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A systematic review and meta-analysis reveals altered drug pharmacokinetics in humans during acute exposure to terrestrial high-altitude; clinical justification for dose adjustment?

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Abstract

Objective: While the physiological responses during acute ascent to terrestrial high-altitude (HA) have the potential to alter the pharmacokinetics (PK) that define the absorption and disposition of medicinal drugs, there have been no systematic reviews and meta-analyzes performed to date.

Methods: We conducted a systematic literature search in June 2017 using NCBI PubMed, EMBASE, Web of Science and Ovid MEDLINE databases to identify relevant observational studies. Studies were deemed eligible based on the following criteria: [1] *participants*: healthy non-acclimatised male or female lowlanders (born and bred at sea-level) and 2] *environment*: exposure to low-altitude (LA, ≤ 600 m) followed by terrestrial high-altitude (HA, ≤ 24 h to ≥ 2,500 m), the time course specifically selected to avoid interpretive complications associated with erythrocytosis. All PK parameters were standardized to be in the same units and the weighted standardised mean difference (SMD) calculated via a combination of fixed and random effects models with heterogeneity evaluated using χ^2 and I^2 statistics.

Results: Of 20,840 studies reviewed, 6 prospective cohort studies ($n = 75$) qualified for inclusion with participants exposed to a mean altitude of 4,025 (mean) ± 380 (SD) m. We observed increases for absorption half-life (SMD: 0.40, 95% CI: 0.01-0.80, $P = 0.04$], elimination half-life (SMD: 0.89, 95% CI: 0.30-1.48, $P = 0.003$) and erythrocyte binding (SMD: 0.52, 95% CI: 0.16-0.88, $P = 0.004$) and reduction in clearance (SMD: -0.56, 95% CI: -1.13-0.00, $P = 0.05$).

Conclusions: Collectively, these findings reveal impairments in both the oral absorption and corresponding clearance of an albeit limited sample of drugs at HA that may potentially require closer patient monitoring and dose adjustments in order to maintain therapeutic efficacy and avoid incidental toxicity.

Introduction

The complex interplay between environmental and physical stressors encountered during acute ascent to terrestrial high-altitude (HA) initiates a cascade of physiological responses that collectively serve to defend oxygen (O_2) delivery to the most metabolically active organ systems (Bailey and others 2017). However, coupling of O_2 delivery to demand is imperfect and severe arterial hypoxemia can ultimately lead to medical complications ranging from mild symptoms of acute mountain sickness (AMS) to the potentially fatal syndromes of high-altitude pulmonary (HAPE)/cerebral (HACE) edema (Bailey and others 2009) that necessitate the use of medicinal drugs.

These physiological adjustments have the capacity to alter the pharmacokinetics (PK) that define the absorption and disposition of drugs subsequent to alterations in, amongst others, cytochrome P (CYP)-450 activity, pH, protein binding, distribution volumes and perfusion (Figure 1 A-B). This is clinically relevant given the millions of lowlanders who sojourn to HA for occupational, recreational, or religious purposes (Li and others 2009) and increasing number of mountaineers who prophylax with a cocktail of drugs in an attempt to accelerate acclimatization and improve summit success (Donegani and others 2016; Nieto Estrada and others 2017).

However, to what extent drug PK change in response to the multiple stressors encountered at terrestrial HA (hypoxia, exercise, cold, see Figure 1) remains unclear, complicated in part by conflicting findings from a limited number of studies constrained by small sample sizes and limited ability to detect treatment effects with participants exposed to different drugs, altitudes and exposure times. Thus, for the first time, a systematic review and meta-analysis was conducted to summarize the results of relevant studies in an attempt to increase sample size and corresponding statistical power. The primary aim was to determine the effects of acute exposure ($\leq$ 24 h) to terrestrial HA on drug PK with a secondary aim of determining optimal sample sizes to help guide the design of future trials.

