CLINICAL PHARMACIST PARTICIPATION IN PREVENTING ADVERSE DRUG REACTIONS IN HOSPITALISED PATIENTS

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Learn from yesterday

Live for today

Hope for tomorrow

The important thing is not to stop questioning.

Albert Einstein

ABSTRACT

Adverse drug reactions (ADRs) are a specific type of drug therapy problem which leads to patient morbidity, mortalities and adds to the overall cost of treatment. Although for many years, Thai hospital pharmacists have been involved in ADR reporting, they have not been active in attempts to prevent them from happening. For this reason, we wished to establish whether a clinical pharmacist's intervention could reduce or prevent ADRs from occurring on two medical wards at Ramathibodi Hospital, a large teaching hospital in Thailand.

Initially, the baseline number of ADRs occurring were determined over a 10 month period. This was followed by an intervention period of 10 months during which a research clinical pharmacist joined the ward medical teams. A total of 1,548 patients were monitored retrospectively for ADRs in the initial phase with 985 patients being studied in the intervention period. It was found that the rate of preventable ADRs was 5.20 per 1,000 patient-days (95% confidence interval, 5.60-4.80) during the baseline period compared with 1.72 patient-days (95% confidence interval, 2.24-1.20) in the intervention period. Thus, the clinical pharmacist's interventions resulted in a reduction of the number of preventable ADRs by 67% ($p<0.001$). In total, the research clinical pharmacist made 143 recommendations to the medical team physician resulting in the prevention of an ADR. These included dosage modification (48.2%), avoidance of a drug-drug interaction (18.9%), inappropriate medication for the disease being treated (14.0%), a request for therapeutic drug monitoring (13.3%) and identification of a history of drug-induced allergy (5.6%). Eighty percent of all research clinical pharmacist recommendations were accepted by the physician and implemented by the medical care team.

In conclusion, the data from the present study showed the value of providing a clinical pharmacy service in reducing the number of drug-induced ADRs. This led to a significant improvement in patient care and cost savings to the health service.

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DEFINITIONS

Adverse Drug Event (ADE)

"an injury due to a medication" (Morimoto *et al.*, 2004).

"an injury resulting from the administration of a drug" (Bates *et al.*, 1993; Hepler and Segal, 2003).

"an injury resulting from a medical intervention related to a drug" (Bates *et al.*, 1995a,b; Hepler and Segal, 2003).

"an injury from a medicine (or lack of intended medicine)" (American Society of Health-System Pharmacists, 1998; Ninno and Ninno, 2001).

"An untoward occurrence after exposure to a drug that is not necessarily caused by the drug" (Pirmohamed *et al.*, 1998).

Adverse Drug Reaction (ADR)

"A response to a drug that is noxious and unintended and occurs at doses normally used in man for the prophylaxis, diagnosis or therapy of disease, or modification of physiological function" (World Health Organization Technical Report Series 1969, 1970; Uppsala Monitoring Centre, 2000; 2002a,b,c; 2004).

"An unwanted or harmful reaction experienced following the administration of a drug or combination of drugs under normal conditions of use and which is suspected to be related to the drug" (Committee on Safety of Medicines, 2002; Royal Pharmaceutical Society of Great Britain, 2003a,b).

"An appreciably harmful or unpleasant reaction, resulting from an intervention related to the use of a medicinal product, which predicts hazard from future administration and warrants prevention or specific treatment, or alteration of the dosage regimen, or withdrawal of the product" (Edwards and Aronson, 2000).

"Any undesirable effect of a drug beyond its anticipated therapeutic effects occurring during clinical use" (Pirmohamed *et al.*, 1998).

"Any unexpected, unintended, undesired, or excessive response to a drug that:

1) requires discontinuing the drug (therapeutic or diagnostic),
2) requires changing the drug therapy,
3) requires modifying the dose (except for minor dosage adjustment),
4) necessitates admission to a hospital,
5) prolongs stay in a health care facility,
6) necessitates supportive treatment,
7) significantly complicates diagnosis,
8) negatively affects prognosis, or
9) results in temporary or permanent harm, disability or death" (American Society of Health-System Pharmacists, 1995).

"Any response to a drug that was noxious and unintended, and that occurred at doses used in humans for prophylaxis, diagnosis or therapy, excluding failure to accomplish the intended purpose" (Karch and Lasagna, 1975).

Adverse event or adverse experience

"Any untoward medical occurrence that may appear during treatment with a pharmaceutical product but which does not necessarily have a causal relationship with the treatment" (Uppsala Monitoring Centre, 2000; 2002a; 2004).

Adverse event

"An injury resulting from medical intervention" This was defined by the Harvard Medical Practice Study (MPS) (Hepler and Segal, 2003).

Adverse reaction or adverse effect

"An adverse outcome that can be attributed to some action of a drug" (Edwards and Aronson, 2000).

Benefit

"An estimated gain for an individual or a population" (Uppsala Monitoring Centre, 2004).

Benefit-risk analysis

"Examination of the favourable (beneficial) and unfavourable results of undertaking a specific course of action. (While this phrase is still commonly used, the more logical pairing of benefit-harm and effectiveness-risk are slowly replacing it)" (Uppsala Monitoring Centre, 2004).

Effectiveness/risk

"The balance between the rate of effectiveness of a medicine versus the risk of harm is a quantitative assessment of the merit of a medicine used in routine clinical practice" (Uppsala Monitoring Centre, 2004).

Efficacy

"The ability of a drug to produce the intended effect as determined by scientific methods, for example in pre-clinical research conditions (opposite of hazard)" (Uppsala Monitoring Centre, 2004).

Harm

"The nature and extent of actual damage that could be caused by a drug. It should not be confused with risk" (Uppsala Monitoring Centre, 2004).

Medication error (ME)

"Any preventable event that may cause or lead to inappropriate medication use or patient harm while the drug is in the control of the health care professional, patient or consumer. Such events may be related to professional practice, health care products, procedures, and systems, including prescribing; order communications; product labelling, packaging, and nomenclature; compounding; dispensing; distribution; administration; education; monitoring and use". This was defined by National

Coordination Council for Medication Error Reporting and Prevention (NCC MERP) (Ninno and Ninno, 2001; Anon., 2005a).

"Inappropriate use of a drug that may or may not result in harm" (Nebeker *et al.*, 2004).

"Any preventable event that may cause or lead to inappropriate medication use or patient harm while the medication is in the control of health professional, patient or consumer" (Department of Health, 2004).

"An unintended act, either of omission or commission, or an act that does not achieve its intended outcome". This was defined by the Joint Commission on Accreditation of Healthcare Organization (JCAHO) (Ninno and Ninno, 2001).

"Any error in the process of prescribing, dispensing or administering a drug, whether their are adverse consequences or not (Van den Bemt *et al.*, 2000a).

Pharmacoepidemiology

"The study of the use and effects of drugs in large populations" (Uppsala Monitoring Centre, 2004).

Pharmacovigilance

"The study of the safety of marketed drugs under the practical conditions of clinical usage in large communities" (Mann and Andrews, 2002a).

"Involves the monitoring, detection, evaluation and responding to drug safety hazards in humans during premarketing development and post-marketing (Shakir and Layton, 2002).

"The science of collecting, researching, assessing and evaluating information from healthcare providers and patients on the adverse effects of medicines, biological products, herbals and traditional medicines" (Uppsala Monitoring Centre, 2002c).

The science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other drug-related problem" (Uppsala Monitoring Centre, 2004).

Potential adverse drug event

"Circumstances that could result in harm by the use a drug but did not harm the patient" (Nebeker *et al.*, 2004).

"A medication error with the potential to cause an injury but which does not actually cause any injury, either because of specific circumstances, chance, or because the error intercepted and corrected" (Morimoto *et al.*, 2004).

"Incidents with potential for injury related to a drug. An example is a patient who received penicillin despite a known allergy to penicillin, but did not react. Included in this category were drug errors that intercepted before the order was actually carried out" (Bates *et al.*, 1995b).

Preventable adverse drug event

"An injury that is the result of an error at any stage in the medication use" (Morimoto *et al.*, 2004).

Risk

"The probability of harm being caused; the probability (chance, odds) of an occurrence" (Uppsala Monitoring Centre, 2004).

Side effect

"Any unintended effect of a pharmaceutical product occurring at a dose normally used in man, which is related to pharmaceutical properties of the drug" (Uppsala Monitoring Centre, 2004).

ABBREVIATIONS

ADE	=	Adverse drug event
ADR	=	Adverse drug reaction
AIDS	=	Acquired immune deficiency syndrome
ASHP	=	American Society of Health-System Pharmacists
ATC	=	Anatomical Therapeutic Chemical
CI	=	Confidence interval
CPOE	=	Computerised physician order entry
DoTS	=	Dose-Time-Susceptibility
EMR	=	Electronic medical record
EU	=	European Union
FDA	=	Food and Drug Administration
G6PD	=	Glucose 6 phosphate dehydrogenase
HIV	=	Human immunodeficiency virus
IOM	=	Institute of Medicine
ICU	=	Intensive care unit
ICH	=	International Conference Harmonisation
JCAHO	=	Joint Commission on Accreditation of Healthcare Organization
LOS	=	Length of stay
ME	=	Medication error
MHRA	=	Medicines and Healthcare products Regulatory Agency
MOPH	=	Ministry of Public Health
MPS	=	The Harvard Medical Practice Study
NCC MERP	=	National Coordinating Council for Medication Error Reporting and Prevention
NHS	=	National Health Service
NPSA	=	National Patient Safety Agency
PEM	=	Prescription Event Monitoring
PMS	=	Post-marketing surveillance
PMR	=	Patient medical record
PSUR	=	Periodic safety update report

RCT	=	Randomized controlled trial
RUCAM	=	Roussel Ulcaf Causality Assessment Method
SD	=	Standard deviation
SLE	=	Systemic lupus erythematosus
SRS	=	Spontaneous reporting system
SJS	=	Steven-Johnsons syndrome
TB	=	Tuberculosis
TDM	=	Therapeutic drug monitoring
UMC	=	Uppsala Monitoring Centre

Chapter 1

General Introduction

CHAPTER 1

GENERAL INTRODUCTION

"If it is preventable then why don't you prevent it?" King Edward VII said when introduced to patients with TB as a preventable disease (Stephens, 2004).

1. BACKGROUND

An adverse drug reaction (ADR) is just one of many drug-related problems which have been recognized in clinical pharmacy practice (Hepler and Strand, 1990; Hepler 2004). In addition, recent publications from the Uppsala Monitoring Centre (UMC) has strengthened ADR awareness by stating "that no drug is 100% safe for all people in all circumstances" (Uppsala Monitoring Centre, 2002a; 2002b; 2004; Hugman, 2005). The extent of the ADR problem has also been highlighted by a meta-analysis carried out by Lazarou *et al.* (1998). It was reported that of all ADRs that occur some 0.32% are fatal, this being between the fourth and sixth most frequent cause of death (Lazarou *et al.*, 1998).

In the USA, following the report "To err is human" by the Institute of Medicine's Committee on the Quality of Health Care in 2000 (Hepler and Segal, 2003; Leape and Berwick, 2005), a number of strategies were developed for preventing drug-related mortality and morbidity and for improving patient safety. Likewise, the National Patient Safety Agency (NPSA) was established by the UK Government in 2001 in order to reduce medication safety problems (Department of Health, 2004; 2005).

The consequences of suffering an ADR are clearly undesirable. They affect patient morbidity and mortality, impact on health care professional management and unquestionably add to the cost of health care. Therefore, health care professionals have a duty to eliminate or reduce drug-induced ADRs. Drug safety is paramount in all aspects of the drug development process. Pre-marketing and post-marketing drug safety monitoring are vitally important processes in establishing the safety profile of a drug and are helpful in identifying potential and real ADRs. Specifically, pharmacovigilance has been developed to cover drug safety monitoring especially post-marketing surveillance (PMS) in order to provide drug safety information once a

medicine has been released onto the market (Lawson, 1997; Meyboom *et al.*, 1997; Talbot and Nilsson, 1998). On the other hand, patient safety involves the concept of quality of care. Patient safety is not confined only to the quality of medication usage. It comprises all procedures related to patient care, such as infection control, anaesthesia, surgery and perioperative medicine. However, prevention of ADRs is one of the most important components of patient safety. Thus, improvement in a drug's safety profile and improved medication management are important if ADRs are to be reduced to a minimum. Clinical pharmacists are experts on medicines because they possess knowledge about all aspects of drug development, pharmacotherapy, and are well-trained in medication usage. Moreover, the pharmaceutical care concept defines a clinical pharmacist's responsibility for optimizing drug therapy in order to improve the quality life of a patient. Without doubt, the clinical pharmacist has a major role to play in decreasing drug-related problems, including a reduction in drug-induced ADRs.

This first chapter will provide essential background information about the general area of ADRs and their prevention or reduction.

2. DEFINITION OF AN ADR

Several definitions have been published for the term "adverse drug reaction". For the purpose of this thesis, it is defined as "any unexpected, unintended, undesired, or excessive response to a drug that: 1) requires discontinuing the drug (therapeutic or diagnostic), 2) requires changing the drug therapy, 3) requires modifying the dose (except for minor dosage adjustment), 4) prolongs stay in a health care facility, 5) necessitates supportive treatment, 6) significantly complicates diagnosis, 7) negatively affects prognosis, or 8) results in temporary or permanent harm, disability or death". This definition is a modification of the ASHP definition (American Society of Health-System Pharmacists, 1995). Common side effects of chemotherapeutic agents such as nausea/vomiting and chill from amphotericin B are not included. The relationship between ADRs, adverse drug events (ADEs), and medication errors (MEs) are shown in Figure 1.1, whilst ADRs which do not cause by MEs and will not be used in this thesis are illustrated in Figure 1.2. Potential drug related harm terms associated with ADRs/ADEs are presented in Table 1.1.

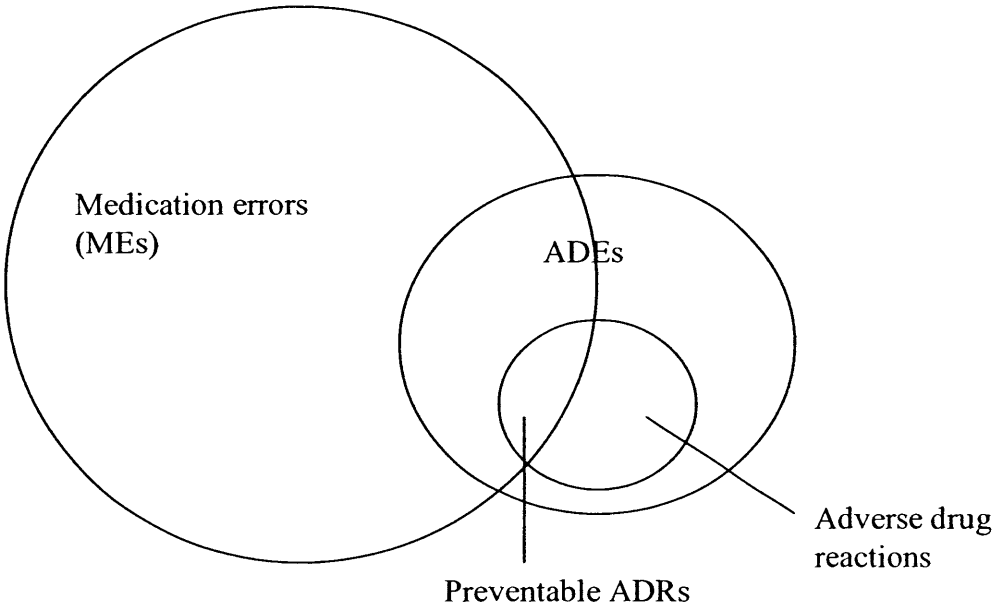

Figure 1.1 Relationship between ADRs, ADEs and MEs shows preventable ADRs result from MEs (American Society of Health-System Pharmacists, 1998; Greory and Kier, 2001).

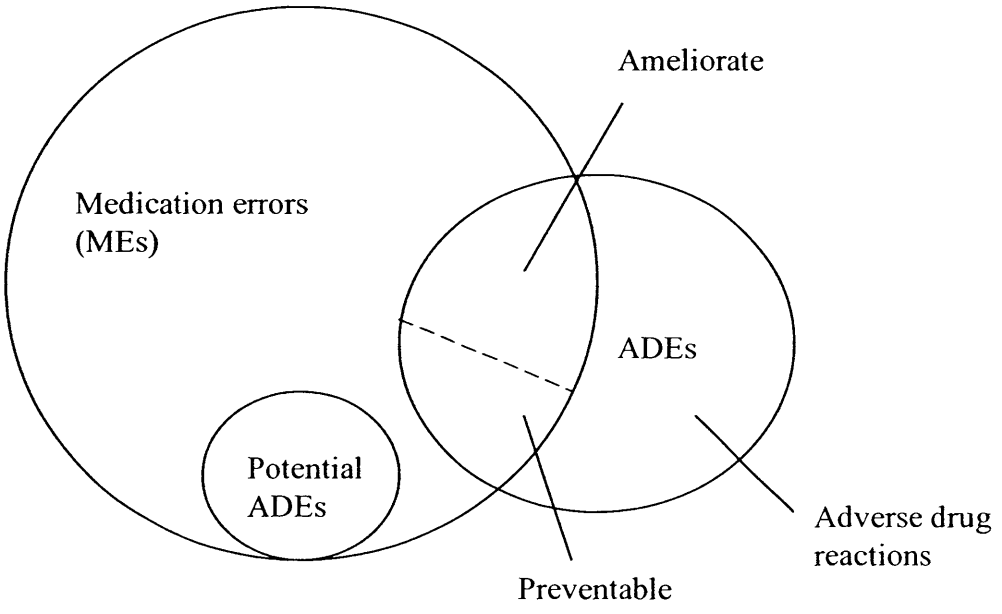

Figure 1.2 Relationship between ADRs, ADEs and MEs shows preventable ADRs which do not result from MEs (Morimoto *et al.*, 2004).

Table 1.1 Drug-related harm terms (Modified from Nebeker *et al.*, 2004)

Terms	Definition
Harm occurred	
Adverse event	Harm in a patient administered but not necessarily caused by a drug.
Adverse drug reaction	Harm directed caused by a drug at normal doses.
Adverse drug event	Harm caused by the use of a drug.
Harm may have occurred	
Medication error	Inappropriate use of a drug that may or may not result harm.
Harm did not occur	
Potential adverse drug event	Circumstances that could result in harm by the use a drug but did not harm the patient.

3. CLASSIFICATION

Drug-induced ADRs can be classified either by their pharmacological mechanism, the severity of the ADR or their preventability.

3.1 Pharmacological mechanism

This relatively simple classification was proposed by Rawlins (1981), ADRs being divided into Type A and Type B. The characteristics of a Type A effect include dose related, predictable with the majority being discovered before drug registration or product launch. In contrast, Type B are not dose related, are unpredictable and the majority are discovered once on the marketing (Rawlins, 1981; Rawlins and Thompson, 1991) as presented in Table 1.2.

Although classifying ADRs into Type A or Type B has been widely accepted, there are several other methods of classifying ADRs. The predictability classification is one such type, and is essentially similar to the Type A/Type B classification. Predictable ADRs include overdoses, adverse effects and interactions between two drugs and between drug and the disease. On the other hand, unpredictable ADRs may result from intolerance, idiosyncrasy, allergy or pseudo-allergy. This classification has been found useful in ADR diagnosis by Hess and Rieder (1997). Details of this classification are presented in Table 1.3. A similar predictability classification has been recommended by Gruchalla (2000) as is presented in Table 1.4.

The predictability classification and Type A/Type B classification are virtually the same as Gharaibeh and colleague's classification which divided ADRs into Type 1 and Type 2 instead of Type A and Type B (Gharaibeh *et al.*, 1998) (see Table 1.5). Although both Type A or Type 1 and Type B or Type 2 are simple to explain, there are some ADRs which do not fit into these classifications. Type C and Type D are used to describe chronic and delayed ADRs, respectively (Royer, 1997; Stephens, 2004) as presented in Table 1.6. Furthermore, Wills and Brown (1999) proposed acronyms for 9 subtypes of ADR. This classification included: - Type A-augmented, Type B-bugs, Type C-chemical, Type D-delivery, Type E-exit, Type F-familial, Type G-genetotoxicity, Type H-hypersensitivity and Type U-unclassified (Table 1.7).

Table 1.2 Pharmacological classification of ADRs by Rawlins (1981).

Features	Type A	Type B
Pharmacology	Augmented	Bizarre
Predictable	Yes	No
Dose-dependent	Yes	No
Morbidity	High	Low
Mortality	Low	High

Table 1.3 Pharmacological classification of ADRs by Hess and Rieder (1997).

Predictable (dose-dependent)	
Overdose	Toxic reaction to specific organ systems due to excessive dose or impaired excretion
Adverse effects	Undesirable pharmacologic effects by mechanisms related to the desired effect
Interactions	
Drug-drug	Action of the drug on the effectiveness or toxicity of another drug
Drug-disease	Certain disease processes interfere with drug metabolism or action
Unpredictable (dose-independent)	
Intolerance	Exaggerated, often disabling effects when medications are given in usual doses
Idiosyncrasy	Genetically determined abnormal reaction to a drug related to metabolic or enzyme deficiency, or altered activation/detoxification pathways
Allergy	Severe, recurrent, immunologically mediated reactions specific to a given agent
Pseudoallergy	Clinically similar to allergic reactions but involve an unknown immune mechanism

Table 1.4 Pharmacological classification of ADRs by Gruchalla (2000).

Type of ADRs	Examples
Type A reactions: Predictable	
Toxicity or overdose	Hepatic failure with high-dose paracetamol
Side effect	Sedation with antihistamines
Secondary effect	Development of diarrhoea with antibiotic therapy due to altered gastrointestinal bacterial flora
Drug interaction	Theophylline toxicity in the presence of erythromycin therapy
Type B reactions: Unpredictable	
Intolerance	Tinnitus with aspirin use
Idiosyncratic reaction	Development of anaemia with the use of antioxidant drugs in the presence of glucose-6-phosphate dehydrogenase deficiency
Hypersensitivity (immunological) reaction	Anaphylaxis with penicillin administration
Pseudoallergic (non-immunological) reaction	Radiocontrast dye reaction

Table 1.5 Pharmacological classification of ADRs (Gharaibeh *et al.*, 1998).

	Type 1	**Type 2**
Synonyms	Augmented, predictable, toxic, quantitative, dose-related	Bizarre, unpredictable, allergic, idiosyncratic, or drug intolerance, qualitative, dose-independent
Mechanism	Predictable, understood	Usually poorly understood
Site	1. Same site of primary drug action 2. Another site for primary and secondary actions	Unrelated to the site of action
Incidence	High (70%)	Low (30%)
Morbidity	Mild	Severe
Mortality	Low	High
Causes:		
Pharmaceutical	Increased availability at site of absorption: quantity and release of dosage form	Decomposition products, additives, excepients, etc.
Pharmacokinetic	Increased level at site of action due to abnormalities of "A, D, M, E"*	Liberation of an abnormal metabolite
Pharmacodynamic	1. Enhanced organ or tissue responsiveness due to enhanced number or sensitivity of receptors 2. Homeostatic imbalance 3. Disease state	1. Genetic 2. Immunologic 3. Neoplastic 4. Teratologic
Reproducibility	Reproducible	Not reproducible
Treatment	Adjust the dose	Stop treatment

*A, D, M, E = Absorption, distribution, metabolism, and elimination.

Table 1.6 Type A/ Type B/ Type C and Type D pharmacological classification of ADRs (Royer, 1997; Stephens, 2004).

Type A (augmented)	Reactions that result from an exaggeration of a drug's normal pharmacological actions when given in the usual therapeutic doses; normally dose dependent. Sometimes referred to as Type 1.
Type B (bizarre)	Those that represent a novel response not expected from known pharmacological action. Sometimes referred to as Type 2.
Type C (chronic)	Adaptive changes, rebound phenomena, other long-term effects.
Type D (delayed)	Carcinogenesis, effects concerned with reproduction (impaired fertility), teratogenesis (adverse effects on the foetus during the early stages of pregnancy), adverse effects on the foetus during the later stages of pregnancy, drugs in breast milk.

Table 1.7 Pharmacological classification of ADRs by Wills and Brown (1999).

Type A	Pharmacologically predictable, dose related, improves if medicine withdrawn, common
Type B	Pharmacologically predictable, involves interaction with a micro-organism, improves if medicine withdrawn
Type C	An irritant reaction, related to drug concentration
Type D	Caused by method of administration or nature of formulation, improved if medicine withdrawn of delivery changed
Type E	Pharmacologically predictable, begins only when medicine stopped or dose reduced
Type F	Only occurs in those genetically predisposed, improves if medicine withdrawn
Type G	Causes irreversible genetic damage
Type H	Requires activation of immune system, improves if medicine withdrawn
Type U	Mechanism not understood

Interestingly, these subtypes are not the same as Edwards and Aronson proposed (Edwards and Aronson, 2000). Their classification consisted of Type A-dose-related, Type B-non-dose-related, Type C-dose-related and time-related, Type D-time-related, Type E-withdrawal and Type F-unexpected failure of therapy (Table 1.8). Recently, Aronson and Ferner (2003) developed a new approach to classifying ADRs being related to a three dimensional approach. Based on dose related, time related and susceptibility (DoTS), they considered that the old classification which was based on dose response was inadequate. Examples of this new three dimensional classification are presented in Table 1.9.

3.2 Severity classification

Stephens (2004) proposed that the severity of an ADR could be divided into mild, moderate and severe. He defined severity as follows:

Mild	Slightly bothersome; relieved with symptomatic treatment.
Moderate	Bothersome, interferes with activities; only partially relieved with symptomatic treatment.
Severe	Prevents regular activities; not relieved with symptomatic treatment.

Previously, others divided severity into four levels (Bergman *et al.*, 1971; Bennett and Lipman, 1977):

Mild or minor	No antidote, therapy or prolongation of hospitalisation required.
Moderate	A change in drug therapy, specific treatment or an increase in hospitalisation by at least one day required.
Severe	Potentially life threatening causes permanent damage or required intensive medical care.
Lethal	Directly or indirectly contributed to the death of the patient.

In contrast, Harwig *et al.* (1992) divided ADR severity into seven levels as presented in Table 1.10.

Table 1.8 Pharmacological classification of ADRs by Edwards and Aronson (2000).

Type of reaction	Mnemonic	Features	Example
A: Dose-related	Augmented	Common Related to a pharmacological action of the drug Predictable Low mortality	• Toxic effects: Digoxin toxicity; serotonin syndrome with SSRIs • Side effects: Anticholinergic effects of tricyclic antidepressants
B: Non-dose-related	Bizarre	Uncommon Not related to a pharmacological action of the drug Unpredictable High mortality	• Immunological reactions: penicillin hypersentivity • Idiosyncratic reactions: Acute porphyria Malignant hyperthermia Pseudoallergy (e.g. ampicillin rash)
C: Dose-related and time-related	Chronic	Uncommon Related to the cumulative dose	• Hypothalamic-pituitary-adrenal axis suppression by corticosteroids
D: Time-related	Delayed	Uncommon Usually dose-related Occurs or becomes apparent some time after the use of the drug	• Teratogenesis (e.g. vaginal adenocarcinoma with diethylstilbestrol) • Carcinogenesis • Tardive dyskinesia
E: Withdrawal	End of use	Uncommon Occurs soon after withdrawal of the drug	• Opiate withdrawal syndrome • Myocardial ischemia (β-blocker withdrawal)
F: Unexpected failure of therapy	Failure	Common Dose-related Often caused by drug interactions	• Inadequate dosage of an oral contraceptive, particularly when used with specific enzyme induces

SSRIs = Serotonin-selective reuptake inhibitors

Table 1.9 Example of the DoTS (dose-time-susceptibility) classification by Aronson and Ferner (2003).

Drugs	ADRs	DoTS classification
Osteoporosis	Corticosteroids	Do-collateral effect; T-late; S-age, sex
Anaphylaxis	Penicillin	Do-hypersensitivity; T-first dose; S-not understood; requires previous sensitisation
Hepatotoxicity	Isoniazid	Do-collateral effect; T-intermediate; S-genetic (drug metabolism), age, exogenous (alcohol), disease (malnutrition)

Table 1.10 Severity classification of ADRs (Hartwig *et al.*, 1992).

Level	Features
1	An ADR occurred but required no change in treatment with suspected drugs.
2	The ADR required that treatment with the suspected drug be held, discontinued, or otherwise changed. No antidote or other treatment required: no increase in length of stay (LOS).
3	The ADR required that treatment with the suspected drug be held, discontinued, or otherwise changed, and/or an antidote or other treatment was required. No increase in LOS.
4	(a) Any level 3 ADR which increases LOS by at least one day, or (b) The ADR was the reason for admission.
5	Any level 4 ADR which required intensive medical care.
6	The adverse reaction caused permanent harm to the patient.
7	The adverse reaction either directly or indirectly led to the death of the patient.

LOS = Length of stay

3.3 Preventability classification

In determining whether an ADR can be prevented, Schumock and Thornton (1992) proposed that seven questions should be posed. Answering yes to one or more of these questions indicated that the ADR was preventable. For example,

i) Was the drug involved in the ADR not considered appropriate for the patient's clinical condition?

ii) Was the dose, route, and frequency of administration not appropriate for the patient's age, weight and disease state?

iii) Was required therapeutic drug monitoring or other necessary laboratory test not performed?

iv) Was there a history of allergy or previous reactions to the drug?

v) Was a drug interaction involved in the reaction?

vi) Was a toxic serum drug level documented?

vii)Was poor compliance involved in the reaction?

4. CAUSALITY ASSESSMENT

The relationship between adverse events and suspected drugs namely ADR causality assessment is vitally important. Unfortunately, as a result of incomplete patient information and a lack of full drug safety information (i.e. frequency, mechanism and risk factors of ADR occurring) an ADR causality assessment is difficult (Meyboom *et al.*, 1997). Causality assessment is helpful in patient care since it helps health care providers to decide appropriate effectiveness/risk management and optimization of drug therapy. Shakir (2004) has recently suggested that an ADR causality assessment should be based on five situations; whether the ADR was identified as a result of a clinical research project, a regulatory authority or a pharmaceutical company initially receiving an ADR report, then the receipt of follow-up information, signal generation and an investigating safety issue or writing in a safety update report.

In general, the methods for assessing ADR causality are based on three types (Naranjo, 1986; Naranjo *et al.*, 1992; Shakir, 2004) as follows:

i) A global introspection or a clinical judgement

This method depends on the ability or experience of the assessor or health care provider who took the initial decision. Because it has no structural establishment, it is

not difficult to assess. However, use of this approach needs to be cautiously interpreted due to its inconsistency, unreliably and lack of transparency (Naranjo *et al.*, 1992; Shakir, 2004).

ii) A structured set of questions or an algorithm

As a consequence of the non-structural method of clinical judgement, a number of structured questions have been developed. In fact, more than 20 causality algorithms have been published in the literature (Stephens, 1987). Although there are many algorithms for causality assessment of adverse events, basically they are categorised into two major types i.e. flow charts or table types, and scoring systems. Karch and Lasagna (1977) and Jones's algorithm (Michel and Knodel, 1986) are well known examples of the first group whilst Kramer's algorithm (1979), Naranjo's algorithm (1981) and the Roussel Ulcaf Causality Assessment Method (RUCAM) (Benichou *et al.*, 1993; Danan and Benichou, 1993; Benichou, 1994) are examples of the scoring algorithm group. Moreover, the European Union (EU) pharmacovigilance method and WHO's causality assessment technique have also been widely used (Meyboom *et al.*, 1997; Uppsala Monitoring Centre, 2000; 2004). Interestingly, the table type causality assessment method has been used in Thailand (Pummangura, 2001), although to date it has not yet been tested for reliability and validity in practice.

iii) The Bayesian probability approach

The probability of an association existing between a suspected drug and an adverse event is calculated according to Bayesian theory (Naranjo *et al.*, 1992; Meyboom *et al.*, 1997). Although this method is reproducible, it is not suitable for practical use because it is labour intensive and time consuming.

Although there are various methods for assessing ADR causality, the principle concepts originate from six themes (Shear, 1990; Recchia and Shear, 1994). A clinical diagnosis is obtained as the first step. Secondly, a detailed drug history and the timing of any medication to which the patient has been exposed are analysed to establish if a time-line relationship between the adverse event and drug exposure exists. Thirdly, a differential diagnosis is conducted in order to distinguish between possible diseases. Fourthly, de-challenge is performed by stopping any suspected drug or drugs. Fifthly, the drug/drugs are reintroduced (re-challenge). Lastly, all available laboratory data is

examined. Unfortunately, the last two approaches are not easily conducted in daily practice because of ethical issues and the fact that frequently no laboratory test data are available (Naranjo *et al.*, 1992; Edwards and Aronson, 2000). These basic principles have been reviewed by Gruchalla (2000). Nevertheless, ADR causality assessment is often controversial with inter- and intra-rates rarely reaching full agreement. For example, the agreement between expert physicians and a probability scale was found to be less than 50% (Gharaibeh *et al.*, 1998). Furthermore, the recent work of Arimone *et al.* (2005) failed to find full agreement with global introspection at any level of causality assessment. Others have similarly published disagreements between expert opinion and published causality assessment data (Macedo *et al.*, 2003).

5. METHODS OF DETECTING ADVERSE DRUG REACTIONS

Although licensed medicines have already received approval from a regulatory agency (i.e. the Medicines and Healthcare products Regulatory Agency (MHRA) in the UK or the Food and Drug Administration (FDA) in the US), this do not guarantee that the medicine is completely safe. This is because at the clinical trial stage of the pre-registration development process, too few and highly specific subjects are recruited, the studies are for short periods and are only for certain indications (Edwards, 1987; Edwards, 1997; Stricker and Psaty, 2004; Gough, 2005; Okie, 2005). As a consequence, post-marketing surveillance or ADR monitoring is important to add to the safety profile of a medicine. This surveillance consists of several different approaches such as anecdotal reporting, voluntary organized reporting, intensive event monitoring, cohort studies, case-control studies, case-cohort studies, population statistics, record linkage and meta-analysis. The strengths and weaknesses of each of these methods is summarised in Table 1.11. Clearly voluntary organized reporting or the spontaneous reporting system (SRS) is the backbone of this type of surveillance. This is due to its simplicity, low cost and the fact that it is not time consuming (Edwards, 1997). Thus, this process is extremely valuable (Ahmad, 2003). An anecdotal reporting system or case report method provides an important source of information when considering drug withdrawal (Arnaiz *et al.*, 2001). However, due to

Table 1.11 Strengths and weaknesses of surveillance methods used to detect ADRs from Edwards and Aronson (2000).

Method	Strength	Weakness
Anecdotal reporting	Simple; cheap	Relies on individual vigilance and astuteness
Voluntary organized reporting	Simple	Under-reporting
Intensive event monitoring	Easily organized	Selected population studied for a short time
Cohort studies	Can be prospective; good at detecting effects	Very large numbers required; very expensive
Case-control studies	Excellent for validation and assessment	Will not detect new effects; expensive
Case-cohort studies	Good for studying rare effects with high power	As for cohort and case-control studies; complex calculations
Population statistics	Large numbers can be studied	Difficult to coordinate; retrospective; relies on accurate records
Record linkage	Excellent if comprehensive	Time-consuming; expensive; relies on accurate records
Meta-analysis	Uses data that have already been obtained	Need to obtain unpublished data; heterogeneity of different studies

under-reporting (Edwards and Aronson, 2000; Gough, 2005), other methods have been developed such as Prescription Event Monitoring (PEM) in the UK (Sue Wood Symposium, 1999; Wong, 1999), and Japan-PEM (Kubota, 2002) although their data been does not cover hospitalised patients (Wong, 1999; Breckenridge *et al.*, 2005). In brief, the current methods of detecting an ADR are categorised into hypothesis-generating methods and hypothesis-testing methods. Spontaneous reporting and Prescription Event Monitoring (PEM) are both useful for generating a signal of a potential ADR. On the other hand, epidemiological studies including cohort and case-control studies, and randomized controlled trials (RCTs) are the methods best suited to hypothesis testing (Mann and Andrews, 2002b).

6. EPIDEMIOLOGY AND CONSEQUENCES

An ADR is simply just one type of drug-induced disease. Thus, the principle of frequency measurement can be applied (i.e. prevalence, incidence and rate). However, there are some drugs which can cause more than one ADR which complicates the relationship between numerator and denominator. A "ratio" is calculated when the numerator is divided by the denominator which generates three different epidemiology terms: "proportion", "percentage" and "rate". Proportion is used when the numerator is a subset of the denominator, whereas rate is used when the numerator is distinguishable from the denominator (Hennekens and Buring, 1987).

As one might expect, the exact frequency of an ADR occurring (i.e. prevalence, incidence and rate) is generally unknown due to variations in the pattern of national prescribing, definitions and causality assessment, the method used to identify a suspected ADR, the type of health institution and the general problem of under-reporting (Stephens, 2004). The frequency of a new or serious ADR occurring in the general population has been reported to be only 0.6-2.0%, whilst it has been estimated to be 10-30% for hospitalised patients (Sweet and Ryan, 1994). In fact, the frequency of an ADR occurring covers a wide spectrum of values as presented in Tables 1.12, 1.13, and 1.14, where frequencies of ADRs occurring in ambulatory patients, the number of ADRs resulting in hospital admission and ADRs occurring during hospitalisations can be compared.

Table 1.12 Examples of the ADE frequencies in ambulatory patients.

Countries (References)	Setting	Sample selection	Methods to detect an ADE	Definition and causality assessment of an ADE	Number of ADEs
USA (Gandhi *et al.*, 2003)	Four adult primary care practices in two hospital based and two community based	661 patients	Patient survey and chart review	-Two dependent reviewers	162 (25%) ADE patients; 20 out of 181 ADEs (11%) were preventable
USA (Gurwitz *et al.*, 2003)	Ambulatory care clinics	All Medicare enrollees i.e. 30,397 elderly person-years	-Reports from health care providers; -review of hospital discharge summaries; -review of emergency department notes; -computer-generate signals; -automated free-text review of electronic note; -and review of administrative incident reports	-An ADE by Bate's definitions -Dependent reviewers	1,523 ADEs; 421 (27.6%) were preventable ADEs

Table 1.13 Examples of the frequencies ADRs or ADEs resulting in hospital admission.

Countries (References)	Setting	Sample selection	Methods to detect an ADR/ADE	Definition and causality assessment of an ADR/ADE	Number of ADRs/ADEs
Australia (Dartnell *et al.*, 1996)	A tertiary hospital	965 admissions during 30 consecutive days	Medical record review	-WHO's ADR definition -Karch and Lasagna algorithm	55 ADRs (5.7%); definitely preventable 5.5%, possible preventable 60.0%
France (Olivier *et al.*, 2002)	A teaching hospital	671 admissions during 4 weeks	Medical record review	-WHO's ADR definition -French causality assessment	44 ADRs in 41 patients
UK (Pirmohamed *et al.*, 2004)	Two large general hospitals	18,820 patients admissions over 6 months	Medical record review	-Edwards and Aronson's definition -Naranjo's algorithm and Jones' algorithm	1,225 admissions related to an ADR

Table 1.14 Examples of the frequencies ADRs or ADEs during hospitalisation.

Countries (References)	Setting	Sample selection	Methods to detect an ADR/ADE	Definition and causality assessment of an ADR/ADE	Number of ADRs/ADEs
UK (Hurwitz and Wade, 1969)	A general hospital, 7 selected wards	1,160 patients	Medical record review	-ADRs: any adverse response to medication undesired or unintended	129 ADRs in 118 patients
USA (Classen *et al.*, 1991; 2005)	A teaching hospital	36,653 hospitalised patients	SRS and computerised ADE signal	-WHO's definitions -Naranjo's algorithm	731 ADEs in 648 patients
USA (Suh *et al.*, 2000)	A teaching hospital	9,311 admissions	SRS	-WHO's definition -Naranjo's algorithm	146 patients occurred during hospitalisation & 50 patients were admitted by ADRs
Germany (Dormann *et al.*, 2000)	A university hospital, a medical ward	379 patient admissions during 6 month period	Computerised automatic laboratory signal and stimulated SRS	-WHO's definition -Naranjo's algorithm with some adaptation	34 ADRs by computerised detection and 17 ADRs by stimulated SRS
Switzerland (Fattinger *et al.*, 2000)	Two university hospitals, a medical ward	4,331 hospitalised patients	Computer-supported data entry system and electronic patient record	-Karch and Lasagna's definition and algorithm -A clinical relevant ADR was defined as an ADR resulting in adverse events considerable discomfort, drug withdrawal or dose reduction and/or initiation of therapeutic measures.	11% clinical relevant ADRs of all hospitalisation and 3.3% of all hospitalisation caused by ADRs

SRS = Spontaneous reporting system; WHO = World Health Organisation

Table 1.14 Examples of the frequencies ADRs or ADEs during hospitalisation (cont.).

