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A Novel Research Method for Determining Sedative Exposure in Critically Ill Patients

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Abstract

Background: While potent sedative and opioid drugs are some of the most commonly used medications to manage pain, anxiety, and discomfort in critically ill patients, conducting clinical trials where sedative and opioid medications are outcome variables within a longitudinal research design can be a methodological challenge.

Objectives: The purpose of this paper is to provide in detail a conceptual discussion of the concept and analysis of *sedative exposure*: A novel research analysis method for aggregating sedative and opioid medication doses from disparate drug classes commonly administered to critically ill patients, and used by our team in several clinical research studies.

Methods: Comparing the dose of each sedative and opioid administered to an individual patient (within a defined time interval) to all other patients in a research study receiving the same medications allows for ranking of dosages for each medication by quartiles. Rank values for all sedatives and opioids received can be summed to a single value resulting in a Sedation Intensity Score. In addition, a simple count of how many hours at least one dose of a sedative or opioid medication has been administered can determine sedation frequency.

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Ethical Conduct of Research:
The research analysis method described in this paper was developed during several research grants, which were carried out following standards of ethical research conduct and with IRB approval. The data presented in this paper are for illustrative purposes only and not actual data obtained from a research study.

Results: This method can allow for comparison of sedative exposure with medications from disparate drug classes and for analysis of estimates of change in medication use over time.

Discussion: This novel research analysis method can overcome the challenges and limitations of determining changes in sedative and opioid medication regimens in cohort and clinical trial study designs.

Keywords

critical care; opioids; sedation; sedation intensity score

Potent sedative and opioid drugs are some of the most commonly used medications to manage pain and anxiety in critically ill patients, as well as promote comfort with invasive therapies such as mechanical ventilation; therefore, it is not surprising that they are a focus in much research. However, conducting clinical trials where sedative and opioid medications are outcome variables within a longitudinal research design can be a methodological challenge. The amount of medications administered, including both sedatives and opioids, can vary from patient to patient in terms of provider medication orders (e.g., type of medications ordered and administration parameters), provider expectations of patient response and goals, provider experience, severity of patients' symptoms, or behavior and patient/family requests and expectations. It is often unclear which medications are being used to manage which patient symptom; for example, a continuous opioid infusion might be used to treat pain while simultaneously taking advantage of the opioid's sedation properties (i.e., calming effect). Sedative dosages can vary enormously as well within an individual patient related to physiological function, tolerance, anxiety levels over time, procedures performed, time of day, efficacy of medication, and patient/family expectations. Intensive care unit (ICU) nurses have reported that workloads, experience level, and attitudes towards sedation management influence how they administer sedatives (Guttormson, Chlan, Weinert, & Savik, 2010).

Sedatives and opioid medications from differing drug classes (e.g., opioids, benzodiazepines, general anesthetics, and antipsychotics) and multiple routes of administration (e.g., oral, intravenous [IV] continuous infusion, and IV intermittent infusion or bolus) create additional challenges to measuring the use of these medications in a clinical research study. Further, current clinical practice guidelines emphasize the management of pain, agitation, and delirium with a focus on the assessment of these signs and symptoms as well as concurrent administration of opioid/analgesic medications prior to the administration of sedatives (Barr et al., 2013). There is an increasing emphasis on achieving and maintaining comfort with multimodal analgesia with the goal to minimize and target use of sedatives (Vincent et al., 2016).

One of the significant challenges in performing longitudinal research in the ICU then is how to standardize analysis of the total amount of sedative and opioid medications across a range of drug classes that patients receive during routine care or clinical trials. This standardization is necessary to compare aggregate sedative and opioid doses for individuals or groups of ICU subjects. This is particularly important if medications are a primary study outcome or have the potential to affect other important outcome variables.

The purpose of this paper is to describe in detail the concept and analysis of *sedative exposure*: A novel research analysis method we developed for aggregating sedative and opioid medication doses from disparate drug classes commonly administered to critically ill, mechanically ventilated (MV) patients. We have used this research analysis method in several clinical research studies; therefore, this paper is a *conceptual* discussion of the method and will provide examples of its use. These examples are not a report of actual data from any specific research trial, but rather data selected to provide context and clarity for the analysis method.

