Clozapine induced constipation – a service evaluation

Background

Clozapine is a second-generation antipsychotic (SGA) with an impressive track record in the treatment of severe and enduring mental health conditions, including psychoses and schizophrenia (Warnez and Alessi-Severini, 2014). It is reserved for, and licensed to, those patients who are unresponsive or intolerant to other antipsychotic medications, its use being determined by an unsatisfactory response to at least two other previous antipsychotics with at least one being another SGA drug (National Institute for Health and Care Excellence, 2015).

The side effect profile of clozapine includes a number of adverse events notably agranulocytosis and because of this risk its use requires a strict regimen of blood monitoring in an attempt to prevent any such blood dyscrasias. The monitoring regime (conducted by the one of the *Clozaril, Denzapine* or *Zaponex* patient monitoring services) requires regular FBC blood tests starting on a weekly basis for 18 weeks at the commencement of the drug then fortnightly to the end of the year and monthly thereafter. Additionally, because of concerns regarding cardiomyopathy, ECGs are suggested to be undertaken prior to clozapine starting, at dose changes and then annually. Metabolic tests including measuring weight and girth, blood tests (e.g., lipids, glucose) as well as other blood test such as U&Es, LFTs and CK are also necessary at varying intervals (Taylor et al, 2015). Other side effects associated with clozapine include siallorhea (i.e., excess dribbling, having great intra-individual variability and varying in intensity from being hardly noticeable to almost daily pillow replacement), and constipation which may be a benign side effect but might also be potentially more sinister. Poorly managed constipation can lead to life threatening situations and it now appears that the effectiveness of the clozapine haematological monitoring programmes has resulted in death from constipation surpassing death from agranulocytosis.

Literature review

The systematic review and meta-analysis conducted by Cohen and colleagues (2012) suggested that whilst agranulocytosis may be up to twice as likely as gastro-intestinal hypo-mobility, the case-fatality rate of the latter is estimated as being approximately 10 times higher than the former. Death is considered to result from two main mechanisms – through the inhalation of feculent vomitus and bowel necrosis from severe faecal impaction. Other constipation-related adverse events include haemorrhoids, faecal or urinary incontinence, UTIs, hernias, worsening of reflux, TIAs and syncope (Rege and Lafferty, 2008). The mechanism for this effect is unknown but appears to stem from a decrease in peristalisis from an anticholinergic (muscarinic) or possibly serotinergic effect of the drug (Hibbard et al, 2009) with metabolic associations including impaired blood glucose which can impair gut motility (Rege and Lafferty, 2008). In a cross sectional study by Every-Palmer et al (2012) where the colonic transit time (CTT) of 37 patients were measured, it was found that patients taking clozapine had a significantly longer CTT than those who were taking other antipsychotics. The median CTT in the

non-clozapine-treated group was 23h whereas the clozapine-treated group was more than 4 times longer at 104.5h. CTT was increased in all segments of the bowel suggesting that there is pancolonic hypomotility. The true incidence of constipation is difficult to ascertain due to the differences in study designs and of the 32 studies reviewed in Shirazi and colleagues paper (2016) only two used the Rome III criteria (considered the most appropriate measure for constipation; Drossman and Dumitrascu, 2008) and the analysis of clozapine associated constipation in these two studies showed a prevalence of 43.1%. Overall data for the 32 studies was 32.1%, being higher for inpatient studies (40.5%) than outpatient (26.2%). Other results revealed that constipation is thought to be three times greater from clozapine than other antipsychotics (Shirazi et al, 2016).