Countries (References)	Setting	Sample selection	Methods to detect an ADR/ADE	Definition and causality assessment of an ADR/ADE	Number of ADRs/ADEs
France (Lagnaoui *et al.*, 2000)	A teaching hospital, a medical ward	444 admissions (2,569 patient-days)	Medical record review	-An ADR was defined as a clinical or biological abnormality associated with the use of a drug. -Panel assessment	21 patients (4.7%) developed 26 ADRs during hospitalisation
USA (Senst *et al.*, 2001)	Four teaching hospitals	3,187 admissions during 53-day period	Medical record review	Bates's ADE definition	74 ADEs and 11 preventable ADEs
UK (Emerson *et al.*, 2001)	A teaching hospital	303 hospitalised patients who received newly marketed drugs during 10 month period	Medical record review by a clinical pharmacist		21 suspected ADRs (7%)
USA (Gurwitz *et al.*, 2005)	Two academic long-term care setting	1,247 long-term care residents	Medical record review	-Bate's ADE definition -Expert reviewers	815 ADEs, 42% preventable and thus, overall rate ADEs was 9.8 per 100 resident-months with rate of 4.1 preventable ADEs per 100 resident-months.

Lazarou *et al.* (1998) carried out a meta-analysis based on ADRs occurring at thirty-nine hospitals in the USA and showed that 0.32 percent (95% CI; 0.23-0.41) of hospitalised patients suffered a fatal ADR. Elsewhere, it has been reported that ADRs led to between 4.2 and 6.0 percent of hospital admissions and approximately 5.0 percent of outpatients suffer an ADR (Stephens, 2004). In addition, a recent UK study of ADRs causing hospital admission indicated that 1,225 admissions related to an ADR in a total of 18,820 patients. This results in a prevalence of 6.5 percent (Pirmohamed *et al.*, 2004). Stephens (2004) also provided an overall ADR incidence rate during hospitalisation of between 1.7 and 29.0 percent.

The financial cost of an ADR has also been studied and demonstrates the economic burden caused to society by an ADR. The costs of ADRs were viewed from the patient, the physician, the manufacturer and the nation by Stephens (2004), while the cost of treating illness resulting from an ADR and the cost of avoiding them was published by Lundkvist and Jonsson (2004). In England and Wales, as a consequence of drug prescribing errors causing an ADR, an additional stay in hospital of 8.5 days was recorded at a cost to the NHS of £1.1 billion (Eaton, 2002). Conversely, at a teaching hospital in the USA it was found that an ADR resulted in an additional mean length of stay per patients of 3.8 days with increased total hospital costs of $5,483 (Suh *et al.*, 2000).

7. PREDISPOSING FACTORS

As a consequence of the significant burden to society of ADRs occurring, health care providers have no choice but to eliminate or reduce this problem to a minimum. Thus, identifying risk factors of an ADR occurring is a key step to reducing or "preventing" an ADR occurring and to ameliorate its severity (Kelly, 2001a,b; Calis and Young, 2004). Furthermore, knowledge of risk modifications has been suggested for predicting an ADR (Holland and Degruy, 1997). The Uppsala Monitoring Center (2004) defined predisposing factors as "any aspect of the patient's history (other than the drug) which might explain reported adverse events i.e. genetic factors, diet, alcohol consumption, disease history, polypharmacy or use of herbal medicines". Such risk factors might be grouped into prescribing factors, drug factors and patient factors (Ritter *et al.*, 1994).

An ADR is an aspect of drug responsiveness which nobody wants and is associated with one's genes, the environment and behaviour (Tucker, 2004). Predisposing factors tend to be related to the basic principles of clinical pharmacology, pharmacokinetics and pharmacodynamics and will have been studied in the development of a new drug (Atuah *et al.*, 2004; Walker, 2004). To date, a knowledge of pharmacogenetics and pharmacogenomics has only just been integrated into drug development in order to reduce ADRs occurring (Ozdemir, 2001; Atuah *et al.*, 2004; Haga and Burke, 2004). Individualization of drug responses is the major role of pharmacogenetics, this being related to the concentration of drug at its site of action. Polymorphism can affect drug responsiveness via the process of drug metabolism, drug transportation and drug targeting (Meyer, 2000; Ingelman-Sundberg, 2001; Pirmohamed and Park, 2001; Evans and McLeod, 2003; Pirmohamed and Park, 2003; Ingelman-Sundberg, 2004; Severino and Zompo, 2004). The relationship between drug response and pharmacogenetics, pharmacokinetics and pharmacodynamics is shown in Figure 1.3. It should also be noted that therapeutic failure might occur if there is an inadequate drug receptor response (Johnson, 2003).

Interestingly, ADRs were originally classified as Type A and Type B according to the Rawlins and Thompson pharmacological classification (Rawlins and Thompson, 1991). Then, risk factors were presented as Type A and Type B risk factors. Because Type A ADRs were classified by pharmacological action, all factors which could affect concentrations of the drug at its site of action are determined as Type A risk factors. Routledge (2004) reviewed risk factors and separated them into Type A and Type B risk factors. Type A risk factors consisted of pharmacological and pharmaceutical factors, pharmacokinetic factors, pharmacogenetic factors and pharmacodynamic factors. On the other hand, Type B risk factors might include drug allergies and all factors predisposed to drug allergy. In addition, G6PD deficiency and long QT syndrome are also affected by a pharmacogenetic factor.

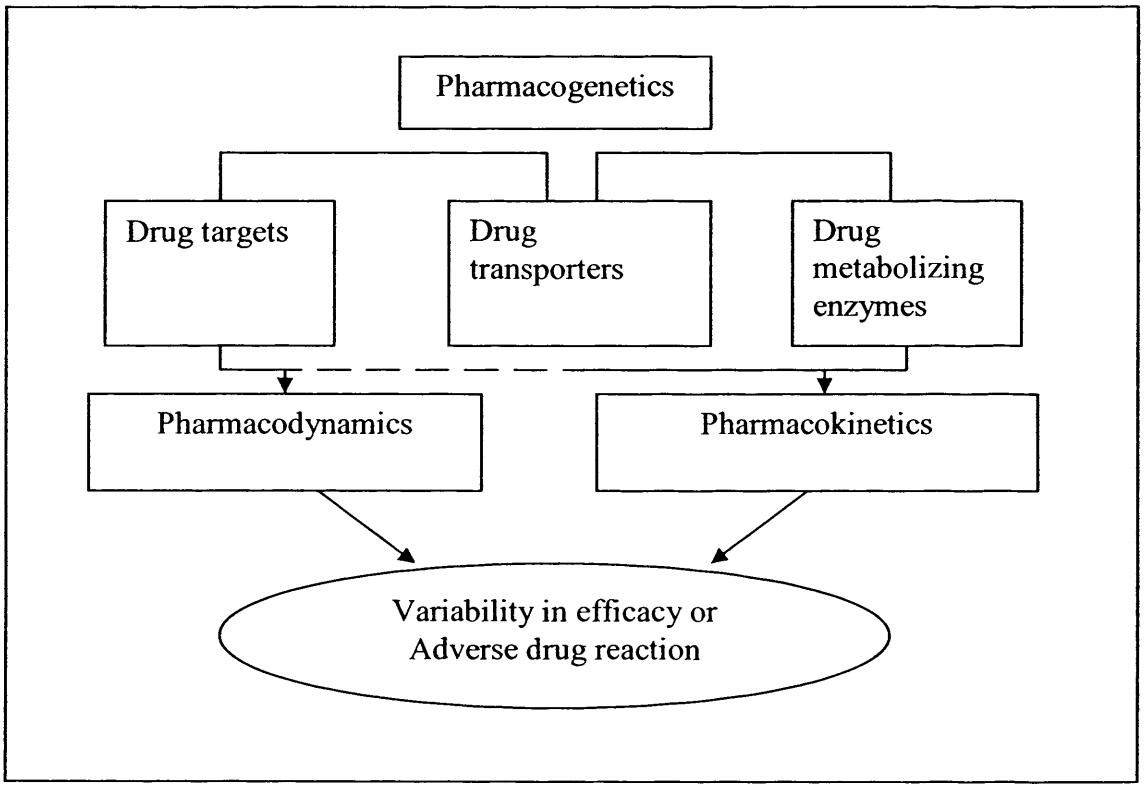

Figure 1.3 Relationship between pharmacogenetics and ADRs (Johnson, 2003) (The broken line indicates that drug transporters are also occasionally the drug target, in addition contributing to drug pharmacodynamics).

Other risk factors focus on immune and non-immune events. Non-immune related ADRs include gender, serious illness, renal insufficiency, liver disease, polypharmacy, HIV infection, Herpes infection, alcoholism and systemic lupus erythematosus. On the other hand, hypersensitivity drug reaction risk factors include the female gender, adult, HIV infection, concomitant viral infection, previous hypersensitivity to a chemically-related drug, asthma when using a beta-blocker, specific genetic polymorphisms and systemic lupus erythematosus (Riedl and Casillas, 2003). According to Callis and Young (2004), risk factors for an ADR occurring include the concurrent use of multiple medications, the presence of multiple co-morbid conditions, the drug dose and duration of exposure, extremes of age (i.e. neonates, children, and the elderly), the female gender, genetic predisposition, prior history of drug hypersensitivity and drug reactions, end-organ dysfunction, altered physiology, inappropriate medication prescribing or use of monitoring, lack of patient education and other systems failure. Reviews related to gender and pharmacokinetics/ pharmacodynamics (Harris *et al.*, 1995; Kando *et al.*, 1995; Gandhi *et al.*, 2004; Anderson, 2005) confirm that being female is a predisposing factor for an ADR occurring being associated with differential physiological and pharmacokinetic parameters. The long QT syndrome is a good example of a significant pharmacodynamic gender difference (Drici and Clement, 2001). Anti-retroviral drugs have also been found to result in an ADR more frequently in female patients than males (Ofotokun and Pomeroy, 2003).

Physiological changes resulting from ageing may also be a predisposing factor for an ADR occurring (Routledge *et al.*, 2003; McLean and Le Couteur, 2004). Indeed, in a cohort study, it was found that elderly patients are strongly predisposed to an ADR occurring (Martin *et al.*, 1998). Risk factors have also been investigated by intensive ADE monitoring in hospitalised patients. It was found that the number of drugs used per patient and the starting of a new drug treatment regime were the most important risk factors for an ADE occurring (Van den Bemt *et al.*, 2000b). Recently, socio-demographic factors have been investigated in elderly patients. It was found that worse nutrition, the number of drugs consumed and renal disease were important factors relating to the prevalence of ADR in hospital admissions (Caamano *et al.*, 2004). Interestingly, Evans *et al.* (2005) identified a number of predisposing factors when comparing 4,291 cases of an ADR with 64,544 controls. This study categorised

predisposing factors into three main groups; patient characteristics, drug administration and patient type. It also divided ADRs occurring according to the most common groups of drugs causing ADRs and the severity of ADRs. The important findings of this study and other predisposing factors for an ADR occurring are presented in Table 1.15.

8. ADR PREVENTABILITY ASSESSMENTS

Although many ADRs can be predicted and thus avoided, not all of them can be prevented. Olivier *et al.* (2002) suggested that there is no gold standard for preventability assessment, whereas use of the "so-called" expert reviewer was one of the methods reported by Bates *et al.* (1995b) this being suggested as being the gold standard by Hepler and Segal (2003). As the result, preventability assessment is not generally easy and frequently it is complicated.

Schumock and Thornton (1992) suggested a number of criteria to be considered in preventability assessment. These included seven specific questions that related to ADR clinical situations and the medication use process. Details of the questions are described earlier (see page 14). This preventability assessment process results in an ADR being classed as either "preventable" or "non-preventable".

Olivier *et al.* (2002) described a preventability assessment process which consisted of three sets of questions based on drug factors, patient factors and prescription factors. Details of each question are presented in Table 1.16. A summated score of under or equal to -2 was judged as an ADR "definitely not preventable", -1 to 8 indicated a "potentially preventable" ADR and a score of 9 and over indicated an ADR which was "definitely preventable". A little later, Dartnell *et al.* (1996) measured avoidability relating to drug therapy by asking six questions:

i) was the suspected drug judged to be indicated or contraindicated?
ii) did the dosage used differ from the accepted recommendations?
iii) had there been adequate monitoring?
iv) had there been adequate counselling?
v) could an alternative or no drug therapy have been undertaken?
vi) was admission likely regardless of the inappropriate use of drug therapy?

Table 1.15 Predisposing factors for an ADR or ADE occurring.

Countries (References)	Predisposing factor assessing methods	Number of ADR/ADE patients	Predisposing factors
UK (Hurwitz, 1969)	Comparing patients with and without ADRs	118 patients with ADRs and 1,160 controls	Significantly more patients of 60 years and over, more women than men, patients receiving more drugs, a previous ADRs and a previous drug allergy
UK (Martin *et al.*, 1998)	48 PEM cohort studies in general practice	513,608 patients (221,781 males)	Suspected ADRs more common with age between 30-59 years and 60% in women
USA (Tran *et al.*, 1998)	Compared percentage male and female patient who occurred ADRs	2,367 patients who visited at ADR clinic	Female gender
Switzerland (Fattinger *et al.*, 2000)	Comparing 1) patient without ADRs 2) patient admitted for ADRs and 3) patient with clinically relevant ADRs	1) 3,193 patients without ADRs 2) 134 patients with ADRs related to admission 3) 297 patients with clinically relevant ADRs	Female gender, polypharmacy
The Netherlands (Van den Bemt *et al.*, 2000b)	Logistic regression analysis determined the relationship between ADEs and proposed risk factors	149 patients who occurred at least one ADR out of 539 patients.	The number of drugs used per patient and the starting of a new drug during hospitalisation
France (Montastruc *et al.*, 2002)	Spontaneous ADR reports from French pharmacovigilance centre	927 ADRs	Female gender

PEM = Prescription event monitoring

Table 1.15 Predisposing factors for an ADR or ADE occurring (cont.).

Countries (References)	Predisposing factor assessing methods	Number of ADR/ADE patients	Predisposing factors
Italy (Caamano *et al.*, 2004)	Logistic regression analysis determined the association between ADRs and socio-demographic variables	878 ADRs resulted in hospital admissions out of 19,070 elderly patients	Nutritional problems, renal failure, using two or more drugs, cognitive impairment
USA (Evans *et al.*, 2005)	Conditional logistic regression analysis from match case-control comparison	4,291 cases and 64,544 controls	1) patient characteristics – female, age, weight, and number of co-morbidities 2) drug administration – dosage, administration route, and number of concomitant drugs and 3) patient type – service, nursing division, and diagnosis-related group
USA (Gurwitz *et al.*, 2005)	Multivariate analysis by matched case-control comparison	476 cases and 476 controls	Patients taking antipsychotic agents, anticoagulants, diuretics and antiepileptics

Table 1.16 Preventability assessment scores by Imb (Olivier *et al.*, 2002).

Questions	Score
The drugs	
Knowledge about the drug and its possible role	
Hypothesis, still debated	+1
A matter of worry, diffused by publications or work in progress	+2
Causality established	+3
Communication about this knowledge	
Reassuring about a lack of danger	0
Relatively worrying	+2
Serious cause for concern about presence of danger	+3
The patient	
Clinical case: risk factors	
No risk factors	0
Risk factors hardly detectable	+2
Presence of risk factors, easy to detect	+3
Drug management	
Respect of recommendation(s) or lack of precaution(s) has played any role in this case	0
Recommendation(s) not applies easily in this patient	+2
Neglect of recommendation(s), easy to apply by the prescriber or the patient	+3
Prescription	
Conditions of prescription	
Prescription indispensable to the patient	-12
Questionable prescription but acceptable	-4
Needless or absolutely contra-indicated prescription (or inappropriate prescription)	+3
Management of the adverse reaction	
Excellent, with prevention of the aggravation of the adverse reaction	0
Inadequate	+2
Absent, with aggravation of the reaction	+3

Although Petersen *et al.* (1994) reported a scaling system for assessing the preventability of adverse events, the rating scale for this assessment was based on the opinions of a panel of three physicians.

9. CHARACTERISTICS OF PREVENTABLE ADRs

In this section, only the characteristics of preventable ADRs in hospitalised patients have been reviewed. The selected studies have focused on preventing ADRs and/or ADEs. For example, Bates *et al.* (1993) found that there were 73 drug-related incidents out of 420 patient admissions during a 37-day period in a tertiary care hospital. Drug-related incidents consisted of 27 ADEs, 34 were potential ADEs and 12 consisted of problem orders. Preventability assessment was categorised as being definitely preventable, probably preventable, probably not preventable and definitely not preventable, this assessment being performed by two independent reviewers. The definitely or probably preventable ADEs accounted for 15 out of 27 events (56%).

Pearson *et al.* (1994) assessed ADR reports using the Schumock and Thornton criteria (1992). They found that thirty-eight out of 203 ADR reports were preventable. The majority of these preventable ADRs consisted of medication usage in known with a drug allergy history, the absence of anticoagulant or thrombolytic drug therapy monitoring and poor renal dosage adjustment in renal insufficiency patients.

Bates *et al.* (1995b) randomized 4,031 patient admissions from two tertiary care hospitals in order to detect ADEs and potential ADEs. The characteristics of each ADE was assessed by two physician reviewers. Preventability assessment was classified as in an earlier study (Bates *et al.*, 1993) as definitely preventable, probably preventable, probably not preventable and definitely not preventable. It was found that there were 247 ADEs and 194 potential ADEs which when extrapolated was equal to 6.5 ADEs per 100 non-obstetric admissions and 5.5 potential ADEs per 100 non-obstetric admissions. Preventable ADEs accounted for 70 out of 247 ADEs (28%). The top three drug-groups involved in preventable ADEs were analgesics (30%), antibiotics (24%) and sedative drugs (8%). Seeger *et al.* (1998) reported that preventable ADRs accounted for 117 out of 612 spontaneous ADR reports. Schumock and Thornton criteria were again used in this study. Preventable ADRs related mostly to dosing and a history of drug allergy. Gholami and Shalviri (1999) randomized 370

patients who were admitted to medical wards in a teaching hospital in Iran. In this study it was found that 60 out of 102 patients suffered a preventable ADR. Characteristics of these preventable ADRs included an inappropriate dosing interval, the poor choice of drug and dosage, poor or no drug plasma concentration monitoring and poor laboratory tests. Winterstein *et al.* (2002) reviewed the ADR reports in a teaching hospital, assessing preventability using Schumock and Thornton criteria. There were 317 preventable ADRs in 275 patients from a total of 2,571 ADR reports. Preventable ADRs related to the dosage adjustment of anticoagulants, drug-drug interactions of opiate agonists and inappropriate insulin usage. It is clear that there is a wide range of actions that can be taken to prevent ADRs from occurring as presented in Table 1.17. Furthermore, Kanjanarat *et al.* (2003) reported on the nature of ADRs and/or ADEs which had been published between 1991 and 2001. Because it included paediatric patients and heterogeneous patient groups, the median of preventable ADEs was found to be only 1.8% (range 1.3 to 7.8) but the preventable rate was 35.2% (range 18.7 to 73.2). The characteristics of typical preventable ADRs and/or ADEs are summarized in Table 1.18.

In conclusion, it is clear that the consequences of an ADR occurring poses a crucial type of health problem and according to a previous literature many of them can be avoided or prevented. Clearly, it is one of the major components of providing a clinical pharmacy service to monitor and attempt to reduce the number of ADRs occurring in hospitalised patients.

Table 1.17 Number and frequencies of preventable ADRs or ADEs in hospitalised patients.

Countries (References)	Setting	Sample selection	Method to detect an ADR/ADE	An ADR/ADE definition, causality assessing and preventability assessment	Number of ADRs/ADEs	Number of preventable ADRs/ADEs
USA (Bates *et al.*, 1993)	A tertiary hospital,7 units	420 admissions 37 days, 2,967 patient-days	Medical record review	-Two dependent reviewers	73 drug-related incidents 27 ADEs, 34 potential ADEs, 12 problem orders	15 (56%) definitely or probable preventable
USA (Pearson *et al.*, 1994)	A community hospital	Reported ADRs in 1 year	SRS	-WHO's definition -Schumock and Thronton criteria	203 ADR reports	38 reports out of 203 reports (18.7%)
USA (Bates *et al.*, 1995b)	Two tertiary hospitals, 10 units	4,031 adult patient admissions during 6 months 21,412 patient-days	Medical record review	-Two dependent reviewers	247 ADEs, 194 potential ADEs, Extrapolated to 6.5, 5.5 ADEs, potential ADE per 100 non-obstetrical admissions	70 out of 247 ADEs (28%)
USA (Seeger *et al.*, 1998)	A teaching hospital	Reported ADRs in 4 years	SRS	-WHO's definition, -Naranjo's algorithm, Schumock and Thronton criteria	612 ADR reports	117 reports out of 612 reports (19%)
Iran (Glolami and Shalviri, 1999)	A teaching hospital	Random in 10 months, 370 patients	Medical record review	-WHO's definition, -Narnajo's algorithm Schumock and Thronton criteria	102 ADR patients	60 preventable ADR out of 102 patients (59%)
USA (Winterstein *et al.*, 2002)	A teaching hospital	Reported ADRs in 6 years	SRS	Schumock and Thronton criteria	2,571 ADR reports	317 ADRs in 275 reports

SRS = Spontaneous reporting system

Table 1.18 Characteristics of preventable ADR and/or ADE in hospitalised patient.

Drugs or drug groups	Preventable types
Penicilliins, macrolides	Drugs given despite a history of allergy of poor documentation of allergic history
Insulin	Patient had NPO orders or starving from hospital routine but insulin dose was not adjusted
Warfarin, heparin	Drugs were given despite positive occult blood test, lack of therapeutic drug monitoring
Analgesics and opiates	Overdose
Beta-blocker, ACE inhibitors	Underdose, overdose, lack of therapeutic drug monitoring
Opiates, benzodiazepines, tricyclic antidepressants, antipsychotropics	Concurrent use of multiple psychotropic drugs

NPO = Nothing by month

AIMS OF THE PRESENT STUDY

In Thailand, although there is a national Adverse Drug Reaction (ADR) spontaneous reporting scheme and clinical pharmacy services have been adopted in recent years, few research studies have focused on the role of clinical pharmacists in "preventing" ADRs from occurring. For this reason, the aim of the present research project is to establish the role of a clinical pharmacist in preventing or reducing the number of ADRs occurring in hospitalised patients. The research is based on two medical wards at the Ramathibodi Hospital, a large teaching hospital in Thailand. In the first place, all ADRs will be monitored on the wards in the absence of a research clinical pharmacist. Following this "control" or baseline study, an intervention study will be conducted in which a research clinical pharmacist will be added to the medical care team and interventions related to preventing ADR from occurring will be brought to the attention of the medical care team. A comparison of the ADR occurring in the two 10 month period studies will be carried out to determine whether the presence of the clinical pharmacist will result in a reduction in the number of drug-induced ADRs occurring on the two wards.

Chapter 2

Problems of Adverse Drug Reactions in Hospitalised Patients

CHAPTER 2

PROBLEMS OF ADVERSE DRUG REACTIONS IN HOSPITALISED PATIENTS

INTRODUCTION

In Thailand, the national Adverse Drug Reaction (ADR) spontaneous reporting scheme was established in 1984 in collaboration with WHO (Olsson, 1998; Anon., 2004a; Grootheest *et al.*, 2004). Importantly, the number of reports substantially increased from 234 in 1984 to 11,000 reports in 2000, mainly as a consequence of pharmacist reporting. However, hospital pharmacists were not involved in attempts to prevent ADRs from occurring they simply reported those that had already occurred. For this reason, it was decided to perform the present research project to determine whether a clinical pharmacist has a role to play in preventing ADRs. Initially, a research clinical pharmacist will review the drug charts of all patients on two medical wards of the Ramathibodi Hospital and assess the number of actual ADRs that occurred, characterise them into types, and assess the number of ADRs that were judged preventable. In this chapter, the total ADRs occurring on the two medical wards will be monitored by an investigating clinical pharmacist without any direct intervention. This will provide baseline/control data. ADRs will be assessed for preventability using the criteria proposed by Schumock and Thornton (1992).

METHODS

Study design

This study was performed using a prospective observational technique. All patients admitted or transferred to the 1st Male Medical Ward and the 1st Female Medical Ward at Ramathibodi Hospital between 7th December 2001 and 6th October 2002 were recruited into the study, the exception being those admitted for less than 1 day.

Ethics approval

Before commencing the study, ethics approval was cleared by the Ethical Board Committee, Ramathibodi Hospital which was the document **ID 09-44-14** ***No.*** 508/2001 on 19th September 2001 (see overleaf).

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Documentary Proof of Ethical Clearance Committee on Human Rights Related to Researches Involving Human Subjects
Faculty of Medicine, Ramathibodi Hospital, Mahidol University

No. 508/2001(I)

Title of Project	PHARMACIST PARTICIPATION AND CHARACTERISTIC OF PREVENTABLE ADVERSE DRUG REACTIONS IN MEDICAL PATIENTS, RAMATHIBODI HOSPITAL
Protocol Number	ID 09-44-14
Principal Investigator	Prof.Sming Kaojarern,M.D.
Official Address	Department of Medicine Faculty of Medicine,Ramathibodi Hospital Mahidol University

The aforementioned project has been reviewed and approved by Committee on Human Rights Related to Researches Involving Human Subjects, based on the Declaration of Helsinki.

Signature of Chairman
Committee on Human Rights Related to Researches Involving Human Subjects

Prof. Krisada Ratana-olarn, M.D., FRCST, FICS.

Signature of Dean

Prof. Prakit Vathesatogkit, M.D., ABIM.,FRCP.

Date of Approval September 19, 2001

Sample size estimation

In a preliminary study, Tragulpiankit (1995) found that the rate of preventable ADRs on the 1st Male Medical Ward and 1st Female Medical Ward at Ramathibodi Hospital was 7 events per 100 admissions (7%). This occurrence was calculated from 515 patients during a three and a half month period of surveillance. The aim of the present study was to reduce the percentage of preventable ADRs by at least 50%. Thus, the expected percentage of preventable ADRs in the intervention period will be 3.5%. The sample size estimation was calculated by determining the standardized difference (Petrie and Sabin, 2000; Schulz and Grimes, 2005) as follows:

$$\text{Standardized difference} = \frac{(p_1-p_2)}{\sqrt{p(1-p)}}$$

Proportion of preventable ADRs in the baseline period (p_1) = 0.07

Proportion of preventable ADRs in the intervention period (p_2) = 0.035

An average of a proportion of preventable ADRs (p) = 0.0525

Therefore, standardized difference was 0.156927. The power of detection two periods preventable ADR difference was 80% at the 5% level of significance. Therefore, required sample size in each group is:

$$= \frac{16}{(\text{standardized difference})^2}$$

i.e. the sample size in each group will need to be at least 650 patients. The duration of the patient study will need to be at least 9 months in each ward.

Data collection

An investigating clinical pharmacist monitored the patients who were admitted to the two selected wards from patient admission through to discharge. Demographic and clinical data was entered onto a "Patient monitoring form" (Table 2.1). Data included the patient's name, hospital number (HN), gender, age, any coexisting diseases, their social history (cigarette smoking and alcohol drinking), drug allergy history, provisional diagnosis, past medication history and current medication. All chart data which included signs/symptoms and laboratory results were reviewed daily in order to detect any ADRs until their discharge from the medical wards.

Table 2.1 Patient monitoring form.

Patient monitoring form (page 1)

☐M ☐F Patient Name_____ HN_____ Physician name_____

Date of birth_____ Age____ Weight___(kg) Height____(cm) IBW___(kg) BMI___

Admission Date_____ Discharge Date_____ LOS_____ Bed No.___

Chief complains _____

Present illnesses _____

_____

_____

Past medication history or coexisting diseases _____

_____

Past medical history _____

_____

Social history _____Drug allergy history _____

Investigations_____

_____

_____

_____

Problem lists or Provisional diagnosis_____

_____

_____

Discharge diagnosis_____

_____

_____

_____

Hospital courses _____

_____

_____

_____

_____

Table 2.1 Patient monitoring form (cont.).

Medication profile page__

Patient name____________ HN_________ Age______ Physician name_____________

Drugs	Dosage and administrations	Date																					

Length of stay (LOS)

The length of stay was defined as the number of days that the patients stayed on the 1st Male Medical Ward or 1st Female Medical Ward. The numbers of days were counted from the first day of ward admission until the patient's discharge from the ward, or transfer to another ward or death. The day that a patient who was transferred from another ward onto the 1st Male or 1st Female medical ward was counted as the first day of ward admission.

Detection of ADRs

Adverse events were retrospectively identified by an investigating clinical pharmacist being judged as any undesired events or abnormal laboratory results which as indicated on patient charts.

Causality assessment

The Roussel Ulcaf Causality Assessment Method (RUCAM) as presented in Table 2.2 (Benichou, 1994) was used to assess the probability of an ADR having taken place. This was carried out by the investigating clinical pharmacist. The RUCAM was also used retrospectively by an independent clinical pharmacist staff of the Pharmacy Faculty of Mahidol University after the patients were discharged from the hospital. The results from the two assessors were then compared for reproducibility and consistency.

Preventability assessment

All ADRs were assessed by the investigating clinical pharmacist for preventability using the Schumock and Thornton criteria (1992). An independent clinical pharmacist also retrospectively assessed each ADR for preventability. Again the results of the two assessors were compared for reproducibility and consistency.

ADRs data collections

ADR data were recorded on an "ADR monitoring form" as presented in Table 2.3. These data consisted of drugs causing the ADRs, organs affected, causality assessments, type and mechanism of the ADRs, severity, and preventability assessments.

Table 2.2 The Roussel Ulcaf Causality Assessment Method (RUCAM) (Benichou, 1994).

Criteria		Score[d]
1. TIME TO ONSET OF THE REACTION	highly suggestive	+3
	suggestive	+2
	compatible	+1
	inconclusive	0
If incompatible, then case "unrelated"		
If information not available, then case "insufficiently documented"		
2. COURSE OF REACTION	highly suggestive	+3
	suggestive	+2
	compatible	+1
	against the role of the drug	-2
	inconclusive OR not available	0
3. RISK FACTOR(S) FOR DRUG REACTION	presence	+1 to +2[a]
	absence	0
4. CONCOMITANT DRUG(S)[c]	Time to onset incompatible	0
	Time to onset compatible but unknown reaction	-1
	Time to onset compatible and known reaction	-2
	Role proved in this case	-3
	None or information not available	0
5. NON DRUG RELATED CAUSED[c]	Ruled out	+2
	Possible or Not investigated[b]	+1 to -2
	Probable	-3
6. PREVIOUS INFORMATION ON THE DRUG	Reaction unknown	0
	Reaction published but unlabelled	+1
	Reaction labelled in the product's characteristics	+2
7. RESPONSE TO READMINSTRATION	Positive	+3
	Compatible	+1
	Negative	-2
	Not available or Not interpretable	0
or PLASM CONCENTRATION of the drug known as toxic		+3
or VALIDATED LABORATORY TEST with high specificity, sensitivity and predictive values		
	Positive	+3
	Negative	-3
	Not interpretable or not available	0
TOTAL		

[a] one additional point for every validated risk factor (maximal value +2)

[b] depending on the nature of the reaction

[c] Sum of negative values of criteria 4 and 5 cannot be lower than -4

[d] The score are classified in 4 degrees: score above 8, relationship "highly probable"; 6-8, relationship "probable"; 3-5 relationship "possible"; 1-2, relationship "unlikely".

Table 2.3 ADR monitoring form.

ADR monitoring form

☐M☐F Patient name_____ HN_____ Date of ADRs occurring_____

Adverse events _____

_____

Suspected drugs _____

_____

Drug group causing: _____

Organ affected: _____

Causality assessment:

☐highly probable ☐probable ☐possible ☐unlikely

Type of an ADR: ☐Type A ☐Type B

Mechanism of an ADR:

☐side effect ☐toxicity ☐secondary effect ☐drug interaction

☐intolerance ☐allergy ☐pseudo-allergy ☐idiosyncracy

Severity of an ADR:

☐ Level 1: An ADR occurred but required no change in treatment with the suspected drug.

☐ Level 2: The ADR required that treatment with the suspected drug be held, discontinued, or otherwise changed. No antidote or other treatment required. No increase in LOS.

☐Level 3: The ADR required that treatment with the suspected drug be held, discontinued, or otherwise changed, AND/OR an antidote or other treatment was required. No increase in LOS.

☐ Level 4: Any level 3 ADR which increases LOS by at least one day.

☐ Level 5: Any level 4 ADR which required intensive medical care.

☐ Level 6: The ADR caused permanent harm to the patient.

☐ Level 7: The ADR either directly or indirectly led to the death of the patient.

Preventability assessment:

1) Was the drug involved in the ADR <u>not</u> considered appropriate for the patient's clinical condition?

2) Was the dose, route, and frequency of administration <u>not</u> appropriate for the patient's age, weight and disease state?

3) Was required therapeutic drug monitoring or other necessary laboratory test <u>not</u> performed?

4) Was there a history of allergy or previous reaction to the drug?

5) Was a drug interaction involved in the reaction?

6) Was a toxic serum drug level documented?

7) Was poor compliance involved in the reaction?

☐Yes, if one or more of above are chosen. ☐No

Data analysis

The data were analysed by SPSS 11.0 version as followings:

i) Demographic data

ii) Frequencies of ADRs

iii) Characteristics of any ADRs

iv) Patients at risk of an ADR occurring

Frequencies of ADRs

The following definitions were used to describe the frequencies with which ADRs occurred:

- Cumulative incidence - the number of ADR patients divided by the total number of patients who were monitored, multiplied by 100 (i.e. ADR patients per 100 admissions).
- Incidence density - the number of ADR patients divided by the total number of patient-days monitored, multiplied by 1,000 (i.e. ADR patients per 1,000 patient-days).
- Rate of admissions - the number of ADR problems (events) divided by the total number of patients who were monitored, multiplied by 100 (i.e. events per 100 admissions).
- Rate of events per 1,000 patient-days - the number of ADR problems (events) divided by the total patient-days monitored, multiplied by 1,000 (i.e. events per 1,000 patient-days).
- Percentage of preventable ADRs - the number of preventable ADR problems (events) divided by the total of number of ADR problems (events), multiplied by 100.
- Rate of preventable ADRs per 100 admissions - the number of preventable ADRs divided by the total number of patients who were monitored, multiplied by 100.
- Rate of preventable ADRs per 1,000 patient-days - the number of preventable ADRs divided by the total of patient-days monitored, multiplied by 1,000.

Characteristics of ADRs in hospitalised patients

Causality assessment was determined using the RUCAM. Agreement about causality assessment between the investigating clinical pharmacist and an independent clinical

pharmacist was tested by kappa weight agreement. Characteristics were analysed as follows:

- Drugs causing an actual ADR were classified into a main group and sub-group using the Anatomical Therapeutic Chemical (ATC) classification system (Anon., 1992).
- The organ system affected was classified according to the system-organ classification issued by WHO (Anon., 2003).
- The type of ADR was classified according to Rawlins and Thompson as either Type A or Type B (Rawlin and Thompson, 1991).
- The mechanism involved in the ADR was classified according to Rieder as being either predictable or unpredictable (Rieder, 1994; Hess and Rieder, 1997). Predictable ADRs included side effects, toxicity, secondary effects, and drug interactions. Unpredictable ADRs included intolerance, allergy, pseudo-allergy and idiosyncratic reactions.
- The severity of an ADR was categorised according to Hartwig *et al.* (1992).
- The characteristics of preventable ADRs were classified according to Schumock and Thornton (1992) criteria. The extent of agreement of preventability assessment between the investigating clinical pharmacist and an independent clinical pharmacist expert was tested using kappa weight agreement.

Patients at risk

The number of patients who experienced an ADR and those who did not was tested statistically using the Chi-squared test and unpaired Student's *t*-test with mean difference (95% CI) depending on the type of patient factor. Statistical significance was set at 0.05.

RESULTS

The baseline or control study covered a 10 month period from 7th December 2001 until 6th October 2002. During this period a total of one thousand five-hundred and forty-eight (1,548) patients were recruited and their demographic data, frequencies of ADRs occurring, the characteristics and identification of patients at risk from suffering an ADR, were analysed.

Demographic data

During the 10 month period (304 days), 1,548 patients were monitored on two medical wards at Ramathibodi Hospital. Some 765 patients (49.42%) were admitted to the 1st Male Medical Ward with 783 patients (50.58%) admitted to the 1st Female Medical Ward. Their ages and gender are presented in Table 2.4. The youngest patient was only 13 years old whilst the oldest one was 101 years. The mean ± SD age was 51.6 ± 18.9 years (male 51.9 ± 18.6 years, female 51.3 ± 19.2 years), there being no significant difference between the male and female groups for age ($p = 0.577$; Mann-Whitney *U*-test).

The minimum length of stay (LOS) was found to be 1 day and the maximum was 103 days. On average, each patient was monitored for 9.07 ± 8.06 days (male 8.80 ± 7.43 days, female 9.34 ± 8.64 days). There was no significant age differences between the male and female groups ($p = 0.204$; Mann-Whitney *U*-test), LOS and gender distributions are presented in Table 2.5. The total number of patient-days was calculated to be 6,731 for male patients and 7,314 for females. The number of concomitant drugs administered in terms of gender distribution are shown in Table 2.6. Some patients did not receive any medication whilst the maximum of number medicines administered concomitantly was 70 items. The mean ± SD number of concomitant drugs was 10.92 ± 7.88 items (male 10.84 ± 7.63 items, female 11.00 ± 8.12 items), there being no significant difference between the males and females ($p = 0.967$; Mann-Whitney *U*-test).

Of 1,548 patients studied, some 862 patients suffered from at least one coexisting disease. The frequency distributions of coexisting diseases are shown in Tables 2.7 and 2.8. Eighty percent of all patients (1,253 out of 1,548 patients) had no history of either alcohol drinking or cigarette smoking. The number of patients in terms of social history and gender distribution is shown in Table 2.9. One hundred and thirty-two of the 1,548 patients (8.5%) had a history of drug allergy. Table 2.10 shows the number of patients with a previous history of drug allergy with respect to gender distribution.

Characteristics of ADRs occurring during hospitalisation

During the 10 month baseline period there were 1,548 patient admissions and of these 249 ADR problems occurred in 187 patients (Table 2.11). The cumulative incidence

Table 2.4 Number of patients in terms of age group and gender.

Age group (years)	Number of patients		
	Male (%)	Female (%)	Total (%)
Less than 20	30 (3.9)	32 (4.1)	62 (4.0)
20-29	81 (10.6)	104 (13.3)	185 (12.0)
30-39	109 (14.3)	122 (15.6)	231 (14.9)
40-49	120 (15.7)	91 (11.6)	211 (13.6)
50-59	123 (16.1)	117 (14.9)	240 (15.5)
Over than 59	302 (39.5)	317 (40.5)	619 (40.0)
Total	765	783	1548

Table 2.5 Number of patients in terms of length of stay and gender.

LOS (days)	Number of patients		
	Male (%)	Female (%)	Total (%)
Less than 10	548 (71.6)	545 (69.6)	1093 (70.6)
10-19	161 (21.1)	170 (21.7)	331 (21.4)
20-29	32 (4.2)	42 (5.4)	74 (4.8)
30-39	17 (2.2)	14 (1.8)	31 (2.0)
40-49	5 (0.7)	6 (0.8)	11 (0.7)
50-59	0 (0.0)	3 (0.4)	3 (0.2)
Over than 59	2 (0.3)	3 (0.4)	5 (0.3)
Total	765	783	1548

Table 2.6 Number of concomitant drugs in term of gender.

Range of drugs (items)	Number of patients		
	Male (%)	Female (%)	Total (%)
Less than 10	401 (52.4)	409 (52.2)	810 (52.3)
10-19	270 (35.3)	266 (34.0)	536 (34.6)
20-29	70 (9.2)	84 (10.7)	154 (10.0)
30-39	16 (2.1)	15 (1.9)	31 (2.0)
40-49	4 (0.5)	6 (0.8)	10 (0.7)
Over than 49	4 (0.5)	3 (0.4)	7 (0.5)
Total	765	783	1548

Table 2.7 Number of patients and their coexisting diseases.

Number of coexisting diseases	Number of patients		
	Male (%)	Female (%)	Total (%)
None	331 (43.3)	355 (45.3)	686 (44.3)
One	338 (44.2)	358 (45.7)	696 (45.0)
Two	90 (11.8)	59 (7.5)	149 (9.6)
Three	6 (0.8)	10 (1.3)	16 (1.0)
Four	0	1 (0.1)	1 (0.1)
Total	765	783	1548

Table 2.8 Number of patients in terms of coexisting disease and gender.

Coexisting disease	Number of patients		
	Male (%)	Female (%)	Total (%)
AIDS	69 (12.9)	37 (7.3)	106 (10.1)
Cancer	142 (26.5)	145 (28.4)	287 (27.4)
Renal disease	167 (31.2)	146 (28.6)	313 (29.9)
Liver disease	104 (19.4)	73 (14.3)	177 (16.9)
CHF	47 (8.8)	44 (8.6)	91 (8.7)
SLE	7 (1.3)	65 (12.8)	72 (6.9)
Total	536	510	1046

Table 2.9 Number of patients in terms of alcohol consumption, cigarette smokers and gender.

Social history	Number of patients		
	Male (%)	Female (%)	Total (%)
Alcohol drinker	35 (4.6)	16 (2.0)	51 (3.3)
Cigarette smoker	94 (12.3)	12 (1.5)	106 (6.9)
Smoker and alcohol drinker	129 (16.9)	9 (1.2)	138 (8.9)
None	507 (66.3)	746 (97.6)	1253 (80.9)
Total	765	783	1548

Table 2.10 Number of patients in terms of drug allergy history and gender.