Methods

Database and search strategy

A systematic review of the published literature was conducted (Figure 2) in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) Statement as a guide (Knobloch and others 2011). Specific care was taken to fulfil key requirements to ensure the validity of our meta-analysis, namely, [1] well-defined objectives, including precise definitions of clinical variables and outcome, [2] an appropriate and well-documented study identification and selection strategy, [3] evaluation of bias in the identification and selection of studies, [4] description and evaluation of heterogeneity, [5] justification of data analytic techniques and [6] use of sensitivity analysis (Walker and others 2008). Two independent investigators interrogated NCBI PubMed, EMBASE, Web of Science and Ovid MEDLINE databases before June 27th (2017) using the following key words and Boolean connectors: (pharmacokinetics OR pharmacodynamics OR drugs OR medicines) AND (altitude OR high-altitude).

Selection and quality assessment

Inclusion criteria: Studies were deemed eligible for meta-analysis based on the following criteria: 1] *participants*: healthy non-acclimatised male or female lowlanders (born and bred at sea-level) and 2] *environment*: exposure to low-altitude (LA, ≤ 600 m) followed by terrestrial high-altitude (HA, ≤ 24 h to ≥ 2,500 m).

Exclusion criteria: We excluded studies that were 1] performed on animals, 2] duplicates (originating from the same participants by the same investigators but published in different journals), 3] letters to editors, reviews, commentaries, case reports, unpublished articles and articles providing insufficient information relating to PK parameters, 4] simulated normobaric hypoxic (laboratory-based) studies given the acknowledged physiological differences compared

to hypobaric hypoxia (Millet and others 2012) and 5] those incorporating chronic (> 24 h) exposures to avoid interpretive (PK) complications associated with erythrocytosis.

Quality: Study quality could not be formerly assessed given that none of the studies were randomised, blinded or provided sample size calculations. Final decision about inclusion or exclusion was achieved through mutual agreement.

Data extraction

The two investigators extracted data using structured data collection tables. All data entries were double-checked manually and all discrepancies resolved through discussion. The following information was extracted from selected studies: authors, publication year, experimental design, drug examined, sample size, altitude and PK parameters. The PK parameters were standardised to be in the same units and included: absorption rate constant (k_A), volume of distribution as a function of bioavailability (V_d/F), mean residence time (MRT), absorption ($t½_A$) and elimination ($t½$) half-lives, clearance as a function of bioavailability (CL/F), elimination rate constant (K), time to peak plasma concentration (T_{MAX}) and erythrocyte binding (C_E).

Statistical analysis

Statistical analyses were conducted using the Cochrane Review Manager software (RevMan Version 5.3.5 for Windows, Cochrane Collaboration, Oxford, UK, http://www.cc-ims.net/RevMan) to pool data for each of the PK parameters and associated variables. Continuous outcomes were presented as a standardized mean difference (SMD, Hedges *g*) along with 95% confidence intervals (CI). Effect sizes of <0.2, <0.5, <0.8 and >0.8 were considered trivial, small, moderate and large, respectively (Cohen 1992). Heterogeneity was evaluated using the Cochran χ^2-based Q and Higgins I^2 statistics that assess the appropriateness of pooling individual study results (Higgins and others 2003). Random-effects models (DerSimonian and Laird 1986) were

applied if heterogeneity was evident (χ^2 $P < 0.10/I^2 > 50\%$) otherwise fixed-effects models (Mantel and Haenszel 1959) were employed. Publication bias was assessed using a Funnel Plot in combination with Egger *et al*.'s test (Egger and others 1997). Power and sample size calculations were performed using G*Power (version 3.1.9.2). Significance was established at $P < 0.05$ for all two-tailed tests and data presented as mean ± SD unless otherwise stated.

Results

Study identification and characteristics

Applying the search terms, a total of 20,840 publications were identified, out of which ten were considered relevant after initial screening by title and abstract (Figure 2). After applying the inclusion and exclusion criteria, six full-text articles employing separate drugs were selected for meta-analysis (Table 1). The general properties of the six drugs are summarized in Table 2. These articles constituted non-randomized single-arm studies comprising a total of 75 healthy males of either Chinese or Chilean descent. Participants were 21 ± 3 years old and exposed to both LA (267 ± 301 m) and HA (4,025 ± 380 m) for 14.2 ± 1.7 h. There was no consistent evidence of systematic publication bias ($P > 0.05$).