Background

Our team of researchers has conducted several studies with MV ICU patients to test interventions with the aim to reduce patient anxiety and decrease the amount of sedative medications administered to patients; the ultimate goal is to optimize recovery and patient participation in care while decreasing potential complications (Chlan et al., 2017; Chlan et al., 2013; Chlan, Weinert, Skaar, & Tracy, 2010). One of the main justifications sedatives—and in some cases opioid medications (due to their sedating properties)—are used in this population is to reduce patient anxiety while receiving life-support treatments.

A common manner by which researchers compare opioid and sedative dosing amounts is to use morphine or lorazepam "equivalents." This method of converting doses within a drug class is inadequate with the addition of newer nonbenzodiazepine sedatives such as propofol (a general anesthetic) and dexmedetomidine (an alpha-2 agonist). These medications are from distinct pharmacologic classes and have specific pharmacodynamic properties that make assigning a dose equivalent problematic. Additionally, even aggregating doses within a single drug class using "dose equivalents" conversions is mathematically simple but, for reasons described below, is pharmacologically and clinically problematic. Examples of sedative and analgesic medications (and their classifications) discussed in this paper include morphine, fentanyl and hydromorphone (opioids), midazolam and lorazepam (benzodiazepines), propofol (general anesthetic), dexmedetomidine (alpha-2 agonist), and haloperidol (antipsychotic).

Benzodiazepine Dose Equivalency Studies

Most benzodiazepine dose equivalency studies were performed in healthy, nonICU patients with normal kidney and liver function that involved dose conversion of various oral benzodiazepines used to treat alcohol withdrawal symptoms. For example, one investigator compared the calming effects of diazepam to chlordiazepoxide and lorazepam (Sachdeva, Choudhary, & Chandra, 2015). While relevant to the care of patients with alcohol dependence and liver disease (thereby introducing the confounding factors of alcohol cross-tolerance and impaired drug metabolism), these medications are rarely used as sedatives for mechanically ventilated patients or are available only in oral form.

A study in ICU patients concluded that the sedation dose equivalence (potency) of IV lorazepam to midazolam was 1:2 (Barr, Zomorodi, Bertaccini, Shafer, & Geller, 2001). This study performed pharmacokinetic modeling using specialized infusion pumps, serum drug concentrations, and standardized sedation scores to estimate differences in drug clearance

and time to awakening after cessation of a continuous infusion. However, the study sample was small and narrowly defined: Only 24 subjects were studied and all were immediately postoperative from elective surgery; they had no liver or kidney disease or shock, no chronic alcohol or benzodiazepine use, and the drug infusion duration was short (mean of 25 hours). The authors also noted that the modeling was significantly affected for the first 24 hours by the effects of general anesthetics and IV opioids administered during the prior surgery. This study also highlights the importance of specifying which "effect" is to be measured when converting sedatives or opioid formulations, as they are not interchangeable. The potency of the drugs' "sedative" effect (i.e., lorazepam or midazolam drug serum concentration relative to a Ramsay sedation score level) was measured at 1:1.8, but the average infusion rate to achieve similar sedation levels was significantly different at 1:2.8 (Barr et al., 2001). Given that serum drug levels are not routinely measured in clinical practice, 1:2.8 is probably the more relevant ratio. However, benzodiazepines have other effects that might differ between specific drugs. For instance, the potency of the "amnestic" effect (recall of drawings) was 1:4—nearly twice that of the "sedative" effect.

Among research studies investigating benzodiazepine therapy in ICU patients, authors have used very different conversion factors. For instance, midazolam 1: lorazepam 7.4 in one study (Zaal et al., 2015) versus midazolam 1: lorazepam 3 in another (Cammarona, Pittet, Weitz, Schlobohm, & Marks, 1998). Tracing the historical citations for dose conversion tables used in ICU studies show that the conversion ratios were derived from subjects sometimes quite different from critically ill patients. For example, the benzodiazepine conversion ratios used in a 2014 paper (Dale et al., 2014) that described changes in sedation practice in a surgical ICU were derived from a 1992 paper (Wilson, Smedira, Fink, McDowell, & Luce, 1992) examining sedation practices after terminal extubation. In turn, the conversion ratios in the Wilson paper (1992) were derived, in part, from short-term studies of benzodiazepine effects on respiratory effort in healthy adults (Berggren, Eriksson, Mollenholt, & Sunzel, 1987) or the relative potency of benzodiazepines as premedications for endoscopy (Bianchi Porro, Barroni, Parente, & Lazzaroni, 1988).