Drug allergy history	Number of patients		
	Male (%)	Female (%)	Total (%)
Drug allergy history	49 (6.4)	83 (10.6)	132 (8.5)
Not known drug allergy history	716 (93.6)	700 (89.4)	1416 (91.5)
Total	765	783	1548

Table 2.11 Adverse drug reactions occurring in the baseline period (249 ADRs in 187 patients).

Problem no.	Case no.	Adverse events	Suspected drug(s)	Causality assessment	Preventability	Criteria
1	1	Hypotension	Captopril	Probable	Preventable	2
2	2	Constipation	Morphine	Probable	Non preventable	
3	3	Tongue rigidity	Phenytoin	Possible	Non preventable	
4	4	Hyperglycaemia	Dexamethasone/ methylpredisolone	Probable	Preventable	3
5	5	Prolong INR	Enoxaparin	Probable	Preventable	2
6	6	Renal impairment	Amphotericin B	Probable	Preventable	3
7	7	Hypotension	Captopril	Probable	Non preventable	
8	8	Angioedema	Xylocaine	Probable	Non preventable	
9	9	Acute renal failure	Amphotericin B	Probable	Preventable	3
10	9	Hypomagnesaemia	Amphotericin B	Probable	Non preventable	
11	10	Haematoma	Enoxaparin	Probable	Preventable	3
12	11	Prolong INR	Warfarin	Probable	Preventable	3
13	12	Extrapyramidal syndrome	Metoclopramide	Probable	Non preventable	
14	12	Tumor lysis syndrome	Etoposide/doxorubicin	Probable	Preventable	3
15	12	Echymosis	Etoposide/doxorubicin	Probable	Non preventable	
16	13	Hyperglycaemia	Dexamethasone	Probable	Preventable	3
17	14	Hypoglycaemia	Insulin	Probable	Preventable	3
18	15	Anaphylaxis	GM-CSF	Probable	Preventable	4
19	15	Rash	G-CSF	Probable	Non preventable	
20	15	Acute renal failure	Amikacin	Possible	Preventable	2,3
21	15	Jaundice	Amphotericin B	Possible	Non preventable	
22	16	Nausea/vomiting	Pethidine	Probable	Non preventable	
23	17	Dry throat	Gabapentin	Possible	Non preventable	
24	18	Pancytopenia	Co-trimoxazole	Probable	Non preventable	
25	19	Vomiting	Mitoxantrone/etoposide	Probable	Non preventable	
26	20	Pancytopenia	Co-trimoxazole	Probable	Non preventable	
27	21	Redman syndrome	Vancomycin	Possible	Preventable	2
28	22	Nausea	Clarithromycin	Probable	Non preventable	
29	23	Phlebitis	Cloxacilline	Probable	Non preventable	
30	24	Dypnea/pruritis	Ara-C/idarubicin	Probable	Non preventable	
31	25	Prolong INR	Warfarin	Probable	Preventable	3

Table 2.11 Adverse drug reactions occurring in the baseline period (cont.).

Problem no.	Case no.	Adverse events	Suspected drug(s)	Causality assessment	Preventability	Criteria
32	26	Acute tubular necrolysis	Gentamicin/amikacin/ Diclofenac	Probable	Preventable	3
33	27	Prolong INR	Warfarin	Probable	Preventable	3
34	27	Digoxin intoxication	Digoxin	Highly probable	Preventable	2
35	28	Phlebitis	Ceftriaxone	Probable	Non preventable	
36	29	Hand pain	Cloxacillin	Probable	Non preventable	
37	30	Pruritis	Ceftazidime/imipenem	Possible	Non preventable	
38	31	Digoxin intoxication	Digoxin	Probable	Preventable	2,3
39	32	Acute renal failure	Vancomycin	Probable	Preventable	2,3
40	33	Diarrhoea	Itraconazole	Possible	Non preventable	
41	33	Acute renal failure	Tacrolimus	Probable	Preventable	2,3
42	34	Volume overload	IV fluid	Probable	Preventable	2
43	35	Cough	Enalapril	Probable	Non preventable	
44	36	Prolong INR	Warfarin	Probable	Preventable	2,3
45	37	Acute liver injury	Phenytoin	Possible	Non preventable	
46	37	Maculopapular rash	Cefepime	Probable	Non preventable	
47	38	Phlebitis	Partial Parenteral Nutrition	Probable	Non preventable	
48	39	Erythromatous rash	PGS	Possible	Non preventable	
49	40	Thrombophlebitis	Vancomycin	Probable	Non preventable	
50	40	Drowsiness	Fluconazole	Probable	Non preventable	
51	41	Exfoliative dermatitis	Levofloxacin	Unlikely	Non preventable	
52	42	Prolong INR	Warfarin	Probable	Preventable	2,3
53	43	Nausea/vomiting	Ara-C/idarubicin	Probable	Non preventable	
54	43	Phlebitis	Ara-C/idarubicin	Probable	Non preventable	
55	44	Hypokalemia/VT	Amphotericin B	Highly probable	Preventable	2,3
56	44	Phlebitis	Cefepime	Possible	Non preventable	
57	44	Rash	Vancomycin	Possible	Non preventable	
58	44	Nausea/vomiting	Mitoxantrone	Highly probable	Non preventable	
59	45	Nausea/vomiting	Ara-C/idarubicin	Probable	Non preventable	

Table 2.11 Adverse drug reactions occurring in the baseline period (cont.).

Problem no	Case no	Adverse events	Suspected drug(s)	Causality assessment	Preventability	Criteria
60	46	Phlebitis	Piperacillin/ vancomycin	Probable	Non preventable	
61	46	Fever	Piperacillin/tazobactam	Possible	Non preventable	
62	47	Myopathy	Prednisolone	Probable	Non preventable	
63	48	Hypokalemia	Penicillin	Possible	Non preventable	
64	49	Vomiting	Morphine	Probable	Non preventable	
65	50	Proximal muscle weakness	Prednisolone	Probable	Non preventable	
66	51	Extrapyramidal syndrome	Metoclopramide	Probable	Non preventable	
67	52	Neutropenia	Gancyclovir	Possible	Non preventable	
68	53	Pancytopenia	Itraconazole	Probable	Non preventable	
69	54	Gastritis	Prednisolone	Probable	Non preventable	
70	55	Phlebitis	TPN/vancomycin	Probable	Non preventable	
71	56	Palpitation	Terbutaline	Probable	Preventable	2
72	57	Acute renal failure	Amphotericin B	Probable	Preventable	2,3
73	58	Leucopenia	Ceftriaxone	Probable	Non preventable	
74	58	Vomiting	Olfloxacin	Probable	Non preventable	
75	59	Prolong INR	Warfarin	Probable	Preventable	2,3
76	60	Prolong INR	Warfarin	Probable	Preventable	2,3
77	61	Nausea/vomiting	Doxorubicin/ara-C	Probable	Non preventable	
78	61	Phlebitis	PPN	Probable	Non preventable	
79	61	Hypokalemia	Amphotericin B	Probable	Preventable	3
80	61	Renal impairment	Amphotericin B	Probable	Preventable	3
81	62	Hypotension	Hydralazine/isosorbide dinitrate	Probable	Preventable	2
82	63	Bronchospasm	Atenolol	Probable	Non preventable	
83	64	Juctional bradycardia	Verapamil/flecainide	Probable	Non preventable	
84	65	Phlebitis	Augmentin^{R}	Possible	Non preventable	
85	66	Vomiting	Vincristine/doxorubicin	Probable	Non preventable	
86	67	Hypokalemia	Amikacin	Possible	Preventable	3
87	68	Hypokalemia	Amikacin/ amphotericin B	Possible	Non preventable	
88	69	Febrile neutropenia	Cyclophosphamide/ vincristine/doxorubicin	Probable	Non preventable	

Table 2.11 Adverse drug reactions occurring in the baseline period (cont.).

Problem no.	Case no.	Adverse events	Suspected drug(s)	Causality assessment	Preventability	Criteria
89	69	Hypokalemia	Amikacin/ amphotericin B	Possible	Non preventable	
90	70	Nausea/vomiting	Isoniazid	Probable	Non preventable	
91	71	Fever	Phenytoin	Probable	Non preventable	
92	71	Thrombophlebitis	Ceftriaxone	Highly probable	Non preventable	
93	72	Acute renal failure	Enalapril	Unlikely	Non preventable	
94	73	Thrombophlebitis	Ceftriaxone	Highly probable	Non preventable	
95	74	Parkinsonism	Haloperidol	Probable	Preventable	4
96	75	Acute renal failure	Amphotericin B	Probable	Non preventable	
97	76	Thrombophlebitis	Ceftazidime	Probable	Non preventable	
98	77	Diarrhoea	Lactulose	Probable	Non preventable	
99	78	Thrombophlebitis	Ceftriaxone/cloxacillin	Highly probable	Non preventable	
100	79	Leucopenia	Cyclophosphamide	Probable	Non preventable	
101	80	Retroperineal bleeding	ASA/enoxaparin	Probable	Non preventable	
102	80	Hypotension	Atenolol	Possible	Non preventable	
103	81	Myopathy	Prednisolone	Probable	Non preventable	
104	82	Nystagmus	Phenytoin	Highly probable	Preventable	3,5,6
105	82	Cholestatic jaundice	Phenytoin	Probable	Non preventable	
106	83	Hypokalemia	Lactulose	Possible	Non preventable	
107	84	Upper GI bleeding	Aspirin	Probable	Non preventable	
108	85	Hyperglycaemia	Methyprednisolone	Probable	Non preventable	
109	86	Thrombophlebitis	Amphotericin B	Highly probable	Non preventable	
110	87	Nausea/vomiting	Augmentin®	Probable	Non preventable	
111	88	Hypoglycaemia	Insulin	Probable	Preventable	2
112	88	Hypokalemia	Amphotericin B	Highly probable	Non preventable	
113	88	Renal impairment	Amphotericin B	Probable	Non preventable	
114	89	Prolong INR	Warfarin	Highly probable	Preventable	2,3

Table 2.11 Adverse drug reactions occurring in the baseline period (cont.).

Problem no.	Case no.	Adverse events	Suspected drug(s)	Causality assessment	Preventability	Criteria
115	90	Prolong INR	Warfarin	Highly probable	Preventable	3
116	91	Hyperglycaemia	Dexamethasone	Highly probable	Non preventable	
117	92	Acute renal failure	Acyclovir	Possible	Preventable	1
118	93	Acute renal failure	Amphotericin B/ imipenem	Probable	Non preventable	
119	94	Leucopenia	Sulfadiazine/ pyrimethamine	Probable	Non preventable	
120	94	Confusion	Trihexyphenydyl/ Baclofen	Possible	Non preventable	
121	94	Acute renal failure	Amphotericin B	Highly probable	Non preventable	
122	95	Prolong INR	Warfarin	Highly probable	Preventable	1
123	96	Hyperglycaemia	Dexamethasone/ Prednisolone	Probable	Non preventable	
124	97	Diarrhoea	Nefinavir	Possible	Non preventable	
125	98	Toxic level	Cyclosporin	Highly probable	Preventable	2,3,6
126	98	Serum sickness	ATG	Highly probable	Non preventable	
127	98	Maculopapular rash	ATG	Probable	Non preventable	
128	98	Febrile neutropenia	ATG	Unlikely	Non preventable	
129	99	Urticaria	Ceftriaxone	Highly probable	Non preventable	
130	100	Leucopenia	Mycophenolate mofetil/ cyclophosphamide	Highly probable	Non preventable	
131	100	Gastritis	Mycophenolate mofetil	Possible	Non preventable	
132	101	Hypokalemia	Amphotericin B	Probable	Non preventable	
133	102	Stevens-Johnson syndrome	Phenytoin	Highly probable	Non preventable	
134	103	Hypokalemia	Amikacin/ amphotericin B	Possible	Non preventable	
135	104	Dehydration	Furosemide	Probable	Preventable	2

Table 2.11 Adverse drug reactions occurring in the baseline period (cont.).

Problem no.	Case no.	Adverse events	Suspected drug(s)	Causality assessment	Preventability	Criteria
136	105	Febrile neutropenia	Etoposide/cytarabine/ cisplatin	Probable	Non preventable	
137	106	Febrile neutropenia	Etoposide/cisplatin	Highly probable	Non preventable	
138	107	Acute renal failure	Enalapril	Probable	Non preventable	
139	108	Thrombophlebitis	Augmentin^{R}/cefazolin	Highly probable	Non preventable	
140	109	Toxic level	Cyclosporin	Highly probable	Preventable	3,5
141	110	Prolong INR	Warfarin	Highly probable	Preventable	5
142	110	Hypokalemia	Amphotericin B	Probable	Non preventable	
143	110	Hemorrhagic cystitis	Cyclophosphamide	Probable	Non preventable	
144	111	Maculopapular rash	Cefazidime/amikacin	Possible	Non preventable	
145	112	Constipation	Morphine/amitriptyline	Probable	Preventable	2
146	113	Maculopapular rash	Pyrazinamide	Highly probable	Preventable	4
147	114	Tachycardia	Theophylline	Possible	Preventable	3
148	115	Febrile neutropenia	Cytarabine/idarubicin	Highly probable	Non preventable	
149	115	Maculopapular rash	Sulperazone/ amphotericin B	Highly probable	Non preventable	
150	116	Acute renal failure	Amikacin	Possible	Preventable	3
151	116	Thrombophlebitis	Amikacin/ceftazidime	Highly probable	Non preventable	
152	117	Febrile neutropenia	Ceftazidime/idarubicin	Highly probable	Non preventable	
153	117	Fever	Cytarabine	Probable	Non preventable	
154	118	Febrile neutropenia	Asparaginase	Highly probable	Non preventable	
155	119	Pancytopenia	Co-trimoxazole	Probable	Preventable	1
156	120	Thrombophlebitis	Ceftrixone	Probable	Non preventable	
157	121	Seizure	Ifosfamide	Possible	Non preventable	
158	122	Nausea/vomiting	Theophylline	Probable	Preventable	3

Table 2.11 Adverse drug reactions occurring in the baseline period (cont.).

Problem no.	Case no.	Adverse events	Suspected drug(s)	Causality assessment	Preventability	Criteria
159	123	Maculopapular rash	Ceftriaxone	Probable	Non preventable	
160	124	Acute liver injury	Phenytoin	Probable	Preventable	1
161	125	Maculopapular rash	Itraconazle	Probable	Non preventable	
162	126	Hyperglycaemia	Dexamethasone	Probable	Non preventable	
163	127	Toxic level	Cyclosporin	Highly probable	Preventable	5
164	128	Nausea/vomiting	Augmentin^{R}/olfloxacin	Possible	Non preventable	
165	129	Thrombophlebitis	Ceftazidime	Probable	Non preventable	
166	130	Maculopapular rash	Ceftriaxone	Probable	Non preventable	
167	131	Acute liver injury	Dapsone	Probable	Non preventable	
168	132	Hyperglycaemia	Prednisolone	Highly probable	Non preventable	
169	132	Serum sickness	ATG	Probable	Non preventable	
170	132	Cholestatic jaundice	Halotestine	Probable	Non preventable	
171	133	Leucopenia	Metrotrexate/cytarabine	Highly probable	Non preventable	
172	133	Fever	Cytarabine	Probable	Non preventable	
173	134	Nystamus	Carbamazepine	Probable	Preventable	3
174	135	Acute renal failure	Acyclovir	Probable	Non preventable	
175	136	Toxic level	Vancomycin	Highly probable	Preventable	2,3,6
176	137	Acute renal failure	Amphotericin B	Possible	Non preventable	
177	138	Nausea/vomiting	Theophylline	Probable	Preventable	3
178	139	Fever	Ciprofloxacin/ augmentin^{R}	Probable	Non preventable	
179	140	Fever	Mitoxantrone/ Cytarabine	Unlikely	Non preventable	
180	140	Acute renal failure	Amikacin/ amphotericin B	Possible	Non preventable	
181	141	Prolong INR	Warfarin	Highly probable	Preventable	2
182	141	Vision disorders	Digoxin	Probable	Non preventable	

Table 2.11 Adverse drug reactions occurring in the baseline period (cont.).

Problem no.	Case no.	Adverse events	Suspected drug(s)	Causality assessment	Preventability	Criteria
183	142	Leucopenia	Cyclophosphamide	Probable	Non preventable	
184	143	Thrombophlebitis	Ceftazidime	Highly probable	Non preventable	
185	144	Thrombophlebitis	Ceftriaxone	Highly probable	Non preventable	
186	145	Pancreatitis	Asparaginase	Probable	Non preventable	
187	145	Hyperglycaemia	Dexamethasone	Probable	Non preventable	
188	146	Bicytopenia	Cyclophosphamide	Probable	Non preventable	
189	147	Acute renal failure	Amikacin/ amphotericin B	Highly probable	Non preventable	
190	147	Diarrhoea	Cefepime	Probable	Non preventable	
191	147	Maculopapular rash	Vancomycin	Probable	Non preventable	
192	147	Thrombophlebitis	Amphotericin B	Probable	Non preventable	
193	148	Diarrhoea	Cefipime	Possible	Non preventable	
194	148	Ataxia	Cytarabine	Possible	Non preventable	
195	148	Thrombophlebitis	Amphotericin B	Possible	Non preventable	
196	149	Renal impairment	Vancomycin	Highly probable	Preventable	2,3,6
197	150	Hydration	Furosemide/atenolol	Highly probable	Preventable	2
198	151	Hypotension	Streptokinase	Highly probable	Preventable	2
199	152	Hypokalemia	Amikacin/ amphotericin B	Probable	Non preventable	
200	153	Prolong INR	Warfarin	Highly probable	Preventable	2
201	153	Cholestatic jaundice	Ceftriaxone/warfarin	Probable	Non preventable	
202	154	Febrile neutropenia	Cytarabine/ mitoxantrone	Highly probable	Non preventable	
203	155	Febrile neutropenia	Cyclophosphamide/ vincristine/doxorubicin	Highly probable	Non preventable	
204	156	Thrombophlebitis	Ceftriaxone/ clarithromycin/PGS	Highly probable	Non preventable	

Table 2.11 Adverse drug reactions occurring in the baseline period (cont.).

Problem no.	Case no.	Adverse events	Suspected drug(s)	Causality assessment	Preventability	Criteria
205	157	Thrombophlebitis	Amphotericin B/ imipenem/acyclovir	Highly probable	Non preventable	
206	158	Toxic level	Cyclosporin	Highly probable	Preventable	3,5
207	159	Maculopapular rash	Imipenem	Probable	Preventable	4
208	159	Febrile neutropenia	Cytarabine/ mitoxantrone	Highly probable	Non preventable	
209	159	Maculopapular rash	Cefazolin	Probable	Non preventable	
210	159	Acute renal failure	Amphotericin B/ amikacin	Probable	Non preventable	
211	159	Acute renal failure	Amphotericin B/ imipenem	Probable	Non preventable	
212	160	Toxic level	Cyclosporin	Highly probable	Preventable	5,6
213	160	Serum sickness	ATG	Probable	Non preventable	
214	160	Acute renal failure	Amikacin/amphotericin B/imipenem	Highly probable	Non preventable	
215	161	Maculopapular rash	Omeprazole	Possible	Preventable	4
216	161	Thrombophlebitis	Cloxacillin	Highly probable	Non preventable	
217	162	Hypokalemia	Amikacin	Possible	Preventable	3
218	163	Toxic level	Tacrolimus	Highly probable	Preventable	3,5
219	163	Hypomagnesaemia	Amphotericin B	Probable	Preventable	1
220	163	Fever	Amphotericin B/ Cloxacillin/sulperazone	Probable	Non preventable	
221	163	Thrombophlebitis	Amphotericin B	Highly probable	Non preventable	
222	164	Seizure	Pethidine	Possible	Preventable	4,5
223	165	Prolong INR	Warfarin	Highly probable	Preventable	2
224	165	Hyperglycaemia	Dexamethasone	Probable	Non preventable	
225	166	Acute renal failure	Amphotericin B	Probable	Non preventable	

Table 2.11 Adverse drug reactions occurring in the baseline period (cont.).

Problem no.	Case no.	Adverse events	Suspected drug(s)	Causality assessment	Preventability	Criteria
226	167	Hypokalemia/ Hypomagnesaemia	Amphotericin B	Probable	Non preventable	
227	168	Thrombophlebitis	Ceftriaxone	Highly probable	Non preventable	
228	169	Upper GI bleeding	ASA/enoxaparin	Probable	Non preventable	
229	170	Bradycardia	Propranolol	Probable	Preventable	2
230	171	Serum sickness	ATG	Probable	Non preventable	
231	171	Maculopapular rash	Imipenem	Probable	Non preventable	
232	172	Toxic level	Cyclosporin	Highly probable	Preventable	3,5
233	173	Maculopapular rash	Amikacin	Probable	Non preventable	
234	173	Acute renal failure	Amphotericin B/ imipenem	Highly probable	Non preventable	
235	174	Constipation	Morphine	Probable	Non preventable	
236	175	Febrile neutropenia	Etoposide/ciplatin/ Cytarabine	Probable	Non preventable	
237	176	Thrombophlebitis	Amphotericin B/ Piperacillin	Highly probable	Non preventable	
238	177	Hypokalemia/ Hypomagnesaemia	Amikacin/acyclovir	Possible	Preventable	2
239	178	Stevens-Johnson syndrome	Co-trimoxazole/ Ceftriaxone	Probable	Non preventable	
240	179	Prolong INR	Warfarin	Highly probable	Preventable	2,5
241	180	Acute renal failure	Acyclovir	Probable	Non preventable	
242	181	Maculopapular rash	Ciprofloxacin	Highly probable	Non preventable	
243	182	Hypomagnesaemia /hypokalemia	Amphotericin B	Possible	Non preventable	
244	183	Thrombophlebitis	Augmentin^{R}	Highly probable	Non preventable	
245	184	Prolong INR	Warfarin	Highly probable	Preventable	2

Table 2.11 Adverse drug reactions occurring in the baseline period (cont.).

Problem no.	Case no.	Adverse events	Suspected drug(s)	Causality assessment	Preventability	Criteria
246	185	Thrombophlebitis	Ceftriaxone/ clarithromycin	Highly probable	Non preventable	
247	186	Thrombophlebitis	TPN/meropenem/ aminosol	Highly probable	Non preventable	
248	187	Febrile neutropenia	Cytarabine	Highly probable	Non preventable	
249	187	Hypokalemia/ Hypomagnesaemia	Amikacin/ amphotericin B	Probable	Non preventable	

Ara-C = cytarabine; ASA = aspirin; ATG = antithrombocyte globulin; GI = gastrointestinal; G-CSF = granulocyte colony stimulating factor; GM-CSF = granulocyte-monocyte colony stimulating factor; INR = international normalised ratio; IV = intravenous; PGS = penicillin G sodium; PPN = partial parenteral nutrition; TPN = total parenteral nutrition; VT = ventricular tachycardia

of ADRs was 12.08 per 100 admission whist the incidence density was 13.31 per 1,000 patient-days. In addition, the rates of ADRs were 16.09 per 100 admissions and 17.73 per 1,000 patient-days.

Two hundred and forty-nine ADRs were assessed using the RUCAM algorithm which categorises ADRs into highly probable, probable, possible and unlikely. Approximately 80% of ADR problems were categorised as highly probable (25.7%) or probable (57.0%) as illustrated in Figure 2.1. The ADR causality assessment carried out by the investigating clinical pharmacist was then compared with the assessment of an independent clinical pharmacist who was on the staff of the Faculty of Pharmacy. One hundred and fifty-nine out of 249 ADRs were compared and the results between the two assessors are illustrated in Figure 2.2. The kappa coefficient (Ka) was found to be 0.11 when four categories of the probability scale were compared (highly probable, probable, possible and unlikely). When the highly probable and probable scales, and the possible and unlikely scales, were combined, into either "yes an ADR had occurred" or "no it had not", the kappa coefficient increased to 0.41. Interestingly, some patients developed more than one ADR-related problem. However, the majority of ADR patients during hospitalisation experienced just one ADR (147 patients, 78.6%). The maximum number of ADRs seen in a patient during hospitalisation was five ADRs. Details of the recorded number of ADR experienced by each patient are presented in Table 2.12.

ADR Characteristics

The characteristics of each ADR are presented as follows:

Drug group causing the ADR based on the ATC classification system

Two hundred and forty-nine ADR problems occurred during hospitalisation. Sixty-one ADR problems were caused by two or more suspected drugs administered concurrently to the patient. The balance of 188 ADRs caused by a single drug were classified according to the ATC system as presented in Table 2.13. General anti-infectives for systemic use caused the greatest number of ADRs (82: 43.6%). These ADR problems were then sub-classified according to the ATC subgroup system as presented in Table 2.14. Approximately 40% of all drug-induced ADRs resulted from antibiotics for systemic use (48: 25.5%) and antimycotics for systemic use (26: 13.8%).

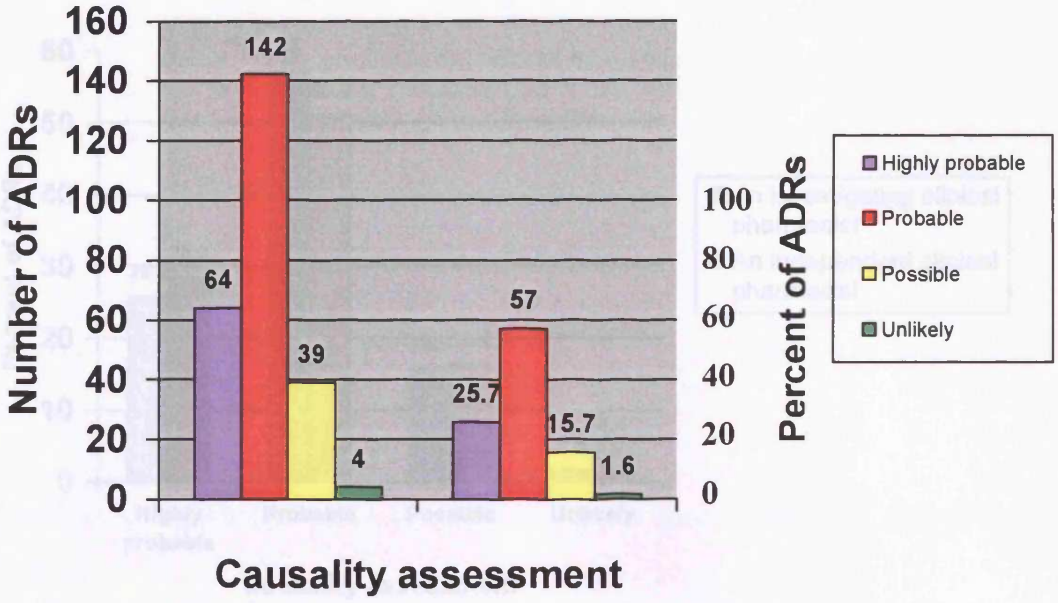


Figure 2.1 Causality assessment of ADRs using the RUCAM algorithm.

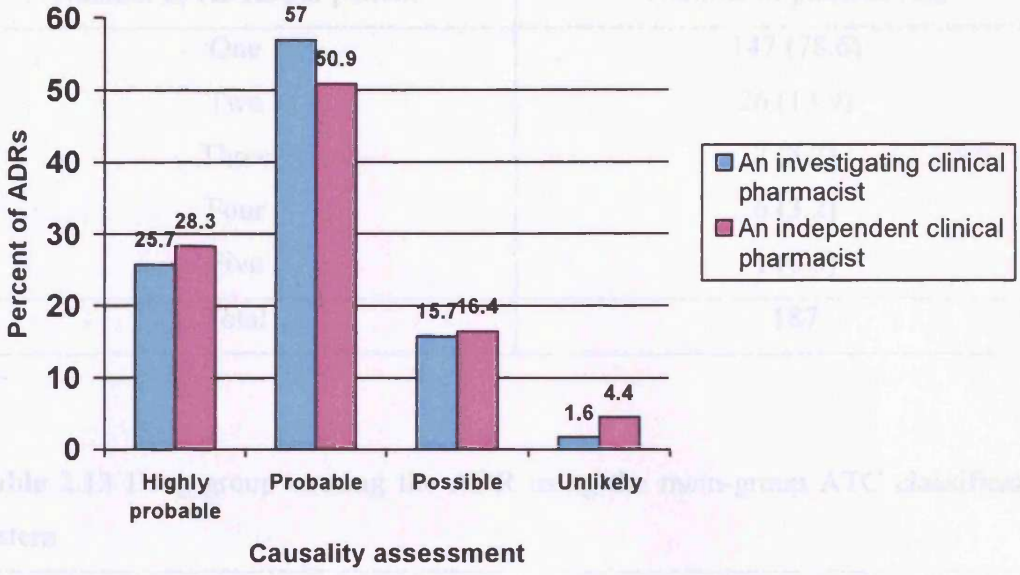


Figure 2.2 Causality assessment of ADRs: comparison between two assessors.

Table 2.12 Number of ADR problems per patient.

Number of ADRs per patient	Number of patients (%)
One	147 (78.6)
Two	26 (13.9)
Three	7 (3.7)
Four	6 (3.2)
Five	1 (0.5)
Total	187

Table 2.13 Drug group causing the ADR using the main-group ATC classification system

Drug groups causing an ADR	No. of ADRs (%)
i) Alimentary tract and metabolism	7 (3.7)
ii) Blood and blood forming organs	22 (11.7)
iii) Cardiovascular system	13 (6.9)
iv) Genito-urinary system and sex hormones	1 (0.5)
v) Systemic hormonal preparations, excl. sex hormones	12 (6.4)
vi) General anti-infective for systemic use	82 (43.6)
vii) Antineoplastic and immunomodulating agents	14 (7.5)
viii)Central nervous system	17 (9.0)
ix) Respiratory system	4 (2.1)
x) Various	16 (8.5)
Total	188

ATC = Anatomical Therapeutic Chemical

Table 2.14 Drug group causing an ADR using the ATC subgroup classification.

Drug group causing an ADR	No. of ADRs (%)
1 Antacids, drugs for treatment of peptic ulcer and flatulence	1 (0.5)
2 Antiemetics and antinaueants	2 (1.1)
3 Bile and liver therapy	2 (1.1)
4 Antidiabetic therapy	2 (1.1)
5 Antithrombotic agents	20 (10.6)
6 Antianemic preparations	2 (1.1)
7 Cardiac therapy	3 (1.6)
8 Antihypertensives	7 (3.7)
9 Diuretics	1 (0.5)
10 Beta blocking agents	2 (1.1)
11 Sex hormones and modulators of the genital system	1 (0.5)
12 Corticosteroids for systemic use	12 (6.4)
13 Antibiotics for systemic use	48 (25.5)
14 Antimycotics for systemic use	26 (13.8)
15 Tuberculostatic, excl. streptomycin	3 (1.6)
16 Antivirals for systemic use	5 (2.7)
17 Cytostatics	8 (4.3)
18 Immunostimulating agents	6 (3.2)
19 Anaesthetics	1 (0.5)
20 Analgesics	5 (2.7)
21 Antiepileptics	9 (4.8)
22 Psycholeptics	1 (0.5)
23 Psychoanaleptics	1 (0.5)
24 Antiasthmatics	4 (2.1)
25 Immunosuppressive agent	13 (6.9)
26 General nutrients	2 (1.1)
27 All other-nontherapeutic products	1 (0.5)
Total	188

ATC = Anatomical Therapeutic Chemical

ADR problems classified by organ affected

Using the WHO adverse reaction classification, 249 ADR problems were classified according to the organ system that was affected. Details are presented in Table 2.15. General disorders of the whole body were the most affected (16.1%). The next most affected parts of the body were gastro-intestinal system disorders (15.7%) and injection site disorders (13.7%).

ADR problems classified by types of ADRs

Some 249 ADR problems were classified according to the Rawlins and Thompson (1991) classification. Approximately 80% of all ADRs were found to be Type A reactions as illustrated in Figure 2.3.

ADR problems classified by mechanism of ADRs

The 249 ADRs were next classified by mechanism of action as shown in Table 2.16. The majority of ADRs appeared to result from side effects (72.3%).

ADR problems classified by severity

The severity of the 249 recorded ADRs are illustrated in Figure 2.4. Most (42.2%) were classified as level 3 (i.e. of moderate severity).

Characteristics of preventable ADRs

Two hundred and forty-nine ADR problems were assessed to determine whether they could have been prevented using the criteria published by Schumock and Thornton (1992). A total of 73 (29.3%) were found to be classified as preventable (Figure 2.5). The retrospective reproducibility of preventability assessment was carried out by an independent clinical pharmacist. The kappa coefficient was found to be 0.41. A comparison of the two assessors findings are illustrated in Figure 2.6. These 73 preventable ADRs occurred in a total of 1,548 patients with a LOS of 14,045 patient-days. Thus, the rate of preventable ADRs was 4.72% or 5.20 per 1000 patient-days. Of the 176 non-preventable ADR problems, a total of 31 were related to thrombophlebitis. It was noted that of the 73 preventable ADRs, 49 (67.1%) were decided by one criteria, 20 (27.4%) by two and 4 (5.5%) by three as illustrated in Figure 2.7. There were none relating to poor compliance.

Table 2.15 ADR problems classified by organ affected.

Organ system affected	No. of ADRs (%)
1 Skin & appendages disorders	23 (9.2)
2 Musculo-skeletal system disorders	4 (1.6)
3 Central & peripheral nervous system disorders	9 (3.6)
4 Autonomic nervous system disorders	1 (0.4)
5 Gastro-intestinal system disorders	39 (15.7)
6 Liver & biliary system disorders	6 (2.4)
7 Metabolic & nutritional disorders	27 (10.8)
8 Endocrine disorders	2 (0.8)
9 Heart rate & rhythm disorders	5 (2.0)
10 Vascular (extracardiac) disorders	6 (2.4)
11 Respiratory system disorders	2 (0.8)
12 Pancytopenia	5 (2.0)
13 White cell and RES disorders	10 (4.0)
14 Platelet, bleeding & clotting disorders	15 (6.0)
15 Urinary system disorders	21 (8.4)
16 Body as a whole-general disorders	40 (16.1)
17 Application site disorders	34 (13.7)
Total	249

RES = Reticuloendothelial system

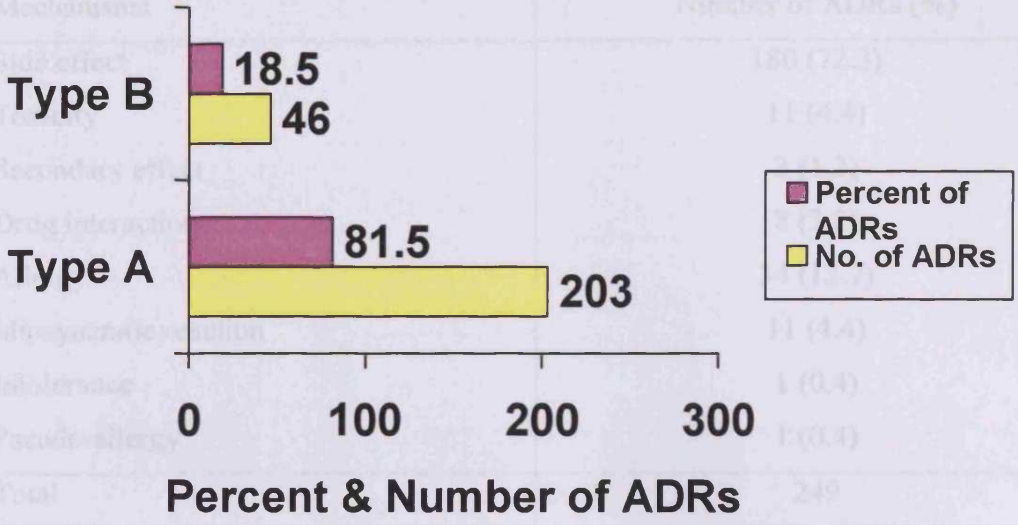


Figure 2.3 Type of ADR problems according to the Rawlins and Thompson (1991) classification.

Table 2.16 Mechanisms of ADR problems.

Mechanisms	Number of ADRs (%)
Side effect	180 (72.3)
Toxicity	11 (4.4)
Secondary effect	3 (1.2)
Drug interaction	8 (3.2)
Allergy	34 (13.7)
Idiosyncratic reaction	11 (4.4)
Intolerance	1 (0.4)
Pseudo-allergy	1 (0.4)
Total	249

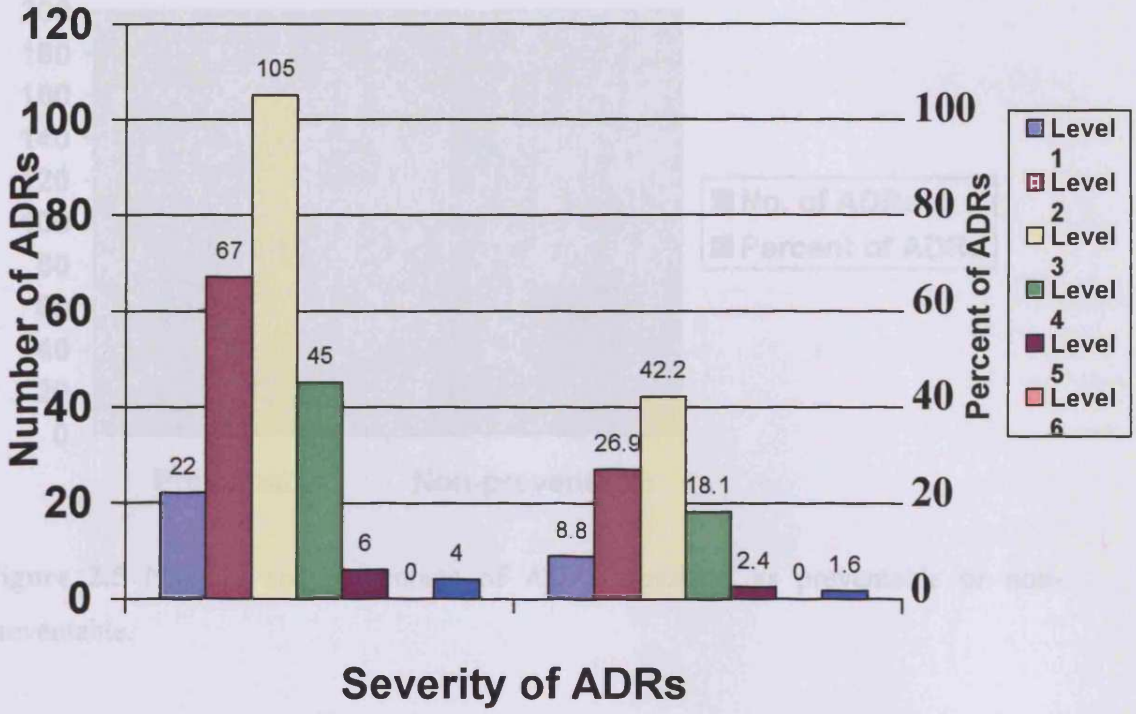


Figure 2.4 Severity of ADR problems.

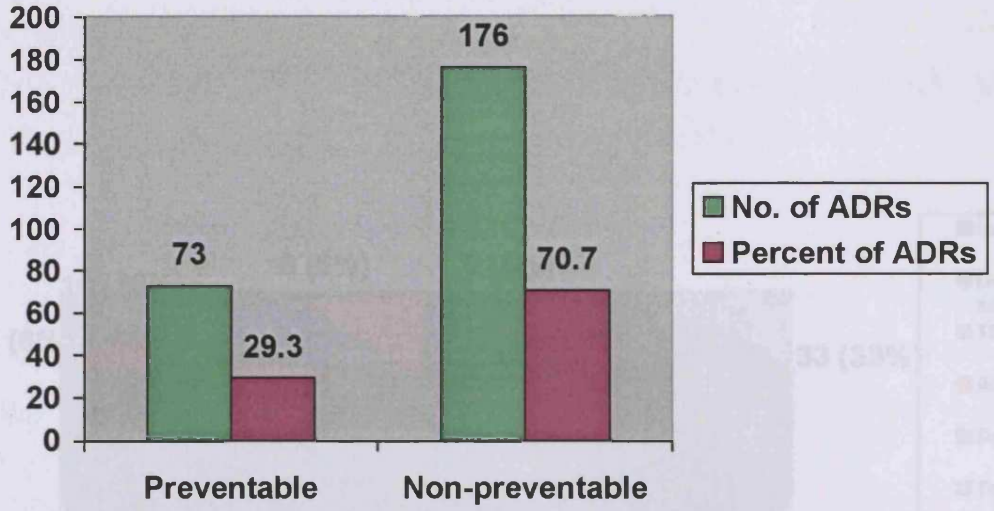


Figure 2.5 Number and percentage of ADRs classified as preventable or non-preventable.