Outcomes

The drugs appeared to be well tolerated since there were no serious adverse events reported. Figure 3 provides a summary of the mean changes (SMD) observed in each of the PK parameters documented at HA based on the individual studies (Supplementary Figures, S1a-S1j). We observed significant increases for $t½_A$ (SMD: 0.40, $P = 0.04$) and t½ (SMD: 0.89, $P = 0.003$) while the hybrid parameter CL/F showed a corresponding reduction (SMD: -0.56, $P = 0.05$). These were considered of potential physiological significance given the SMD "cut-off" of ≥ 0.50 standardized units as illustrated (Figure 3). In contrast, no changes ($P > 0.05$) were observed in the remaining parameters, notably k_A, T_{MAX}, Vd/F or K (latter SMD: -0.53). Similarly MRT while not significant, showed a marked tendency to be increased (SMD: 0.56, $P = 0.09$). Finally and as expected, significant increases in Hct (SMD: 1.02, $P = 0.01$) and C_E (SMD: 0.52, $P = 0.004$) were observed.

Statistical power and sample size

Post-hoc analyses revealed that studies were generally underpowered with no singular pharmacokinetic parameter achieving the (minimal) requisite power of 0.8 (Figure 4). Prospective calculations indicated that sample sizes needed to be in the order of ~2 to over 1,500 fold larger in order to be adequately powered to detect a treatment effect.

Discussion

This systematic review and meta-analysis has revealed important changes in PK parameters that define the absorption and disposition of an albeit limited selection of medicinal drugs displaying diverse physico-chemical and PK properties that may be indicative of a broader impact of the HA environment upon the body's handling of pharmaceuticals. First, by pooling relevant studies and improving statistical power, our analysis extends original works described in a published review (Hui and others 2016) highlighting impairments in both the oral absorption and corresponding clearance of drugs that from a clinical perspective, encourage the need for closer patient monitoring and dose adjustments in order to maintain therapeutic efficacy and avoid incidental toxicity. Second, prospective calculations have helped inform the design of future trials highlighting the need for considerably larger sample sizes to more rigorously address PK changes and ultimately define safer, more effective pharmacological interventions at HA.

The overall outcomes of our analysis highlighted a significant prolongation in $t^1/_{2A}$ at HA. This change in rate is not necessarily underpinned by any change in the extent of absorption [bioavailability (F)], a parameter not reported in any of the primary studies forming this meta-analysis. Our analysis would suggest that the data for sulfamethoxazole, meperidine and lithium made the greatest contribution to the overall absorption outcomes of our study. These drugs possess different biopharmaceutical characteristics in respect to the Biopharmaceutics Classification System (BCS) for orally administered drugs (Kasim and others 2004). Sulfamethoxazole is a Class IV drug (low permeability and low solubility) whereas meperidine and lithium (WHO 2005) are Class I drugs (high permeability and high solubility). The other drugs in the analysis being: acetazolamide (Class IV), furosemide (Class IV) and prednisolone (Class I). However, there is little that can be concluded from such biopharmaceutical characteristics in terms of a unifying mechanism to support a slower absorption rate at HA and the BCS system itself does not provide a definitive measure of in-vivo absorption outcomes.

Acute exposure to HA is often associated with gastrointestinal complaints attributed to delayed gastric emptying, although more severe hypoxemia associated with higher elevations (>5000 m) is typically required before nutrient malabsorption becomes apparent (Bailey and others 2004; Bailey and others 2001; Bailey and others 2000). The absorption of Class IV drugs such as sulfamethoxazole are generally not affected by gastric emptying but by other complex and variable issues acting on the drug formulation within the gastro-intestinal tract. Further, the meperidine data in this analysis was represented as a drug delivered via the intra-muscular route. Changes in hemodynamics at the absorption site (intestinal or intra-muscular) could be responsible for slowed drug absorption as indicated by one study that reported a reduction in superior mesenteric blood flow both before and following a standard meal in response to acute exposure (2h) to hypobaric hypoxia equivalent to a simulated altitude of 4,800 m (Loshbaugh and others 2006). Similarly, subtle effects of a hypobaric hypoxic environment upon local capillary pressures and epithelial-luminal biochemistry including membrane carriers, metabolism and local intestinal secretions that influence pH could be highly relevant to the drug absorption process.