One web-based clinical calculator, clincalc.com, (ClinCalc.com, n.d.) converts lorazepam to midazolam in a 1:2 ratio citing the Barr paper (Barr et al., 2001). However, the website has multiple cautionary statements indicating that most conversion ratios are based only on oral formulations, can vary as much as tenfold, do not account for tolerance, cross-tolerance, or drug accumulation and are not adjusted for age, organ function, and metabolism. Unlike opioids, the Food and Drug Administration does not require manufacturers to provide dose equivalents or relative potencies on benzodiazepine package inserts.

Opioid Dose Equivalency Studies

Conversion ratios for opioids may appear to be more evidence-based; however, they still have significant limitations. First, almost all studies examining the relative potencies of opioids refer only to their analgesic effects, such as studies examining changes in pain scores after single opioid doses given for acute surgical pain. There is much less research on opioid conversion ratios related to opioids' sedative or relief of dyspnea effects even though these are common reasons opioids are administered to MV patients. Second, in chronic

opioid dosing, there is evidence of nonequivalent bidirectionality (Pereira, Lawlor, Bigano, Dorgan, & Bruera, 2001). This means that a conversion ratio of, for instance, 1:2 used to switch from Opioid X to Opioid Y is not the equivalent to a 2:1 ratio when switching from Opioid Y to Opioid X. Conversion ratios for analgesia can also be dose-dependent; converting low chronic doses of Opioid X to Opioid Y may have a conversion ratio three times lower than switching to the same Opioid Y, but Opioid X is at a higher chronic dose (Patanwala, Duby, Waters, & Erstad, 2007). Third, almost all opioid conversion studies examined much lower doses than are used in MV patients where respiratory depression is often a beneficial effect rather than a feared adverse effect.

In summary, despite years of research, simple conversion ratios within drug classes cannot accurately characterize overall sedative burden in ICU patients with altered drug metabolism and who may develop tolerance quickly when high drug doses are administered to manage severe respiratory failure. In addition, some metabolic effects of the patient's underlying illness (e.g., liver failure, sepsis, central nervous system disease) may mimic or compound the administered drug effect making it difficult to define associations between drug dose and sedation level except in the least ill patients. ICU patients who frequently receive co-sedation with two or three opioid or sedative medications also complicate the situation. Throughout our research, we have come to think more about the concept of *total sedative exposure,* defined as a combination of both the *frequency* of sedative administration as well as the *intensity* of daily sedative regimens. It has become increasingly clear that simply using 'dose equivalency' concepts in order to quantify sedatives received is an inadequate approach.

Methods

Conceptual Approach

An alternative method of evaluating the receipt of sedative and opioid medications for ICU patients is needed. One method that avoids the conversion ratio and disparate drug class problem is to rank subjects within a clinical sample (Weinert & Calvin, 2007). Ranking permits aggregation of sedative medications from disparate drug classes that will never have conversion ratios, for instance, propofol and opioids or dexmedetomidine and benzodiazepines. Since the predominant assessment scale used to titrate sedatives (i.e., the Richmond Agitation-Sedation Scale [RASS], [Sessler et al., 2002]) measures levels of motor movement and arousability (level of consciousness measured mostly by eye opening), ICU care providers naturally develop a practice range constituting low, medium, or high doses for each benzodiazepine, propofol, opioid, or dexmedetomidine that is expected to achieve the desired sedation level. Ranges may be reinforced by dose limits in electronic order sets, where an out-of-the-usual dose might result in an electronic warning about excessive dosing. Although this has not been well studied, it is likely that intensivists, nurses, and pharmacists can identify which patients are receiving "a lot" of sedatives (e.g., multiple sedatives simultaneously or high doses of a single sedative) and which patients are receiving "not much" sedation (e.g., low dose of a single sedative).