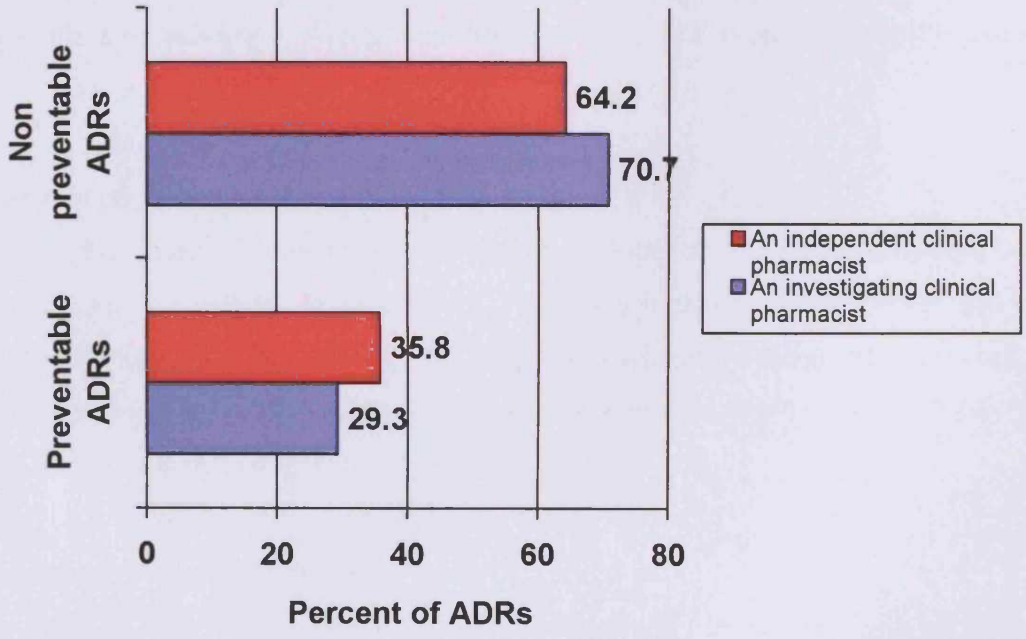


Figure 2.6 Comparison of ADRs classified as preventable by two assessors.

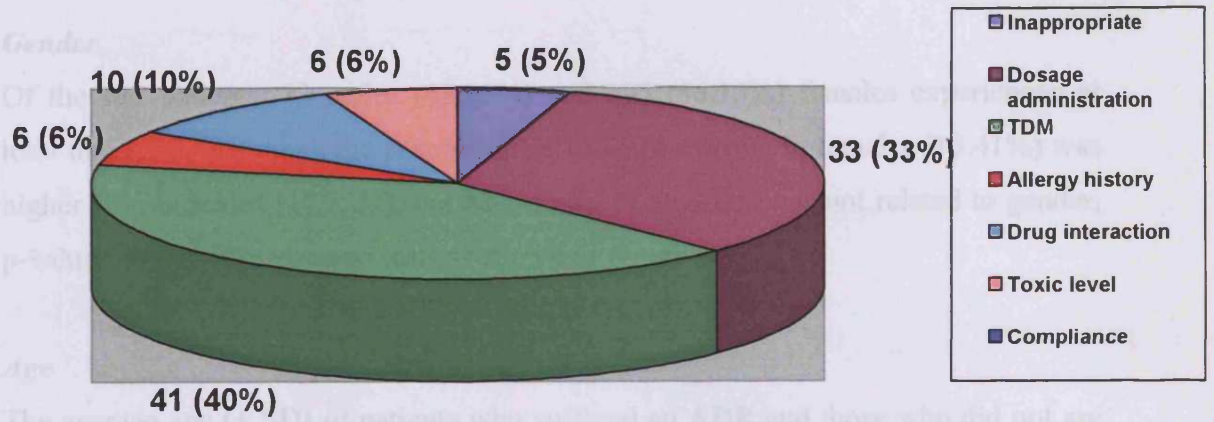


Figure 2.7 Number and percentage of preventable ADRs in each criterion.

Patients at risk from an ADR

The following parameters were tested as possible risk factors for experiencing an ADR:- gender, age, LOS, number of concomitant drugs, coexisting diseases, cigarette smoking and/or alcohol consumption, and previous drug allergy history.

Gender

Of the 187 patients, 82 males (43.85%) and 105 (56.15%) females experienced at least one ADR. Although the proportion of ADRs occurring in females (13.41%) was higher than in males (10.72%), the occurrence of an ADR was not related to gender, p-value = 0.104 (Chi-squared test) as shown in Figure 2.8.

Age

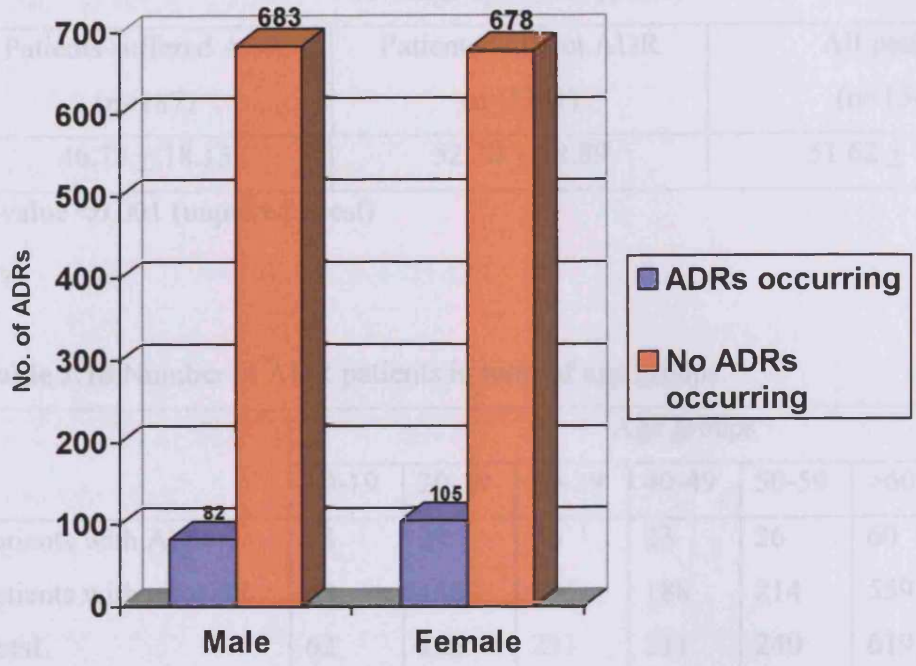
The average age (± SD) of patients who suffered an ADR and those who did not are presented in Table 2.17. The average age of patients without an ADR was found to be greater than the age of patients with an ADR by 5.57 years (95% CI 2.69-8.45). There was a significant difference between age and the occurrence of an ADR (unpaired *t*-test). The patient's age was categorised into six groups as presented in Table 2.18. The highest proportion of ADRs were found to occur in the age range 10-19 years of age.

Length of stay (LOS)

Mean (± SD) length of stay of patients who experienced an ADR compared with those who did not is presented in Table 2.19. There was a significant difference (p-value <0.001) between the two groups. As might be expected, patients who suffered an ADR were required to stay longer in hospital by 9.49 days (95% CI 8.36-10.64). The LOS for patients in each group are presented in Table 2.20.

Number of concomitant drugs

The mean (± SD) number of drugs taken concomitantly in patients with an ADR is presented in Table 2.21. Patients who suffered an ADR received more concomitant drugs than patients who did not by 8.45 items (95% CI 7.32-9.58). The number of drug items that patients were taking was divided into six groups as shown in Table 2.22.



p-value = 0.104 (Chi-squared test)

Figure 2.8 Number of ADRs in male and female patients.

Table 2.17 Average age of patients who suffered an ADR compared with those who did not.

Average age ± SD (years)		
Patients suffered ADR (n=187)	Patients without ADR (n=1361)	All patients (n=1548)
46.73 ± 18.13	52.30 ± 18.89	51.62 ± 18.88

p-value <0.001 (unpaired *t*-test)

Table 2.18 Number of ADR patients in term of age groups.

	Age groups						
	10-19	20-29	30-39	40-49	50-59	>60	All
Patients with ADR	13	29	36	23	26	60	187
Patients without ADR	49	156	195	188	214	559	1361
Total	62	185	231	211	240	619	1548
Proportion	21.0%	15.7%	15.6%	10.9%	10.8%	9.7%	12.1%

p-value = 0.019 (Chi-squared test)

Table 2.19 Average LOS of patients who suffered an ADR compared with those who did not.

Average LOS ± SD (days)		
Patients suffered ADR (n=187)	Patients without ADR (n=1361)	All patients (n=1548)
17.42 ± 12.93	7.93 ± 6.34	9.07 ± 8.06

p-value < 0.001 (unpaired *t*-test)

Table 2.20 LOS for patients in each group.

	LOS groups						
	< 10	10-19	20-29	30-39	40-49	>50	All patients
Patients with ADRs	53	81	24	18	6	5	187
Patients without ADRs	1040	250	50	13	5	3	1361
Total	1093	331	74	31	11	8	1548
Proportion	4.9%	24.5%	32.4%	41.9%	54.5%	62.5%	12.1%

p-value < 0.001 (Chi-squared test)

Table 2.21 Average number drug items taken by patients who suffered an ADR compared with those patients who did not.

Number of drug items per patient		
Patients suffered ADR (n=187)	Patients without ADR (n=1361)	All patients (n=1548)
18.35 ± 10.28	9.90 ± 6.89	10.92 ± 7.88

p-value < 0.001 (unpaired *t*-test)

Table 2.22 Number of drug items taken by patients in various groups.

	Number of drug items taken						
	< 10	10-19	20-29	30-39	40-49	>50	All patients
Patients with ADRs	35	76	56	13	4	3	187
Patients without ADRs	775	460	98	18	6	4	1361
Total	810	536	154	31	10	7	1548
Proportion (%)	4.3	14.2	36.4	41.9	40.0	42.9	12.1

p-value < 0.001 (Chi-squared test)

Coexisting diseases

Coexisting diseases which might predispose patients to an ADR such as AIDS, cancer, renal disease, liver disease, CHF and SLE are presented in Tables 2.23 to 2.28. Only cancer was found to be a predisposing factor.

Cigarette smoking and/or alcohol consumption

The number of ADRs in patients who smoked and consumed alcohol are shown in Table 2.29. Neither of these factors appear to predispose patients to an ADR.

Previous history of drug allergic reaction

Presented in Table 2.30 are the number of ADRs that occurred in patients with a history of drug allergy. There was a significant relationship between the two indicating that a history of drug allergy is a predisposing factor for an ADR.

Table 2.23 Number of patients with AIDS experiencing an ADR.

	Number of patients		
	Patient with AIDS	Patient without AIDS	All patients
Patients with ADR	13	174	187
Patients without ADR	93	1268	1361
Total	106	1442	1548
Proportion	12.3%	12.1%	12.1%

p-value = 0.878 (Chi-squared test)

Table 2.24 Number of patients with cancer experiencing an ADR.

	Number of patients		
	Patients with cancer	Patients without cancer	All patients
Patient with ADR	61	126	187
Patient without ADR	226	1135	1361
Total	287	1261	1548
Proportion	21.3%	10.0%	12.1%

p-value <0.001 (Chi-squared test)

Table 2.25 Number of patients with renal disease experiencing an ADR.

	Number of patients		
	Patients with renal disease	Patients without renal disease	All patients
Patient with ADR	47	140	187
Patient without ADR	266	1095	1361
Total	313	1235	1548
Proportion	15.0%	11.3%	12.1%

p-value = 0.074 (Chi-squared test)

Table 2.26 Number of patients with liver disease who experienced an ADR.

	Number of patients		
	Patients with liver disease	Patients without liver disease	All patients
Patient with ADR	28	159	187
Patient without ADR	149	1212	1361
Total	177	1371	1548
Proportion	15.8%	11.6%	12.1%

p-value = 0.111 (Chi-squared test)

Table 2.27 Number of CHF patients who experienced an ADR.

Patient factor	Number of patients		
	Patients with CHF	Patients without CHF	All patients
Patient with ADR	14	173	187
Patient without ADR	77	1284	1361
Total	91	1457	1548
Proportion	15.4%	11.9%	12.1%

p-value = 0.319 (Chi-squared test)

Table 2.28 Number of patients with SLE who experienced an ADR.

Patient factor	Number of patients		
	Patients with SLE	Patients without SLE	All patients
Patient with ADR	13	174	187
Patient without ADR	59	1302	1361
Total	72	1476	1548
Proportion	18.1%	11.8%	12.1%

p-value = 0.111 (Chi-squared test)

Table 2.29 Number of patients who smoked cigarettes and/or consumed alcohol.

Patient factor	Number of patients		
	Patients with ADR (% in each group)	Patients without ADR (% in each group)	All patients
Cigarette smokers	14 (13.2%)	92 (86.8%)	106
Alcohol drinkers	5 (9.8%)	46 (90.2)	51
Smoker and drinker	13 (9.4%)	125 (90.6%)	138
None	155 (12.4%)	1098 (87.6%)	1253
Total	187	1361	1548

p-value =0.707 (Chi-squared test)

Table 2.30 Number of patients with a history of drug allergy.

Patient factor	Number of patients		
	Patients with previously history of allergy	Patient unknown history of drug allergy	All patients
Patient with ADR	28	159	187
Patients without ADR	103	1258	1361
Total	131	1417	1548
Proportion	21.4%	11.2%	12.1%

p-value <0.001 (Chi-squared test)

DISCUSSION

Disease frequency is generally referred to in terms of prevalence and incidence (Hennekens and Buring, 1987; Knapp and Miller, 1992). The prevalence represents the number of existing cases with the disease, divided by the total population at a given point in time. In contrast, the incidence represents the number of existing cases who suffer from the disease (the numerator) divided by the total population (the denominator) at a specified period of time. Because in the present study, frequency refers only to the number of ADRs noted during the study periods, the prevalence cannot be measured. In addition, an ADR can be considered a drug-induced disease in terms of disease frequency measurement and clearly one patient could suffer more than one ADR. For this reason, the frequency of an ADR occurring is presented both in terms of incidence and rate. To provide further information, this number is quoted per 100 patient hospital admissions or with reference to the length of patient study in hospital (i.e. per 1,000 patient-days). In the present study, the frequency with which ADRs occurred was found to be 12.1 patients who experience an ADR per 100 patient admissions on two medical wards at the Ramathibodi Hospital. In comparison, Hurwitz and Wade (1969) reported the incidence of ADRs occurring at a UK general hospital as being 118 out of 1,160 patients or 10.2 patients experienced an ADR per 100 patient admissions. This was during a stay on a general medical, surgical, dermatology and psychiatry ward following intensive monitoring. Although the present results are slightly higher, they are of the same order of magnitude. Interestingly, in a study carried out in Switzerland, Fattinger *et al.* (2000) reported the incidence of ADRs occurring on two medical wards at a teaching hospital, using a computer-support data entry system and electronic patient record retrieving, as 11.0 patients who experienced an ADR per 100 admissions. Remarkably similar to the finding in the present study.

In contrast, Van den Bemt *et al.* (2000b) reported an incidence of ADRs on the internal medicine wards of two Dutch general hospitals as 27.7 per 100 admissions. This higher incidence was said to result from an increased focus on ADR detections. Collaboration of doctors and nurses in spontaneous reporting schemes with intensive patient reviews by hospital pharmacists was said to lead to the high detections rates. Moreover, it found that the mean age of 68.7 years and a LOS of 16.5 days were both considerably higher than in the present study where the mean age was 51.6 years with

a LOS of 9.1 days. Since the elderly are more likely to suffer an ADR than their younger counterparts this may be the reason for the higher incidence of ADRs in the Van den Bemt study.

In France, Lagnaoui *et al.* (2000) reported that the incidence of ADRs was 5.9 patients per 100 admissions or 10.1 patients per 1,000 patient-days during hospitalisation in the internal medicine department of a university hospital. This study included subjects with an average LOS of 5.8 days who received on average 5.2 drugs concurrently. As a result of this, the frequency of an ADR occurring might have been expected to be less than the present study. In a further study by Bates *et al.* (1995b), the number of ADEs were reported to be 6.5 per 100 admissions and 11.5 per 1,000 patient-days. In this study, the severity of the ADEs were categorised into fatal, life-threatening, serious and significant. This study did not include mild ADEs which probably explains why the frequency was lower than in the present study, even though this study included medication errors which resulted in an ADE. Interestingly, the incidence of ADEs in two large academic long-term care facilities was found to be as high as 815 in a total of 1,247 long-term care residents (or 8,336.4 resident-months) equating to 29.4 ADEs per 1,000 patient-days (Gurwitz *et al.*, 2005). These subjects were on average aged 86 years old. The fact that this study was in elderly patients who were long-term care patients doubtless resulted in the high number of ADEs observed. This study included medication errors which would also inflate the number of ADEs occurring.

In the above studies, the frequency of ADRs/ADEs reported were determined following systemic chart review and/or intensive surveillance. Although this method is regarded as being highly sensitive, it is also time consuming and costly which is a major limitation if carried out daily. In contrast, spontaneous reporting methods are easy to carry out and cost less but suffer from under-reporting. As a consequence, a trigger system using both computerised and non-computerised detection methods has been developed in order to capture suspected ADRs in daily practice (Gandhi *et al.*, 2000; Thurmann, 2001; Rozich *et al.*, 2003). Perhaps not surprisingly, the frequencies of ADR occurring vary according to which of these different methods was used for detecting ADRs. Importantly, the methods described in the classic paper of Classen *et al.* (1991; 2005) have been developed into computerised surveillance of ADRs over

an 18 month period at a tertiary care centre in a US hospital affiliated to a university faculty. However, the frequency of ADRs was reported to be only 1.77 per 100 admissions. This was probably as a consequence of the computerised surveillance system not being able to detect all ADRs. In summary, the incidence rate of ADRs found in the present study were not very different from those reported in previous studies. This is despite variations in the definitions used of an ADR, the use of a variety of methodologies and different patterns of medication usage (Sweet and Ryan, 1994; Dean, 2003; Stephens, 2004).

In a meta-analysis of ADR incidence in US hospitalised patients carried out by Lazarou *et al.* (1998), it was found that the incidence for all ADRs was 10.9%, in a patient population of 34,463. Interestingly, this incidence is close to the incidence found in the present study (12.1%) even though there were differences in the definition of an ADR in both studies. Furthermore, in the present study the incidence density was found to be 13.31 per 1,000 patient-days. It was estimated that there were approximately 0.8 patients experiencing a drug-induced ADR every day on two medical wards investigated in the present study. Thus, it is a challenge to reduce ADRs. Clearly, understanding the risk factors leading to an ADR is fundamental if drug-induced ADRs in hospital patients is to be related to a minimum.

Importantly, anti-infective agents were found to be the drug group most likely to lead to an ADR (i.e. 43.6% in the present study). However, Classen *et al.* (1991; 2005) reported that analgesics led to 31.0% of all ADRs, more than any other drug group. This difference may have resulted from the different methods used for ADR detection; computer-based surveillance against daily intensive chart review. The computerised ADR detection method is affected by the limitation of signal alerting. Perhaps surprisingly, this result was similar to that published by Bates *et al.* (1995b), who also found that the drug group most likely to cause ADEs were analgesics (i.e. 30%). Needless to say, the recruitment of critical care and surgical patients would be expected to result in high analgesic usage. However, Gurwitz *et al.* (2005) reported that warfarin was the prime drug causing an ADE in their study (i.e. 15% of all ADEs). The long-stay care patients studied in this particular investigation was probably was the cause of the different pattern of medication usage seen from the previous studies.

As a result of intensive patient surveillance, all ADRs should be detected, and hence avoided. Interestingly, the body in general and disorders of the gastro-intestinal system were most affected by ADRs. This was similar to the findings of Van den Bemt (2000b) and Fattinger (2000), although other organs affected were different from those quoted by Van den Bemt *et al.* (2000b) and Fattinger *et al.* (2000). These discrepancies probably resulted from different medication usage in the different patient populations.

Although the incidence of ADRs quoted in the study by Lazarou *et al.* (1998) resulted from a meta-analysis of ADR studies carried out in the USA, it was reported that Type A accounted for 76.2% of ADRs. This was the same order as the 81.5% found the present study. In contrast, Lagnaoui *et al.* (2000) found Type A ADRs accounted for only 42.3% of events in his study. These discrepancies probably resulted from the recruitment of different types of patient. For example, Lazarou *et al.* (1998) recruited in a variety of hospitals in the USA, whereas Lagnaoui *et al.* (2000) carried out his study in a 23-bed ward in a University hospital in France.

In an early study carried out by Hurwitz and Wade (1969), side effects were found to be responsible for 52% of all ADRs. In contrast, this mechanism accounted for 72% of ADRs in the present study. Thus, the majority ADRs in the present study could be regarded as predictable and thus should have been preventable. Hurwitz and Wade (1969) also reported that out of 129 ADRs, 3.1% were severe, 79.8% moderate and 17.1% were of mild severity. In the present study, the percentage of level 3 and 4 severities were combined together giving a figure of 60.3% for ADRs of moderate severity. This level of severity was similar to that found earlier by Hurwitz and Wade (1969). Bates *et al.* (1995b) in their later study classified severity of ADEs as fatal, life-threatening, serious, and significant. Thus, it was difficult to compare their study results with the present one. Interestingly, although Classen *et al.* (1991; 2005) did not detect ADRs by systematic chart review or intensive surveillance, they did find that Type A reactions accounted for 90.8% of all ADRs detected. ADRs of moderate severity accounted for 82.1% of the 731 ADRs. These results were closely related to the present study. There were suggestions that many ADRs could have been prevented and later work was developed in order to bring about a reduction in ADRs occurring (Evans *et al.*, 1994).

It was an important part of the present study to determine the number of so-called preventable ADRs. In fact, all ADRs were classified as preventable according to the criteria published by Shumock and Thornton (1992). Although this is possibly not the best method of assessment (Olivier *et al.*, 2002), it was used to assess ADRs which were considered preventable as part of the process for developing methods of ADR prevention. Interestingly, in the clinical situation it was found that it was not easy to respond to the questions used in the assessment process. For example, the first criterion was based on a question asking about inappropriate clinical conditions! It was not easy to justify the appropriateness of medication under some clinical situations because a definitive diagnosis had not always been established. Vague clinical conditions resulted in difficulties in assessment. Inadequate drug monitoring also led to difficulties with assessment. For instance, although patients were checked for blood electrolytes after using amphotericin B, they were also hypokalemic. Moreover, there were ADRs which were could not be matched to any criteria or were incomplete and so it was unclear whether these ADRs could be regarded as preventable. Antimicrobial-induced thrombophlebitis or phlebitis was an example. As a result of difficulties in assessment and relatively incomplete patient information, when an independent clinical pharmacist retrospectively assessed ADRs for preventability to determine reproducibility of this assessment process it was found to be only moderately reproducible (kappa coefficient 0.41).

In the same way, the frequency of preventable ADRs reported can be virtually the same as the frequency of ADRs occurring. Furthermore, the characteristics of preventable ADRs relies on the definition of preventable ADRs, the methodologies used and the pattern of medication usage. The rates of preventable ADRs in this study were judged to be 4.72 per 100 admissions or 5.20 per 1,000 patient-days. This was lower than quoted in the Gurwitz (2005) study, where the rate of preventable ADRs was found to be as high as 12.3 per 1,000 patitent-days (Gurwitz *et al.*, 2005). In addition, the percentage of preventable ADEs (42%) was likewise higher than seen in the present study (29%). Because the majority of subjects in the Gurwitz study were elderly patients in long-term care, these patients were probably more likely to suffer an ADR due to a high medication load resulting in more preventable ADRs. In addition, the most common drug causing an ADE in this study was warfarin which was relatively easy to "control" with appropriate prescribing and monitoring.

Interestingly, although preventability assessment in the Bates study (Bates *et al.*, 1995b) was performed by an expert panel, it was found that preventable ADEs were estimated to be 28% which was close to the percentage of preventable ADRs estimated in the present study.

Lagnaoui *et al.* (2000) found that the percentage of preventable ADRs in their study was 50%, almost twice that seen in the present study. Differences in patient recruitment, medication usage and preventability assessment probably resulted in the high percentage seen. In another study, the percentage of preventable ADRs was estimated to be 34% (Oliver *et al.*, 2002). This was a study carried out in out-patients where the level of care and monitoring is likely to be less than in hospitalised patients, resulting in a higher percentage of preventable ADRs. Pearson *et al.* (1994) and later Seeger *et al.* (1998) reported on the characteristics of preventable ADRs, as assessed by the Schumock and Thornton criteria in a community hospital and large university hospital in USA. The rate of preventable ADRs in both studies was 19% following the spontaneous reporting of ADRs. Interestingly, the voluntary report system tended to result in a number of unpredictable ADRs being collected. The most frequently observed criteria for preventable ADRs were associated with therapeutic drug monitoring and laboratory tests (39.4%). This was different from the Seeger *et al.* (1998) and Pearson *et al.* (1994) studies. Seeger *et al.* (1998) reported that preventable ADRs were associated mainly with dosing and a history of drug allergies whilst Pearson *et al.* (1994) reported that most of the preventable ADRs were involved solely with documented allergic responses to drugs.

Not only the characteristics of ADRs have been determined but patients at risk have also been investigated. In the present study, risk factors included patient age, length of stay in hospital, whether patients had cancer or not, the number of medications being taken and whether they had a history of drug allergy. Recently, Evans *et al.* (2005) determined inpatient risk factors for ADEs using a matched case-control study design. ADEs which were considered to be ADRs were detected by computerization over a 10-year period in a large teaching hospital. The matched cases of 4,291 ADEs were analysed by conditional logistic regression, being compared with 64,544 control patients. Inpatient risk factors were divided into three categories i.e. patient characteristics, drug administration and patient type. Not only drugs causing ADEs

were identified but also risk factors associated with different therapeutic classes of drug while severe ADEs were likewise identified as risk factors. This study identified analgesics, morphine, anti-infectives, cardiovascular agents, anticoagulants and anti-platelets as high risk drugs which should be closely monitored. Moreover, gender (female), age, weight, creatinine clearance and a number of co-morbidities increased the risk of an ADE occurring.

The present study differed from the Evans *et al.* (2005) study in terms of methodology, subjects and types of risk factor, the mean age of patients, and number of medications being administered; therefore patient risk factors in the present study were not similar to the large subject study, whilst cancer disease and drug allergy patient risk factors were not specifically performed by Evans *et al.* (2005). The length of hospital stay was not determined in the large study because this factor was a matching parameter. However, the length of stay in the present study was similar to the finding of Bates *et al.* (1999) who found ADEs occurred more often in patients who stayed longer in hospital although the method of investigating risk factors was not the same as used in the present study. Moreover, the number of drugs administered per patient was found to be the factor which most frequently contributed to ADEs (Van den Bemt *et al.*, 2000b), a finding similar to that found in the present study. Although cancer and a history of drug allergy were not compared in the above original research articles, these factors were found to be predisposing factors as summarised in the comprehensive review articles later published by Riedl and Casillas (2003) and Calis and Young (2004).

The number of drug items being taken by patients with an ADR were more than twice those being taken in patients who did not experience an ADR. This result might be explained by the increased chance of drug-drug interactions taking place. This finding confirmed that the more drugs taken concomitantly the greater the risk of an ADR occurring (Veehof *et al.*, 1999). Although age is a predisposing factor for an ADR to occur in this study the average age of patients without an ADR was more than that in patients who experienced an ADR. This result might be explained by the fact that patients aged 10-19 years old had the highest incidence of ADRs (21.0%) patients aged over 60 experienced the lowest (9.7%). This result was at variance with the

theory that elderly patients are at greatest risk of ADRs due to such problems as organ failure (Routledge *et al.*, 2003; Routledge, 2004).

Gender was not found to be a predisposing factor in the present study. This somewhat surprising result was different from that published by Martin *et al.* (1998), Tran *et al.* (1998), Montastruc *et al.* (2002) and Evans *et al.* (2005). Monstastruc *et al.* (2002) and Martin *et al.* (1998) identified gender differences in a voluntary report to the Pharmacovigilance Centre in France and General Practice database in England, respectively, while Tran *et al.* (1998) investigated patients who were referred to an ADR clinic. One of the possible explanation for this finding might be the small sample size in the present study. The Evans, Monstastruc, and Tran studies included 4,291, 927 and 2,367 ADR patients, respectively, while Martin *et al.* (1998) included a total of 513,608 patients. Recent reviews by Routledge *et al.* (2003) and Anderson (2005) confirm that females are more at risk from experiencing an ADR than their male counterparts.

Variations in ADR causality assessment methods frequently result in differences in whether not a specific drug caused an ADR (Macedo *et al.*, 2003). Although Naranjo's algorithm is one of the most widely used methods of determining causality (Oberg, 1999), it is not easy to use. For this reason, the RUCAM was used in this study because it provides more detail for assessments carried out in practice. Causality assessment using RUCAM resulted in more than 80% of ADRs being classified as probable or highly probable. The intense monitoring system and availability of complete information for patients allowed all questions in the RUCAM method to be answered. Despite this, in the retrospective reproducibility study where assessment was repeated by an independent clinical pharmacist, the kappa coefficient was calculated to be only 0.11. Although this value became 0.41 when highly probable and probable, and possible and unlikely were combined, agreement was far from perfect.

The present study was the longest patient safety monitoring study so far carried out in Thailand. In order to detect all the ADRs that occurred in the study, a dedicated research clinical pharmacist had surveyed all patient data on a daily basis. However, this high level of surveillance is not practical in pharmacy practice. Instead, a

stimulated spontaneous reporting system (SRS) and/or trigger system should be developed for daily practice in the near future.

SUMMARY

- During a 10 month baseline period, a total 1,548 patients were monitored for ADRs. Two hundred and forty-nine ADR problems were identified in 187 patients. Thus, the cumulative incidence and incidence density of overall ADRs were 12.08 per 100 admissions and 13.31 per 1,000 patient-days, respectively. The rate of overall ADRs was 16.09 per 100 admissions or 17.73 per 1,000 patient-days, respectively.
- It was found that 73 of the 249 ADRs could have been prevented (i.e. 29.3%). Thus, the rate of preventable ADRs was 4.72 per 100 admissions or 5.20 per 1,000 patient-days.
- General anti-infectives for systemic use led to the most ADRs (43.6%). Antibiotics (25.5%) and antimycotics (13.8%) for systemic use and antithrombotic agents (10.6%) were the most common drug groups causing an ADR.
- Some 81.5% of ADRs were Type A while 42.2% of all ADRs were classified as level 3 severity (i.e. the ADR required that treatment with the suspected drug be held, discontinued, or otherwise changed).
- It was estimated that many ADRs could have been prevented by therapeutic drug monitoring, laboratory test (39.4%) and close attention to using the correct dose, route, frequency of administration for a patient's age, weight, and disease state (32.7%).
- Predisposing factors for an ADR consisted of length of hospital stay, the number of concomitant drugs being administered, whether or not there was a history of drug allergy and whether a patient was suffering from cancer.

Chapter 3

Preventing Adverse Drug Reactions in Hospitalised Patients by Clinical Pharmacist interventions

CHAPTER 3

PREVENTING ADVERSE DRUG REACTIOS IN HOSPITALISED PATIENTS BY CLINICAL PHARMACIST INTERVENTIONS

INTRODUCTION

Having established the extent to which ADRs occur in the absence of a research clinical pharmacist on two medical wards at the teaching hospital, the aim of this present study was to determine whether the presence of a research clinical pharmacist as a member of the medical care team, could reduce the number of ADRs occurring. Described in this chapter are the findings of an intervention study in which a ward-based clinical pharmacy service was provided for a 10-month period, the same length of time as the baseline/control period (as described in Chapter 2), on the same two medical wards at Ramathibodi Hospital.

METHODS

Study design

A prospective intervention study was carried out on two medical wards at the Ramathibodi Hospital, a research clinical pharmacist being present as a member of the medical care team.

Sample size estimation

In the previous preliminary study (Tragulpiankit, 1995), it was found that the rate of preventable ADRs in patients on the 1st Male Medical and 1st Female Medical Wards at Ramathibodi Hospital was 7 events per 100 admissions (7%). This occurrence resulted from 515 patients during a three and a half month period of surveillance. The hypothesis of the present study was to reduce the percentage of preventable ADRs by 50%. Thus, the expected percentage of preventable ADRs in the intervention period will be 3.5%. The sample size estimation was calculated by determination of the standardized difference (Petrie and Sabin, 2000; Schulz and Grimes, 2005) as follows:

$$\text{Standardized difference} = \frac{(p_1-p_2)}{\sqrt{p(1-p)}}$$

Proportion of preventable ADRs in the baseline period (p_1) = 0.07

Proportion of preventable ADRs in the intervention period (p_2) = 0.035

An average of a proportion of preventable ADRs (p) = 0.0525

Therefore, the standardized difference was 0.156927. The power of detecting preventable ADR difference in the two studies was 80% at the 5% level of significant. Thus, the required sample size in each group will be =

$$\frac{16}{(\text{standardized difference})^2}$$

Thus, the sample size in each group will need to be at least 650 patients and the duration of the patient study will need to be at least 9 months for each ward. It was therefore decided to study all patients admitted to the two wards for two ten month periods.

Patient selection

The study included all patients who were admitted or transferred to the 1st Male Medical Ward and the 1st Female Medical Ward at Ramathibodi Hospital from 7th December 2002 to 8th October 2003. Any patient who was admitted for less than 1 day was not included.

Ethics approval

Before commencing the study, ethics approval was given by the Ethical Board Committee at Ramathibodi Hospital (see **ID 09-44-14** ***No.*** 508/2001 dated 19th September 2001- see overleaf).

Medical care teams

Medical care teams at Ramathibodi Hospital are made up of undergraduate and postgraduate medical students. For each 30 bed ward, three principle medical care teams are appointed. Each of these teams consists of a 1st year resident, an extern and six or seven undergraduate medical students, supervised by a 2nd year resident doctor (specialty doctor) and a 3rd year resident doctor (ward advisor).

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Documentary Proof of Ethical Clearance Committee on Human Rights Related to Researches Involving Human Subjects
Faculty of Medicine, Ramathibodi Hospital, Mahidol University

No. 508/2001(I)

Title of Project	PHARMACIST PARTICIPATION AND CHARACTERISTIC OF PREVENTABLE ADVERSE DRUG REACTIONS IN MEDICAL PATIENTS, RAMATHIBODI HOSPITAL
Protocol Number	ID 09-44-14
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The aforementioned project has been reviewed and approved by Committee on Human Rights Related to Researches Involving Human Subjects, based on the Declaration of Helsinki.

Signature of Chairman
Committee on Human Rights Related to Researches Involving Human Subjects

Prof. Krisada Ratana-olarn, M.D., FRCST, FICS.

Signature of Dean

Prof. Prakit Vathesatogkit, M.D., ABIM.,FRCP.

Date of Approval September 19, 2001

Data collection

An investigating clinical pharmacist monitored all patients admitted to the two selected wards from patient admission through to discharge from the medical ward. Clinical data were entered into a "Patient monitoring form" (Table 3.1). The clinical data consisted of the patient's name, hospital number (HN), gender, age, coexisting diseases, social history (smoking and alcohol drinking), drug allergy history, provisional diagnosis, past medication history and current medication. Responses to treatment including signs/symptoms and laboratory results were reviewed daily.

Detection of potential ADRs

Potential ADRs were identified according to Schumock and Thornton's criteria (1992). In the case of a potential ADR, this would be investigated thoroughly by the investigating ward-based clinical pharmacist. Any recommendations made to the medical care team were on a face to-face basis, in order to prevent a potential ADR from occurring. The investigating clinical pharmacist's recommendations were recorded on a "Clinical pharmacist intervention form" (Table 3.2).

ADR causality assessment, preventability assessment and ADR data collection

Adverse events were retrospectively detected by an investigating clinical pharmacist based on any undesired events or abnormal laboratory noted during intensive patient surveillance.

Causality assessment

Roussel's Ulcaf Causality Assessment Method (RUCAM) (Table 3.3) was used to assess the probability of a particular drug causing an ADR. This was carried out by the investigating clinical pharmacist. This method was also used retrospectively for validation when an expert member of the clinical pharmacist staff at the Pharmacy Faculty at Mahidol University, independently assessed causality.

Table 3.1 Patient monitoring form.

Patient monitoring form (page 1)

□M □F Patient Name_____ HN_____ Physician name_____

Date of birth_____ Age___ Weight__(kg) Height____(cm) IBW___(kg) BMI___

Admission Date_____ Discharge Date_____ LOS_____ Bed No.____

Chief complains_____

Present illnesses_____

_____

_____

Coexisting diseases or Past medical history_____

_____

Past medical history_____

_____

Social history_____ Drug allergy history_____

Investigations_____

_____

_____

_____

Problem lists or provisional diagnosis_____

_____

_____

Hospital courses_____

_____

_____

_____

Discharge diagnosis_____

_____

_____

_____

Table 3.1 Patient monitoring form (cont.).

Medication profile page__

Patient name___________ HN________ Age______ Physician name____________

Drugs	Dosage and administrations	Date																					

Table 3.2 Clinical pharmacist intervention form.

Clinical pharmacist intervention form

☐M ☐F Patient name_____ HN_____ Date of record_____

A Potential ADR/ clinical pharmacist intervention_____

_____

_____

Drug(s) related interventions_____

_____

Type of clinical pharmacist's recommendations:

☐ 1) The drug involved in the ADR was not considered appropriate for the patient's clinical condition.

☐2) The dose, route, and frequency of administration was not appropriate for the patient's age, weight and disease state.

☐3) Therapeutic drug monitoring or other necessary laboratory test was not performed.

☐4) There was a history of allergy or previous reaction to the drug.

☐ 5) A drug interaction was involved in the reaction.

☐6) A toxic serum drug level was documented.

☐7) Poor compliance was involved in the reaction.

Potential severity:

- ☐ Potential fatal
- ☐ Potential serious
- ☐ Potential significant

Outcome of recommendations:

- ☐ Accepted and changed
- ☐ Accepted but unchanged
- ☐ Not accepted

Patient outcomes:

- ☐ Improve or no ADR occurred
- ☐ Worse or ADR occurred
- ☐ Dead

Table 3.3 The Roussel Ulcaf Causality Assessment Method (RUCAM) (Benichou, 1994).

Criteria		Score[d]
1. TIME TO ONSET OF THE REACTION	highly suggestive	+3
	suggestive	+2
	compatible	+1
	inconclusive	0
If incompatible, then case "unrelated"		
If information not available, then case "insufficiently documented"		
2. COURSE OF REACTION	highly suggestive	+3
	suggestive	+2
	compatible	+1
	against the role of the drug	-2
	inconclusive OR not available	0
3. RISK FACTOR(S) FOR DRUG REACTION	presence	+1 to +2[a]
	absence	0
4. CONCOMITANT DRUG(S)[c]	Time to onset incompatible	0
	Time to onset compatible but unknown reaction	-1
	Time to onset compatible and known reaction	-2
	Role proved in this case	-3
	None or information not available	0
5. NON DRUG RELATED CAUSED[c]	Ruled out	+2
	Possible or Not investigated[b]	+1 to -2
	Probable	-3
6. PREVIOUS INFORMATION ON THE DRUG	Reaction unknown	0
	Reaction published but unlabelled	+1
	Reaction labelled in the product's characteristics	+2
7. RESPONSE TO READMINSTRATION	Positive	+3
	Compatible	+1
	Negative	-2
	Not available or Not interpretable	0
or PLASM CONCENTRATION of the drug known as toxic		+3
or VALIDATED LABORATORY TEST with high specificity, sensitivity and predictive values		
	Positive	+3
	Negative	-3
	Not interpretable or not available	0
TOTAL		

[a] one additional point for every validated risk factor (maximal value +2)

[b] depending on the nature of the reaction

[c] Sum of negative values of criteria 4 and 5 cannot be lower than -4

[d] The score are classified in 4 degrees: score above 8, relationship "highly probable"; 6-8, relationship "probable"; 3-5 relationship "possible"; 1-2, relationship "unlikely".

Preventability assessment

All ADRs were assessed for preventability using Schumock and Thornton criteria (1992) by the investigating clinical pharmacist. Latter, a clinical pharmacy expert retrospectively assessed preventability as a means of determining reproducibility of the technique and accuracy of the assessment made initially by the investigating ward-based clinical pharmacist.

ADR data collection

ADR data was entered onto an "ADR monitoring form" (Table 3.4). These data consisted of drugs causing an ADR, organs affected, either Type A or Type B, the mechanism of action of the ADR, its severity, causality and preventability assessment.

Data analysis

The data were analysed by SPSS 11.0 version for the following:

i) Demographic data

ii) Frequencies of potential ADRs

iii) Characteristics of the clinical pharmacist's interventions

iv) Frequencies and characteristics of ADRs occurring

RESULTS

The intervention period covered a 10 month period from 7th December 2002 until 8th October 2003. A total of nine hundred and eighty-five patients were recruited, 514 patients (52.18%) being admitted to the 1st Male Medical Ward with the remaining 471 patients (47.82%) admitted to the 1st Female Medical Ward.

Their ages and genders are shown in Table 3.5. The youngest patient was only 15 years old whilst the oldest one was 94 years. The mean $\pm$ SD age was 52.1 $\pm$ 18.9 years (male 51.0 $\pm$ 18.9 years; female 53.2 $\pm$ 18.7 years). Statistically, there was no significant difference in the ages of the male and female group ($p = 0.059$; Mann-Whitney *U*-test).

Table 3.4 ADR monitoring form.