Patients prescribed clozapine are in an invidious situation – not only may the clozapine medication directly cause constipation by the above suggested mechanisms, the illnesses themselves for which it is prescribed may have an indirect influence on constipation. People who experience psychotic illnesses often suffer greatly with negative symptoms of psychoses such as lethargy, amotivational states or a blunted affect and may neglect their activities of daily living. They may follow a poor lifestyle, not having what would be considered a healthy diet with an over-reliance on convenience foods and lack of dietary fibre and may have sedentary behaviour and be unlikely to exercise regularly (Brown et al, 1999). Additionally, those with a psychotic illness may have impaired pain recognition so that when they experience constipation they may not recognise the pain or discomfort associated with it (Stubbs et al, 2015). These factors and other side effects of clozapine such as sedation and weight gain only go to increase the burden. Furthermore, they may take a myriad of other drugs in an attempt to maintain some degree of mental health stability – such as antidepressants or other antipsychotics – or drugs to counteract some of the side effects of clozapine (such as the antihistamine pirenzepine for siallorhea or the anticholinergic procyclidine for dyskinesia) which may themselves add to the dangers of constipation.

When at clinic appointments clozapine patients might be too embarrassed to talk about their bowel habit; they may even believe the constipation is part of a complex florid thought disorder which should not be disclosed. Without direct questions from clinical staff about bowel habit it may ultimately be overlooked by clinicians who may be distracted trying to actively manage psychotic symptoms or there may be a genuine ignorance that the effect clozapine can have on bowel function. Whilst there are good intentions to provide physical health care to those who experience SMIs, constipation should not be overlooked as part of this monitoring and should be discussed as normally as their diet. All members of the team should be aware of the complications of constipation so that everyone is aware of the potential danger. This is particularly pertinent to note as the study reported by De Hert and colleagues (2016) reported that only ~50% of psychiatric nurses knew clozapine caused constipation.

Aim

This study aims to discover the rate of constipation amongst clozapine treated patients in the Cardiff and Vale UHB and in doing so raise the importance and awareness among all clinical staff, and their patients, of the need for proper and thorough assessment and treatment it.

Method

Patients were interviewed whilst at their normal clinic appointments during June 2017 using an extension of the mostly unstructured typical assessment of constipation (which could consist of asking about bowel habit since the last time they were seen and any use of laxatives) by using a 9-question structured interview form, shown in Table 1. Supporting these questions visual prompts were used including the Bristol stool chart and laminated pictures of packaging from laxative products to help ascertain and identify laxative use (if patients could not recall the name of the products prescribed). Constipation was identified with the Rome III criteria (Table 2). Patients were recruited from the clozapine clinics held within the Cardiff and Vale UHB. Inclusion in the study was entirely opportunistic – patients who were at their routine appointments were asked if they would like to participate in it by the researcher and the nurses who undertake the clinics at the time. Approximately 175 patients were approached to take part in the study, 155 agreed to participate and were interviewed and one patient was excluded because they had difficulty explaining their bowel habit. There are approximately 330 clozapine treated patients within the UHB. A pilot study including 18 patients preceded the main data collection, without amendment to the study questionnaire, and this served as a useful interviewer training opportunity; those in the pilot study were included in the study sample.

The authors approached both the Ethics and the Audit offices within the UHB for clarification that this was a service evaluation and the relevant offices within the UHB gave consent for the study to proceed. The data was collated and analysed with SPSS v.20 using binary logistic regression to assess predictor significance.

Table One

Clozapine/Constipation questionnaire

1. Gender
2. Age
3. Clozapine dose
4. Years on clozapine
5. Use of other medication which may worsen constipation (anticholinergics, antihistamines or opioid based analgesia)
6. Functional constipation (Rome III diagnostic criteria)
7. Identification of laxatives used
8. Is there a family history of constipation (first or second generation) or bowel disorder?
9. Do you currently smoke

Table Two
Rome III diagnostic criteria (must include *two or more* of the following)
Criteria fulfilled for the last three months with symptom onset at least six months prior to diagnosis

a. Straining during at least 25% of defecations

b. Lumpy or hard stools in at least 25% of defecations

c. Sensation of incomplete evacuation for at least 25% of defecations

d. Sensation of anorectal obstruction/blockage for at least 25% of defecations

e. Manual maneuvers to facilitate at least 25% of defecations (e.g., digital evacuation, support of the pelvic floor)

f. Fewer than three defecations per week

Results

Male= 108 (70%) Female= 46 (30%)