Therefore, in clinical research comparing a patient's sedative dose (within a defined time interval such as a 4-hour time block or per day) against all other patients in the research

study receiving the same medication would rank subjects from those receiving very little to those receiving the highest doses. If a patient receives more than one sedative medication within the time interval, they are assigned a rank for each medication. To estimate total sedative exposure within the time interval, rank values for all drugs received are summed to a single value. We refer to this as the Sedation Intensity Score (SIS). If desired, the ranks within each time interval could be summed across an entire MV episode or ICU stay. It is important to understand that the intent of the SIS is to estimate sedative dose intensity received by the patient, not its observed sedative effects as used by other researchers (Shehabi et al., 2018).

For instance, within a sample of 200 MV patients a researcher wants to characterize the distribution of seven sedative and opioid medications: 160 subjects might have received propofol, 150 received fentanyl, 50 morphine, 25 hydromorphone, 75 dexmedetomidine, 50 midazolam, and 20 lorazepam. Starting with propofol, within a 4-hour time block where any dose of propofol was administered to any patient, the weight-adjusted propofol dose within each time block is ranked across all patients' 4-hour time blocks and then divided into quartiles. Doses in the highest quartile (e.g., 60 mcg/kg/minute) are assigned a rank score of 4, with scores of 3, 2, and 1 given to those in lower quartiles. There will be thousands of these ranked propofol doses because one patient receiving a continuous propofol infusion would have 6 ranked doses per day (and patients may be on propofol for several days); although, for a single 4-hour interval the propofol dose, ranking may vary from 1 to 4. The same dose calculation and rankings are completed for time intervals across the entire sample in which any of the seven medications were administered. Next, for an individual patient, within a single 4-hour time block, the drug ranking score for all drugs is summed creating the SIS. The lowest nonzero score for each 4-hour interval would be 1 (single drug given at the lowest quartile dose) the highest possible score would be 28 (all seven sedative doses given simultaneously and all at the highest quartile dose). Depending on the study aims or goals of the analysis, the SIS could be used in different ways. For example, daily changes in the SIS over an episode of respiratory failure would identify periods of high or low sedation drug intensity. If the researcher wished to characterize the total sedative burden received by each patient to correlate sedation exposure with postextubation recovery or amnesia for the ICU stay, then the SIS for all time blocks during intubation for each patient would be summed. If the study design was a randomized trial of music listening by MV patients, then a reduction in the SIS over the duration of mechanical ventilation would demonstrate the benefits of music listening in reducing overall sedative administration (Chlan et al., 2013).

Calculating the Sedation Intensity Score

Calculating aggregate amounts.—The sedation intensity score aggregates administration frequency and dose (usually mg or mcg/kg/minute) of medications from disparate drug classes over a 24-hour day. The first step is to calculate sedation doses given in distinct time intervals for all sedative/opioid medications received by a cohort of subjects each 24-hour day. Researchers can determine the medications they define as "sedatives." Some might include IV antipsychotic medications such as haloperidol, others might include enteral benzodiazepines or opioids, but others might exclude enteral medications. In the

examples provided below, we included eight IV medications: morphine, fentanyl, midazolam, lorazepam, propofol, hydromorphone, haloperidol, and dexmedetomidine.

Each 24-hour timeframe is divided into six, 4-hour time blocks. Total doses given by bolus of any of the eight medications are summed for each 4-hour block. The same time blocks are used for continuous infusions where the hourly infusion rate is summed for the 4-hour timeframe for those infusions that had a consistent infusion rate over the 4 hours. Medications are treated similarly regardless of whether or not they are dosed by weight-based calculations (See Table 1). For instance, a morphine infusion administered at 2 mg/ hour would be summed to a value of "8" for that particular 4-hour timeframe. Fentanyl boluses doses of 50 mcg and 25 mcg would be summed to "75" for the 4-hour time block. An infusion of propofol at 25 mcg/kg/ min would be summed to equal a value of "100" for that same specific 4-hour time block. Summing of actual hourly calculations is important rather than taking a 4-hour total and dividing by four in order to treat infusion values consistent with bolus dose values.

