Clinical Sedation Scores as Indicators of Sedative and Analgesic Drug Exposure in Intensive Care Unit Patients

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ABSTRACT

Background: It is unclear how best to measure sedative/analgesic drug exposure in the clinical care of critically ill patients. Large doses and prolonged use of sedatives and analgesics in the intensive care unit (ICU) may lead to oversedation and adverse effects, including delirium and long-term cognitive impairment. These issues are of particular concern in elderly patients (aged ≥65 years), who account for at least half of all ICU admissions and nearly two thirds of ICU days.

Objective: This pilot study explored the relationships between clinical sedation scores, sedative/analgesic drug doses, and plasma drug concentrations in critically ill patients, the majority of whom were elderly.

Methods: This was a prospective, observational study conducted in a 500-bed, tertiary care community hospital. Study patients included a cohort of mechanically ventilated, medical ICU patients who were admitted to the hospital between April and June 2004 who required use of fentanyl, lorazepam, or propofol. Sedative/analgesic medications were administered according to clinical guidelines. Patients' sedation levels were measured twice daily using the Richmond Agitation-Sedation Scale (RASS). Dosing of fentanyl, lorazepam, and propofol was recorded. Blood was sampled twice daily for up to 5 days to analyze plasma drug concentrations. To specifically evaluate the effects of acute, extended (rather than chronic) sedative and analgesic exposure, the study focused on an ICU population receiving these agents for at least 48 hours but <2 weeks.

Results: Eighteen medical ICU patients (11 females, 7 males; mean [SD] age, 66.1 [18.1] years) on mechanical ventilation comprised the study cohort. Fifteen patients were aged >62 years, and 11 of those were aged ≥71 years. Plasma drug concentrations (median and interquartile range) were as follows: fentanyl—2.1 ng/mL, 0.9–3.4 ng/mL; lorazepam—266 ng/mL, 112–412 ng/mL; and propofol—845 ng/mL, 334–1342 ng/mL. Maximum concentrations were 3- to 12-fold higher than medians (fentanyl, 7.3 ng/mL; lorazepam, 3108 ng/mL; propofol, 10,000 ng/mL). Medication doses were only moderately correlated with RASS scores (Spearman ρ): fentanyl—$\rho = -0.39$, $P = 0.002$; lorazepam—$\rho = -0.28$, $P = 0.001$; and propofol—$\rho = -0.46$, $P < 0.001$. Plasma drug concentrations of fentanyl and lorazepam demonstrated moderate correlations with sedation scores (fentanyl—$\rho = -0.46$, $P = 0.002$; lorazepam: $\rho = -0.49$, $P < 0.001$), while propofol concentrations correlated poorly with sedation scores ($\rho = -0.18$, $P = 0.07$). Associations between interval drug doses and plasma concentrations were as follows: fentanyl, $\rho = 0.84$; lorazepam,

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ρ = 0.76; and propofol, ρ = 0.61 (all, $P < 0.001$). Instructive examples of discrepant dose versus plasma concentration profiles and drug interactions are provided, including 3 cases with patients aged ≥64 years.

Conclusions: Elderly patients are commonly encountered in the ICU setting. Only moderate correlations existed between clinical sedation levels and dose or plasma concentration of sedative/analgesic medications in this study population. Further work is needed to understand appropriate and feasible measures of exposure to sedatives/analgesics relating to clinical outcomes. (*Am J Geriatr Pharmacother.* 2007;5:218–231)

Key words: intensive/critical care, mechanical ventilation, delirium, aging/elderly care, sedatives, analgesics.

INTRODUCTION

Elderly patients aged ≥65 years account for at least half of all intensive care unit (ICU) admissions and nearly two thirds of ICU days.[1,2] The quantity and dosing intervals of sedative and analgesic medications used in the ICU are often empiric and rudimentary, and it is common to find both young and old patients receiving similar dosing regimens to ensure comfort via a drug-induced coma.[3] It is clear that large doses and prolonged use of sedatives and analgesics frequently result in oversedation, which may be reduced (but usually not eliminated) through protocols using clinical sedation scores.[3–6] However, it is not known if these sedation scores adequately inform the managing team about individual patients' drug exposures. Knowledge of drug exposure is important because of its relationship with oversedation and accompanying acute adverse effects (such as delirium). Furthermore, sedatives and analgesics may be a modifiable source of the recently recognized long-term cognitive impairment (to which the geriatric population appears particularly susceptible) that persists for months to years in up to 60% of patients after an ICU stay.[7–12] Whether drug exposure itself or an associated pharmacodynamic response of protracted sedation could be responsible for such outcomes remains uncertain.

Past investigations of relationships between sedatives and analgesics and clinical outcomes in ICU patients have most often used drug dose to estimate medication exposure.[13–16] Pandharipande et al,[17] for example, recently described the temporal association of lorazepam dose as an independent risk factor (odds ratio, 1.2; $P = 0.03$ per unit dose) for developing delirium in a group of 198 mechanically ventilated patients. In the same cohort, statistically significant (or trending toward significant) associations between sedative/analgesic drug doses and observed sedation levels were found (ρ = −0.13 to −0.32; $P < 0.01$ to 0.10), but correlations were low, disparate between drugs, and difficult to use practically.[18] These observations are explained, in part, by the presence of marked interindividual variability when drug dose is considered as a lone predictor of drug response.

In contrast, drug plasma concentration, as determined by modulation of drug disposition (pharmacokinetics) through intrinsic drug properties—as well as metabolic, genetic, environmental, drug interaction, and disease factors—frequently exhibits a good relationship with drug response (pharmacodynamics) in the non-ICU setting. Studies involving short-term infusions of lorazepam, morphine, and propofol in healthy volunteers or surgical patients have demonstrated good correlations between plasma concentrations and sedation levels.[19–21]

Conversely, for critically ill patients receiving drug infusions beyond 60 hours, limited data exist regarding clinical sedation scores as indicators of drug dose, plasma drug concentration, and effective drug exposure, particularly in the elderly.[22,23] Accordingly, this pilot study was undertaken to evaluate these relationships and assess sedation score as an easily obtainable metric of drug exposure in a cohort of mechanically ventilated, medical ICU patients from a tertiary care community hospital where fentanyl, lorazepam, and propofol were the standard sedative and analgesic medications. To specifically evaluate the effects of acute, extended (rather than chronic) sedative and analgesic exposure, the study focused on an ICU population receiving these agents for at least 48 hours but <2 weeks.

PATIENTS AND METHODS

Study Protocol

Enrollment criteria included any adult, mechanically ventilated patient admitted to the medical ICUs of the 500-bed Saint Thomas Hospital (Nashville, Tennessee) between April and June 2004 who required use of fentanyl, lorazepam, or propofol. Midazolam is not used for continuous sedation at this hospital. Predetermined study exclusion criteria were dependence on mechanical ventilation for >2 weeks and a decision to withdraw care or extubate before enrollment. To reflect existing ICU use patterns and better mimic the clinical conditions and population encountered by community-based practitioners, there were no age-specific study entry requirements. The institutional review boards of Saint Thomas Hospital and the study coordinating center, Vanderbilt