ADR monitoring form

☐M☐F Patient name_____ HN_____ Date of ADR occurring_____

Adverse events _____

_____

Suspected drugs _____

_____

Drug group causing: _____

Organ affected: _____

Causality assessment:

☐highly probable ☐probable ☐possible ☐unlikely

Type of an ADR: ☐ Type A ☐Type B

Mechanism of an ADR:

☐side effect ☐toxicity ☐secondary effect ☐drug interaction

☐intolerance ☐allergy ☐pseudo-allergy ☐idiosyncracy

Severity of an ADR:

☐Level 1: An ADR occurred but required no change in treatment with the suspected drug.

☐Level 2: The ADR required that treatment with the suspected drug be held, discontinued, or otherwise changed. No antidote or other treatment required. No increase in LOS.

☐Level 3: The ADR required that treatment with the suspected drug be held, discontinued, or otherwise change, AND/OR an antidote or other treatment was required. No increase in LOS.

☐Level 4: Any level 3 ADR which increases LOS by at least one day.

☐Level 5: Any level 4 ADR which required intensive medical care.

☐Level 6: The ADR caused permanent harm to the patient.

☐Level 7: The ADR either directly or indirectly led to the death of the patient.

Preventability assessment:

1) Was the drug involved in the ADR <u>not</u> considered appropriate for the patient's clinical condition?

2) Was the dose, route, and frequency of administration <u>not</u> appropriate for the patient's age, weight and disease state?

3) Was required therapeutic drug monitoring or other necessary laboratory test <u>not</u> performed?

4) Was there a history of allergy or previous reaction to the drug?

5) Was a drug interaction involved in the reaction?

6) Was a toxic serum drug level documented?

7) Was poor compliance involved in the reaction?

☐ Yes, if one or more of above are chosen ☐No

Table 3.5 Number of patients in terms of age and gender.

Age group	Number of patients		
	Male (%)	Female (%)	Total (%)
Less than 20 years	18 (3.5)	11 (2.3)	29 (2.9)
20-29	64 (12.5)	53 (11.3)	117 (11.9)
30-39	81 (15.8)	64 (13.6)	145 (14.7)
40-49	74 (14.4)	60 (12.7)	134 (13.6)
50-59	88 (17.1)	89 (18.9)	177 (18.0)
More than 60 years	189 (36.8)	194 (41.2)	383 (38.9)
Total	514	471	985

The minimum length of stay (LOS) in hospital was 2 days whilst the maximum was found to be 77 days. On average, each patient was monitored for 8.84 $\pm$ 8.35 days (male 8.64 $\pm$ 8.37 days, female 9.06 $\pm$ 8.32 days). There was no significant differences between the length of stay of male and female patients (p=0.352; Mann-Whitney *U*-test). LOS and gender distribution is shown in Table 3.6. The total number of patient-days were 8,710 patient-days (male 4,443 patient-days; female 4,267 patient-days).

The number of concomitant drugs administered to male and female patients is shown in Table 3.7. Some patients did not receive any medication whilst the maximum number of medicines administered concomitantly was 51 items. The mean $\pm$ SD number of concomitant drugs was 11.35 $\pm$ 7.18 items (male 10.90 $\pm$ 6.56 items, female 11.85 $\pm$ 7.77 items), there being no significant difference between the number of items in the two groups (p = 0.244; Mann-Whitney *U*-test).

Of the 985 patients studied, some 580 patients suffered from at least one coexisting disease as shown in Tables 3.8 and 3.9. Most patients (660 out of 985 patients) had no history of either alcohol drinking or cigarette smoking. The number of patients in terms of social history and gender distribution are shown in Table 3.10.

One hundred of the total of 985 patients reported a history of drug allergy and of these, a total of 59 (12.5%) were female with the remaining 41 (8.0%) being male.

Frequencies of potential ADRs

During the 10 month intervention period there were 985 patient admissions with 143 recommendations being made for "preventing ADRs" affecting a total of 110 patients covering a LOS of 8,710 patient-days. Details of the investigating clinical pharmacist's recommendations are presented in Table 3.11. Thus, the cumulative incidence for a potential ADR was 11.17 per 100 admissions whilst the incidence density was 12.63 per 1,000 patient-days. In addition, the rate of potential ADRs was calculated to be 14.52 per 100 admissions or 16.42 per 1,000 patient-days.

Some 29 patients were recommended for more than one action, while most patients (81 out of 110 patients) were recommended for a single intervention.

Table 3.6 Number of patients in term of LOS.

LOS (days)	Number of patient		
	Male (%)	Female (%)	Total (%)
Less than 10	372 (72.4)	328 (69.6)	700 (71.1)
10-19	108 (21.0)	113 (24.0)	221 (22.4)
20-29	21 (4.1)	15 (3.2)	36 (3.7)
30-39	4 (0.8)	6 (1.3)	10 (1.0)
40-49	3 (0.6)	5 (1.1)	8 (0.8)
50-59	3 (0.6)	3 (0.6)	6 (0.6)
More than or equal 60	3 (0.6)	1 (0.2)	4 (0.4)
Total	514	471	985

Table 3.7 Number of concomitant drugs administered.

Items	Number of patients		Total (%)
	Male (%)	Female (%)	
Less than 10	244 (47.5)	222 (47.1)	466 (47.3)
10-19	220 (42.8)	180 (38.2)	400 (40.6)
20-29	39 (7.6)	52 (11.0)	91 (9.2)
30-39	10 (1.9)	13 (2.8)	23 (2.3)
40-49	1 (0.2)	3 (0.6)	4 (0.4)
More than or equal 50	0 (0.0)	1 (0.2)	1 (0.1)
Total	514	471	985

Table 3.8 Number of patients with coexisting diseases.

Number of coexisting diseases	Number of patients (%)		
	Male	Female	Total
None	196 (38.1)	209 (44.4)	405 (41.1)
One	239 (46.5)	206 (43.7)	445 (45.2)
Two	70 (13.6)	50 (10.6)	120 (12.2)
Three	9 (1.8)	6 (1.3)	15 (1.5)
Total	514	471	985

Table 3.9 Number of patients with specific coexisting diseases.

Coexisting diseases	Number of patients		
	Male (%)	Female (%)	Total (%)
AIDS	44 (8.6)	29 (6.2)	73 (10.0)
Cancer	102 (19.8)	95 (20.2)	197 (27.0)
Renal disease	103 (20.0)	77 (16.3)	180 (24.7)
Liver disease	101 (19.6)	41 (8.7)	142 (19.5)
CHF	49 (9.5)	48 (10.2)	97 (13.3)
SLE	7 (1.4)	34 (7.2)	41 (5.6)
Total	514	471	730

Table 3.10 Alcohol consumption and smoking in patients involved in the intervention study.

Social history	Number of patients		
	Male (%)	Female (%)	Total (%)
Alcohol drinker	49 (9.5)	14 (3.0)	63 (6.4)
Cigarette smoker	78 (15.2)	15 (3.2)	93 (9.4)
Smoker and alcohol drinker	163 (31.7)	6 (1.3)	169 (17.2)
None	224 (43.6)	436 (92.5)	660 (67.0)
Total	514	471	985

Table 3.11 Clinical pharmacist's interventions (143 interventions in 110 patients).

Problem no.	Case no.	Pharmacist interventions	Drug(s) related interventions	Criteria
1	1	Allergy history reviewed	Sulfonamides	4
2	2	Reduced dosing	Digoxin	2
3	3	Allergy history reviewed	Penicillins	4
4	4	Allergy history reviewed	Cefipime	4
5	4	Reduced rate of infusion	Acyclovir	2
6	5	Allergy history reviewed	NSAIDs	4
7	6	Avoided drug interaction	Amlodipine/clarithromycin/simvastatin	5
8	7	Renal dosage adjusted	Hydralazine	2
9	8	Allergy history reviewed	Penicillins	4
10	9	Avoided drug interaction	Clozapine/ciprofloxacin	5
11	10	Avoided drug allergy	Co-trimoxazole	4
12	11	Avoided drug interaction	Trazodone/fluoxetine	5
13	12	Reduced rate/dose	Fluconazole	2
14	13	Avoided drug interaction	Warfarin/ciprofloxacin	5
15	14	Reduced dosing	Digoxin	2
16	15	Avoided drug interaction	Theophylline/metronidazole	5
17	16	TDM	Cyclosporin	3
18	17	Reduced dosing	Glipizide	2
19	17	Changed to NSS	5%D/W	1
20	18	TDM	Phenytoin	3
21	19	Avoided drug interaction	Warfarin/ciprofloxacin	5
22	20	Avoided drug interaction	Warfarin/ciprofloxacin	5
23	21	Changed to NSS	5%D/W	1
24	22	Suggested infusion over 24 hour	Amphotericin B	2
25	23	Suggested infusion rate	Phenytoin	2
26	24	Monitored drug therapy	Methypredinisolone	3
27	25	Reduced dosing	Ciprofloxacin	2
28	26	Reduced dosing	Atenolol	2
29	27	Suggested IV loading	Cyclophosphamide	2
30	28	Reduced dosing	Amikacin	2
31	29	Reduced dosing	Ciprofloxacin	2
32	30	Changed drug	Ceftriaxone	1
33	31	Avoided drug interaction	Warfarin/levofloxacin	5
34	32	Allergy history reviewed	Sulfonamides	4
35	33	Spitted dosing	Phenytoin	2

Table 3.11 Clinical pharmacist's interventions (cont.).

Problem no.	Case no.	Pharmacist interventions	Drug(s) related interventions	Criteria
36	34	Reduced dosing	Fluconazole	2
37	35	Suggested rate infusion	Acyclovir	2
38	36	Avoided drug interaction	Theophylline/clarithromycin	5
39	37	Suggested IV loading	Cyclophosphamide	2
40	38	Monitored drug therapy	Enoxaparin	3
41	39	Monitored drug therapy	Pheyntoin	3
42	40	Changed to 5%D/W	NSS	1
43	41	Monitored drug therapy	Enalapril	3
44	42	Avoided drug interaction	Warfarin/clarithromycin	5
45	43	Renal dosage adjusted	Digoxin	2
46	44	Renal dosage adjusted	Augmentin®	2
47	44	Reduced dose	Atenolol	2
48	45	Renal dosage adjusted	Augmentin®	2
49	46	Renal dosage adjusted	Ceftazidime	2
50	46	Renal dosage adjusted	Imipenem	2
51	47	Renal dosage adjusted	Acyclovir	2
52	48	Renal dosage adjusted	Augmentin®	2
53	48	Renal dosage adjusted	Allopurinol	2
54	48	Reduced dosing	Phenytoin	2
55	48	Avoided drug interaction	Phenytoin/isoniazid	5
56	49	Renal dosage adjusted	Ceftazidime	2
57	49	Renal dosage adjusted	Co-trimoxazole	2
58	50	Dosage adjusted	Paracetamol	2
59	51	Renal dosage adjusted	Augmentin®	2
60	52	Renal dosage adjusted	Augmentin®	2
61	53	Renal dosage adjusted	Allopurinol	2
62	54	Renal dosage adjusted	Cefotaxime	2
63	54	Renal dosage adjusted	Cefotaxime	2
64	55	Held from liver injury	Levofloxacin	1
65	55	Monitored first dose	Doxazosin	2
66	56	Reduced dosing	Felodipine	2
67	56	TDM	Phenytoin	3
68	57	Renal dosage adjusted	Ciprofloxacin	2
69	58	Suggested loading dose	Warfarin	2
70	59	Inappropriated use	Co-trimoxazole	1
71	59	Renal dosing adjusted	Allopurinol	2

Table 3.11 Clinical pharmacist's interventions (cont.).

Problem no.	Case no.	Pharmacist interventions	Drug(s) related interventions	Criteria
72	60	Reduced dosing	Warfarin	2
73	61	Avoided drug interaction	Warfarin/clarithromycin	5
74	61	Avoided drug interaction	Warfarin/amiodarone	5
75	61	Renal dosing adjusted	Cefixime	2
76	62	Renal dosing adjusted	Amlodipine	2
77	63	Penicillin allergy history reviewed	Augmentin®	4
78	64	Renal dosing adjusted	Atenolol	2
79	65	Inappropriated in hypokalemia, hyponatremia	Moduretic	1
80	66	Avoided drug interaction	Warfarin/amiordarone	5
81	67	Sulfa allergy history reviewed	Glipizide	4
82	67	Inappropriated in liver disease	Rogistazone	1
83	68	Reduced dosing	Gentamicin	2
84	69	Suggested rate of infusion	Vancomycin	2
85	70	Reduced dosing	Augmentin®	2
86	71	Inappropriated in hyponatremia	HCTZ	1
87	71	Inappropriated in hyponatremia	Amitrytyline	1
88	72	Reduced dosing	Augmentin®	2
89	73	TDM	Gentamicin	3
90	74	Drug therapy monitored	Warfarin	3
91	74	Avoided drug interaction	Warfarin/co-trimoxazole/fluconazole	5
92	75	TDM	Theophylline	3
93	75	Avoided drug interaction	Theophylline/clarithromycin	5
94	76	Reduced dosing	Allopurinol	2
95	77	Avoided drug interaction	Phenytoin/co-trimoxazole/fluconazole	5
96	77	TDM	Phenytoin	3
97	78	Reduced dosing	Ceftazidime	2
98	79	Avoided drug interaction	Phenytoin/fluconazole/efavirenz	5
99	79	TDM	Phenytoin	3
100	80	Avoided drug interaction	Digoxin/amiodarone	5
101	81	Inappropriated in stool occult blood positive	Indomethacin	1
102	82	Reduced dosing	Allopurinol	2
103	83	Inappropriated in renal impairment	Enalapril	1

Table 3.11 Clinical pharmacist's interventions (cont.).

Problem no.	Case no.	Pharmacist interventions	Drug(s) related interventions	Criteria
104	83	Reduced dosing	Allopurinol	2
105	84	Reduced dosing	Co-trimoxazole	2
106	85	Avoided drug interaction	Digoxin/diltiazem	5
107	85	TDM	Digoxin	3
108	86	Inappropriated in hypokalemia	Enalapril	1
109	87	Inappropriated in pancytopenia	Co-trimoxazole	1
110	88	Reduced dosing	Ethambutol	2
111	89	Reduced dosing	Ciprofloxacin	2
112	89	Reduced dosing	Amikacin	2
113	90	Inappropriate in hyponatremia	Furosemide	1
114	91	Laboratory monitored	Dexamethasone	3
115	92	Reduced dosing	Ciprofloxacin	2
116	92	Reduced dosing	Ciprofloxacin	2
117	93	Reduced dosing	Warfarin	2
118	94	Avoided drug interaction	Warfarin/clarithromycin	5
119	95	Drug interaction	Cyclosporin/ciprofloxacin	5
120	95	TDM	Cyclosporin	3
121	96	Suggested pre-medication	Amphotericin B	2
122	97	Reduced dosing	Co-trimoxazole	2
123	98	Selected laxative for prevention	Morphine	1
124	99	Reduced dosing	Amikacin	2
125	99	Inappropriated in disease condition	Allopurinol	1
126	99	Drug therapy monitored	Magnesium chloride	3
127	100	Avoided drug interaction	DDI/gancyclovir	5
128	101	Avoided drug interaction	Phenytoin/efavirenz	5
129	101	TDM	Phenytoin	3
130	102	Held inappropriate drugs	Isoniazid/rifampicin/pyrazinamide	1
131	102	Held inappropriate drug	Omeprazole	1
132	103	Avoided drug interaction	Carbamazepine/fluconaole	5
133	103	TDM	Carbamazepine	3
134	104	Held in hyperuricemia	Furosemide	1
135	105	Suggested pre-medication	Amphotericin B	2
136	105	Suggested hydration	Amphotericin B	2
137	106	Suggested hydration	Amphotericin B	2
138	107	Avoided drug interaction	Tacrolimus/diltiazem	5

Table 3.11 Clinical pharmacist's interventions (cont.).

Problem no.	Case no.	Pharmacist interventions	Drug(s) related interventions	Criteria
139	107	TDM	Tacrolimus	3
140	108	Reduced dosing	Amphotericin B	2
141	108	Reduced dosing	Amphotericin B	2
142	109	Reduced dosing	Ceftazidime	2
143	110	Suggested pre-medication	Amphotericin B	2

DDI = didanosine; 5%D/W = 5% dextrose in water; HCTZ = hydrochlorothiazide; IV = intravenous; NSAIDs= non-steroidal anti-inflammatory drugs; NSS = normal saline solution; TDM = therapeutic drug monitoring

Characteristics of the research clinical pharmacist's interventions

Most of the investigating clinical pharmacist's recommendations (69 out of 143 recommendations) related to dosage adjustment or modification to drug administration. There were no recommendation relating to drug toxicity or compliance. The number and types of recommendation are illustrated in Figure 3.1.

The total of one hundred and forty-three recommendations were classified according to drug group using the ATC classification system as presented in Table 3.12. Only the main causal drug was categorised when interventions related to drug-drug interaction criterion. General anti-infectives for systemic use were the most common (58 out of 143 recommendations) drug group mentioned in the investigating clinical pharmacist's recommendations. Antibiotics for systemic use (24.5%), anti-epileptics (10.5%) and anti-thrombotic agents (9.8%) were frequently mentioned by the investigating clinical pharmacist as being involved in an ADR (Table 3.13).

Potential severity of recommendations

Recommendations were classified according to the potential harm they would cause if they occurred in the patient. Potentially serious ADRs would occur if the investigating clinical pharmacist's recommendations were rejected by the medical care team. Of the recommendations, some 12.6% were judged to be of seriously significant severity, while the majority (approximately 79.7%) were considered to be potentially significant. Some 7.7% were classed as of unknown significance.

Outcome of recommendations

The outcome of recommendations made are presented in Figure 3.2. Approximately 80% of all the investigating clinical pharmacist's recommendations were accepted by the medical care team and fully implemented. There were 36 patients for whom it was not possible to make an assessment due to the limitations of the data available. The remaining 107 patient outcomes were classified as patient's improving or no ADR occurring (95: 88.8%), patient deterioration (6: 5.6%) or death (6: 5.6%).

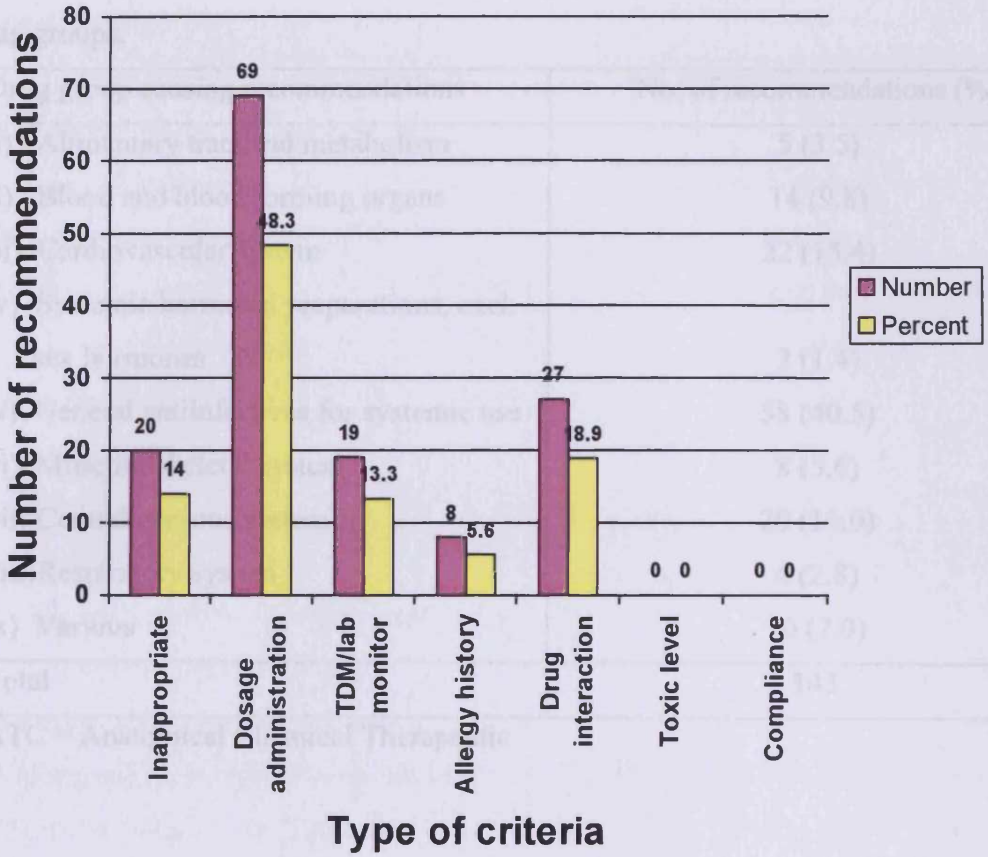


Figure 3.1 Number of recommendations for preventing ADRs in each criterion.

Table 3.12 Number of interventions by drug group using the ATC classification of drug groups.

Drug group causing recommendations	No. of recommendations (%)
i) Alimentary tract and metabolism	5 (3.5)
ii) Blood and blood forming organs	14 (9.8)
iii) Cardiovascular system	22 (15.4)
iv) Systemic hormonal preparations, excl. sex hormones	2 (1.4)
v) General antiinfectives for systemic use	58 (40.5)
vi) Musculo-skeletal system	8 (5.6)
vii) Central nervous system	20 (14.0)
viii)Respiratory system	4 (2.8)
ix) Various	10 (7.0)
Total	143

ATC = Anatomical Chemical Therapeutic

Table 3.13 Drug groups resulting in an intervention using the ATC subgroup classification.

Drug groups causing recommendations	No. of recommendations (%)
a) Antacids, drugs for treatment of peptic ulcer and flatulence	1 (0.7)
b) Antidiabetic therapy	3 (2.1)
c) Mineral supplements	1 (0.7)
d) Antithrombotic agents	14 (9.8)
e) Cardiac therapy	7 (4.9)
f) Antihypersentives	8 (5.6)
g) Diuretics	4 (2.8)
h) Beta blocking agents	3 (2.1)
i) Corticosteroids for systemic use	2 (1.4)
j) Antibiotics for systemic use	35 (24.5)
k) Antimycotics for systemic use	10 (7.0)
l) Chemotherapeutics for systemic use	7 (4.9)
m)Tuberculostatics, excl. streptomycin	2 (1.4)
n) Antivirals for systemic use	4 (2.8)
o) Antiinflammatory and antirhematic products	3 (2.1)
p) Antigout preparations	5 (3.5)
q) Analgesics	2 (1.4)
r) Antiepileptics	15 (10.5)
s) Psycholeptics	2 (1.4)
t) Psychoanaleptics	1 (0.7)
u) Anti-asthmatics	4 (2.8)
w) Immunosuppressive agent	7 (4.9)
x) All other-nontherapeutic products	3 (2.1)
Total	143

ATC = Anatomical Therapeutic Chemical

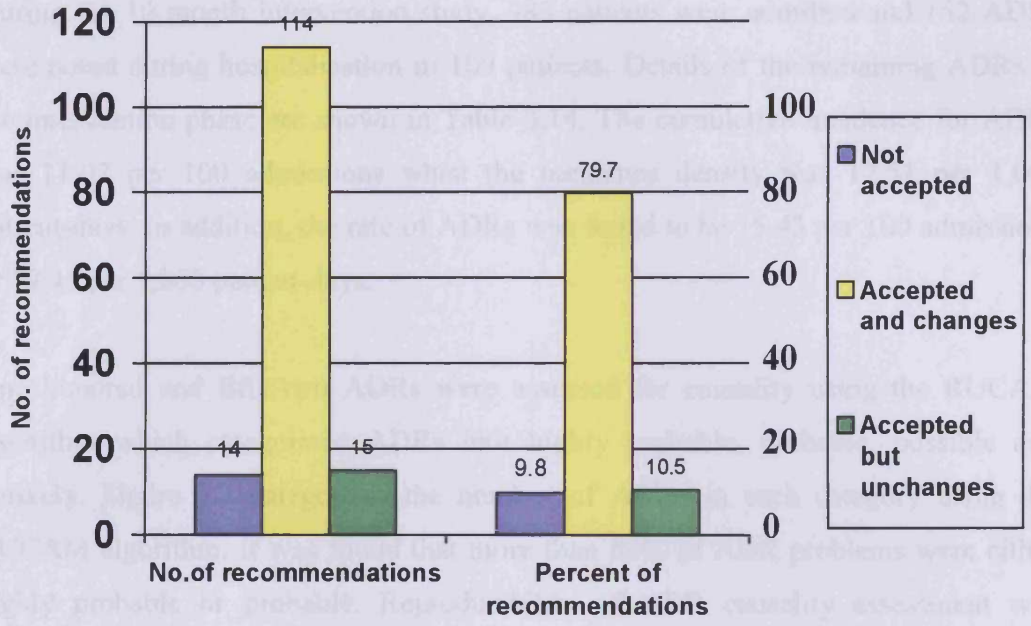


Figure 3.2 Type of recommendation classified by outcome of recommendations.

Characteristics of ADRs during hospitalisation

During the 10 month intervention study, 985 patients were admitted and 152 ADRs were noted during hospitalisation in 109 patients. Details of the remaining ADRs in the intervention phase are shown in Table 3.14. The cumulative incidence for ADRs was 11.07 per 100 admissions whist the incidence density was 12.51 per 1,000 patient-days. In addition, the rate of ADRs was found to be 15.43 per 100 admissions or 17.45 per 1,000 patient-days.

One hundred and fifty-two ADRs were assessed for causality using the RUCAM algorithm which categorised ADRs into highly probable, probable, possible and unlikely. Figure 3.3 categorises the number of ADRs in each category using the RUCAM algorithm. It was found that more than 80% of ADR problems were either highly probable or probable. Reproducibility of ADR causality assessment was carried out by a clinical pharmacy expert resident in the Faculty of Pharmacy. This validation was retrospectively performed on 109 out of the 152 ADR problems identified (72%), the medical charts of the balance of 43 not being available. Figure 3.4 compared the data from two assessors. The kappa coefficient was found to be 0.33 when the four probability scales of the RUCAM were calculated (i.e. highly probable, probable, possible and unlikely). However, when the highly probable and probable scale, and possible and unlikely scale, were combined into "yes" and "no" categories, the kappa coefficient increased to 0.40.

Although the majority of patients experienced only one ADR during hospitalisation (i.e. 78 patients, 71.6%), a number of patients experienced more than one drug-induced ADR, the maximum number of ADR being five (Table 3.15).

Drug groups causing ADRs according to the ATC classification system

One hundred and fifty-two ADR problems occurred during hospitalisation. Twenty-one ADR problems were caused by more than one suspected drugs being concurrently administered to a patient. Of the 131 ADR problems relating to a single drug, these were classified according to the ATC classification system as shown in Table 3.16, with the subgroup classification being presented in Table 3.17. General anti-infectives for systemic use were the most common drug group involved in an ADR (57.3%) with antimycotics in particular causing problems (35.1%).

Table 3.14 Adverse drug reactions in the intervention period (152 ADRs in 109 patients).

Problem no.	Case no.	Adverse events	Suspected drug(s)	Causality assessment	Preventability	Criteria
1	1	Hypoglycaemia	Insulin	Highly probable	Preventable	2
2	2	Severe vomiting	Doxycycline	Possible	Non preventable	
3	3	Phlebitis	Cefepime	Possible	Non preventable	
4	4	Hypoglycaemia	Insulin	Probable	Preventable	2
5	5	BM suppression	Azathioprine	Probable	Non preventable	
6	6	Acute liver injury	Simvastatin	Possible	Non preventable	
7	7	Dyspepsia	Naproxen	Probable	Non preventable	
8	7	Thrombophlebitis	Diazepam	Possible	Non preventable	
9	8	Pancytopenia	Cotrimoxazole/ amphothericin B	Probable	Non preventable	
10	9	Leg edema	Nifedipine	Possible	Non preventable	
11	10	Thrombophlebitis	Amphotericin B	Probable	Non preventable	
12	10	Hypokalemia	Amphotericin B	Probable	Non preventable	
13	11	Upper GI bleeding	Aspirin	Probable	Preventable	1
14	12	Urticaria	Co-trimoxazole	Probable	Non preventable	
15	13	Maculopapular rash	Ceftriaxone	Possible	Non preventable	
16	14	Erythemotous rash	INH/rifampicin/PZA/ ethambutol	Possible	Non preventable	
17	15	Rash	Ibuprofen	Possible	Non preventable	
18	16	Depression	Efavirenz	Probable	Non preventable	
19	16	Acute liver injury	ARV/phenytoin	Possible	Non preventable	
20	16	Hypokalemia	Amphotericin B	Probable	Non preventable	
21	17	Hypokalemia	Amphotericin B	Probable	Non preventable	
22	17	Thrombophlebitis	Piperacillin/amikacin	Probable	Non preventable	
23	18	Cholestatic jaundice	Ceftriaxone	Unlikely	Non preventable	
24	19	Erythromatous MP rash	ATG	Probable	Non preventable	
25	19	Thrombophlebitis	ATG	Probable	Non preventable	
26	20	Hypokalemia/ Hypomagnesaemia	Amphotericin B	Probable	Non preventable	
27	21	Diarrhoea	Ceftriaxone	Unlikely	Non preventable	
28	22	Hyperglycaemia	Dexamethasone	Probable	Non preventable	

Table 3.14 Adverse drug reactions in the intervention period (cont.).

Problem no.	Case no.	Adverse events	Suspected drug(s)	Causality assessment	Preventability	Criteria
29	23	Maculopapular rash	Ceftriaxone/phenytoin	Probable	Non preventable	
30	24	Gastritis	Prednisolone	Probable	Non preventable	
31	25	DM	Dexamethasone	Probable	Non preventable	
32	26	Hypokalemia	Amphotericin B	Probable	Non preventable	
33	27	Hypotension	Captopril	Probable	Non preventable	
34	28	Nausea/vomiting	Etoposide/platinum	Probable	Non preventable	
35	29	Hypokalemia	Furosemide	Possible	Non preventable	
36	29	Echymosis	Enoxaparin	Probable	Preventable	3
37	30	Acute liver injury	INH+rifampicin/PZA	Probable	Non preventable	
38	31	Upper GI bleeding	ASA	Probable	Non preventable	
39	32	Hypokalemia	Amphotericin B	Probable	Non preventable	
40	33	Vomiting	Etoposide/cisplatin	Probable	Non preventable	
41	34	Phlebitis	ATG	Probable	Non preventable	
42	35	Echymosis	Enoxaparin	Probable	Preventable	3
43	36	Diarrhoea	Ciprofloxacin	Possible	Non preventable	
44	37	Palpitation	Nifedipine	Probable	Non preventable	
45	38	Maculopapular rash	Cefpirome	Probable	Non preventable	
46	38	Erythematous rash	Ara-C	Probable	Non preventable	
47	39	Constipation	Morphine	Probable	Non preventable	
48	40	Diarrhoea	Ampicillin/gentamicin	Possible	Non preventable	
49	41	Acute renal failure	Amikacin	Probable	Non preventable	
50	42	Prolong INR	Warfarin	Probable	Preventable	2
51	43	Fatty liver	TPN	Probable	Non preventable	
52	43	Hypoglycemia	Insulin	Possible	Preventable	2
53	44	Rash	Cefpirome	Probable	Non preventable	
54	44	Bicytopenia	Co-trimoxazole	Highly probable	Non preventable	
55	45	DM	Prednisolone	Possible	Non preventable	
56	46	Hypokalemia/ hypomagnesaemia	Amphotericin B	Probable	Non preventable	
57	46	Renal insufficiency	Amphotericin B	Probable	Non preventable	
58	47	Hypophosphatemia	Pamidronate	Probable	Non preventable	

Table 3.14 Adverse drug reactions in the intervention period (cont.).

Problem no.	Case no.	Adverse events	Suspected drug(s)	Causality assessment	Preventability	Criteria
59	48	Renal injury	Cyclosporin	Highly probable	Preventable	3
60	48	Phlebitis	Clindamycin	Probable	Non preventable	
61	49	Pruritis	Ceftriaxone	Probable	Non preventable	
62	50	Phlebitis	Augmentin^{R}	Probable	Non preventable	
63	51	Thrombophlebitis	Augmentin^{R}	Probable	Non preventable	
64	52	Hypokalemia/ hypomagnesaemia	Amphotericin B	Probable	Non preventable	
65	52	Gastritis	Prednisolone	Possible	Non preventable	
66	53	Hypomagnesaemia	Amphotericin B	Probable	Non preventable	
67	54	Hypokalemia/ hypomagnesaemia	Amphotericin B	Probable	Non preventable	
68	54	Renal insufficiency	Amphotericin B	Probable	Non preventable	
69	54	Maculopapular rash	Imipenem	Probable	Non preventable	
70	54	Cholestatic jaundice	Imipenem	Probable	Non preventable	
71	54	Febrile neutropenia	Idarubicin	Highly probable	Non preventable	
72	55	Nausea/vomiting	Digoxin	Highly probable	Preventable	5
73	56	Drug eruption	Ceftriaxone	Probable	Non preventable	
74	57	Hypoglycaemia	Glibenclamide	Probable	Non preventable	
75	58	Prolong INR	Warfarin	Highly probable	Preventable	3
76	59	Diarrhoea	Colchicine	Possible	Non preventable	
77	59	Prolong INR	Warfarin	Highly probable	Preventable	3
78	60	Prolong INR	Warfarin	Highly probable	Preventable	3
79	61	Prolong INR	Warfarin	Highly probable	Non preventable	
80	62	Hypokalemia/ hypomagnesaemia	Amphotericin B	Probable	Non preventable	
81	62	Pancytopenia	Imatinib	Probable	Non preventable	
82	63	Hypokalemia	Amphotericin B	Possible	Non preventable	
83	64	Anaphylaxis	Paclitaxel	Probable	Non preventable	

Table 3.14 Adverse drug reactions in the intervention period (cont.).

Problem no.	Case no.	Adverse events	Suspected drug(s)	Causality assessment	Preventability	Criteria
84	65	Hypoglycaemia	Hydrocortisone	Highly probable	Non preventable	
85	66	Prolong INR	Warfarin	Highly probable	Preventable	3
86	67	Prolong INR	Warfarin	Highly probable	Preventable	3
87	68	Phlebitis	Cloxacillin	Probable	Non preventable	
88	69	Phlebitis	Amphotericin B	Probable	Non preventable	
89	69	Diarrhoea	Colchicine	Highly probable	Non preventable	
90	69	Erythomatous rash	Fluconazole	Probable	Non preventable	
91	70	Pancytopenia	Bactrim^{R}/gancyclovir	Probable	Non preventable	
92	71	Hypokalemia/ hypomagnesaemia	Amphotericin B	Probable	Non preventable	
93	71	Renal impairment	Amphotericin B	Highly probable	Non preventable	
94	72	Acute liver injury	INH/rifampicin/PZA	Probable	Non preventable	
95	73	Psychosis	Methyprednisolone	Highly probable	Non preventable	
96	73	EPS	Haloperidol	Probable	Non preventable	
97	73	Febrile neutropenia	Endoxan	Possible	Non preventable	
98	74	Hyperglycaemia	Dexamethasone	Probable	Non preventable	
99	75	Hypokalemia/ hypomagnesaemia	Amphotericin B	Probable	Non preventable	
100	75	Febrile neutropenia	Ara-C	Probable	Non preventable	
101	76	Acute renal failure	Amikacin	Probable	Non preventable	
102	77	Hypokalemia/ hypomagnesaemia	Amphotericin B	Probable	Non preventable	
103	77	Acute renal failure	Amphotericin B /amikacin	Probable	Non preventable	
104	78	Maculopapular rash	Ciprofloxacin/ ceftazidime	Probable	Non preventable	
105	79	Hyperglycemia	Dexamethasone	Possible	Non preventable	
106	80	Neutropenia	Bactrim^{R}/gancyclovir	Probable	Non preventable	
107	81	Hypokalemia/ hypomagnesaemia	Amphotericin B	Probable	Non preventable	

Table 3.14 Adverse drug reactions in the intervention period (cont.).

Problem no.	Case no.	Adverse events	Suspected drug(s)	Causality assessment	Preventability	Criteria
108	82	Diarrhoea	Colchicine	Highly probable	Non preventable	
109	83	Acute liver injury	INH/rifampicin/PZA	Probable	Non preventable	
110	84	Acute renal failure	Acyclovir	Probable	Preventable	2
111	85	Febrile neutropenia	Ara-C/idarubicin	Higly probable	Non preventable	
112	86	Hypokalemia/ hypomagnesaemia	Amphotericin B	Probable	Non preventable	
113	86	Thrombocytopenia	Co-trimoxazole	Probable	Non preventable	
114	87	Hyperglycaemia	Dexamethasone/ prednisolone	Probable	Non preventable	
115	88	Maculopapular rash	Carbamazepine	Possible	Non preventable	
116	89	Acute renal failure	Enalapril	Probable	Non preventable	
117	89	Hyperuricemia	Furosemide	Probable	Non preventable	
118	90	Maculopapular rash	Ara-C	Probable	Non preventable	
119	91	Acute renal failure	Acyclovir	Probable	Non preventable	
120	92	Hypokalemia	Amphotericin B	Probable	Non preventable	
121	93	Hyperglycaemia	Dexamethasone	Probable	Non preventable	
122	94	Hypokalemia/ hypomagnesaemia	Amphotericin B	Probable	Non preventable	
123	95	Hypokalemia/ hypomagnesaemia	Amphotericin B	Highly probable	Non preventable	
124	96	Hypokalemia	Amphotericin B	Probable	Non preventable	
125	96	Febrile neutropenia	Ara-C/idarubicin	Highly probable	Non preventable	
126	97	Hypokalemia	Amphotericin B	Probable	Non preventable	
127	97	Acute renal failure	Amphotericin B	Probable	Non preventable	
128	98	Hypokalemia	Gentamicin	Possible	Non preventable	
129	99	Febrile neutropenia	Ara-C/idarubicin	Highly probable	Non preventable	
130	99	Hypokalemia	Amphotericin B	Possible	Non preventable	
131	99	Phlebitis	Amphotericin B	Possible	Non preventable	
132	100	Hypokalemia	Amphotericin B	Probable	Non preventable	
133	100	Phlebitis	Amphotericin B	Highly probable	Non preventable	
134	100	Acute renal failure	Amphotericin B	Probable	Non preventable	

Table 3.14 Adverse drug reactions in the intervention period (cont.).

Problem no.	Case no.	Adverse events	Suspected drug(s)	Causality assessment	Preventability	Criteria
135	101	Hypokalemia/ Hypomagenesemia	Amphotericin B	Probable	Non preventable	
136	101	Maculopapular rash	G-CSF	Probable	Non preventable	
137	102	Hyperglycaemia	Dexamethasone/ prednisolone	Probable	Non preventable	
138	103	Hypokalemia/ Hypomagnesaemia	Amphotericin B	Probable	Non preventable	
139	104	Hypokalemia/ hypomagnesaemia	Amphotericin B	Probable	Non preventable	
140	105	Hypoglycaemia	Amphotericin B	Proabable	Non preventable	
141	105	Renal insufficiency	Amphotericin B	Possible	Non preventable	
142	105	Hyperglycaemia	Dexamethasone	Highly probable	Non preventable	
143	106	Febrile neutropenia	Ara-C/idarubicin	Highly probable	Non preventable	
144	106	Hypokalemia	Amphotericin B	Possible	Non preventable	
145	106	Diarrhoea	Piperacillin/imipenem	Possible	Non preventable	
146	107	Hypokalemia/ hypomagnesaemia	Amphotericin B	Highly probable	Non preventable	
147	107	Febrile neutropenia	Ara-C	Highly probable	Non preventable	
148	107	Drug fever	Amphotericin B	Possible	Non preventable	
149	108	Hypokalemia/ hypomagnesaemia	Amphotericin B	Probable	Non preventable	
150	109	Hypokalemia	Amphotericin B	Highly probable	Non preventable	
151	109	Acute renal failure	Amphotericin B	Highly probable	Non preventable	
152	109	Diarrhoea	Multi-antibiotics	Probable	Non preventable	

Ara-C = cytarabine; ARV = antiretroviral; ASA= aspirin; ATG = antithrombocyte globulin; BM = bone marrow; DM = diabetes mellitus; EPS = extrapyramidal syndrome; GI = gastrointestinal; G-CSF = granulocyte colony stimulating factor; GM-CSF = granulocyte-monocyte colony stimulating factor; INH = isoniazid; INR = international normalised ratio; PZA = pyrazinamide; TPN = total parenteral nutrition

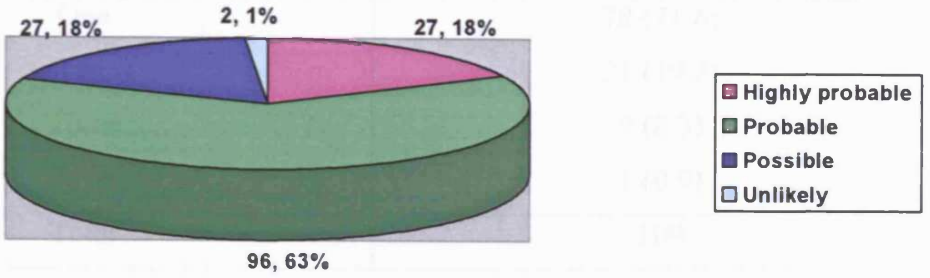


Figure 3.3 Causality assessment of ADRs using the RUCAM algorithm.

