Original Article

A novel factor influencing perioperative midazolam administration: The effect of presentation dose on administration dose

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Abstract

Background and Aims: Determinants of pharmaceutical unit presentations are not well understood and often appear indiscriminate. However, the dose administered may play a key role in the patient's anesthetic course. A recent change in a pharmaceutical vendor at our institution resulted in a change in midazolam presentation. In this study, we sought to determine whether the dose in which midazolam was dispensed to anesthesiologists was associated with the quantity of midazolam administered perioperatively.

Material and Methods: In this retrospective, observational study, we examined 310 adult patients who underwent general anesthesia at a single site, tertiary care, university hospital before and after a change in midazolam presentation from 2 mg to 3 mg. The primary outcome was the quantity of midazolam administered during the anesthetic. Additional clinical variables measured included patient age, weight, gender, and American Society of Anesthesiology (ASA) classification.

Results: The mean dose of midazolam administered to the 3 mg presentation cohort was 2.67 mg compared to 1.99 mg to the 2 mg presentation cohort (mean difference: 0.68 mg, 95% CI: 0.46–0.9 mg; *P* value <0.001). According to a logistic regression model, the odds of receiving a dose of 3 mg or greater in the 3 mg presentation cohort was 22 times greater than the odds of receiving such a dose in the 2 mg presentation cohort (OR: 22.3; 95% CI: 10.6–47.0; $P < 0.001$). This effect of presentation dose on administration dose was not observed in patients greater than or equal to 65 years of age.

Conclusions: Midazolam presentation dose influences the administration dose.

Keywords: Administration dose, dosage, midazolam, presentation dose

Introduction

Midazolam, a rapidly acting benzodiazepine, is one of the most commonly administered drugs to achieve preoperative anxiolysis.[1] Although midazolam is effective in alleviating preoperative anxiety, adverse effects may include excessive post-operative sedation, increased risk of post-operative respiratory depression and hypoxia,[2] and increased risk of cognitive impairment.[3] Multitudes of factors are associated with a patient's response to midazolam including the administration dose, age, and co-morbidities.[4] Given the variability in baseline anxiety and sensitivity to midazolam, the anesthesia provider must determine the proper dose of midazolam to maximize anxiolysis while minimizing adverse effects. Thus, understanding factors that contribute to midazolam administration doses may help anesthesia providers achieve this balance.

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Although one recommended midazolam dosing guideline for preoperative anxiolysis is 0.02–0.04 mg/kg,[5] anesthesia providers often administer less or more depending on their clinical judgment. In March 2013, our hospital system instituted a change in the outsourced compounding pharmacy providing midazolam. Because of this change, the presentation dose of midazolam changed from 2 mg to 3 mg per unit dose. We hypothesized that the change in the presentation dose of midazolam led to an increase in the administration dose. In this retrospective observational study, we examined the association between the presentation dose of midazolam and the administration dose to determine whether the manner in which midazolam was presented to anesthesia providers influenced their administration practices in the peri-operative period.

Material and Methods

After obtaining approval from our institutional review board (IRB #14-000142), we conducted a retrospective observational study designed to evaluate the association between the presentation dose of midazolam and the administration dose of midazolam. We defined the presentation dose as the dose of midazolam, in milligrams, dispensed to the anesthesia provider; additional midazolam could be given to the provider by dispensing an additional presentation dose. Administration dose was defined as the total dose of midazolam, in milligrams, administered to the patient from anesthesia start time to anesthesia end time as documented on the anesthesia record. Although midazolam administration dosing at our institution generally adheres to suggested guidelines,[5] there is no specific dosing protocol or maximum dosing limit, as some patients require higher doses depending on the severity of preoperative anxiety levels or tolerance from chronic benzodiazepine use.

Prior to March 2012, midazolam was dispensed to anesthesia providers in 2 mg vials. After March 2013, midazolam was dispensed to anesthesia providers in 3 mg pre-filled syringes. The change in presentation dose was a result of a change in the outsourced pharmacy supplying the drug and was implemented to facilitate the ease of administration and improve efficiency. The change was not related to any other policy changes in the main operating rooms.