We observed a consistent increase in C_E that has traditionally been attributed to an increase in Hct and/or total protein including albumin assuming C_E includes all sources of binding in blood (Hui and others 2016). In the current study, we specifically chose to focus our attention on acute HA exposure (< 24 h) and thus confident that the increase in C_E was unrelated to any increase in erythrocyte mass given the 2-3 day time-lag between erythropoiesis and *de novo* appearance of reticulocytes in the circulation. Thus, the increased Hct observed likely reflects an apparent hemoconcentration subsequent to hyperventilation/diuresis-induced plasma volume contraction, notwithstanding potential increases in capillary hydrostatic and interstitial osmotic pressures that collectively drive fluid from the intravascular to the extravascular space (Fall and others 2011).

The analysis revealed a consistent and significant trend for the CL/F parameter to be reduced at HA. The decrease in CL/F could reflect decreases in CL and/or increases in F. However increases

in F would not be consistent with a trend for a reduced rate of absorption and moreover the Vd/F parameter remained essentially unchanged indicating neither Vd or F to have changed significantly, or both parameters to have changed in a simultaneous and directly proportional manner, i.e. if F were to have increased then Vd would also need to have increased in direct proportion. In this context while acute HA exposure can be associated with fluid extravasation any such conductive fluid transfer would not in its own right change the effective estimate for Vd, when this estimate is based upon total drug plasma concentrations, which is indeed the case in the primary studies underpinning the analysis of this systematic review. As such we interpret the reduced CL/F to reflect a decrease in CL per se, entirely consistent with the prolonged t½ and indeed the trend for MRT to be prolonged in the studies, although it is important to note that the method of calculation of the MRT parameter was not explicitly defined in most of the primary works. The apparent discrepancy between t½ and K (the latter not significant), although trending towards an (expected) inverse relationship, is a likely consequence of the marked heterogeneity of the SMDs associated with each of the selected studies.

Previous observed or presumed decreases in drug CL at HA have more often than not been interpreted in the context of altered capacity for enzymatic metabolism, particularly diminished monooxygenase activity of CYP-450 for which O_2 is a substrate (Fradette and Du Souich 2004). However, a drug's CL (i.e. one based on measurement of total protein-bound and free drug levels) may also be impacted by changes in drug plasma protein binding. This is particularly the case for those drugs displaying medium to low extraction efficiencies across an organ(s) of elimination where a change in the fraction of unbound drug in plasma (Fu) may deliver concordant change in a drug's total (bound and unbound) plasma CL. In the context of the current molecules and with respect to metabolism-mediated elimination, any potential HA-induced changes in Fu could possibly impact upon the CL of prednisolone and sulfamethoxazole, as examples of medium to low extraction drugs. However, the CL/F of prednisolone, a drug recognized to display

concentration-dependent changes in Fu (Al-Habet and Rogers 1980; Frey and others 1986), did not change at HA in the primary study (Arancibia and others 2005). A number of drugs in the present analysis have limited or no metabolic elimination but rather substantial renal excretion (acetazolamide, furosemide and lithium) but nevertheless displayed in the primary studies significantly reduced CL/F with HA exposure. Collectively, this raises the potential role of altered hemodynamics in HA-induced changes in CL either through direct or indirect mechanisms. The extent by which HA alters renal hemodynamics remains equivocal (Goldfarb-Rumyantzev and Alper 2014) despite some evidence for a reduction in glomerular filtration rate at comparable elevations (Pichler and others 2008). Collectively, our findings are broadly consistent with those reported in the animal/in-vitro literature with the reduction in drug clearance classically attributed to hypoxia though the additional impact of other environmental stressors typically encountered at HA such as exercise and cold (highlighted in Figure 1A) warrant investigation (Bailey 2017).