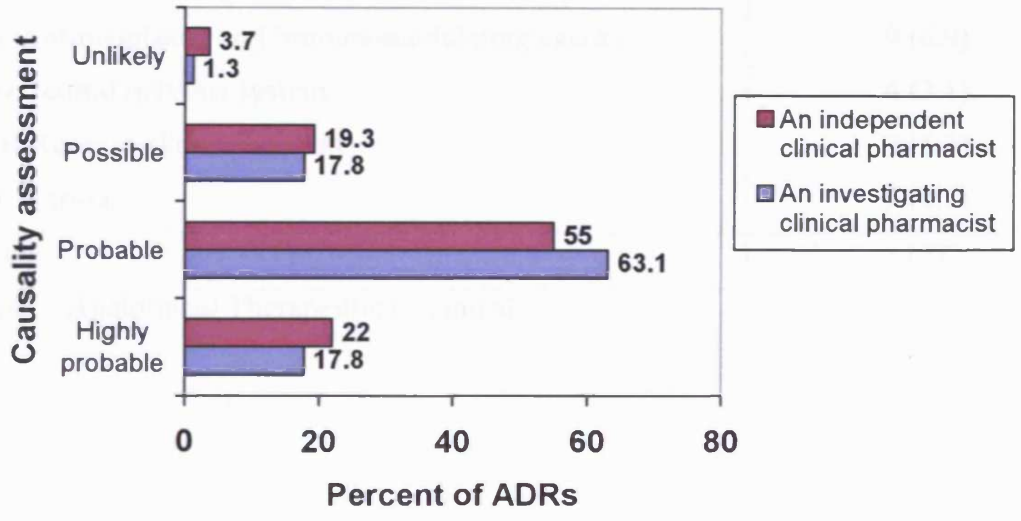


Figure 3.4 Causality assessment of ADRs for the two assessors.

Table 3.15 Number of ADR problems for each patient.

Number of ADRs for each patient	Number of patients (%)
One	78 (71.6)
Two	21 (19.3)
Three	9 (8.3)
Five	1 (0.9)
Total	109

Table 3.16 Drug group causing an ADR using the ATC classification system.

Drug groups causing ADRs	No. of ADRs (%)
i) Alimentary tract and metabolism	4 (3.1)
ii) Blood and blood forming organs	10 (7.6)
iii) Cardiovascular system	7 (5.3)
iv) Systemic hormonal preparations, excl. sex hormones	13 (9.9)
v) General antiinfectives for systemic use	75 (57.3)
vi) Antineoplastic and immunomodulating agents	9 (6.9)
vii) Central nervous system	4 (3.1)
viii)Musculo-skeletal system	7 (5.3)
ix) Various	2 (1.5)
Total	131

ATC = Anatomical Therapeutic Chemical

Table 3.17 Drug groups causing an ADR using the ATC subgroup classification.

Drug group causing an ADR	No. of ADRs (%)
a) Antidiabetic therapy	4 (3.1)
b) Serum lipid drug agents	1 (0.8)
c) Antithrombotic agents	9 (6.9)
d) Cardiac therapy	1 (0.8)
e) Antihypersentives	4 (3.1)
f) Diuretics	2 (1.5)
g) Corticosteroids for systemic use	10 (7.6)
h) Calcium homeostasis	1 (0.8)
i) Antibiotics for systemic use	22 (16.8)
j) Antimycotics for systemic use	46 (35.1)
k) Chemotherapeutics for systemic use	1 (0.8)
l) Antivirals for systemic use	4 (3.1)
m)Immune sera and immunoglobulin	3 (2.3)
n) Cytostatics	7 (5.3)
o) Immunostimulating agents	2 (1.5)
p) Antiinflammatory and antirheumatic products	4 (3.1)
q) Antigout preparations	3 (2.3)
r) Analgesics	2 (1.5)
s) Antiepileptics	1 (0.8)
t) Psycholeptics	2 (1.5)
u) Immunosuppressive agent	1 (0.8)
w) General nutrients	1 (0.8)
Total	131

ATC = Anatomical Therapeutic Chemical

ADR problems classified by organ affected

Using the WHO adverse reaction classification, 152 ADR problems were classified according to organ system affected. The detailed classification is shown in Table 3.18. Importantly, thirty-six out of 152 ADR problems (23.7%) related to metabolic and nutritional problems.

ADR problems classified by type of ADR

Of the 152 ADR problems identified, 123 (80.9%) ADRs were found to be of the Type A variety according to the classification of Rawlins and Thompson (1991).

ADR problems classified by mechanism of action

Using the system for determining the mechanism of action of an ADR suggested by Rieder (1994), of the 152 ADR problems side effects were found to account for the majority (76.3%) while twenty-eight ADR problems were related to allergic and idiosyncratic reactions (Table 3.19).

ADR problems classified by severity

The severity of ADR problems are illustrated in Figure 3.5. Sixty-four out of 152 ADR problems (42.1%) were considered to be of level 3 severity. On the other hand, there was no ADRs with a severity level of 6 or 7.

Characteristics of preventable ADRs

One hundred and fifty-two ADR problems were assessed for preventability using Schumock and Thornton criteria (1992). Table 3.14 shows details of all preventable ADRs in the intervention phase. The number of ADRs problems classified by type of preventability are shown in Figure 3.6. The percentage of preventable ADRs was 9.9%. These preventable ADRs occurred in 985 patients equating to 8,710 patient-days. Thus, the rate of preventable ADRs was 1.52 per 100 admissions or 1.72 per 1,000 patient-days. In addition, the retrospective reproducibility of preventability assessment was found to produce a kappa coefficient of 0.33 for 109 out of 152 ADRs assessed. Figure 3.7 illustrates the data for the two assessors.

Table 3.18 ADR problems classified according to organ affected.

Organ systems affected	No. of ADRs (%)
1 Skin & appendages disorders	20 (13.2)
2 Central & peripheral nervous system disorders	2 (1.3)
3 Psychiatric disorders	1 (0.7)
4 Gastro-intestinal system disorders	23 (15.1)
5 Liver & biliary system disorders	7 (4.6)
6 Metabolic & nutritional disorders	36 (23.7)
7 Endocrine disorders	14 (9.2)
8 Heart rate & rhythm disorders	1 (0.7)
9 Vascular (extracardiac) disorders	1 (0.7)
10 Red blood cell disorders	1 (0.7)
11 Pancytopenia	5 (3.3)
12 White cell and RES disorders	7 (4.6)
13 Platelet, bleeding & clotting disorders	9 (5.9)
14 Urinary system disorders	10 (6.6)
15 Body as a whole-general disorders	2 (1.3)
16 Application site disorders	13 (8.6)
Total	152

RES = Reticuloendothelial system

Table 3.19 Mechanism of action resulting an ADR.

Mechanism of action	Number of ADRs (%)
Side effect	116 (76.3)
Toxicity	1 (0.7)
Secondary effect	5 (3.3)
Drug interaction	1 (0.7)
Allergy	18 (11.8)
Idiosyncratic reaction	10 (6.6)
Intolerance	1 (0.7)
Total	152

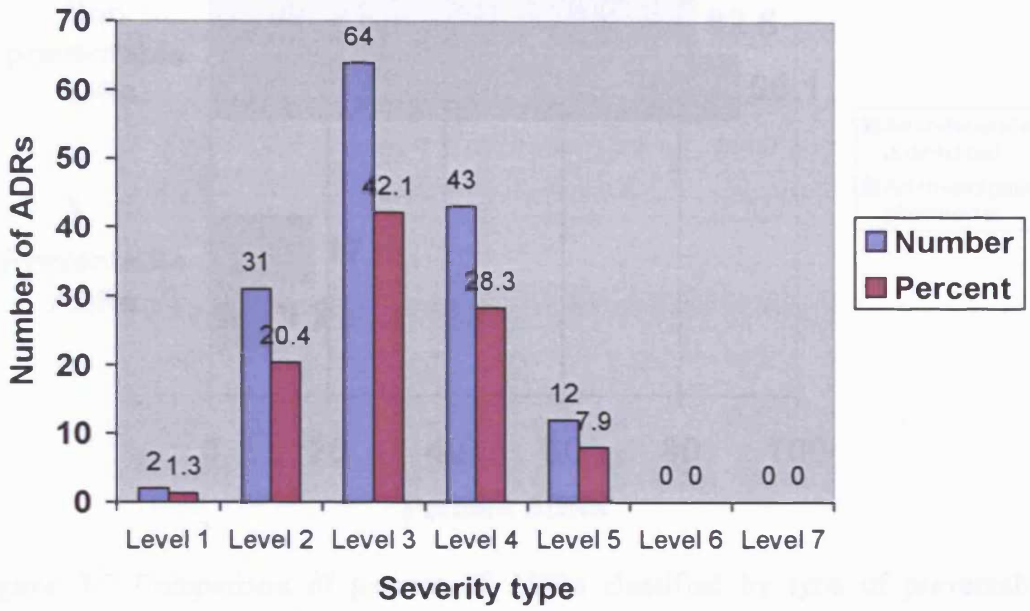


Figure 3.5 Number of ADRs classified by severity.

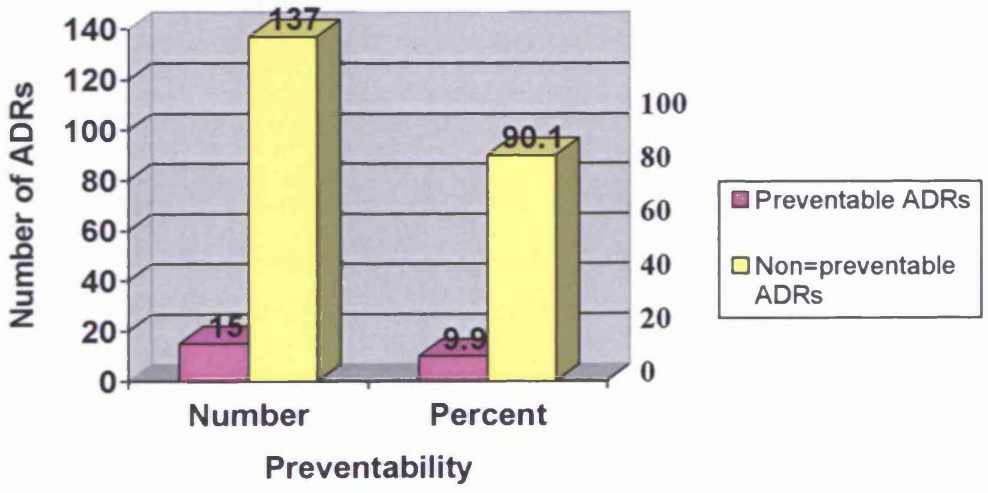


Figure 3.6 Number of ADRs classified by type of preventability.

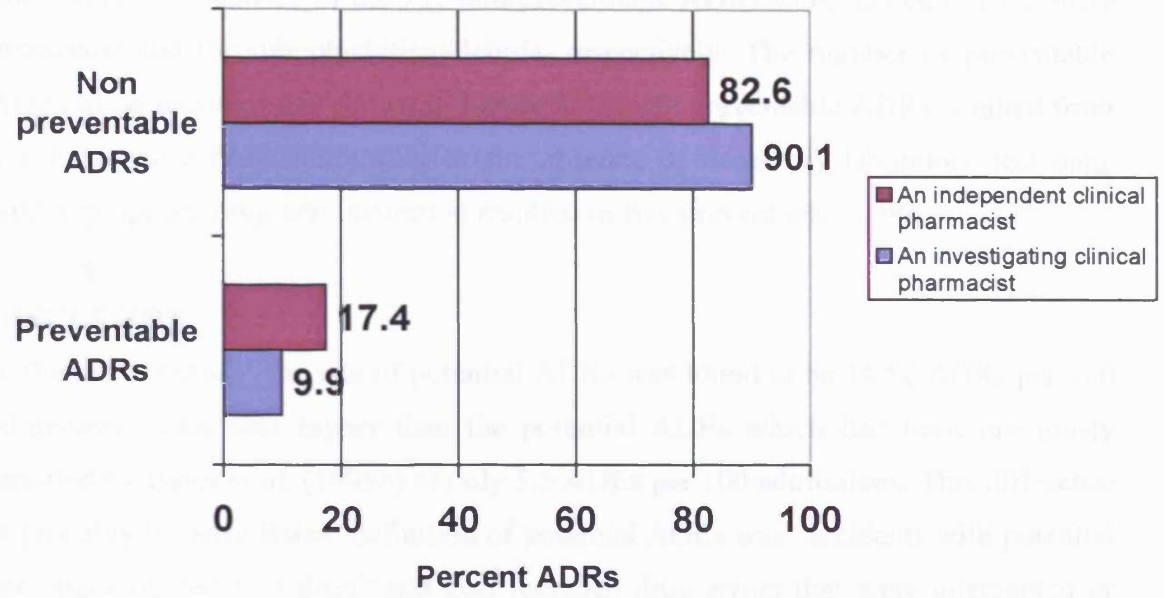


Figure 3.7 Comparison of percent of ADRs classified by type of preventability between two assessors.

Interestingly, 35 and 12 of the 137 non-preventable ADRs were related to electrolyte imbalance and thrombophlebitis/phlebitis, respectively. The number of preventable ADRs in each criterion is shown in Figure 3.8. Eight preventable ADRs resulted from non-therapeutic drug monitoring or the absence of necessary laboratory test data. Non-appropriate drug administration resulted in five preventable ADRs.

DISCUSSION

In the present study, the rate of potential ADRs was found to be 14.52 ADRs per 100 admissions. This was higher than the potential ADEs which had been previously reported by Bates *et al.* (1995b) of only 5.5 ADEs per 100 admissions. This difference is probably because Bates' definition of potential ADEs was "incidents with potential for injury related to a drug" and also included drug errors that were intercepted or which were detected by chance. This probably explains the lower value reported by these workers compared with the highly intensive method of surveillance of patients in the present study. In fact, the rate of potential ADEs was calculated as the ratio of the number of research clinical pharmacist's recommendations to the total number of monitored patients in the study. Thus, this rate should be compared with other studies in terms of a clinical pharmacist's ability to prevent ADRs. Fertleman *et al.* (2005) reported that a pharmacist member of a medical care team in a general district hospital in the UK made 109 recommendations concerning only 53 patients. The high ratio resulted from the fact that the clinical pharmacist's interventions were not limited to only "preventing" ADRs. It included all recommendations for improving medication management such as reviewing drug needs and the selection of drugs. Likewise, Leape *et al.* (1999) and Kucukarslan *et al.* (2003) reported that 398 and 150 pharmacist recommendations resulted from only 75 and 86 patients, respectively. The types of intervention included drug information recommendations, which doubtless explains the high number of pharmacist interventions per patient in those study. Whilst the presence of a research clinical pharmacist as a member of the medical care team in the present study resulted in many non-ADR type recommendations as well as those directly related to an ADR, unfortunately, these were not recorded.

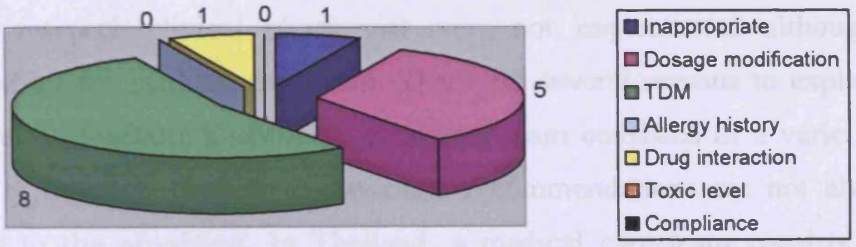


Figure 3.8 Number of preventable ADRs in each criterion.

Importantly, the acceptance rate of changes recommended by the research clinical pharmacist was 79.7%. Interestingly, some 15 (10.5%) of the recommendations made by the research clinical pharmacist were not implemented although they were accepted by the medical care team. There are several reasons to explain this result. Because the teaching hospital medical care team consisted of a variety of levels of doctor, a research clinical pharmacist's recommendations are not always reported directly to the physician. In Thailand, a medical care team consists of a 1st year resident, as well as externs and medical students, all of whom provide a 24 hour service. Although the medical care team might have accepted the pharmacist's suggestion, it might not have been implemented by the 2nd year residents or the specialty residents simply because they did not interact with the research clinical pharmacist directly on the ward at the time. Moreover, the research clinical pharmacist's recommendations which were focused on patient safety might not have been accepted in terms of drug efficacy. For example, it was recommended that with amphotericin B, the duration of infusion should be extended in order to reduce nephrotoxicity. However, the aspergillosis infection might have been serious and any extension of the infusion time might have reduced the overall efficacy of amphotericin B. Thus, although the clinical pharmacist's suggestion was accepted in principal it was not implemented. Furthermore, it was found that 14 (9.8%) recommendations which were not accepted, because they would have resulted in increases in the cost of drug treatment. For example, the research clinical pharmacist often recommended more frequent blood level monitoring but it was repeatedly rejected due to the increased costs. The acceptance rate of the research clinical pharmacist's recommendations in the present study was lower than the acceptance rate published by Leape *et al.* (1999) and Kucukarslan *et al.* (2003). In both these studies almost 99% of all recommendations were accepted. These high values were probably because their studies included medication errors which would obviously have been accepted. The greater experience of US clinical pharmacists may have been another possible reason why the acceptances were higher than seen in the present study.

It was found that for approximately one-quarter of all patients (29 out of 110 patients) more than one recommendation per patient was made by the research clinical pharmacist. Obviously, a patient is able to develop more than one ADR problem,

requiring more than one recommendation being made by the research clinical pharmacist. Interestingly, no recommendation involved compliance. As drug administration was carried out by nurses, it was assumed that inpatients took their medication as expected. Therapeutic drug monitoring was recommended when an ADR related to toxic blood concentrations was suspected.

Many different methods have been used to classify/categorise a clinical pharmacist's interventions depending largely on their practice setting, and the reasons for measuring their contribution to patient care. For example, both Leape *et al.* (1999) and Kucukarslan *et al.* (2003) classified pharmacist interventions in terms of preventing ADEs by reducing medication errors in the prescribing process. In contrast, in the UK, Fertleman *et al.* (2005) reported only on the impact of a clinical pharmacist in a post-take ward setting, the types of clinical pharmacist intervention consisting of patient counselling, education, and the supply of medicines. Bednall *et al.* (2003) had previously reported on the pharmacist's contributions on post-take ward rounds at a large hospital in the UK, where the pharmacist's interventions were divided into three main types; drug supply, therapy review, patient contact. In contrast, the clinical pharmacist's recommendations in a Veterans Affairs Medical Center in the USA focused on clinical and economic outcomes resulting from the clinical pharmacist's recommendations. Interventions consisted of 15 different types (Lee *et al.*, 2002). As a consequence, any comparisons between the research clinical pharmacist's recommendations in the present study and those published in other studies need to be interpreted with caution.

Most research clinical pharmacist recommendations relate to drug administration. For example, these accounted for about half (48%) of all recommendations made in the present study. Of particular interest was the fact that approximately 40% of all patients were more than 60 years old. Such "elderly" patients are at increased risk of an ADR occurring due to the probability that drug-elimination deteriorates with increasing age. Renal dosage adjustment may need to be considered in order to avoid supra-therapeutic drug effects. This finding supports the findings of Kucukarslan *et al.* (2003) and Fertleman *et al.* (2005) who similarly indicated that modified dosage was the major type of intervention made by a clinical pharmacist (i.e. 52 (35%) out of 150 recommendations and 29 (27%) out of 109 recommendations, respectively).

These were also similar to those reported by Lee *et al.* (2002) who found that the need to adjust dosage and frequency was the most common type of recommendation made (i.e. 129 (51.6%) out of a total of 250 interventions). Moreover, although the method of detecting ADRs was different, the high proportion of drug administration-type recommendations in the present study was similar to those published by Seeger *et al.* (1998), in which ADRs were detected using a spontaneous reporting system and where dosage adjustment was again the most frequent intervention for preventing ADRs. Gholami and Shalviri (1999) who carried out intensive ADR monitoring in hospitalised patients likewise reported that drug administration problems were the most common type of preventable ADRs.

According to the demographic data, it was found that more than 50% of all patients suffered from one or more coexisting diseases such as AIDS, cancer, liver disease, renal disease, CHF and SLE. As a result, these patients were prescribed increased numbers of drugs. It was found that the average number of drugs administered concurrently were 10 items. Needless to say, the more drugs that are prescribed, the more the chances of a drug-drug interaction taking place. As a consequence of this, drug-drug interaction interventions were the second most frequent type of research clinical pharmacist intervention (i.e. 27 (19%) out of 143 recommendations). In comparison, Leape *et al.* (1999) and Kucukarslan *et al.* (2003) indicated that drug-drug interventions accounted for only 4% and 2%, respectively, of interventions. Obviously, these lower percentages stemmed from differences in the scope of their pharmacist interventions which focused on errors related to the prescribing process.

In the present study, it was found that 14% and 13% of all recommendations could be classified as inappropriate medication usage for the patient's clinical condition or there was a need for therapeutic drug monitoring or laboratory tests to be carried out. These interventions were not easy to compare with other studies because this type of recommendation was not categorised in previous studies. However, the former type involves drug selection which contributes to optimum drug efficacy. Similarity, the latter type is important in optimizing drug dosage management (Thomson, 2003; Routledge, 2004). Interestingly, a clinical toxicology consultant service is provided at the Ramathibodi Hospital as part of the medical teaching program. It also provides a

drug level monitoring service but unfortunately to date, hospital pharmacists do not take part in this service. Hopefully, this will be resolved in the near future.

Patients with a history of drug allergy accounted for 100 (10%) out of the total of 985 patients. However, records of drug allergy were not complete, only drug names being included in the medical charts, although this was documented in some medical charts. Details of adverse reactions which resulted from a drug allergy were not provided. As the result of this, some drug allergy histories were vague and may not have been a true drug allergy. Thus, the clinical approach for selecting drugs where there was the drug allergy history was vague was the "better safe than sorry" approach (i.e. avoid prescribing medications which may result in drug-induced allergy) (Shear, 1990; Gruchalla, 2000). For this reason, in the present study, recommendations relating to the prevention of drug allergies or idiosyncratic reactions accounted for only 8 (5.6%) out of the total of 143 recommendations, this being the least frequent type of clinical pharmacist intervention. Usually, in order to prevent the reoccurrence of a drug allergy response, an inappropriate drug may have been given which may have led to drug resistance and an overall increase in the cost of drug therapy (Gruchalla, 2000). Unfortunately, in the present study the appropriateness of medication in drug allergy patients was not studied. Interestingly, it has been reported that a clinical pharmacist had been successfully able to manage penicillin allergic patients (Wall *et al.*, 2004). This will be investigated at the Ramathibodi Hospital in further research.

General anti-infectives for systemic use was the most common drug group mentioned in the research clinical pharmacist's recommendations (i.e. 58 (40.6%) out of 143 drugs). Interestingly, when classified according to subgroup, not only were the antibiotics for systemic use the most common mentioned but antiepileptic drugs and antithrombotic drugs were frequently cited in recommendations made by the research clinical pharmacist. General anti-infectives for systemic use are known to be high risk drugs because of their narrow therapeutic index. Such drugs include the aminoglycosides and vancomycin whilst phenytoin, carbamazepine, valproic acid and warfarin are antiepileptic and antithrombotic drugs which likewise have a narrow therapeutic index and high potential for a drug-drug interaction. As a consequence of the high risk, research clinical pharmacist recommendations frequently involve these drugs in order to prevent ADRs from occurring. This result was not dissimilar to the

earlier findings of Mutnick *et al.* (1999) who measured the value of clinical pharmacist's interventions at a large hospital in the USA. Although all the clinical pharmacist's intervention were monitored and evaluated by Mutnick *et al.* (1999), it was found that high risk drugs such as gentamicin, vancomycin and digoxin were the most common drugs to be involved in interventions.

Although the presence of a research clinical pharmacist as a member of the health care team resulting in a reduction in the number of ADRs, they could not be eliminated. This was partly because the pharmacist was not able to provide full 24 hours per day cover. Bednall *et al.* (2003) found that 60% of all clinical pharmacist contributions on the wards of a large hospital in the UK were made out-of-hours. While the medical care teams provided full patient care for 24 hours per day until similar 24 hour cover is provided by a research clinical pharmacist it is likely that many preventable ADRs will still occur.

SUMMARY

- During a 10 month period, some 985 patients were monitored by a research clinical pharmacist on two medical wards. One hundred and forty-three of the pharmacist's recommendations for preventing an ADR from occurring were made to the medical care team. Of these 79.7% were accepted and implemented.
- One hundred and fifty-two ADR problems were identified in 109 patients.
- The cumulative incidence of potential ADRs was 11.17 per 100 admissions whist the incidence density was 12.63 per 1,000 patient-days.
- Forty-eight percent of the total number of recommendations were related to dose, route, or frequency of administration in appropriated for the patient's age, weight, or disease state.
- General anti-infectives for systemic use was the most frequent drug group resulting in an intervention, whilst more specifically, antibiotics for systemic use (24.5%), antiepileptics (10.5%) and antithrombotic agents (9.8%) were the major drug types resulting in a pharmacist's intervention.
- Eighty percent of all recommendations were considered to be of potentially significant severity.

Chapter 4

Impact of a Clinical Pharmacist's Intervention in Preventing Adverse Drug Reactions

CHAPTER 4

IMPACT OF A CLINICAL PHARMACIST'S INTERVENTION IN PREVENTING ADVERSE DRUG REACTIONS

INTRODUCTION

Although eighty percent of all research clinical pharmacist interventions on two general medical wards were accepted by the medical care teams (as reported: Chapter 3), this did not answer the fundamental question of whether a clinical pharmacist's participation can reduce or "prevent" ADRs from occurring. Because a double-blind study design cannot be conducted in patient research (Shojania *et al.*, 2001), a comparison was made of the frequency of so-called "preventable" ADRs occurring in a before-intervention (control) period and an intervention period. The characteristics of ADRs identified retrospectively when there was no research clinical pharmacist present on the wards was investigated in Chapter 2 whilst in Chapter 3 data was provided on ADRs occurring when a research clinical pharmacist was a resident member of the medical care team and who was actively attempting to prevent ADRs from happening. In this chapter, the impact that the research clinical pharmacist made on reducing ADRs in hospital patients, will be measured by comparing ADR data gathered from the control period with that obtained during the intervention study period.

METHODS

Study design

The demographic data and the characteristics of ADRs in the pre-intervention "control" period (Chapter 2) and intervention period (Chapter 3) have been compared. Information on patient selection, inclusion and exclusion criteria and the classification and characteristics of ADRs has been presented in earlier chapters, likewise details of data collection and analysis.

RESULTS

The pre-intervention (control) period included 1,548 patients (765 males, 783 females) whilst the intervention period included 985 patients (514 males, 471

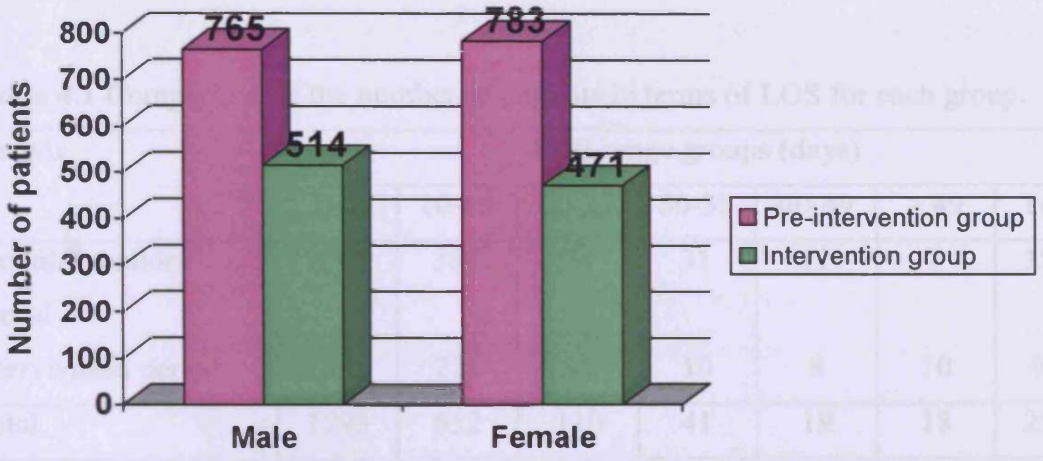
females). Data from these two studies have been compared under the following headings: demographic data, characteristics of ADRs, characteristics of preventable ADRs, frequencies of ADRs and frequencies of preventable ADRs.

Demographic data

Gender distribution in the two periods is illustrated in Figure 4.1. The percentage of male and female patients in the two periods was not statistically significantly different ($p = 0.175$, Chi-squared test). The mean $\pm$ standard deviation of the patient's age in the control group was 51.6 ± 18.9 years whilst in the intervention group it was 52.1 ± 18.9 years. No significant difference was found in the average ages of the two groups ($p = 0.661$; Mann-Whitney *U*-test). The age ranges are compared in Figure 4.2. There was no statistical difference in age for the control and intervention groups ($p = 0.432$, Chi-squared test).

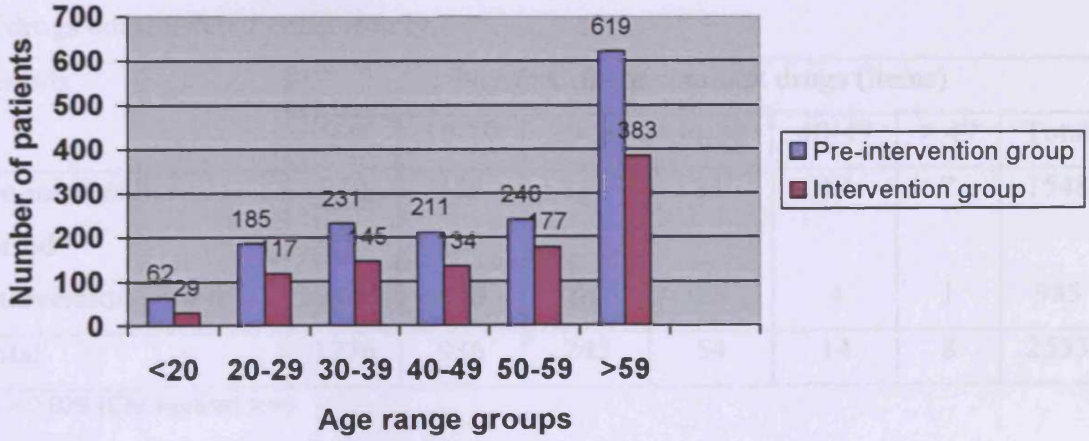
The mean $\pm$ SD of length of stay (LOS) in the control group was 9.07 ± 8.06 days whilst it was 8.84 ± 8.35 days for the intervention group. There was no statistical difference in LOS for the control and intervention groups ($p = 0.174$; Mann-Whitney *U*-test). The range of LOS was grouped and the distribution of these is shown in Table 4.1. No significant difference was found in the LOS for the two groups ($p = 0.257$, Chi-squared test).

The number of drugs administered concurrently to patients in the control group was 10.92 ± 7.88 items whilst in the intervention group it was 11.35 ± 7.18 items. It was significant difference in the average number of drugs administered to the two groups ($p = 0.006$, Mann-Whitney *U*-test) and the range of concomitant drugs administered were also significantly different ($p = 0.029$, Chi-squared test). This distribution is shown in Table 4.2.



p = 0.175 (Chi-squared test)

Figure 4.1 Gender distribution for the two periods.



p = 0.432 (Chi-squared test)

Figure 4.2 Comparison of number of patients in terms of age range for the two periods.

Table 4.1 Comparison of the number of patients in terms of LOS for each group.

Periods	LOS range groups (days)						
	0-9	10-19	20-29	30-39	40-49	> 49	Total
Pre-intervention period	1093	331	74	31	11	8	1548
Intervention period	700	221	36	10	8	10	985
Total	1793	552	110	41	19	18	2533

p = 0.257 (Chi-squared test)

Table 4.2 Comparison of the number of patients in each group in terms of the number of drugs administered concurrently.

Periods	Number of concomitant drugs (items)						
	0-9	10-19	20-29	30-39	40-49	> 49	Total
Pre-intervention period*	810	536	154	31	10	7	1548
Intervention period*	466	400	91	23	4	1	985
Total	1276	936	245	54	14	8	2533

*p = 0.029 (Chi-squared test)

The number of patients who suffered from coexisting diseases is presented in Table 4.3. Except for liver disease and CHF, the percentages of these illnesses in patients in the intervention study were significantly higher than patients in the pre-intervention (control) study.

The number of patients in both groups who smoked and drank alcohol are also presented in Table 4.3. The percentage of patients in each category was found to be significantly different. Again, the number of patients with an allergic history are presented in Table 4.3. No significant difference was found between patients with a history of drug-induced allergy in the pre-intervention and intervention groups.

Characteristics of ADRs

In the pre-intervention period it was found that 187 patients suffered from a total of 249 ADR problems during hospitalisation whilst in the intervention period some 109 patients suffered from 152 ADRs.

Causality assessment of ADRs using RUCAM for the two periods is illustrated in Figure 4.3. The number of highly probable and probable (82.7%) ADRs in the pre-intervention period was of the same order as those (81.0%) found in the intervention period. Presented in Table 4.4 are the kappa coefficients of RUCAM reproducibility for the two study periods. These kappa coefficients are presented both for the four levels of assessment (highly probable, probable, possible, and unlikely) and two levels of assessment (combination of highly probable and probable into "yes" and combination of possible and unlikely into "no").

The number of ADR problems for each patient in the pre-intervention and intervention period are presented in Figure 4.4. There was no significant difference between the two study groups ($0.05 < p < 0.10$; Chi-squared test).

Table 4.3 Comparison of the number of patients who had coexisting diseases, social history and allergy history.

Coexisting diseases/social history/allergy history	Number of patients		P value (Chi-squared test)
	Pre-Intervention period	Intervention period	
Non AIDS	1442	912	0.589
AIDS	106	73	
Non cancer	1261	788	0.362
Cancer	287	197	
Non renal disease	1235	805	0.228
Renal disease	313	180	
Non liver disease	1371	843	*0.027
Liver disease	177	142	
Non CHF	1457	888	*<0.001
CHF	91	97	
Non SLE	1476	944	0.561
SLE	72	41	
Non social history	1253	660	*<0.001
Smoking	106	93	
Alcohol	51	63	
Smoking and alcohol	138	169	
Not known drug allergy	1416	885	0.150
Allergy history	132	100	

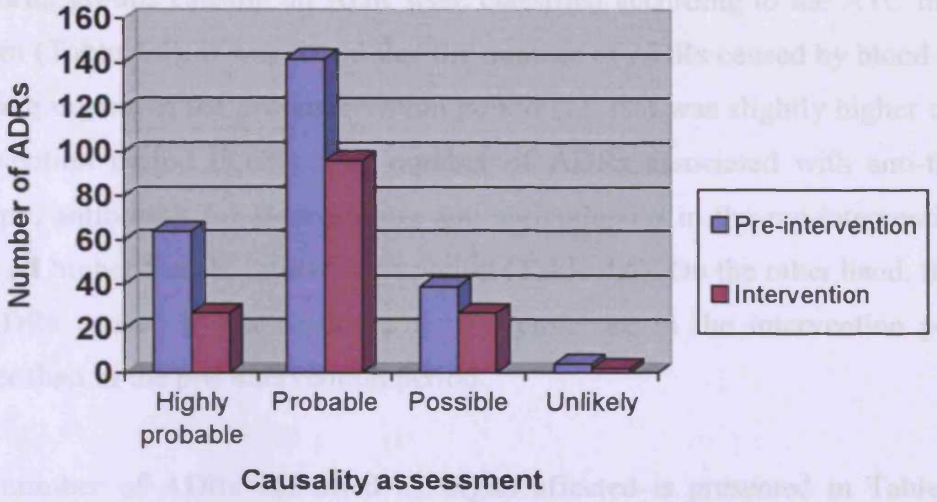


Figure 4.3 Comparison of causality assessment of ADRs using RUCAM.

Table 4.4 Comparison of kappa coefficients for the two study periods.

Causality assessment levels	Kappa coefficients	
	Pre-intervention period	Intervention period
Four level assessments	0.11	0.33
Two level assessments	0.41	0.40

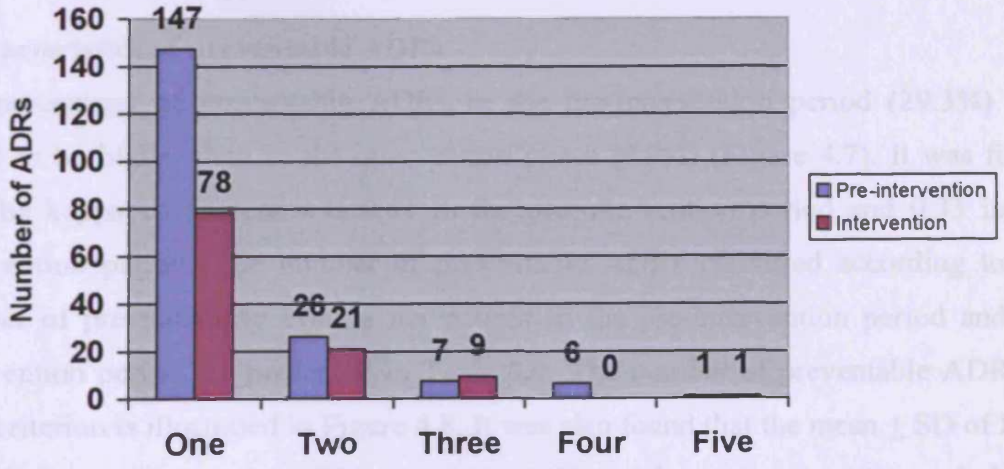


Figure 4.4 Comparison of the number of ADR problems for each patient.

The drug groups causing an ADR were classified according to the ATC main group system (Table 4.5). It was found that the number of ADRs caused by blood and blood forming organs in the pre-intervention period (11.7%) was slightly higher than in the intervention period (7.6%). The number of ADRs associated with anti-thrombotic therapy, antibiotics for systemic use and antiepileptics in the pre-intervention period were all higher than in intervention period (Table 4.6). On the other hand, the number of ADRs caused by antimycotics for systemic use in the intervention period was higher than in the pre-intervention period.

The number of ADRs classified by organ affected is presented in Table 4.7. The number of ADRs associated with "body as a whole-general disorders" in the pre-intervention period was higher than in the intervention period.

The number of ADRs classified as Type A and Type B are presented in Figure 4.5. The number of ADRs resulting from toxicity and drug interactions in the intervention period were lower than in the pre-intervention period. Details of the number of ADRs classified by mechanism of action are shown in Table 4.8, whilst the number of ADRs classified by severity are illustrated in Figure 4.6. Although the number of ADRs of severity level 5 in the intervention period were higher than in the pre-intervention period, no ADR of severity 7 was observed in the intervention study.

Characteristics of preventable ADRs

The percentage of preventable ADRs in the pre-intervention period (29.3%) was found to be higher than in the intervention phase (9.9%) (Figure 4.7). It was found that the kappa coefficient was 0.41 in the pre-intervention period and 0.33 in the intervention period. The number of preventable ADRs classified according to the number of preventability criteria per patient in the pre-intervention period and the intervention period are presented in Table 4.9. The number of preventable ADRs in each criterion is illustrated in Figure 4.8. It was also found that the mean $\pm$ SD of LOS of 69 patients who occurred 73 preventable ADRs in the pre-intervention period was 18.68 $\pm$ 15.13 days whilst it was 13.80 $\pm$ 8.07 days in 15 patients who occurred 15 preventable ADRs in the intervention period. However, the mean difference i.e. 4.88 (95% CI -3.16 to 12.92) was not statistically different (p-value = 0.230; unpaired *t*-test).

Table 4.5 Comparison of the drug groups causing an ADR classified according to the ATC main group classification for the two study periods.

Drug groups causing ADRs	Number of ADRs (%)	
	Pre-intervention period	Intervention period
i) Alimentary tract and metabolism	7 (3.7)	4 (3.1)
ii) Blood and blood forming organs	22 (11.7)	10 (7.6)
iii) Cardiovascular system	13 (6.9)	7 (5.3)
iv) Genito-urinary system and sex hormones	1 (0.5)	0
v) Systemic hormonal preparations, excl. sex hormones	12 (6.4)	13 (9.9)
vi) General anti-infective for systemic use	82 (43.6)	75 (57.3)
vii) Antineoplastic and immunomodulating agents	14 (7.5)	9 (6.9)
viii) Central nervous system	17 (9.0)	4 (3.1)
ix) Respiratory system	4 (2.1)	0
x) Musculo-skeletal system	0	7 (5.3)
xi) Various	16 (8.5)	2 (1.5)
Totals	188	131

ATC = Anatomical Therapeutic Chemical

Table 4.6 Comparison of drug groups causing an ADR using the ATC subgroup classification for the two study periods.