To evaluate the association between presentation dose and administration dose, we compared the total dose of midazolam administered to patients undergoing general anesthesia at our institution before and after the presentation dose was changed from 2 mg vials to 3 mg pre-filled syringes. To reduce the possibility of confounding from the potential for anesthesia residents' dosing practices to change as a function of time throughout the academic year, we selected identical months for comparison. Specifically, we compared midazolam administration doses in August 2012, prior to the policy change, to administration doses in August 2013, after the change.

The study sample included 310 patients who underwent general anesthesia in our institution's main operating rooms in August 2012 and August 2013. Exclusion criteria included patients less than 18 years of age, those who either had a pre-operative regional anesthetic or underwent an awake intubation, as well as patients undergoing cardiac surgery. Patients receiving either a preoperative regional anesthetic or an awake intubation were excluded because midazolam was often administered to achieve sedation for the preoperative procedures as opposed to solely preoperative anxiolysis. Cardiac cases were excluded as midazolam was frequently administered intraoperatively during the case as a component of the anesthetic. Similarly, patients receiving midazolam as a co-induction agent were excluded. Patients who received no midazolam were also excluded. Of the 310 patients, 149 patients comprised the 2 mg presentation dose cohort and 161 patients comprised the 3 mg presentation dose cohort.

The primary outcome was the quantity of midazolam administered for preoperative anxiolysis. This was defined as the total midazolam dose administered from anesthesia start time until anesthesia stop time, excluding midazolam given for co-induction. These data were ascertained by reviewing the anesthetic record. Midazolam administration dose was treated as a continuous outcome variable in the primary analysis. In a secondary analysis, midazolam administration dose was treated as a binary outcome variable with a cut-point of 3 mg. The primary predictor variable was presentation dose, which was 2 mg of midazolam for all patients who underwent an anesthetic in 2012, and 3 mg of midazolam for all patients who underwent an anesthetic in 2013. Data were collected on additional clinical variables including patient weight, age, gender, and ASA classification. For patients who underwent multiple anesthetics within a cohort, only their first anesthetic was included in the analysis.

Statistics

Descriptive statistics for continuous variables were summarized as means ± standard deviations and as proportions for categorical variables. Linear and logistic regressions were used for the analysis of continuous and binary outcome data, respectively. To explore whether the effect of presentation dose on administration dose differed as a function of patient age, an age by administration dose interaction term was included in the regression model. A P value less than 0.05 was considered statistically significant. All statistical analyses were

performed using Stata software, version 15.0 (StataCorp)[6] with collaboration of our departmental statistician.

Results

The mean dose of midazolam administered in the 3 mg presentation cohort was 2.67 mg compared to 1.99 mg administered in the 2 mg presentation dose cohort. The increase in the mean dose of midazolam was statistically significantly (mean difference: 0.68 mg, 95% CI: 0.46 mg –0.9 mg; *P* value: <0.001). Table 1 displays the summary statistics for patient demographics including weight, age, gender, ASA classification, and presence of the emergency modifier for the ASA classification. With the exception of patient weight, there were no statistically significant differences between the 2 mg and 3 mg presentation dose cohorts. To adjust for possible confounding, weight was included as a predictor in the multivariable models. Table 2 displays the regression coefficients, 95% CI, and *P* values for univariate and multiple linear regression models. Of note, the inclusion of weight as a variable in the multiple regression model had no meaningful effect on the association between presentation dose and administration dose. In sensitivity analysis, including each of the other collected clinical variables in the regression models, did not qualitatively affect the results.