However, these findings contrast with those reported during more controlled laboratory-based exposures to normobaric hypoxia. In one of the most rigorous trials conducted to date, 2 h passive exposure to a simulated altitude of 4,500 m failed to alter hepatic blood flow and corresponding metabolism of theophylline (low hepatic extraction ratio metabolized mainly by CYP1A2) and verapamil (high hepatic extraction ratio metabolized mainly by CYP3A4), arguing against the need for dose adjustment (Streit and others 2005). Differences between normobaric versus hypobaric hypoxia (Millet and others 2012) notwithstanding the contributory impact of additional stimuli such as exercise, cold and psychological stress exclusive to terrestrial ascent (Bailey 2017; Peng and Cheung 2009; Peng and Cheung 2011) may contribute at least in part to these conflicting findings and clearly highlight the need for further research.

Limitations

It is important to recognize the limitations associated with the current meta-analysis. Our findings are restricted to participants of either Chilean or Chinese descent and thus the interpretive implications for other ethnic groups remains unclear, especially given established differences in the catalytic activities of CYP-450 isoforms (Yang and others 2012). Furthermore and subject to inclusion/exclusion criteria, our analysis was confined to a limited selection of compounds that exhibit diverse clearance pathways and thus it is unlikely that changes in active tubular ion exchange, oxidative metabolism, phase II pathways such as *N*-acetylation, sulfation, and glucuronidation or active tubular efflux can collectively be ascribed to a single "common mechanism" induced by HA. The situation is clearly more complex, further complicated by exposure to multiple stressors whose independent and combined impact on drug PK remain largely unknown. Equally, it may be considered pharmacologically unfounded to pool study data from such physiochemically diverse compounds, the fundamental basis of a meta-analysis, though we have adhered to stringent guidelines (Knobloch and others 2011; Walker and others 2008) including a description and evaluation of heterogeneity, to optimize the validity of our findings.

Conclusion

This analysis reveals impairments in both the oral absorption and corresponding clearance of an albeit limited sample of drugs that exhibit diverse clearance pathways that may potentially require modifications in dosage regimens to maintain efficacy or prevent toxicity especially for those with a narrow therapeutic index. Given that studies have traditionally been underpowered, characterized by a high degree of variability and relatively small effect sizes, larger scale randomized controlled trials in humans are encouraged to better define safer and more effective pharmacological interventions at HA including the experimental (laboratory-based) isolation of the independent and combined influences of the composite PK-modulating stressors (hypoxia, exercise, cold). Given

the prevalence of drug use at HA (Donegani and others 2016), it would seem reasonable to extend PK research to other commonly used drugs for prevention and treatment of HA illness including AMS, HAPE and HACE as recently highlighted (Nieto Estrada and others 2017), namely, steroids (budesonide, dexamethasone), bronchodilators (salmeterol, theophylline or aminophylline, montelukast), phosphodiesterase 5-inhibitors (tadalafil, sildenafil), calcium channel modulators (nifedipine, flunarizine), non-steroidal anti-inflammatories and other analgesics (aspirin, carbasalate, ibuprofen) . Furthermore, it would be equally important to include those drugs commonly prescribed to treat pre-existing cardiovascular, cerebrovascular, metabolic, endocrine and pulmonary diseases within a tourist population (antiplatelets, statins, β-blockers, nitrates, angiotensin-converting enzyme inhibitors, angiotensin II receptor antagonists).

Contributors

DMB contributed to the conception and design of the study. DMB and BSS contributed to the development of the search strategy. BSS conducted the systematic search. DMB and BSS completed the acquisition of data and performed the data analysis. MG provided specialist pharmacological input. All authors assisted with the interpretation. DMB wrote the first draft of the manuscript. All authors contributed to the drafting and revision of the final article. All authors approved the final submitted version of the manuscript.

Author Disclosure Statement

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