If the infusion dose is titrated during the 4-hour time block, the mean from all documented doses is calculated for each hour (See Table 2). Then, all four 1-hour means are summed for the value for the entire four hours. For benzodiazepine and opioid medications, bolus doses and continuous infusion values are summed for an overall total dose for the 4-hour time block.

Determination of quartile ranks.—Next, the medication doses by 4-hour blocks are divided by the weight of the patient when they entered the study to create a dose/kg measure. These 4-hour time blocks are then summed over the 24-hour period to obtain a daily total dose/kg value. Aggregate doses of all possible 8 IV medications are summarized individually over all patients and 4-hour time blocks in the research study and descriptive statistics are utilized to determine the quartile cut points over all measures of each medication. (See Tables 3a and 3b). These quartiles are used to assign a relative dosing "rank" for each medication by each 4-hour time block: 0 = no drug, 1 = bottom quartile, 2 = second quartile, 3 = third quartile, and 4 = fourth quartile. These relative ranking scores are summed for the day over the six 4-hour blocks to produce a daily SIS for each patient. If a patient did not have data for all six of the 4-hour time blocks on the last day of the study, the sum for that day is adjusted to estimate the full day (e.g., if the patient had sedation data for four of the time blocks, the sum was adjusted by 6/4 to an equivalent of a full day's score.

Calculating Sedation Frequency

Another method that eliminates tedious abstraction of weight-adjusted drug doses is the sedative dose frequency (SF) method. A simple count of how many hours within a 24-hour period at least one dose of a sedative medication administration is abstracted (See Table 4). The maximum frequency count would be 1/medication/hour. For instance, a continuous infusion of propofol would be one dose per hour; a bolus dose of 2 mg of hydromorphone given every hour would be the same. A patient getting both medications simultaneously would have an hourly sedation frequency count of 2. Over a 24-hour day with every hour having an SF count of 2, this patient would have a *daily* sedation frequency of 48. A patient

receiving a low rate of a continuous infusion for only 30 minutes within a 1-hour interval or receiving both a continuous infusion at a high rate, plus two bolus doses within the same hour are considered equivalent in this SF method. The same patient who received propofol for only 12 hours and four doses of hydromorphone would have a daily sedation frequency count of 16. A subject receiving 18 hours of dexmedetomidine, two doses of midazolam, and three doses of fentanyl would have a daily score of 23. A subject receiving no sedatives would have a score of 0.

Data Analysis with Sedation Intensity Scores

Sedative exposure is a conceptual term. SIS and SF are not combined, but analyzed separately using the appropriate analytic methods (e.g., parametric or nonparametric methods). Mixed models can be used for longitudinal data that are nonnormally distributed and where some datapoints may be missing and research participants exit the study at differing timepoints.

Our research measuring the outcomes of an intervention using longitudinal research designs required that we analyze for changes in sedative exposure over time. Therefore, we have used a mixed-models analysis, which accommodates for nonhomogenous variances and correlation of values that arise from repeated measures. Analyses from these models result in an estimation of the slope that is the estimation of the change in SI and SF over time. Using this method of analysis results in estimates of change in medication administered over time while accounting for varying study exit points by patients. It also results in a lower type I error and higher power than imputation methods used for missing data (Chakraboty & Gu, 2009).

Discussion

It is well known that the amount and frequency of sedative and analgesia medication use in MV ICU patients can vary widely in practice for a plethora of reasons, both known and unknown: The intended purpose of the medication, patient condition and acuity, patient response to medications, physician and nurse medication familiarity and preference, provider beliefs about level of required sedation and pain control, and environmental conditions (Guttormson et al., 2010). These clinical practice variations present specific challenges in clinical research studies, particularly in research where interventions are being assessed for their effect on patients' sedative and pain levels and medication usage. Additional limitations arise when assessing the use of these medications in research, such as medications falling into disparate medication classes with no or inadequate equivalencies between medications; potential for wide variations in the numbers, dosages, and frequencies of sedatives and analgesics administered to patients in clinical research studies (as in clinical practice), particularly in multisite trials; and even the weight that is used for each individual patient to determine dosing (i.e., ideal body weight vs. actual weight).