The data were also analyzed by treating the outcome as a binary variable with a cut-point of 3 mg. For the 2 mg presentation dose cohort, a midazolam dose greater than or equal to 3 mg was only administered to 6.0% of the patients. Comparatively, for the 3 mg presentation dose cohort, a midazolam dose greater than or equal to 3 mg was administered to 59.6% of the patients. According to a logistic regression model that included presentation dose and weight as predictors, the odds of receiving a dose of 3 mg or greater in the 3 mg presentation cohort was over 22 times greater than the odds of receiving such a dose in the 2 mg presentation dose cohort (OR: 22.3; 95% CI: 10.6–47.0; *P* value: <0.0001) [Table 3]. A histogram displaying the frequency distribution of administration doses in each presentation dose cohort is shown in Figure 1. The figure illustrates that the 3 mg presentation dose cohort more frequently received higher doses of midazolam compared to the 2 mg presentation dose cohort.

As age is a factor that affects both a patient's risk for anxiety and their responsiveness to benzodiazepines, we sought to determine whether the effect of presentation dose on administration dose differed as a function of the patient's age. Specifically, we hypothesized that for patients greater than or equal to 65 years of age, the association between presentation dose and administration dose would be weaker than that for patients less than 65 years of age. In a multivariable regression model that included presentation dose, age, weight, and an age by presentation dose interaction term, the interaction was statistically significant ($P = 0.007$), indicating that the

Table 1: Patient demographics

	All (*n*=310)	2 mg (*n*=149)	3 mg (*n*=161)	*P*
Age (years)	53.2±17.9	52.6±18.9	53.8±16.9	0.56
Weight (kg)	76.1±20.0 (*n*=307)*	73.6±18.2 (*n*=148)*	78.4±21.4 (*n*=159)*	0.037
Male gender (%)	143 (46.1%)	66 (44.3%)	77 (47.8%)	0.57
ASA classification				
1	31 (10%)	14 (9.4%)	17 (10.6%)	0.1
2	133 (42.9%)	67 (45.0%)	66 (41.0%)	
3	127 (41.0%)	64 (43.0%)	63 (39.1%)	
4	19 (5.1%)	4 (2.7%)	15 (9.3%)	
Emergency modifier for ASA classification	22 (7.1%)	10 (6.7%)	12 (7.5%)	0.83

Patient demographics are shown. Continuous variables are presented as mean±standard deviation. Categorical variables are presented as numbers (percentages). Demographics are provided for the entire sample as well as stratified by the dispensing dose cohort. P between the cohorts are provided. Comparisons for continuous variables were performed using independent samples t test. Comparisons for categorical variables were performed using Fisher's exact test. Weight was not available for 3 patients*

Table 2: Regression analysis models

Predictor	Model 1 (*n*=310)		Model 2 (*n*=307)*		Model 3 (*n*=307)*	
	Coefficient (CI)	*P*	Coefficient (CI)	*P*	Coefficient (CI)	*P*
Presentation	0.68 (0.46, 0.90)	<0.001	0.65 (0.43, 0.88)	<0.001	0.83 (0.57, 1.08)†	<0.001†
Age	N/A	N/A	N/A	N/A	−0.36 (−0.69,−0.04)†	0.03†
Weight	N/A	N/A	0.007	0.019	0.006	0.032
Pres* Age	N/A	N/A	N/A	N/A	−0.64 (−1.10, −0.18)	0.007

*Coefficient, P, and 95% confidence intervals for predictors in univariate and multivariable linear regression models. Pres*Age represents the presentation dose by age interaction. Model 1 is a linear regression model, which only includes presentation dose cohorts as a predictor. Model 2 is a linear regression model that includes presentation dose and weight as predictors. Model 3 is a linear regression model that includes presentation dose cohort, weight, and age (dichotomized at 65 years old) by presentation cohort interaction. *Models 2 and 3 have fewer subjects as weight was not available for 3 patients. †As Model 3 contains an interaction term, the interpretation of the age term in the multivariable model is the effect of age on administration dose for patients within the 2 mg presentation dose cohort. Similarly, the interpretation of the presentation dose predictor in Model 3 is the effect of presentation dose on administration dose among patients <65 years of age*

