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Review

Prolonged infusion of sedatives and analgesics in adult intensive care patients: A systematic review of pharmacokinetic data reporting and quality of evidence

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ABSTRACT

Although pharmacokinetic (PK) data for prolonged sedative and analgesic agents in intensive care unit (ICU) has been described, the number of publications in this important area appear relatively few, and PK data presented is not comprehensive. Known pathophysiological changes in critically ill patients result in altered drug PK when compared with non-critically ill patients. ClinPK Statement was recently developed to promote consistent reporting in PK studies, however, its applicability to ICU specific PK studies is unclear. In this systematic review, we assessed the overall ClinPK Statement compliance rate, determined the factors affecting compliance rate, graded the level of PK evidence and assessed the applicability of the ClinPK Statement to future ICU PK studies. Of the 33 included studies (n = 2016), 22 (67%) were low evidence quality descriptive studies (Level 4). Included studies had a median compliance rate of 80% (IQR 66% to 86%) against the ClinPK Statement. Overall pooled compliance rate (78%, 95% CI 73% to 83%) was stable across time (P = 0.38), with higher compliance rates found in studies fitting three compartments models (88%, P < 0.01), two compartments models (83%, P < 0.01) and one compartment models (77%, P = 0.17) than studies fitting noncompartmental or unspecified models (69%) (P < 0.01). Data unique to the interpretation of PK data in critically ill patients, such as illness severity (48%), organ dysfunction (36%) and renal replacement therapy use (32%), were infrequently reported. Discrepancy between the general compliance rate with ClinPK Statement and the under-reporting of ICU specific parameters suggests that the applicability of the ClinPK Statement to ICU PK studies may be limited in its current form.

Contents

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1. Introduction

Administration of analgesic and sedative agents in the critically ill is either empirical, or titrated to the patient's target sedation scores [1]. However, under and over- sedation is common, occurring in up to 75% of all intensive care unit (ICU) cases requiring sedation for 24 h or more [2]. Non-optimal sedation leads to longer duration of ICU stay [3], increased risk of complications [3,4] and higher cost of care [5].

Overwhelmingly, in modern intensive care practice continuous infusion has become established as the predominant method of administration over bolus injection to achieve optimal plasma steady state in critical ill patients requiring prolonged sedation [6].

Critically ill patients have substantially altered pharmacokinetics (PK) and pharmacodynamics (PD) as a result of hemodynamic instability, medical interventions and impaired organ function [7–11]. The insufficient reporting of basic PK parameters, such as volume of distribution and total clearance in ICU patients given antibiotics has previously been highlighted [12]. Similarly, most sedatives and analgesics have pharmacological properties that are likely to be affected by the pathophysiological changes in critically ill patients [13–15]. The consequent variation in PK in critically ill patients has been described and contributes to substantial heterogeneity in drug handling in a range of therapeutic agents [7,8,16,17]. The systematic reporting of these factors is important for ICU studies to allow proper utilization of research results [8].

Recognition of the need for, and benefits of reporting guidelines for PK studies has been rising [12,18,19]. Reporting guidelines for population PK-PD studies are now available to enhance the readability, reproducibility and interpretation of advance drug-related concentration–time and effect models [18]. In particular, the ClinPK Statement [19], published in 2015, was developed to promote consistent reporting in PK studies. However, the applicability of ClinPK Statement to ICU specific PK studies is unclear as no independent external review of the checklist has been conducted to date.

Therefore, the purpose of this study was to assess the quality of data reporting, evidence available and the extent of applicability of the ClinPK Statement in sedatives and analgesics to gauge the translatability of studies to clinical practice in ICU. The objectives of this systematic review were to identify all relevant PK studies of analgesics and sedatives delivered by continuous or intermittent infusion for more than 24 h in adult critically ill patients to estimate the overall ClinPK Statement compliance rate and grade the level of PK evidence available. The secondary objectives were to determine the factors associated with overall ClinPK Statement compliance rate, and assess the reporting rates of ICU relevant clinical parameters to determine the applicability of the ClinPK Statement to future ICU PK studies.

2. Methods

This systematic review followed the reporting guidelines of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) [20] and the classification for the levels of evidence of PK studies [21]. The levels of evidence ranged from highest (Level 1: systematic review of PK-PD studies) to lowest (Level 5: expert opinion with explicit critical appraisal, or based on physiology, bench research or 'first principles') [21].

2.1. Search strategy

We searched for studies using Ovid MEDLINE (January 1946-October 2015) and Ovid EMBASE (1910-October 2015). We identified further studies from reviewing the reference lists of retrieved studies and performing a search on Institute of Scientific Information Web of Science (January 1900-October 2015). With the assistance of a medical librarian, the first author used the MESH terms and text words for MEDLINE and other headings appropriate in other databases, such as 'Pharmacokinetics', 'Adult', 'Intensive care' and 'Sedation' (Appendix A). Extended searches were conducted after a further refinement of the search strategy, with assistance from a medical librarian, in December 2016 (Appendix B). The results of the electronic searches were saved in EndNote software and exported to Rayyan application (rayyan.qcri.org/) for further screening. We restricted our inclusion criteria to studies published in English, Chinese (Simplified and Traditional) and German. To ensure that we had not missed any studies, we compared our search results to the references cited in a review paper [22].

2.2. Criteria for considering studies

Studies of adults in the intensive care unit receiving sedation with midazolam, lorazepam, propofol, dexmedetomidine, sufentanil, alfentanil, remifentanil, fentanyl or morphine infusion for greater than 24 h that reported PK parameters were included. We arbitrarily chose 24 h as the threshold for prolonged sedation/analgesia as this excludes short term sedation for interventional procedures, and was often listed as an inclusion criterion in the studies [23,24]. We excluded conference abstracts and PK