Drug sub-groups causing an ADR	Number of ADRs (%)	
	Pre-intervention period	Intervention period
1 Antacids, drugs for treatment of peptic ulcer and flatulence	1 (0.5)	0
2 Antiemetics and antinaueants	2 (1.1)	0
3 Bile and liver therapy	2 (1.1)	0
4 Antidiabetic therapy	2 (1.1)	4 (3.1)
5 Antithrombotic agents	20 (10.6)	9 (6.9)
6 Antianemic preparations	2 (1.1)	0
7 Cardiac therapy	3 (1.6)	1 (0.8)
8 Antihypertensives	7 (3.7)	4 (3.1)
9 Diuretics	1 (0.5)	2 (1.5)
10 Beta blocking agents	2 (1.1)	0
11 Sex hormones and modulators of the genital system	1 (0.5)	0
12 Corticosteroids for systemic use	12 (6.4)	10 (7.6)
13 Antibiotics for systemic use	48 (25.5)	22 (16.8)
14 Antimycotics for systemic use	26 (13.8)	46 (35.1)
15 Tuberculostatic, excl. streptomycin	3 (1.6)	0
16 Antivirals for systemic use	5 (2.7)	4 (3.1)
17 Cytostatics	8 (4.3)	7 (5.3)
18 Immunostimulating agents	6 (3.2)	2 (1.5)
19 Anaesthetics	1 (0.5)	0
20 Analgesics	5 (2.7)	2 (1.5)
21 Antiepileptics	9 (4.8)	1 (0.8)
22 Psycholeptics	1 (0.5)	2 (1.5)
23 Psychoanaleptics	1 (0.5)	0
24 Antiasthmatics	4 (2.1)	0
25 Immunosuppressive agent	13 (6.9)	1 (0.8)
26 General nutrients	2 (1.1)	1 (0.8)
27 All other-nontherapeutic products	1 (0.5)	0
28 Serum lipid drug agents	0	1 (0.8)
29 Calcium homeostasis	0	1 (0.8)
30 Chemotherapeutics for systemic use	0	1 (0.8)
31 Immune sera and immunoglobulin	0	3 (2.3)
33 Antiinflammatory and antirheumatic products	0	4 (3.1)
34 Antigout preparations	0	3 (2.3)
Totals	188	131

ATC = Anatomical Therapeutic Chemical

Table 4.7 Comparison of ADR problems classified by target organ affected for the two study periods.

Organ system affected	No. of ADRs (%)	
	Pre-intervention period	Intervention period
1 Skin & appendages disorders	23 (9.2)	20 (13.2)
2 Musculo-skeletal system disorders	4 (1.6)	0
3 Central & peripheral nervous system disorders	9 (3.6)	2 (1.3)
4 Autonomic nervous system disorders	1 (0.4)	0
5 Gastro-intestinal system disorders	39 (15.7)	23 (15.1)
6 Liver & biliary system disorders	6 (2.4)	7 (4.6)
7 Metabolic & nutritional disorders	27 (10.8)	36 (23.7)
8 Endocrine disorders	2 (0.8)	14 (9.2)
9 Heart rate & rhythm disorders	5 (2.0)	1 (0.7)
10 Vascular (extracardiac) disorders	6 (2.4)	1 (0.7)
11 Respiratory system disorders	2 (0.8)	0
12 Pancytopenia	5 (2.0)	5 (3.3)
13 White cell and RES disorders	10 (4.0)	7 (4.6)
14 Platelet, bleeding & clotting disorders	15 (6.0)	9 (5.9)
15 Urinary system disorders	21 (8.4)	10 (6.6)
16 Body as a whole-general disorders	40 (16.1)	2 (1.3)
17 Application site disorders	34 (13.7)	13 (8.6)
18 Psychiatric disorders	0	1 (0.7)
19 Red blood cell disorders	0	1 (0.7)
Totals	249	152

RES = Reticuloendothelial system

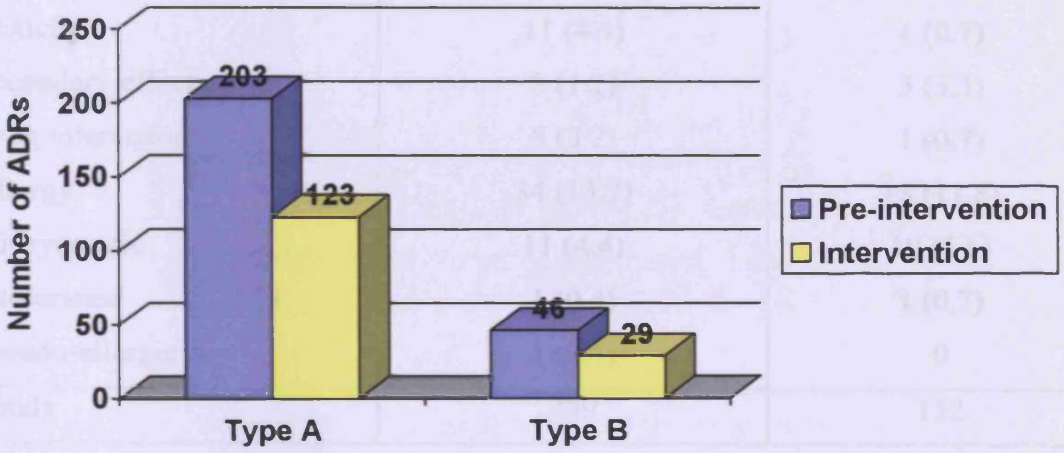


Figure 4.5 Comparison of the number of Type A and Type B ADR problems for the two study periods.

Table 4.8 Mechanism of action of ADR problems experienced in the two study groups.

Mechanism of action	Number of ADRs (%)	
	Pre-intervention period	Intervention period
Side effect	180 (72.3)	116 (76.3)
Toxicity	11 (4.4)	1 (0.7)
Secondary effect	3 (1.2)	5 (3.3)
Drug interaction	8 (3.2)	1 (0.7)
Allergy	34 (13.7)	18 (11.8)
Idiosyncratic	11 (4.4)	10 (6.6)
Intolerance	1 (0.4)	1 (0.7)
Pseudo-allergic	1 (0.4)	0
Totals	249	152

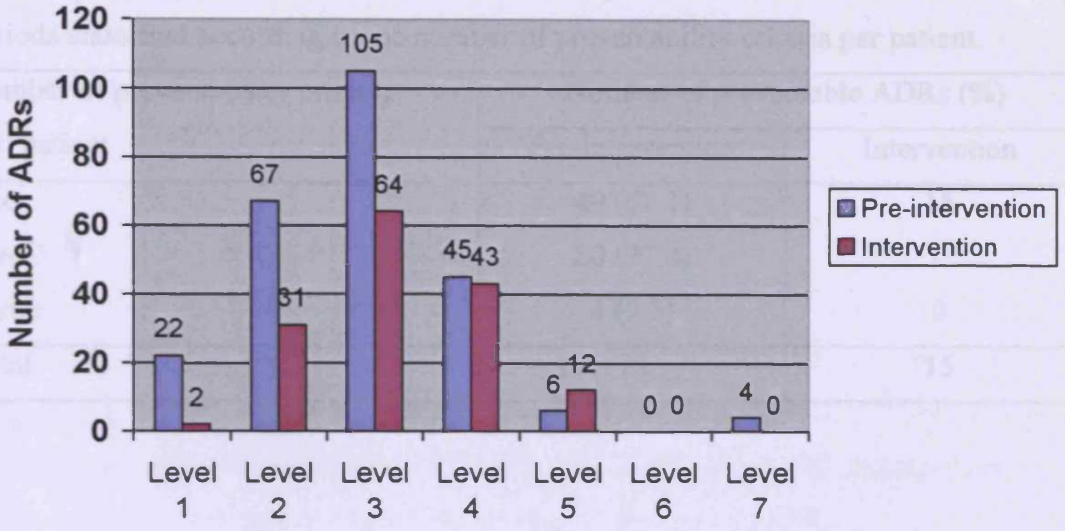


Figure 4.6 Comparison of the severity of ADR problems for the two periods.

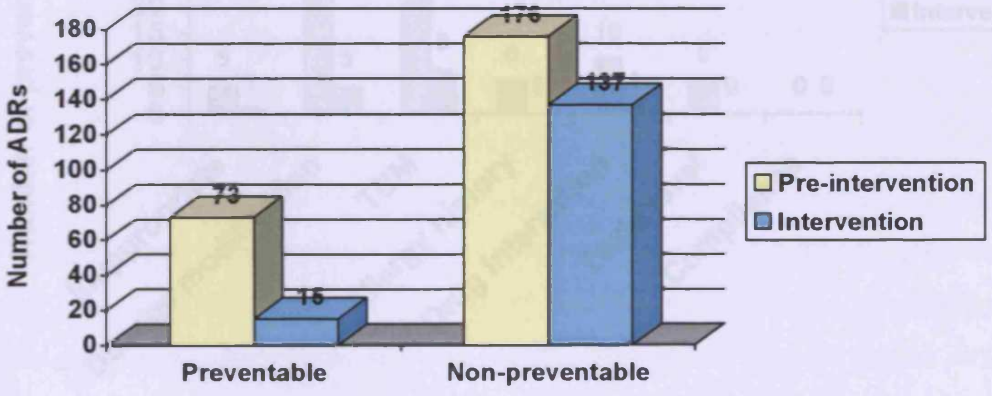


Figure 4.7 Comparison of the number of ADRs classified as preventable and non-preventable for the two study periods.

Table 4.9 Comparison between the number of preventable ADRs in the two study periods classified according to the number of preventability criteria per patient.

Number of preventability criteria per patient	Number of preventable ADRs (%)	
	Pre-intervention	Intervention
One	49 (67.1)	15
Two	20 (27.4)	0
Three	4 (5.5)	0
Total	73	15

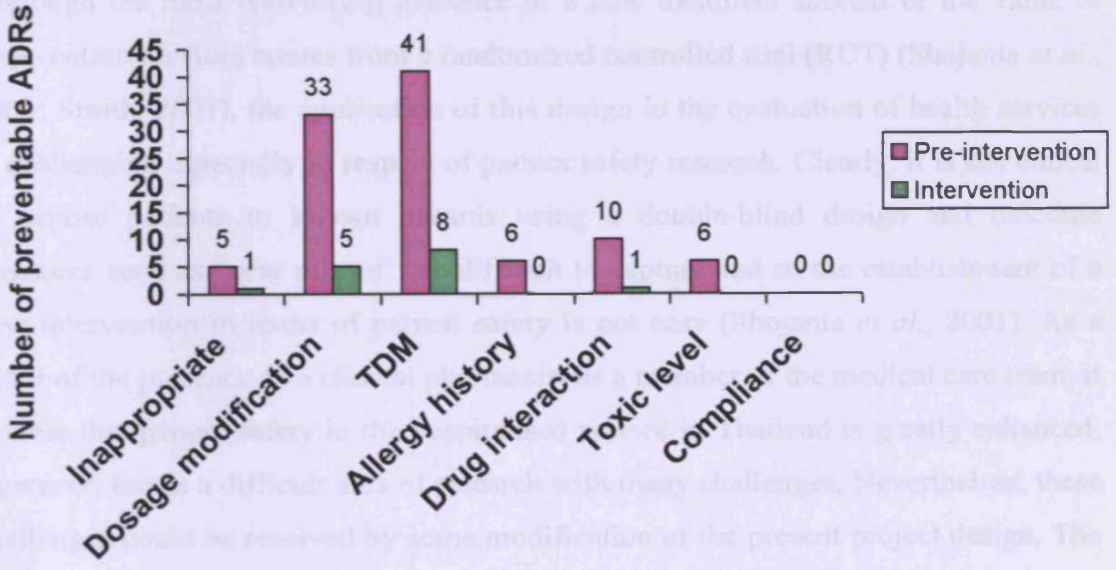


Figure 4.8 Comparison of the number of preventable ADRs in each criterion for the two study periods.

Frequencies of ADRs

The incidence of ADRs for the two study periods is presented in Table 4.10. The rate of ADRs for the two periods was compared in terms of the rate per 100 admissions and the rate per 1,000 patient-days (Table 4.11).

Frequencies of preventable ADRs

The LOS and number of preventable ADRs was calculated using the rate per 100 admissions and rate per 1,000 patient-days (Table 4.12). The average rate reduction of preventable ADRs was from 5.20 (95% CI 5.60-4.80) per 1,000 patient-days in the pre-intervention period to 1.72 (95% CI 2.24-1.20) per 1,000 patient-days in the intervention period, representing a percentage reduction of 66.9%.

DISCUSSION

Although the most convincing evidence of a new treatment success or the value of intervention services comes from a randomized controlled trial (RCT) (Shojania *et al.*, 2001; Smith, 2001), the application of this design in the evaluation of health services is challenging especially in respect of patient safety research. Clearly, it is not ethical to expose patients to known hazards using a double-blind design and outcome measures such as "near misses" are difficult to capture and so the establishment of a new intervention in terms of patient safety is not easy (Shojania *et al.*, 2001). As a result of the presence of a clinical pharmacist as a member of the medical care team, it is clear that patient safety in the hospitalised service in Thailand is greatly enhanced. However, this is a difficult area of research with many challenges. Nevertheless, these challenges could be resolved by some modification of the present project design. The "near misses" or potential for an ADR to occur (see Chapter 3) was determined by intensive monitoring by a research clinical pharmacist in an intervention study. The actual ADRs were also determined both by prospective intensive monitoring and retrospectively by two clinical pharmacists (the researcher and an independent expert assessor) for causality and preventability assessment. A single blind study design was used to reflect the impact of a clinical pharmacist as a member of the medical team in the present study which was not in fact different from that used earlier by Evans *et al.* (1994), Leape *et al.* (1999) and Fertleman *et al.* (2005). In the UK, Fertleman (2005) reported on the impact of a clinical pharmacist on a post-take ward round comparing a control and intervention period, whereas in the USA, Leape (1999) compared the rate

Table 4.10 Cumulative incidence and incidence density of ADRs for the two study periods.

	Pre-intervention period	Intervention period
Total monitored patients (patients)	1548	985
Number of ADRs patients (patients)	187	109
Cumulative incidence (%)	12.08	11.07
Total LOS (patient-days)	14,045	8,710
Incidence density (per 1,000 patient-days)	13.31	12.51

Table 4.11 Rates of ADRs for the two study periods.

	Pre-intervention period	Intervention period
Total monitored patients (patients)	1548	985
Number of ADR problems (events)	249	152
Rate per 100 admissions (%)	16.09	15.43
Total LOS (patient-days)	14,045	8,710
Rate per 1,000 patient-days	17.73	17.45

Table 4.12 Comparison of the rates of preventable ADRs for the two study periods.

	Pre-intervention period	Intervention period
Total monitored patients (patients)	1548	985
Average LOS (days)	9.07	8.84
Total LOS (days)	14,045	8,710
Number of preventable ADRs	73	15
Rate of preventable ADRs (%)	4.72	1.52
Rate of preventable ADRs (per 1,000 patient-days)	5.20*	1.72*
95% CI Rate of preventable ADRs per 1,000 patient-days	(5.60-4.80)	(2.24-1.20)

*p <0.001 (unpaired *t*-test)

of preventable ADEs before and after a clinical pharmacist was added to the medical care team in an ICU unit. Earlier, Evans *et al.* (1994) monitored patients for three consecutive periods to identify the change in number of Type B ADRs and those of a severe nature. The three interventions which were carried out included a computerised alert for drug allergy, standardised antibiotic administration rates, and timely physician notification in order to prevent ADRs from occurring. In comparison, Kucukarslan (2003) conducted a single-blind, standard-care control study in order to determine the rate of preventable ADEs. The comparison between a control and a study group was performed on two identical general medicine units. Unfortunately, there are no identical medical wards at Ramathibodi Hospital, and so this approach was not possible in the present study. Although the number of patients recruited in the pre-intervention period was more than the patients recruited in the intervention period, it was found that the demographic profiles for gender, age, LOS, coexisting diseases (AIDS, cancer, renal disease, SLE) and history of drug allergy were not significantly different between the two study groups. The exceptions were the number of concomitant drugs, the presence of coexisting liver disease, CHF and whether patients were smokers and/or drinkers in the two patient groups. As a consequence of this, the pre-intervention patients represented a good control group in order to provide baseline information.

Interestingly, it was found that the proportion of males and females in both patient groups was approximately 1:1 whilst the mean age of patients was approximately 50 years old. Although the mean LOS in the intervention group was slightly higher than in the pre-intervention group, this was not significantly different. However, it was difficult to interpret whether the presence of a clinical pharmacist in a medical team resulted in changes to the LOS because in the present study it was defined as monitoring days on two medical wards. Obviously, there were some patients who transferred to other wards before their discharge and some patients were transferred from other wards. As a result of this, the real LOS might not have been accurate. With respect to the average number of drugs administered concurrently, the number in the intervention phase was greater than in the pre-intervention phase. This result suggests that the clinical pharmacist's interventions failed to reduce the number of prescribed drugs being administered. If the number of drugs administered concurrently had declined, one might have expected the number of potential ADRs to have been

reduced, since ADRs are more likely to occur with multiple drug therapy. It was found that the clinical pharmacist's interventions did reduce the number of preventable ADRs resulting from drug-drug interactions. It was also noted that although there were significant differences between the patients in the pre-intervention and intervention groups in terms of coexisting diseases such as liver disease and CHF and social drinking and smoking, these patient factors were not a predisposing factor for ADRs (Chapter 2).

One of the limitations of the present study was that whilst at the start of the study, the research clinical pharmacist expected to monitor all 60 patients on two wards during the intervention phase, this was found to create an excessive work load which was unsustainable. For this reason, for most of the intervention phase only one ward was closely monitored by the research clinical pharmacist. However, the ratio of clinical pharmacist to beds (i.e. 1:30) was still higher than reported in other clinical pharmacist intervention studies. Recently, Fertleman *et al.* (2005) reported on the impact of a clinical pharmacist on a 28-bed medical ward in a general hospital in the UK whilst Leape *et al.* (1999) reported on a pharmacist servicing a 17-bed ICU unit in a teaching hospital while a clinical pharmacist to patient ratio of 1:15 was reported by Kucukarslan *et al.* (2003) at a general hospital in the USA. The ratio of clinical pharmacist to patients will probably impact on the effectiveness of the clinical pharmacist in providing health care services. Interestingly, as a consequence of the wide variety and scope of hospital pharmacy practice around the world (LeBlanc and Dasta, 2005), a comparison of clinical pharmacy services in developed and developing countries is difficult. Such services are only slowly developing in countries such as Thailand and are far less comprehensive than in the UK and USA.

Schumock *et al.* (2003) reviewed studies carried out on the economic benefits of providing clinical pharmacy services from 1996-2000. The impact of such services were categorised into five major groups as follows:- disease management, general pharmacotherapeutic monitoring, pharmacokinetic monitoring, targeted drug programmes, patient education programmes or cognitive services. The benefit to cost ratio was estimated in a total of 59 studies and it was found that services related to adverse reaction monitoring were of greatest value. Patient safety which included a reduction of ADRs provided the clinical pharmacist with the greatest opportunity to

directly influence patient care (LeBlanc and Dasta, 2005). In the USA, the American College of Physicians and American Society of Internal Medicine (2002) also published data supporting the role of pharmacists in improving patient safety and reducing medical errors. In comparison, in the UK the clinical pharmacist's role has been described by the patient's journey throughout hospitalisation. In other words, before admission, on admission, during hospital stay, and on discharge. Obviously, all clinical pharmacy activities were provided as part of the concept of pharmaceutical care and led to a reduction in ADRs (Brady, 2003; Child and Cooke, 2003). Furthermore, the Australian Society of Hospital Pharmacists recently published a positional statement which encouraged the integration of clinical pharmacy services into patient care services to improve patient outcomes and reduce ADEs (Anon., 2005b).

Although clinical pharmacy services include patient counselling, the provision of drug information services, patient-drug profile reviews, ADR monitoring, therapeutic drug monitoring, and drug utilization reviews are being developed by the Ministry of Public Health (MOPH) in Thailand (Chan and Ching, 2005), the impact of these services is not well established. This is because patient outcomes and the benefit to cost ratio of the presence of a clinical pharmacist as a member of the health care team has not been investigated. However, it was found that the number of pharmacy practice orientated faculty theses have increased from four in 1991 to 37 theses in 2002 (Anon., 2004b), indicating the increasing focus on pharmacy practice research in Thailand. Furthermore, a clinical pharmacy Master programme now established at Mahidol University includes taking students onto the medical ward at Ramathibodi Hospital. Unfortunately, the impact that clinical pharmacy services has had on patient care has not been conducted to date. Thus, one of the expectations of the present study was that the presence of a research clinical pharmacist as a member of the medical care team would lead to the expansion of clinical pharmacy services and integration of academic research and pharmacy practice in a teaching hospital setting.

A major finding in the present study was that the rate of preventable ADRs was reduced by 66.9%. This impressive reduction was calculated from the difference between the preventable ADR rate in the pre-intervention period (i.e. 5.20 per 1,000 patient-days) and the rate of preventable ADRs during the intervention phase (i.e. 1.72

per 1,000 patient-days). Interestingly, although there were variations in patient outcomes, methodology and patient recruitment in the present study compared with the studies of both Leape *et al.* (1999) and Kucukarslan *et al.* (2003), the percentage reduction of ADRs calculated in the present study was not greatly different from that quoted by Leape *et al.* (1999) and Kucukarslan *et al.* (2003) where the reduction rate of preventable ADEs was 66% and 78%, respectively. Instead of ADRs, both the Leape *et al.* (1999) and Kucukarslan *et al.* (2003) studies measured ADEs as their outcome measure. In the pre-intervention periods it was found that the preventable ADR rate was 5.20 per 1,000 patient-days or 4.72 ADRs per 100 admissions. Importantly, these frequencies should be compared with those of other studies using the same unit of frequency. Leape *et al.* (1999) reported that for the before-intervention period, preventable ADEs were 10.4 per 1,000 patient-days. On the other hand, Kucukarslan *et al.* (2003) quoted the rate of preventable ADEs as 26.5 per 1,000 patient-days in their control group. In comparison, during the intervention phase in the present study, it was found that the rate of preventable ADRs was 1.72 per patient-days or 1.52 ADRs per 100 admissions. These frequencies were compared with these in the Leape *et al.* (1999) and Kucukarslan *et al.* (2003) studies. For example, Leape *et al.* (1999) reported that in their intervention group, the rate of preventable ADEs was 3.5 per 1,000 patient-days, whereas Kucukarslan (2003) quoted preventable ADEs as 5.7 per 1,000 patient-days in their study group. It is interesting to note that in both the Leape *et al.* (1999) and Kucukarslan *et al.* (2003) studies, the rate of preventable ADEs for the two groups were higher than in the present study. This is possibly because their two studies included medication errors as an outcome measure. Perhaps surprisingly, Kucukarslan's preventable ADE rates were higher than stated in Leape's study even though according to Leape their critical care patients would have been expected to suffer more ADEs than seen in general medical patients. This was supported by the fact that the average LOS in Leape's study was approximately 12 days, far longer than Kucukarslan's LOS of approximately 4 days. Probably the greater number of medications each patient was taking in Kucukarslan's study (i.e. approximately 15 items) resulted in the more frequent occurrence of preventable ADEs. Furthermore, there were other discrepancies between the present study and the studies of Leape *et al.* (1999) and Kucukarslan *et al.* (2003). Not only were the study designs different but in the Leape *et al.* (1999) and Kucukarslan *et al.* (2003) studies, they both focused on preventable

ADEs resulting from ordering and prescribing errors. On the other hand, the intervention study in the present study included drug monitoring. Thus, the clinical pharmacist's approach to providing a service in the three studies were dissimilar although the overall outcome was improved patient care.

During the pre-intervention period, it was found that 73 out of 249 (29.3%) ADRs could be categorised as preventable ADRs whilst only 15 out of 152 (9.9%) ADRs could be categorised as preventable in the intervention phase. These percentages were derived from Schumock and Thornton (1992) preventability assessment criteria in which the ADRs were assessed by answering "yes" to seven specific questions. Clearly, this preventability assessment process is not very flexible. It should also be noted that there are a variety of systems used in carrying out preventability assessments published in the literature. An expert panel in preventability assessment according to Bates *et al.* (1995b) originally categorised preventable ADEs into four groups (i.e. definitely probable, probably preventable, probably not preventable, and definitely not preventable). However, the results for their preventable ADEs were represented by only two scales, preventable and non-preventable ADEs. They found that the kappa coefficient agreement when assessed by two physicians was a highly satisfactory 0.92. In comparison, Olivier *et al.* (2002) assessed ADRs leading to hospital admission as being either preventable or non-preventable at a teaching hospital in France. The study compared preventable ADRs using a French causality assessment process composed of a number of structured scoring questions as presented earlier in Table 1.16 with expert opinion. It was found that the expert panels justified preventable ADRs in 54.5% of all instances whilst their standardised preventability scale identified only 9% as definite and 25% as potentially preventable ADRs. Although in the present study, the reproducibility agreement for preventability assessment was not good when based on kappa coefficients, the disagreement between assessments was not far different from that quoted in the earlier Olivier *et al.* (2002) study.

Not only did the percentage of preventable ADRs decrease from 29.3% to 9.9% in our study, those that did remain during the intervention period emphasised the research clinical pharmacist's overall activities. It was found that none of the remaining preventable ADRs were associated with toxic serum drug concentrations and were

associated with drug-induced allergies in the intervention period. Indeed, the research clinical pharmacist's recommendations resulted in the almost total elimination of ADRs. However, some preventable ADRs were still noted mainly resulting from the absence of therapeutic drug monitoring or the carrying out of detailed biochemical and blood tests. Had intensive monitoring been carried out such as INR monitoring following warfarin prescribing, and comprehensive blood profiling then the remaining preventable ADRs might have been completely avoided. However, the added costs of providing such support would have been substantial and are probably unaffordable in Thailand at the present time.

In the pre-intervention period, antithrombotic agents and antiepileptic drugs accounted for 10.6% and 4.8% of all ADRs, these values decreasing to 6.9% and 0.8% during the intervention period. Clearly, these two drug groups pose a high risk of causing an ADR (Calis and Young, 2004) because they possess a narrow therapeutic index, and any interaction with another drug is more likely to lead to unwanted effects. Antimycotic agents accounted for the highest percentage of ADRs (i.e. 35.1%) in the intervention period compared with only 13.8% during the pre-intervention study. The most frequently prescribed drug in this group was amphotericin B which commonly causes ADRs associated with electrolyte imbalance and nephrotoxicity. The controversial method of pre-medication with saline solution in order to prevent these ADRs and non-standardized electrolyte monitoring possibly resulted in the increased frequency of these ADRs.

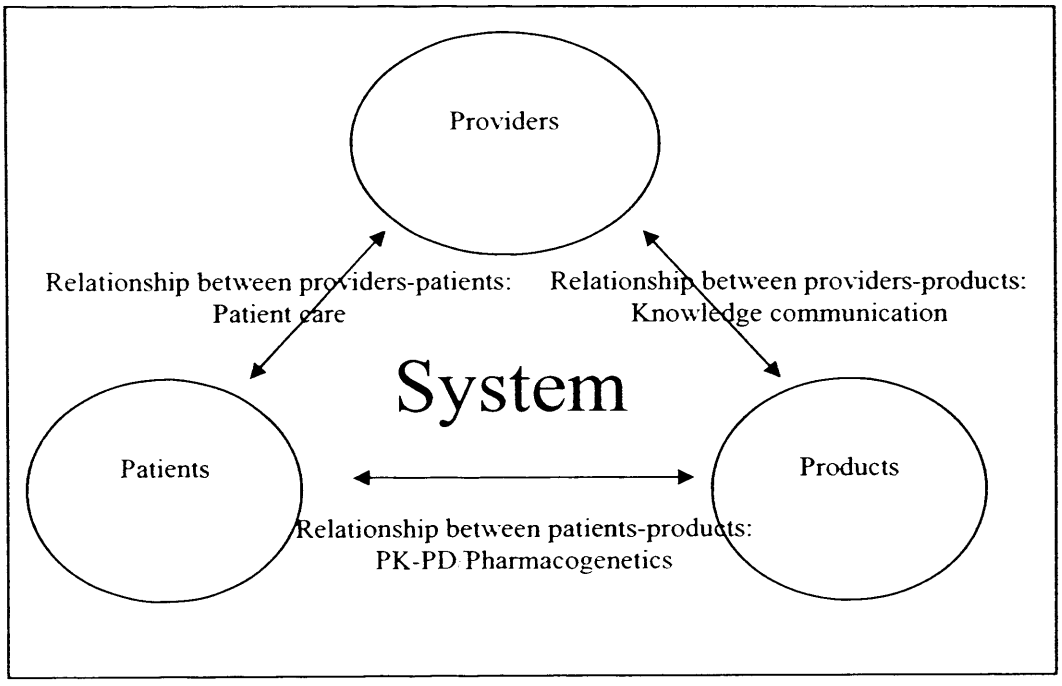
The cumulative incidence of ADRs was found to be 12.08 per 100 admissions with the incidence density being 13.31 per 1,000 patient-days in the pre-intervention period. This compared with a cumulative incidence of 11.07 per 100 admissions and an incidence density of 12.51 per 1,000 patient-days during the intervention period. The small reduction of these incidences was similar to the slight reduction in ADR rates. It is suggested that although the preventable ADRs were substantially reduced, the remaining ADRs were not markedly reduced. This is probably because the research clinical pharmacist's presence as a member of the medical care might have resulted in more frequent ADR detection during the intervention phase. This explanation is similar to the so-called "Hawthorne effect" which is used to describe

practitioners who alter their practices as a result of being observed (Evan *et al.*, 1994; Boardman and Fitzpatrick, 2001).

Interestingly, if the cumulative incidence of potential and actual ADRs is summed (i.e. 22.24 per 100 admissions) and likewise the incidence density of potential and actual ADRs (i.e. 25.14 per 1,000 patient-days) during the intervention phase then these values are approximately twice those seen in the pre-intervention period (i.e. 12.08 per 100 admissions and 13.31 per 1,000 patient-days). This also suggests that the presence as a member of the medical care team increases the detection rate of potential ADRs.

As stated earlier, it is virtually impossible to prevent all ADRs from occurring. The fact that clinical pharmacist services are not always provided on a 24-hour basis, that not all recommendation's are accepted, as well as a reluctance to spend increased amounts of money on blood level monitoring for all patients, doubtless contributed to the remaining 15 preventable ADRs that were identified in the intervention period.

One interesting approach to eliminating ADRs is to use the model as illustrated in Figure 4.9. This model for preventing ADRs conceptualizes all factors involved in ADRs and their relationship to "preventing" ADRs. To begin with, this model is based on three crucial components. The first one is the concept of drug responsiveness which relies on one's genes, environment and behaviour (Tucker, 2004). Secondly, Schumock and Thornton (1992) and Imb's preventability assessments (Olivier *et al.*, 2002) are used to characterise preventable ADRs. Lastly, the predisposing factors for ADRs are factored into the model. Although the model is used to explain the general concept for preventing ADRs, it can be applied to other specific schemes. For example, prevention of drug-induced liver injuries (organ affected scheme), prevention of ADRs in HIV patients (patient group scheme), or prescribing system for preventing ADRs on medical wards (systems scheme). However, the application of this model needs to be evaluated in more detail for each specific scheme, before being used routinely.



PK-PD = Pharmacokinetics-pharmacodynamics

Figure 4.9 A model for preventing ADRs

In Figure 4.9, the three Ps stand for product, patient and provider whilst the three Rs stand for the relationships between each P (i.e. product-patient, product-provider and patient-provider). A product or medicine has a drug included as an active ingredient with a pharmaceutical excipient. The drug development process can lead to the prevention or avoidance of an ADR by integration of knowledge related to the pharmacology, chemistry, drug metabolism and toxicology of the active ingredient through the modification of the drug's structure or the drug delivery process (Li, 2004). Patient factors relate to the concept of patients at risk from an ADR occurring. Identification of patients at risk is one of the first steps in preventing an ADR. Patient factors also include patient knowledge related to ADRs (Fincham, 1991). Providers include all health care providers who take part in the medication use process such as physicians, pharmacists and nurses. It involves their responsibility in the prescribing, dispensing, administration and monitoring of drug use. The "prevention" of ADRs relies on their specific role and collaboration with others (Atuah *et al.*, 2004).

The relationship between a patient and a product is summarised earlier in Figure 1.3. The use of pharmacokinetic and pharmacodynamic data in pre-clinical studies is essential in the assessment of drug safety (Walker, 2004). Recently, in March 2005, the US FDA Patient Safety News reported a new cytochrome P450 genotyping test. This could certainly assist is choosing a patient's medication and to individualise doses (Anon., 2005c). Interestingly, Hughes *et al.* (2004) reported that in the UK, pharmacogenetic testing before abacavir prescribing was able to prevent abacavir hypersensitivity responses from occurring and is a cost-effective procedure. The clinical application of pharmacogenetics will also be helpful for the individualisation of medicine in the future. Furthermore, other basic principles involved in optimising drug therapy according to a drug's clinical pharmacology profile such as therapeutic drug monitoring (TDM) (Cambell, 1999; Steenhoek, 2000; Thomson, 2003) and/or avoidance of adverse drug-drug interactions are important concepts for preventing ADRs.

The product-provider relationship involves drug information being communicated. Not only does incomplete drug safety information, but a lack of communication, may result in an ADR. The reporting of serious ADRs associated with a new drug increases drug safety awareness which hopefully will prevent similar ADRs for

occurring in other patients. Interestingly, delayed withdrawal of Vioxx^{R} (Waxman, 2005) seems to have resulted from a lack of communication between the drug company and health care providers over the toxic cardiovascular effects of this drug. This led to a number of deaths in arthritic patients taking this anti-inflammatory drugs, before the seriousness of these effects became widely known, resulting in the drug's withdrawal.

The relationship between a patient and a provider includes the medical care, nursing care and pharmaceutical care. The pharmacist's opportunity to collaborate with a physician in the selection of drug therapy could lead to a reduction in ADEs for example in ambulatory patients (Tierney, 2003). Leape *et al.* (1999) also demonstrated that pharmacist participation can reduce the risk of an ADE by 66%. In another study (Bates *et al.*, 1995b) it was found that the prescribing process can lead to a variety of problems. Furthermore, Kucukarslan *et al.* (2003) indicated that the rate of preventable ADEs fell by 78% when clinical pharmacists took part in hospital general medicine ward rounds.

A combination of drug development, drug regulation and patient data is reflected in the spontaneous reporting system to evaluate drug safety once a medicine has reached the market. This has resulted in approximately 10% of drugs registered between 1975 and 1999 being withdrawn (Lasser *et al.*, 2002). Moreover, there were 121 product withdrawals worldwide between 1960 and 1999 (Fung *et al.*, 2001). Therefore, a good spontaneous reporting system with comprehensive post-marketing surveillance have prevented many serious ADRs from being repeated. Interestingly, the withdrawal of Vioxx^{R} in September 2004 resulted from drug surveillance and extensive drug safety monitoring, although in hindsight some people considered that this drug should have been withdrawn several years earlier to because of the seriousness of its cardiovascular effects (Dieppe *et al.*, 2004; Kim *et al.*, 2004). This withdrawal was said to have resulted in an FDA crisis in the USA (Anon., 2005d) and discussions to initiate new drug safety monitoring systems took place (Anon., 2005e;f). The result were new guidance notes entitled: "premarketing risk assessment, development and use of risk minimisation action plans and good pharmacovigilance practices and pharmacoepidemiologic assessment" being published.

Nevertheless, no matter how good and appropriate any system is for preventing ADRs, it is doubtful whether ADRs can be totally eliminated. Interestingly, it was found that a computerised physician order entry (CPOE) system can reduce prescribing errors (Jones *et al.*, 2005) although no-one has yet been able to eliminate prescribing and dispensing errors.

SUMMARY

- A research clinical pharmacist was able to reduce the rate of preventable ADRs from 5.20 per 1,000 patient-days during a pre-intervention (control) period where no clinical pharmacist service was provided down to 1.72 per 1,000 patient-days during the intervention phase in which a research clinical pharmacist was present as member of the medical care team.
- The overall rate of reduction in ADRs during the intervention phase was calculated to be 66.9%.
- There was no significant difference in the demographic data in terms of gender, age, LOS, coexisting diseases of AIDS, cancer, renal disease and SLE, and drug allergy history for the pre-intervention and intervention groups although there was a significant difference in terms of number of concomitant drugs, coexisting diseases of the liver and CHF and the smoking and intake of alcohol in the two groups.
- It has been shown that a research clinical pharmacist is able to provide an important contribution to drug safety in hospitalised patients in Thailand.
- A model for preventing ADRs has been described, however, it is unlikely that ADRs can be totally eliminated following medicine usage.

Chapter 5

General Discussion and Conclusions

CHAPTER 5

GENERAL DISCUSSION AND CONCLUSIONS

Adverse drug events are a common problem in hospitalised patients and result mainly from a systems failure such as a lack of sufficient patient information and/or drug information (Leape *et al.*, 1995; Bates, 1999; Hepler and Segal, 2003). The extent to which Thai-hospitalised medical patients suffer from ADRs is reported in Chapter 2. If a clinical pharmacist is added to the patient care team then many of these ADRs can be prevented. In particular, four specific systems (i.e. computerised order entry, the provision of electronic drug information, standardising dosing and administration times) have been recommended for preventing ADRs or ADEs from occurring (Hepler and Segal, 2003). In Thailand, although there is a national ADR monitoring scheme and clinical pharmacist services are being introduced, unfortunately, there is no evidence to date to support the provision of a clinical pharmacist service in attempting to reduce ADRs. For this reason, the present study was performed during a period when ADR monitoring and pharmaceutical care was being developed in Thailand. This followed substantial health system reforms to improve patient care whilst limiting expenditure (Anon., 2004c; Towse et *al.*, 2004). The eventual outcome of the present study was to determine the clinical pharmacist's value as a member of the medical team in a large teaching hospital. Also to create a role model for the clinical pharmacy profession leading to improved clinical pharmacy education and the advancement of clinical pharmacy practice in Thailand.

Important performance indicators of a clinical pharmacist's contribution to the medical care team include acceptance of proposed pharmacist interventions (see Chapter 3) and a reduction in the rate of so-called "preventable" ADRs. Data was gathered following a study in ADRs in an intervention phase (in the presence of a research clinical pharmacist) was compared with a baseline phase, when no research clinical pharmacist was present. Clearly, the acceptance of a clinical pharmacist's interventions by a physician implies a successful measure of the pharmacist's activities whilst a reduction in the number of "preventable" ADRs reflects a measure of clinical outcome success.

Data from the present study indicated that a research clinical pharmacist's participation in a medical team reduced the rate of "preventable" or avoidable ADRs by 66.9%. This reduction was calculated from the difference between the number of preventable ADRs during a control period in the absence of a research clinical pharmacist (5.20 preventable ADRs per 1,000 patient-days) with those seen during an intervention phase (1.72 preventable ADRs per 1,000 patient-days). Although it was found in the present study that this reduction rate was similar to that observed in an earlier study where ADEs accounted for 66.3% in an intensive care unit (Leape *et al.*, 1999), the two studies were quite different in respect of the outcome measures used, the methodology employed and patient recruitment. Firstly, the outcome measure used in the Leape *et al.* (1999) study was ADEs rather than ADRs. Secondly, they involved the pharmacist in the prescribing process whilst in the present study, such a monitoring process was not excluded. Thirdly, all the patient's recruited in the present study were general medical patients, whereas critical care patients were recruited by Leape *et al.* (1999). Clearly, the reduction rate of preventable ADRs relies on the pharmacist's skills and knowledge as well as the ratio of clinical pharmacists to patients. An experienced senior pharmacist carried out rounds on the 17-bed ICU ward in the Leape *et al.* (1999) study. On the other hand, the present study was performed by a junior clinical pharmacist covering a 30-bed internal medicine ward. Doubtless, discrepancies in the two studies are probably explained by the differences in outcome measures used, methodologies and differences in patient recruitment. It is therefore, perhaps surprising that the rates of reduction of ADRs in both studies were quite similar.

A reduction rate of preventable ADEs of 78.5% has been reported in general medical patients by Kucukarslan *et al.* (2003) which is higher than the reduction rate observed in the present study. Their higher reduction rate might have resulted from a higher pharmacist to patient ratio. This was approximately 1:15 in the Kucukarslan *et al.* (2003) study whilst in the present study it was 1:30. Clearly, the more closely the patients are monitored, the greater the quality of patient care is likely to be. Moreover, the use of pharmacotherapy specialist pharmacists in the Kucukarslan *et al.* (2003) study might have resulted in the more effective prevention of ADEs. In addition, although the present and Kucukarslan *et al.* (2003) studies were conducted on internal medicine wards, it is interesting to note that the Kucukarslan *et al.* (2003) and Leape

et al. (1999) studies were quite similar in terms of outcome measures and methodologies used.