Our research team has developed a novel research analysis method to overcome the limitations of aggregating sedative and opioid medication dosing in cohort and clinical trial study designs. The advantages of the sedative exposure concept (utilizing SIS and SF) for use in research study analysis are that it is relatively easy to calculate, can aggregate

sedation drug intensity across disparate nonequivalent drug classes, and avoids conversion ratios—which are imprecise at best—and unusable with medications in unique drug classes. It also has the desirable statistical property of using ranked quartiles, which minimizes the effect of skewed distributions and extreme outliers observed in most ICU sedation studies. A limitation is that it treats quartile rankings as equivalent across drug classes. For example, a patient receiving midazolam at the 2nd quartile rate (SIS = 2) is considered equivalent to a patient receiving the lowest quartile dose of both propofol and fentanyl. In addition, since the method ranks doses within a defined cohort, it cannot be used to compare actual drug amounts from other research studies. However, patterns of sedation intensity over time or identification of risk factors for receiving high intensity or low intensity sedative therapy would be comparable across different studies.

Conclusion

Challenges to quantifying sedative exposure will only increase with time with the likelihood of new sedative and analgesic medications from potentially unique drug classes being developed and administered to patients. With the growing emphasis on improving the quality of life of critically ill patients, both in the ICU environment as well as long-term outcomes, there is increasing scrutiny on balancing the benefits and risks of sedative and opioid administration. It is important that researchers continue to develop methods to better ‘quantify’ sedative exposure for the critically ill population. This paper has described two approaches (sedative intensity and sedative frequency) to determine global sedative exposure for selected IV sedative and opioid medications.

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Table 1

Summing Multiple Medication Doses over a 4-Hour Block

	1200–1300	1300–1400	1400–1500	1500–1600	Summed 4 hour block Sedation Intensity by medication	Total 4 hour block Medication Dose
Propofol Infusion (mcg/kg/min)	25	25	25	25	100	175
Fentanyl Boluses (mcg)	50			25	75	

Table 2

Example of a Dose Rate Calculation within a 4-Hour Block with a Titrated Medication Infusion

	1200	**1215**	**1230**	**1245**	**1300**	**1315**	**1330**	**1345**	**1400**	**1415**	**1430**	**1445**	**1500**	**1515**	**1530**	**1545**
Propofol Infusion (mcg/kg/min)	12	14	30	32	32	32	32	32	33	35	40	36	40	40	40	48
	1200–1300				1300–1400				1400–1500				1500–1600			
	Mean: 12 + 14+ 30 + 32 /4 = 22				32				Mean: 33 + 35 + 40 + 36 /4 = 36				Mean: 40 + 40 + 40 + 48 /4= 42			

*Note.*Total 4-hour block sedation intensity: 22 + 32 + 36 + 42 = 132.

Table 3a

Example of Determining Sedation Intensity Score by Quartile Rank for Fentanyl

Fentanyl Quartiles	Sedation Intensity Score
0 medication given	0
≤ 1.96 mcg/kg	1
>1.96 mcg/kg to ≤ 8.85 mcg/kg	2
> 8.85 mcg/kg to ≤ 21.85 mcg/kg	3
>21.85 mcg/kg	4

Table 3b

Individual Patient – Quartile Rank by Medication for a 24-hour Period

	00 – 0400	0400–0800	0800–1200	1200–1600	1600–2000	2000–2400	Summed Quartile Ranks	Daily Sedation Intensity Score
Fentanyl	3	3	2	2	2	2	14	30
Propofol	2	2	3	4	3	2	16	

Table 4

Example of Sedation Frequency Calculation

	1200–1300	1300–1400	1400–1500	1500–1600	Summed 4 hour block Sedation Frequency Score by medication	Total 4 hour block Sedation Frequency Score
Propofol Infusion (mcg/kg/min)	25	25	25	25	4	6
Fentanyl Boluses (mcg)	50			25, 25*	2	

**Note.* The maximum sedation frequency is 1/medication/hour.