Mean age = 44.26 years (range 21yrs-82yrs)

Mean clozapine dose = 387.5mg (range 37.5mg-800mg)

Mean years taking clozapine = 11 years (range two months- 27 years)

Number of patients taking cholinergic or opiaites = 37 (24%)

Number of patients with a family history of bowel problems = 35 (23%)

Number of patients taking laxatives = 69 (45%)

Current smoker = 85 (55%)

Constipated according to Rome III = 66 (42.8%)

Statistical tests:

Using binary logistic regression, Odds Ratio values revealed that people who take laxatives are between two and four more times more likely to have constipation than those that don't take laxatives (CI=1.9-8.3 significant at p>0.001). All of the other variables are non-significant and therefore don't have a contributing effect (once all other statistical variables have been controlled for) and there were no outliers in the sample.

The Omnibus Tests of Model Coefficients goodness of fit test is significant at 0.009, chi-square value is 20.318 with 8 degrees of freedom whilst the chi-square value for the Hosemor and Lemeshow test

is 5.468 with a significance of 0.707 both supporting the model used. Model summary suggests that between 12% and 16% of the variability is explained by this set of variables.

Limitations

There are a number of caveats to this study. Although the regular clinic nurse was present when the extended questions about constipation were asked during their usual appointments it is possible that the patient was embarrassed when talking about such issues and hence might not be entirely open about it, especially if they do not understand the nature of the complication – or feel that the clozapine was not associated with it. The interviewer asked participants whether they took anticholinergic or opioid based analgesia (which can worsen constipation) and although there was no significant predictor to constipation noted it is still possible that an accumulative effect could result. Patients with serious and enduring mental health conditions may not be the best descriptive historians of their medication regime; they may have the medication provided in blister packs or have other people give it to them – and they may have other medication concurrently from the GP which they forget to describe. For this reason, and for the purposes of the study we did not analyse taking additional different antipsychotics as patients may not be clear what they take because GPs may be prescribing medications which may worsen (or indeed improve) constipation. Further studies should look at how other variables might influence constipation associated with clozapine use.

Discussion

This study produced a 42.8% incidence of constipation among the sample size of 154 patients interviewed, according to the Rome III criteria for diagnosis of constipation. This is a greater figure than shown by the 26.2% constipation incidence in Shirazi and colleagues (2016) review of outpatients but remarkably close to the two studies contained in that paper which also used the Rome III criteria to identify constipation (43.1%). The gender division in the Shirazi et al article was similar (69%) to this paper (70%). Furthermore their meta-regression analyses revealed that the participant's age, diagnosis, gender, smoking status, duration of treatment, clozapine dose or clozapine serum levels did not predict constipation. Our study reflected this lack of prediction where measured.

The only statistically significant predictor of constipation in this study was whether the patient took laxatives (Odds Ratio CI=1.9-8.3, $p>0.001$). This result, and the percentage of patients within the sample who were classed as experiencing constipation, was initially surprising to the authors. It seemed at first a paradox that constipation was so highly significantly associated with laxative use – unless you view the laxative use being associated with constipation and also not being sufficient to manage the constipation. Clinicians – and patients taking clozapine, and those who are close to them – should be aware of this and not feel complacent that because patients are taking laxatives they are not in danger of experiencing constipation. The risk of constipation needs to be monitored very closely during any clinical appointments and should be as routine a question as other activities of daily living that might be asked, such as the patient's diet or sleep, or even (psychotic) symptom control.

Where severe constipation does occur it will need to be managed but it doesn't generally warrant clozapine discontinuation - especially when considering that discontinuation can lead to severe consequences including relapse in a group of patients who can exhibit extreme forms of psychiatric

distress. Monitoring of clozapine associated constipation underscores the importance of ensuring clinicians have sufficient awareness of when withdrawal of treatment should occur (Nielson et al, 2013).