Not only was the clinical outcome measured in terms of reducing the number of preventable ADRs but the variety and characteristics of the research clinical pharmacist's interventions provided another indicator of a hospital pharmacist's activities as a member of the medical care team. In the present study, some 143 recommendations associated with 985 patients were made i.e. 14.5 recommendations per 100 admissions. This is quite low compared with figures published earlier by Leape *et al.* (1999) and Kucukarslan *et al.* (2003). In their studies, a total of 398 recommendations were made for 75 patients or 530.7 per 100 admissions, and 150 recommendations for 86 patients or 174.4 per 100 admissions, respectively. The lower number of clinical pharmacist interventions in the present study probably reflected differences in how ADRs were classified in these studies. The classification used in the present study was based on the Schumock and Thornton preventability assessment method for ADRs (Schumock and Thornton, 1992). In contrast, Leape *et al.* (1999) and Kucukarslan *et al.* (2003) both included writing errors, the provision of drug information and additional drug therapies. Leape and colleagues found that 325 out of 398 interventions could be categorised as writing errors, lack of drug information, and additional drug therapy interventions (Leape *et al.*, 1999). In contrast, Kucukarslan *et al.* (2003) reported that these accounted for 35 out of a total of 150 recommendations. In addition, the critical care patients in the Leape *et al.* (1999) study were more likely to be at risk of an ADE occurring than patients on a general medical ward. Indeed, the ratio of Leape's interventions were more than those quoted in the Kucukarslan *et al.* (2003) study. Clearly, both groups used as their outcome measure, ADEs rather than ADRs, and the clinical pharmacist's interventions included medication errors. Therefore, it is not perhaps surprising that the number of clinical pharmacy interventions were less than found in the present study.

Both Leape *et al.* (1999) and Kucukarslan *et al.* (2003) found that nearly all the clinical pharmacist's recommendations (98.9% and 98.0%, respectively) were accepted by the medical care team. These acceptance rates were a little higher than those determined in the present study (129 out of 143 recommendations or 90.2%). The reason for this marginally lower rate of acceptance in the present study was

probably because in the USA studies, prescribing errors were included and these would most likely be accepted by the physicians. Moreover, the experience of clinical pharmacists in the USA is relatively greater than those working in Thailand where clinical pharmacy is a relatively new practice area.

In Thailand, the presence of a clinical pharmacist as a member of the medical care team has only recently been established even though a more patient focused role has been encouraged for the past 10 years ago. Following substantial health system reforms in the year 2000, attention has also turned to the cost-effectiveness of treatments and the quality of patient care. One result of these reforms is to question whether Thai clinical pharmacists are able to demonstrate value for money or cost effectiveness in terms of providing high quality medication management. Clearly, a number of research studies will need to be carried out in the next few years if indeed the provision of clinical pharmacy services are to be proved to be cost effective.

In the USA, Kucukarslan *et al.* (2003) compared the rate of preventable ADEs between a standard (control) care hospital patient group with that of a clinical pharmacist intervention group. These authors found that clinical pharmacists were able to reduce the rate of so-called "preventable ADEs" by 78.5%. It was also found that patients who experienced an ADE stayed in hospital on average 1.4 days longer than patients who avoided an ADE following a clinical pharmacist's intervention. The extra bed occupancy for a semiprivate room in the hospital amounted to an extra cost of $923 per admission (Kucukarslan *et al.*, 2003). Unfortunately, the authors did not calculate the cost-savings of reducing preventable ADEs in the intervention group in terms of the costs of employing a clinical pharmacist.

In the UK, the impact of having a clinical pharmacist present on ward rounds has recently been demonstrated at a district general hospital by Fertleman *et al.* (2005). This study compared the cost-savings between a pre-intervention group where normal medical care was provided for 50 patients and an intervention group of 53 patients (i.e. with a clinical pharmacist participating on the physician's ward rounds). Cost-savings were calculated as the cost of drugs which were stopped from the moment of admission through to discharge and the actual cost of drugs provided as medication during hospitalisation. The predicted average annual cost-saving which resulted from

drugs being stopped was found to be between £5.52 and £88.60 per patient, in the pre-intervention and intervention groups, respectively. Interestingly, the annual cost of drugs prescribed for each patient increased by £181 and £122 in the two groups. Overall, if all the data was extrapolated, a cost-saving of £500,000 per annum would have been made in providing a weekday service for 25 patient admissions per day. If the cost of employing a full time pharmacist is approximately £48,000 (Fertleman *et al.*, 2005), then the benefit of employing a clinical pharmacist is clear to see and is a highly cost-effective exercise.

Dooley *et al.* (2003) reported cost-savings resulting from a clinical pharmacist's recommendations from a study in eight Australian teaching hospitals. The benefits of a clinical pharmacist's interventions were transposed into cost-savings based on the reduction in length of hospital stay, the probability of readmission, the change in drug therapy management, the cost of laboratory monitoring, and the saving on medical procedures. From a total of 1,399 interventions, 96 could have led to a reduction in length of hospital stay while 156 reduced the potential for readmission. As a consequence, cost-savings of AU$150,307 and AU$111,848 for reduced length of stay and prevention of potential readmissions were made. These represented the majority of the total cost-savings of AU$263,221. Interestingly, although some changes in drug therapy management, laboratory monitoring and medical procedures might have added rather than reduced costs, these were largely counteracted by a reduction in length of hospital stay. It was reported that the clinical pharmacist's recommendations resulted in a decreased length of hospital stay by an average of 2.28 and 2.42 days for high dependency beds and general ward beds, respectively. The overall estimation of a clinical pharmacist's impact was also converted into the cost-benefits of employing such a specialist pharmacist. For every dollar spent on the pharmacist's interventions, approximately AU$23 was saved. In fact, the cost/benefits of a clinical pharmacist's recommendations resulted from only 3.8% of the clinical pharmacist's total time spent on the wards (Dooley *et al.*, 2003). In comparison, although the aim of present study was focused on a clinical pharmacist's recommendations in preventing ADRs, the clinical pharmacist's participation as a full member of the medical care team contributed to patient safety in other ways such as responding to drug information enquiries, providing data on drug availability and checking on the suitability and availability of dosage forms. Unfortunately, the

usefulness of these services were not investigated although this is an important aspect for future research. The clinical pharmacist's recommendations which led to changes in medicines management in the present study totalled 114 in 985 patients (11.57%). This is in contrast to the 1,399 recommendations concerning 24,866 patients (5.63%) recorded in the Dooley *et al.* (2003) study. The higher frequency of clinical pharmacist's recommendations in the present study together with many non-measured contributions indicate the significant benefits of having a clinical pharmacist as a member of the health care team.

Leape *et al.* (1999) compared the rate of preventable ADEs in ICU patients between a before-intervention group (usual practice) and an intervention group in which a clinical pharmacist participated on physician and nurse rounds and was on-call 24 hours a day. Annual cost-savings resulting from a reduction of 58 preventable ADEs were calculated (Leape *et al.*, 1999). The average cost of the total resource utilization associated with these post preventable ADEs, which did not include the cost of injuries to patients or malpractice costs, was $4,685 per ADE (Bates *et al.*, 1997). Thus, the estimated cost-savings were equal to $270,000 for a 17-bed ICU unit in a 700-bed teaching hospital (Leape *et al.*, 1999). These cost-savings were more than the cost of employing a 50% full-time-equivalent clinical pharmacist (Cullen *et al.*, 2000). In addition, this study also established that the average length of stay of patients before-intervention compared to the intervention phase was 13.9 and 12.4 days, respectively. In the present study the equivalent average length of hospital stay was 9.07 and 8.84 days, respectively. This difference was probably associated with the fact that critical care patients can be expected to require longer hospitalisation than the less sick patients usually seen on a general medical ward in a Thai hospital.

Although in the present study there was no statistical difference between the length of hospital stay in the control and intervention phase of the study, the length of hospital stay in the intervention group was reduced. Since the average cost per admission at Ramathibodi Hospital in 2002 was 21,092 Bahts, this represented a cost-saving equivalent to 4,851 Bahts per admission. Furthermore, the research clinical pharmacist prevented 42 ADRs from occurring resulting in a further cost-savings of 203,742 Bahts over the 10 month study. If the cost of a full time pharmacist in Thailand is 10,000 Bahts per month, the benefits of employing a clinical pharmacist

are clearly cost-effective. Unfortunately, to date the exact cost of preventing ADRs has not been investigated in Thailand. However, if the average cost of monitoring ADRs in Thailand is approximately 5,000 Baht per annum, and the reduction of preventable ADRs is 58 ADRs (as in the present study), then the cost-savings would be equivalent to 290,000 Bahts over the 10 month period. In other words, for every Baht spent on a clinical pharmacist's salary, there would be saving of 2.9 Baht; a considerable saving to the hospital service in Thailand. The literature relating to the cost/benefits of employing a clinical pharmacist suggests that there are various methods for transposing the benefits of pharmacist interventions into cost-savings. However, due to limitations in cost-saving data in the present study, the actual cost/benefits of providing a clinical pharmacist service in Thailand is difficult to establish. Nevertheless, the value of a clinical pharmacist in preventing ADRs is not in question. Clearly, the precise cost/benefits of having a clinical pharmacist as a member of the medical care team should be further investigated.

One of the problems encountered in carrying out ADR studies is knowing which of the various classifications of an ADR to use to determine the mechanism of action of the ADR. Many different ways to classify the type of ADR occurring have been published in the literature. For example, Hurwitz and Wade (1969) classified ADRs into those resulting from an overdose, excessive effects, side-effects, hypersensitivity and idiosyncratic reactions while Gholami and Shalviri (1999) divided ADRs into their predictability according to twenty-five in-depth criteria. As a consequence of these various classifications, comparison of the types of ADRs published in the literature is often difficult. It was decided in the present study to classify ADRs according to a basic pharmacological classification (Hess and Rieder, 1997) and into Type A and Type B reactions according to Rawlins (1981). In the pre-intervention phase, Type A ADRs accounted for 81.5% of reactions with side effects (72.3%) being major cause of an ADR occurring. This latter percentage was different from that published by Hurwitz and Wade (1969) and more recently by Gholami and Shalviri (1999) who reported side effects accounting for 57.8% and 96.1% of ADRs, respectively. Both sets of data originated from intensive monitoring and systematic chart review in the same manner as that used in the present study. It was found that the majority of ADRs were Type A or predictable ADRs. On the other hand, spontaneous reporting of ADRs by other authors have indicated that only 35.5%

(Pearson *et al.*, 1994) and 48% (Seeger *et al.*, 1998) of ADRs were considered to be Type A ADRs. This is probably explained by the different methods used for ADR detection. Intensive ADR monitoring should detect most ADRs occurring whilst a voluntary reporting method has a tendency to flag-up mainly Type B ADRs. Furthermore, preventable ADRs in the present pre-intervention phase occurred largely because of a failure to carry out therapeutic drug monitoring or other necessary laboratory tests (39.4%), a failure to adjust dosages or correct drug administration (32.7%), or missed drug-drug interactions (9.9%). These percentages are comparable with those reported by Winterstein *et al.* (2002) in which the corresponding values were 17.0%, 49.5% and 18.6%, respectively. In Winterestein's study, ADRs were retrieved using a voluntary reporting system which probably accounts for the discrepancies with the values found in the present study.

Interestingly, the types of preventable ADRs in the pre-intervention study differed from the types of research clinical pharmacist interventions recommended during the intervention period. The two most frequent were a requirement for therapeutic drug monitoring and laboratory tests (3rd rank) plus dosage adjustment or drug administration (2nd rank) in the control phase, whereas a dosage adjustment and change in drug administration (2nd rank), and drug-drug interactions (5th rank) were the most frequent of the research clinical pharmacist's recommendations (48.3% and 18.9%, respectively). Side-effects accounted for the majority of ADRs (72.3%), these being prevented by modification of dosage administered. This most frequent type of clinical pharmacist intervention was also similar to the pharmacist's recommendations for preventing an ADE published by Kucukarslan *et al.* (2003). They found that dosage or frequency of dosing adjustments were the most frequent type of intervention (35%) although this study did not classify the type of intervention according to Schumock and Thornton (1992) criteria as in the present study. The addition of drugs to therapy (21%) and the identification of potential problems with continuing therapy after discharge (8%) were reported by Kucukarslan *et al.* (2003). Interestingly, although the clinical pharmacist's interventions in the present study were focused on preventing ADRs, recommended dosage adjustments (48.3%) were similar to the clinical pharmacist's interventions as recorded in a Veterans Affairs (VA) Medical Centre by Lee *et al.* (2002). Whilst this study did not focus only on preventing ADRs, it was found that 129 out of 250 recommendations (51.6%) were

classified as adjustments to dosage or frequency. Problems relating to dosage adjustment or drug administration is clearly an area requiring an improved performance by physicians.

In the present study, the severity of ADRs were classified according to the seven interval scale described by Hartwig *et al.* (1992). This severity classification expanded on those reported earlier by Bennett and Lipman (1977) and Bergman *et al.* (1971) in which only 4 levels of severity assessment was used. In contrast, Stephens (2004) divided severity into just three levels. Almost one-half (42.2%) of all ADRs in the present pre-intervention study were judged to be of level 3 severity (i.e. the ADR required that treatment with the suspected drug be with-held, discontinued, or otherwise changed, and/or an antidote or other treatment was required, although there is no increase in length of stay. The result of the present study was different from that reported by Gholami and Shalviri (1992) who classified severity into 7 levels as in the present study. It was found that 52.0% of all ADRs were regarded as level 4 severity (i.e. any level 3 ADR that increased LOS by at least one day, or the ADR was the reason for hospital admission). Whilst 26 out of 62 patient admissions were due to an ADR in the Gholami and Shalviri (1992) study, in the present study only ADRs occurring during hospitalisation were recorded. Thus, it was not surprising that ADR severity in the Gholami study was more severe than in the present study. Severity assessment is difficult to compare between different studies. For example, Suh *et al.* (2000) classified ADR severity into 3 levels (mild, moderate, and severe) and found that 53% of all ADRs were of moderate severity. If level 3 severity had been used in the present study then 42.2% of ADRs would have been classed as moderate severity, this result being similar to that published by Suh *et al.* (2000). Unfortunately, severity assessment could not be compared with that of Bates *et al.* (1995b) because these authors categorised severity into fatal, life-threatening, serious and significant.

For comparison, the severity of potential ADRs was determined for the intervention period of the present study. It was found that the majority (79.7%) of recommendations could be recorded as potentially significant. This severity level was greater than the moderate severity found in the pre-intervention period (42.2%). As a consequence of this, it was suggested that a research clinical pharmacist's intervention is able to prevent ADRs of moderate severity in about 80% of cases. This percentage

is greater than the corresponding value of 42.2% found in the pre-intervention period, but was similar to the results of both Gholami and Shalviri (1999) and Cullen *et al.* (2000) who found that preventable ADRs were judged to be more severe than non-preventable ADRs.

Interestingly, general anti-infectives for systemic use were the most frequent drugs causing an ADR in the pre-intervention period (43.6%) and accounted for 40.5% of the research clinical pharmacist's interventions in the intervention study. Moreover, when this group of drugs was subdivided it was found that antibiotics for systemic use in both studies accounted for 25.5% and 24.5% of ADRs, respectively. These results may of course have been influenced by their high usage. Moreover, anti-infective agents are known to commonly cause ADRs in hospitalised patients (Suh *et al.*, 2000; Calis and Young, 2004; Waedwithan, 2004). Dosage modification was the most frequent of the research clinical pharmacist's interventions accounting for 48.3% of recommendations. The need to avoid toxicity with anti-infective drugs was the most likely reason for a reducing dosage. This was perhaps not surprising because according to the demographic data, some 40% of all patients were elderly, who were more at risk of suffering an ADR.

Recently, a 10-year study of ADRs which had been detected by computer-based surveillance at a 520-bed teaching hospital in the USA focused on the risk factors for experiencing an ADR (Evans *et al.*, 2005). It was found that analgesics, anti-infectives, cardiovascular agents plus anticoagulants and fibrinolytics accounted for 59.8%, 20.1%, 7.2% and 3.6%, respectively, from a total of 4,376 ADRs reported in hospitalised patients. However, the frequency of drugs causing an ADR in the present study was somewhat different to that described in the Evans *et al.* (2005) study. One possible reason for the different rankings of drugs resulting in an ADR, is that computerised ADR detection fails to detect all ADRs in the way that intensive surveillance does.

A review of six studies on drug groups causing preventable ADEs in hospitalised patients was reported by Kanjanarat *et al.* (2003). These authors found that cardiovascular drugs, psychoactive and CNS agents, analgesics, anticoagulants and anti-infective agents most frequently led to ADRs accounting for 17.9%, 15.3%,

12.8%, 9.8%, and 9.6% of ADRs, respectively. These results originated from heterogeneous sources and included ADRs identified from both systemic chart review and voluntary reporting methods. The fact that these studies included preventable ADEs as well as ADRs probably accounts for the differences in the drug groups found to cause ADRs in the current study.

In the pre-intervention period, the majority of organs associated with an ADR included general disorders of the whole body (16.1%), gastrointestinal system disorders (15.7%), application site disorders (13.7%) and metabolic & nutritional disorders (10.8%). Skin and appendage disorders were associated with a further 9.2%. In the present study, intensive monitoring was carried out and thus it was expected that every undesirable effect was detected. Interestingly, our results are similar to those published by Suh *et al.* (2000) who also used intensive monitoring to detect ADRs. In contrast, data collected by the Thai National ADR spontaneous reporting system (Waedwithan, 2004) indicated that skin and appendage disorders and disorders affecting the whole-body accounted for 49.3% and 12.6%, respectively, of a total of 22,785 ADRs. In a study of preventable ADEs in hospitalised patients Kanjanarat *et al.* (2003) found that allergic and cutaneous, hepatic or renal disorders, cardiovascular disorders, and haematological disorders accounted for 34.4%, 14.3%, 13.2% and 13.2%, respectively, of all preventable ADEs. Coexisting diseases or underlying diseases in the patients studied may account for the differences in rankings seen in the various studies.

Although intensive ADR monitoring in the pre-intervention period was time consuming, data collected during this period did provide information about potential predisposing factors leading to ADRs and which a voluntary reporting system would not have been able to detect. Patient characteristics which have been suggested as risk factors for ADRs in the literatures were investigated by comparing the frequency of ADRs occurring in patients who suffered an ADR with those who did not. However, the results were different for each factor when compared with those of a much larger study carried out recently by Evan *et al.* (2005). A relatively small sample size and the fact that the study design was not of the matched case-control type doubtless resulted in this discrepancy between the findings in the two studies.

A comprehensive literature review indicated that there are many definitions of an ADR and related terms such as ADE. However, the World Health Organization (WHO) definition of an ADR has been in use for more than 30 years, being widely accepted. The thalidomide tragedy in the 1960s stimulated drug safety awareness and led to post-marketing surveillance (PMS) systems being set up world-wide. Thus, international ADR monitoring of new medicines after drug registration became established using the WHO definition of an ADR (World Health Organization Technical Report Series 1969, 1970). This definition was later clarified by Karch and Lasagna (1975) who excluded therapeutic failure. In 2000, a new definition was proposed by Edwards and Aronson (2000) who suggested that "noxious" in the original WHO definition was not obvious and should not be included for medicinal products. The new definition also included the withdrawal of a product as well as the unexpected failure of therapy. Other ADR definitions exist which tend to be related to the aims of the institution publishing them, such as the Medicines and Healthcare products Regulatory Agency (MHRA) in the UK and the American Society of Health-System Pharmacists (ASHP) in the USA.

Some researchers use the term adverse drug event (ADE) rather than adverse drug reaction (Hepler and Segal, 2003). In fact, it was suggested that the WHO definition should be confined to the appropriate use of drugs (Bates *et al.*, 1995a; 1995b; Ninno and Ninno, 2001). It has also been suggested that the WHO definition of an ADR should only include unexpected or unpredictable adverse effects and not those as a direct consequence of a medication error. This ADE definition has also been used in the IOM's report "To err is human" under the patient safety scheme (Institute of Medicine, 2000). Surprisingly, there is no definition for an ADE published by the WHO in their glossary of terms (Uppsala Monitoring Centre, 2004).

For the most part, an ADR definition which includes medication errors is very helpful in strategies to prevent ADRs from occurring, although there is an overlap in the definitions of medication error (ME) and adverse drug event (ADE). A medication error is described as part of the medication use process and ADRs and ADEs may result from an ME (American Society of Hospital Pharmacists, 1998; Greory and Kier, 2001; Nebeker *et al.*, 2004). Unfortunately, it is sometimes difficult to distinguish between a medication error and an ADR in some clinical practice

situations (Otero, 1999; Ninno, 2001; Clough, 2001; Hepler and Segal, 2003) leading to differences in the way in which ADRs are sometimes reported.

Interestingly, there are examples in the literature where the same definition is used for ADEs and ADRs (Evans *et al.*, 1994; Classen *et al.*, 1997; Rozich *et al.*, 2003; Evans *et al.*, 2005). Furthermore, the ABC synopsis for primary care providers in the UK uses ADE instead of ADR (Dunn, 2003). It is also somewhat misleading that the ADE term was used for the second step causality assessment approach used by Naranjo *et al.* (1992). However, since this is only used in causality assessment, it is well recognized as such. Other considerations need to be taken account when using the terms ADR and ADE which will be discussed here. Adverse events refer to a response leading to patient harm but not necessarily caused by a drug whilst ADR or ADE are terms used when a patient is harmed by taking a drug. The term "potential" ADE is used when an ADE does not occur but it could have occurred (Nebeker *et al.*, 2004). Therefore, a potential ADE could imply the prevention of an ADE (see Table 1.1). In the present study, the term potential ADR has been used in this way. Others have defined an adverse event as being the same as an adverse experience (Uppsala Monitoring Centre, 2000; 2002a; 2004), while adverse event was defined by Hepler and Segal (2003) and the IOM (Institute of Medicine, 2000) with no mention of an adverse experience. Edwards and Aronson (2000) also addressed the importance of distinguishing between an adverse event and an adverse reaction (or adverse effect). They defined an adverse reaction as "an adverse outcome that can be attributed to some action of a drug (Edwards and Aronson, 2000). A recent UMC publication introduced the terms "risk-effectiveness" and "benefit-harm" instead of the previously used term of risk-benefit (Uppsala Monitoring Centre, 2004).

As a consequence of the various definitions and terms used in ADR studies, much confusion has arisen (Nebeker, *et al.*, 2004). Some terms overlap while others are very different. For example, the "process" of medication usage includes medication errors, while the "outcome" of medication usage is an ADR and ADE (Hepler and Segal, 2003). Clearly, it was very important to understand the relationship between the various terms and is the first step in preventing drug-related morbidity (Morimoto *et al.*, 2004). Consequently, epidemiological studies are often difficult to interpret due to inconsistencies in the definitions used and choice of outcome measures. Thus, in all

ADR studies or other drug safety monitoring schemes, all terms used must be defined and ideally terms should only be used that are widely accepted throughout the world. In the present study, the definition of an ADR was that published by the ASHP. This excluded nausea/vomiting when referring to ADRs induced by chemotherapeutic agents and chill resulting from amphotericin B use. This definition was considered especially suitable for hospitalised patients.

Assessment of causality is also difficult when assigning an ADR to a particular drug. Lack of patient information and incomplete drug safety information especially in the case of unpredictable ADRs makes this task difficult (Meyboom *et al.*, 1997). Moreover, the fact that re-challenge is not often an option on ethical grounds and the absence of any specific laboratory confirmation tests, makes ADR causality assessment extremely difficult to confirm in absolute terms. Perhaps the best method is to use three approaches when attempting to determine the drug causality; global introspection or clinical judgement, structural questionnaires or algorithms, and a Bayesian probabilistic approach (Naranjo, 1986; Shakir, 2004). Although the Bayesian method tends to be reproducible and highly objective, it is difficult to use in practice because it is time consuming and requires an enormous amount of information gathering. The global introspection method is simple to use in practice and can be used daily by physicians. However, it lacks structural assessment and reproducibility (Arimore *et al.*, 2005). In comparison, questionnaires or algorithms are not difficult to use and are more objective than relying solely on clinical judgement. Thus, many algorithms have been developed in order to improve the reproducibility and reliability of ADR causality assessment. Unfortunately, there is currently no gold standard algorithm in use. For this reason, the RUCAM was used in the present study because this method of determining causality is more comprehensive than Naranjo's algorithm and is easier to use in practice.

Perhaps unsurprisingly, the reproducibility of the RUCAM was not good. The kappa coefficients were found to be 0.11 and 0.33 in the pre-intervention period and post-intervention periods, respectively, when the four levels of RUCAM probability were compared. However, the kappa coefficients became 0.41 (moderate agreement) for both groups when highly probable and probable, and possible and unlikely were combined into "yes" and "no" categorises of an ADR occurring. Use of four different

levels (highly probable, probable, possible and unlikely) clearly resulted in higher disagreement than when only two levels were used. The different judgements for each question in the RUCAM depended to some extent on the experience of the assessors. Although in the present study the same algorithm was used, agreement between assessors was not good. A similar situation was observed by Macedo *et al.* (2003) and Arimore *et al.* (2005). Macedo and colleagues compared an expert panel's assessment with fifteen published algorithms using 200 ADR case reports. Agreement based on global introspection was not good at any level of causality assessment (Macedo *et al.*, 2003). Arimore and colleagues reported similarity that agreement between five expert's who assessed one hundred and fifty ADRs, was likewise poor with a kappa coefficient of only 0.20 (Arimore *et al.*, 2005).

Not only is causality assessment of ADRs difficult but ADR preventability assessment is another difficult area although it is a critical step in developing a scheme for preventing ADRs. Preventability assessment is not easy and often leads to confusion (Ninno and Ninno, 2001). Probably the reason for this is because any decision about preventability relies on assumptions (Hepler and Segal, 2003). Moreover, Olivier *et al.* (2002) highlighted the fact that again there is no gold standard for preventability assessment. However, preventability assessments have been used by the Adverse Drug Event Prevention Study group using an expert panel (Hepler and Segal, 2003). Clearly, the expert panel assessments were made according to each assessor's experience. In comparison, the Schumock and Thornton (1992) approach has been widely used for retrospectively assessing ADR reports and is based on seven specific questions being asked. Because the aim of the present study was to reduce "preventable ADRs" between the pre-intervention and intervention phases of the study, preventability assessment was used in the present study. However, the calculated kappa coefficients for both phases was far from good (i.e. 0.41 and 0.33 for the pre-intervention and intervention group, respectively). Causality assessment differences between assessors resulting from differing judgements of the assessors and variability in the interpretation of criteria (especially to the first question of Schumock's and Thorton's criteria) clearly resulted in the large variability of preventability assessments carried out. As a consequence, it is suggested that other methods for preventability assessment should be developed for specific use in hospitals where compliance is not such a problem as in primary care. The addition of

preventability criteria such as inadequate pre-medication and IV-site reactions would also improve the overall accuracy of assessing whether or not an ADR is preventable or not.

There are a number of limitations associated with the present study. Firstly, although the interventions of a research clinical pharmacist were able to reduce the number of preventable ADRs, such ADRs still occurred albeit at a lower level. A major reason for this was doubtless associated with the absence or incomplete drug safety information. In addition, only one research clinical pharmacist was involved and so 24 hours cover per day, for seven days a week, was simply not possible. Furthermore, to monitor 30 patients every day was highly labour intensive. In contrast, three medical care teams worked in eight-hour shifts to provide overall 24 hour patient care. Furthermore, physicians could be called at anytime to provide care at busy times or emergencies. It would certainly help if pharmacists were to provide "out of hours" cover although ideally a full 24 hour clinical pharmacy service would be of greatest benefit to patient care. In Thailand, to date there has not been a study to assess the value of a clinical pharmacist on hospital ward rounds. Thus, employment of a designated clinical pharmacist remains controversial. Although evidence of a clinical pharmacist's value has been proven in the USA and the UK, direct comparisons with Thailand are difficult because of differences in the multi-factorial health care systems in the three countries and differences in the professional backgrounds and training of clinical pharmacists.

Secondly, although documenting ADEs in a patent's chart is helpful for preventing the re-occurrence of an ADE (Nebeker *et al.*, 2004), in the present study no formal documentation of the research clinical pharmacist's intervention were recorded. Clearly, the future documentation of intervention in Thailand will be useful in providing evidence of the clinical pharmacist's ability to problem solve and full acceptance of any recommendations by the health care team. Initially, it is hoped that the clinical pharmacist might share responsibility for patient care in Thailand by being permitted to co-sign the patient charts with the attending physician.

Thirdly, the focus was on "preventing ADRs" in the present study, the efficacy of drug therapy was not assessed even though the optimization of drug therapy does

consist of benefit-harm assessment. Clearly, patient outcomes are not dependent on just one health care professional but many. While interventions which focused only on "preventing ADRs" undoubtedly influenced the overall outcome, some research clinical pharmacist recommendations related to drug availability and drug selections according to the particular situation and time available. This obvious limitation in providing a full clinical pharmacy service restricted the aims of the study and together with a heavy work-load left little or no time to provide extensive pharmaceutical care services. It would have also been interesting to measure the impact of drug therapy and medicines management on a patient's quality of life. It has previously been reported in the literature for example, that patients with reactive airways disease (Weinberger *et al.*, 2002) and congestive heart failure (Gattis *et al.*, 1999) showed improved quality of life associated with the provision of pharmaceutical care.

Fourthly, the present study was labour intensive both during the pre-intervention and intervention phases because the sole research clinical pharmacist had to monitor all patients on two 30-bed wards. Thus, the impact that could be achieved in order to determine the extent to which ADRs occurred in the control period and "in preventing ADRs" in the intervention period was limited. Clearly, it was not possible to provide in addition, a full pharmaceutical care service. The intensive ADR monitoring service was expensive to provide and could probably be justified only as a research project as stated by others (Emerson *et al.*, 2001; Morimoto *et al.*, 2004). The voluntary reporting of suspected ADR relies on a health care provider's awareness of drug safety problems and an ability to communicate these to the relevant authorities. Under-reporting remains a problem with this method. A computerised approach for detecting ADRs provides a more comprehensive service and is more economical and effective than other methods (Emerson *et al.*, 2001; Morimoto *et al.*, 2004; Silverman *et al.*, 2004), while computerised physician order entry (CPOE) and electronic medical records (EMR) have both been shown to reduce ADRs following computerised surveillance (Morimoto *et al.*, 2004). Although Ramathibodi Hospital has an established computerised data connection for administration purpose, the use of computerised data in drug treatment has yet to be implemented. Hence, such computerised methods are out of question for the time being.

Fifthly, although the ideal study design for demonstrating clinical effectiveness is the randomized controlled trial (RCT), in clinical practice, intervention studies are not easy to perform using this approach. Due to the lack of identical medical wards at Ramathibodi Hospital, the control group could not be studied at the same time as the intervention group and it was not possible to randomize patients on recruitment. As a consequence of this, the present study was performed using a before and after design, despite the limitations of this type of study.

Sixthly, assessment of preventability was limited due to lack of a gold standard for this assessment and disagreement between expert assessors about an ideal method for preventability assessment. Physicians have to concentrate most of their energies on diagnosis and thus have littler time for assessing preventable ADRs. Clearly, a physician-pharmacist team should be able to initiate preventability assessment. Improvement of safety is also likely to result from this collaboration because of the recognition that ADRs occur in daily practice and most can be prevented. Thus, communication of ADRs and preventability assessment are a real challenge for pharmacists and physicians in daily practice, if patients are to be protected as best as possible from unwanted drug-induced effects.

Finally, the present study was performed on two general medical wards at a large teaching hospital. Consequently, some patients were admitted immediately to these wards whilst others were transferred to these wards from other wards and some patients were transferred to others wards to continue therapy before discharge. Thus, the LOS noted in the present study did not necessarily represent the actual length of stay in the hospital. Furthermore, ADRs occurring in other medical wards, or even the outpatient department and emergency departments were not recorded. Also a large teaching hospital tends to undertake more academic-type activities and as a result in general, the severity of diseases admitted are worse than seen in other types of hospital. A parallel study in a non-teaching hospital may well have led to a very different set of ADR data, and would be an interesting further project to undertake.

In conclusion, a number of further studies should be carried out to build on the findings in the present study. These include;

- The cost effectiveness of providing a clinical pharmacist service for preventing ADRs needs to be determined in order to establish this role for clinical pharmacists in Thailand as members of the medical care team.
- The integration of hospital computerised clinical data and computerised detection ADRs should be developed in order to prevent ADRs from occurring in daily practice, once hospitals become fully computerised.
- A specific model for preventing ADRs in either high risk patients or patients administered high risk drugs, needs to be established in all Thai hospitals.
- Communication between clinical pharmacists and other health care providers needs to be expanded. For example, pharmacists should report on their activities to physicians and other health care professionals.
- The provision of pharmaceutical care services needs to be studied with physician collaboration in order to measure the clinical pharmacist's impact on improving a patient's quality of life.
- Finally, a fully costed study should be carried out to determine the cost-benefits of providing a comprehensive clinical pharmacy service on all wards at the Ramathibodi Hospital and other hospitals in Thailand.

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Pummangura C., **Tragulpiankit P.**, Kaojarern S., Wananukul W., Montakantikul. P, Luscombe DK. & Pomyen N. (2004). Characteristics of adverse drug reactions and patient at risk in medical wards. *Pharmacy World & Science*, **26**, A97 (abstract).

PEPI – 045 Characteristics of adverse drug reactions and patients at risk in medical wards

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Background and Objective: To determine the characteristics of adverse drug reactions (ADRs) and patient at risk in medical wards.

Design: Six months perspective observation. ADRs were assessed by Roussel Ulcaf Causality Assessment Method (RUCAM). Preventable ADRs were classified using Schumock and Thornton criteria.

Setting: Male and female medical wards in a large university hospital (Ramathibodi Hospital, Bangkok).

Main Outcome Measures: Number of preventable ADRs and ADRs classified by drug group causing and organ affected. The rate of patients with ADRs and without ADRs was compared between each patient at risk.

Results: A total of 928 patients were monitored and 165 ADRs during hospitalization were detected out of 121 patients (70 females and 51 males) whose mean age was 46.11 ± 18.61 years. Thirty-eight ADRs were classifed as preventable. General systemic anti-infective drugs caused the most ADRs (47.3%) and preventable ADRs (30.0%). The ADRs and preventable ADRs mostly expressed as metabolic and nutritional disorders (16.4%) and urinary system disorders (21.0%) as well as platelet, bleeding and clotting disorders (21.0%), respectively. The significant differences between patients with ADRs and without ADRs were age, length of stay, cancer, liver disease, alcohol drinking and positive history of drug allergy ($P < 0.05$). The only significant difference between preventable and non-preventable ADRs was in cancer patients ($P < 0.05$). The most preventable ADRs were caused by no serum drug concentration monitoring or other necessary laboratory tests (27.6%), inappropriate drug administration (25.9%) and drug interaction (22.4%).

Conclusions: ADRs are not uncommon problem in medical wards and that at least one third could be prevented. Pharmacist should identify patients at risk of ADRs and participate in drug therapy monitoring.

Tragulpiankit P., Kaojarern S., Wananukul W. & Luscombe DK. Reducing the risk of drug-induced adverse events in hospitalized patients. *Pharmacy World & Science*, **26**, A100 (abstract).

PEPI – 057 Reducing the risk of drug-induced adverse events in hospitalized patients

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Background and Objective: To evaluate clinical pharmacist interventions in limiting drug-induced adverse events.

Design: Comparison between baseline phase (without pharmacist intervention, 8 weeks in 2 medical wards) and pharmacist intervention phase (4 weeks in 2 medical wards). Preventable adverse events were classified using Schumock and Thornton criteria.

Setting: Male and femal medical wards in a large university hospital.

Main Outcome Measures: Rate of preventable adverse events following clinical pharmacist interventions.

Results: A total of 1,023 patients were studied, 648 patients (320 male, 52 ± 19.18 years) in the baseline phase and 375 patients (180 male, 50.77 ± 18.78 years) in the intervention phase. Initially the rate of preventable adverse events was found 5.75 per 1,000 patient-days (95% confidence interval [CI], 6.31–5.19). Following intervention, the rate of preventable adverse events was found 2.60 per 1,000 patient-days (95% confidence interval [CI], 3.40–1.80; $P < 0.001$). The rate of preventable adverse events has decreased by 55%. The clinical pharmacist made a total of 46 recommendations. Interventions related-to preventing adverse events included modification of the dosage regimen (34.5%), inappropriate clinical patients' situation (27.6%), avoidance of drug–drug interactions (17.2%) and therapeutic drug monitoring or necessary laboratory monitoring (13.8%). Of all recommendation 39 (84.8%) were accpted by medical teams.

Conclusions: Clinical pharmacist participation in the medical patient care team resulted in decreased rate of preventable adverse events leading to significantly improved patient care.

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Tragulpiankit P., Pummangura C., Luscombe DK., Kaojarern S., Wananukul W., Montakantikul P. & Nathisuwan S. Prevention of adverse drug reactions in hospitalised patients by pharmacist participation at a large teaching hospital in Thailand. *Drug Safety*, **28**, 931 (abstract).

6. RETROSPECTIVE ANALYSIS OF DRUG-INDUCED STEVENS JOHNSON SYNDROME (SJS) OR TOXIC EPIDERMAL NECROLYSIS (TEN)

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Objective: To examine reports of drug-induced SJS and TEN in Singapore as dermatological ADRs accounted for >40% of all adverse reactions reports received by the Pharmacovigilance Unit of the Health Sciences Authority in the past 5 years.

Methods: A search of the HSA ADR database was carried out to identify all reports of SJS and TEN from 1993 to 2004. In particular, we were interested in the types of suspected drugs implicated, time taken to develop the reactions, patient's profile and annual reporting rate of these reactions.

Results: Between 1993 and 2004, a total of 151 reports of SJS/TEN (120 SJS and 20 TEN cases) were identified. This comprised 2.28% of the total ADR reports received. The most common suspected drugs were carbamazepine (27 reports), cotrimoxazole (25), phenytoin (14), allopurinol (13) and amoxicillin (13). The average time taken to develop the reactions was 29 ± 61 days. Female patients were affected more (57.6%) than male (42.4%) patients and the average age reported was 48 ± 22 year-old (range 1–88). Chinese patients formed the highest group (56.3%), followed by Malays (16.6%) and Indians (9.9%). Fatal reports accounted for 15.2% of the total SJS/TEN reports and 45% of patients have not yet recovered from the ADRs when reports were submitted.

The annual local reporting rate for SJS/TEN from 1993 to 2004 ranged from 0.58% to 3.16%. Based on the reports received through the spontaneous ADR reporting programme, the estimated rates of SJS/TEN in Singapore are about 7–8 cases per million population per year for 2003 and 2004 compared to 2–4 cases per million population per year for 1993 and 1994.

Conclusions: Serious cutaneous adverse reactions namely SJS and TEN constitute about one-third of all serious ADR submitted to HSA. Preliminary data suggests a higher estimated incidence of SJS/TEN in Singapore compared reported rates in the literature. Further studies are needed to examine the reasons for this observed difference.

7. PREVENTION OF ADVERSE DRUG REACTIONS IN HOSPITALISED PATIENTS BY PHARMACIST PARTICIPATION AT A LARGE TEACHING HOSPITAL IN THAILAND

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Objectives: To determine whether clinical pharmacist participation could lead to the prevention of adverse drug reactions (ADRs) in hospitalised patients in a teaching hospital.

Methodology: Comparison of a 10 month baseline phase (with no pharmacist intervention) with the same period in which a pharmacist attended two general wards at Ramathibodi Hospital. Suspected and preventable ADRs were assessed by Roussel Uclaf Causality Assessment (RUCAM)[1] and Schumock and Thornton criteria[2], respectively. The numbers of preventable ADRs were then compared between the intervention and baseline phases using SPSS version 11.0.

Results: A total of 1,548 (male 49.1%, age 51.6 ± 18.9 years) and 985 (male 52.2%, age 52.1 ± 18.9 years) patients were recruited to the baseline and intervention phases, respectively, there being no statistical difference between these phases in terms of gender and age. During the baseline phase, the rate of preventable ADRs was found to be 5.20 per 1,000 patient-days (95% confidence interval [CI], 5.60-4.80) compared with 1.72 per 1,000 patient-days (95% CI, 2.24-1.20) following pharmacist intervention, a difference of 70% ($p<0.001$). Clinical pharmacist intervention resulted in 143 recommendations. These included dosage modification (48.2%), avoidance of drug-drug interactions (18.9%), inappropriate medication for a disease (14.0%), the need for therapeutic drug monitoring (13.3%) and history of drug allergy (5.6%). Eighty percent of all clinical pharmacist recommendations were accepted and implemented by the medical care team.

Conclusion: Although a national ADR monitoring scheme was established in Thailand in 1984, few steps have been taken to actively prevent ADRs from occurring in hospital patients. Results of the present study indicate that the participation of a clinical pharmacist on hospital ward rounds markedly reduces the number of preventable ADRs from occurring.

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8. POST LICENSURE SAFETY SURVEILLANCE FOR PREVENAR®, A 7-VALENT PNEUMOCOCCAL CONJUGATE VACCINE

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Prevenar® was approved for use in infants (2 months to 2 years old) to prevent invasive diseases caused by pneumococcus of serotypes 4, 6B, 9V, 14, 18C, 19F and 23F. The French Drug Agency entrusted the Pharmacovigilance Regional Center of Tours with a pharmacovigilance monitoring to detect as early as possible, an eventual serious adverse effect not identified yet.

Two methods, an intensive monitoring based on systematic reporting and a pharmacovigilance survey based on spontaneous reporting have been used.

During the 19-month intensive monitoring period conducted by 13% of French office-based pediatricians, 32 cases of serious or unlisted adverse symptoms were collected. During the 3.5-year period of marketing, 153 spontaneous reports of serious or unlisted adverse effects