Clozapine's effects on bowel motility are reported to be both under-appreciated and under recognised with little attention being paid to constipation in clozapine studies (Shirazi et al, 2016). Although usually a benign side effect which can occur at any stage of treatment, it appears more associated with the maintenance phase of treatment; ongoing vigilance of clozapine induced constipation is therefore vital (Neilson and Meyer, 2012). A trusting relationship with clinicians is essential to mediate this in order to avoid any potential dangerous issues but also to ensure that patient's concordance with their medication is not negatively influenced by their bowel discomfort.

Conclusion

This study is a useful reminder of the importance to both monitor constipation with a strong index of suspicion and to treat it with a degree of aggression to prevent it becoming more uncomfortable and ultimately potentially life threatening. Discovering that nearly half the patients included in the study experience constipation was somewhat disconcerting to the authors, especially when considering the concerns constipation can bring, but this figure has been produced by other studies. Clozapine can be an extremely effective medication, being a game changer in managing the more severe forms of serious and enduring mental illness. But in common with many medications it is not without its concerns, but these concerns can be mitigated through good practise. Bowel habit should be enquired regularly at clinic appointments so that this routine reduces embarrassment of talking about it, encouraging an open dialogue. Constipation should not be trivialised because it can have truly devastating consequences.

Recommendations

All nursing staff should be aware of the propensity for clozapine to be associated with constipation, and that although constipation can be a benign side effect it can in some cases can be fatal. The prescription of a laxative does not necessarily mean that any constipation is being treated adequately and clinicians need to be aware that repeated assessment is appropriate. Laxative treatment may need to be aggressive and patients need to be fully involved and concordant with it.

Acknowledgements

College Data Clinics, Cardiff University for guiding the authors through statistics

Ben Ussher, Student Nurse, Cardiff University for his help in the pilot part of this study

Conflict of interest

All authors declare no conflict of interest

References

Brown S., Birtwistle J., Roe L. and Thompson C. (1999) The unhealthy lifestyle of people with schizophrenia Psychological Medicine 29 (3) 697-701

Cohen D., Bogers J., van Dijk D. et al (2012) Beyond white blood cell monitoring: screening in the intial phase of clozapine therapy Journal of Clinical Psychiatry 73 (10) 1307-12

De Hert M., De Beugher A., Sweers K. et al (2016) Knowledge of psychiatric nurses about the potentially lethal side-effects of clozapine Archives of Psychiatric Nursing 30 (1) 79–83

Every-Palmer S., Nowitz M., Stanley J. et al (2016) Clozapine-treated Patients Have Marked Gastrointestinal Hypomotility, the Probable Basis of Life-threatening Gastrointestinal Complications: A Cross Sectional Study EBioMedicine 5 pp 125-134. Accessed 13/05/2017

Nielsen J. and Meyer J. (2012) Risk Factors for Ileus in Patients with Schizophrenia Schizophrenia Bulletin 38(3) pp.592-598

National Institute for Health and Care Excellence (2015) Psychosis and Schizophrenia in Adults, Quality Standard QS80 (4)

Nielson J., Correll C., Manu P. and Kane J (2013) Termination of clozapine treatment due to medical reasons: when is it warranted and how can it be avoided Journal of Clinical Psychiatry 74 (6) 603-13

Rege S. and Lafferty T. (2008) Life-threatening constipation associated with clozapine Australasian Psychiatry 16 (3) 216-219

Shirazi A., Stubbs B., Gomez L. et al (2016) Prevalence and Predictors of Clozapine-Associated Constipation: A Systematic Review and Meta-Analysis International Journal of Molecular Sciences 17, 863, 1-18

Stubbs B., Thompson T., Acaster S. et al (2015) Pain Decreased pain sensitivity among people with schizophrenia: a meta-analysis of experimental pain induction studies 156 (11) 2121-2131

Taylor D., Paton C. and Kapur S. (2015) The Maudsley Prescribing Guidelines in Psychiatry: 12th Edition John Wiley and sons Ltd., Chichester

Warnez S. and Alessi-Severini S. (2014) Clozapine: a review of clinical practice guidelines and prescribing trends BMC Psychiatry 14: 102 1-5