effect of presentation dose on administration dose differed as a function of the patient's age [Table 2]. Specifically, for patients who were less than 65 years of age, a higher presentation dose was associated with a higher administration dose (mean difference: 0.83; 95% CI: 0.57 – 1.08; *P* value: <0.001). However, for patients greater than 65 years of age, dispensing dose was not statistically significantly associated with administration dose (mean difference: 0.19; 95% CI: -0.20 – 0.57; *P* value = 0.34). To graphically appreciate the interaction, Figure 2 plots the mean administration doses within each of the four strata defined by combinations of age category and presentation dose cohort. The figure illustrates that while younger patients in the 3 mg presentation dose cohort received significantly higher midazolam doses than those in the 2 mg presentation dose cohort, the same was not observed with their older counterparts.

Discussion

In this retrospective observational study, we show that the manner in which midazolam is presented to anesthesia providers, influences the dose that is administered to patients. The change from a 2 mg presentation dose to a 3 mg presentation dose led anesthesia providers to administer higher doses to their patients. Although there are several known factors that weigh into a clinician's decision concerning the dose one administers, we are unaware of any studies specifically evaluating how the presentation dose of a drug affects its administration.

Although the nature of this study precludes a definitive determination as to the reason for the higher administration dose in the 3 mg presentation dose cohort, several plausible explanations may account for part of the effect. At our institution, anesthesia providers are responsible for returning unused drug to the pharmacy as midazolam is a controlled substance. When the administration dose equals the presentation dose, or a multiple thereof, the anesthesia provider does not need to return unused medication to the pharmacy, which thereby decreases time spent on documentation. A provider, therefore, may be encouraged to increase the amount of drug he or she would normally administer. Because midazolam is a controlled medication (Schedule IV in United States, Schedule III in United Kingdom, and Schedule IV under the United Nations Convention of Psychotropic Substances of 1971), our notion minimizing waste documentation is widely applicable.[7] There may also be a psychological element to the compulsion to administer the entirety of the presentation dose, similar to how a person will often finish the entirety of food put on one's plate even if they would not have consumed that much food if the meal were smaller. A study examining the effect of food portion size on the amount of food consumed found that larger portion sizes resulted in higher food consumption.[8] Finally, there are situations where a provider may be compelled to administer a lower dose of medication when there exists a

Table 3: Portion of patients who were administered ≥3 mg of midazolam within each presentation dose cohort

Administration dose	Presentation dose cohort	
	2 mg (*n*=149)	3 mg (*n*=161)
Dose ≥3 mg	9 (6.0%)	96 (59.6%)
Dose <3 mg	140 (94.0%)	65 (40.4%)

This table displays the number (percentage) of patients within each presentation dose cohort who were administered ≥3 mg of midazolam versus the number of patient who were administered <3 mg of midazolam

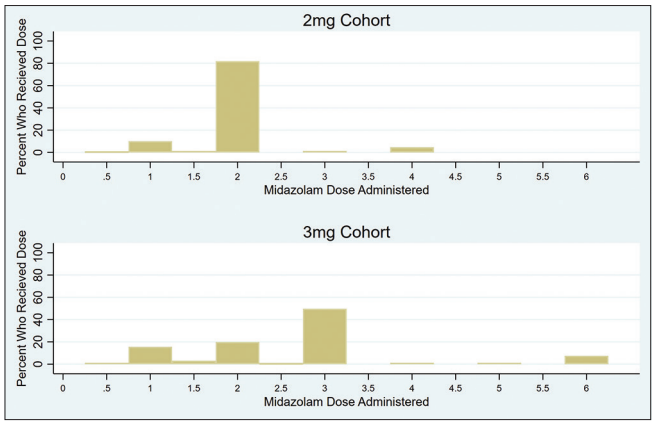

Figure 1: Histogram of administration doses. Source: Original. The histograms display the frequency distributions of administration doses of midazolam for each of the presentation dose cohorts. The figure illustrates that higher midazolam doses (primarily 3 mg and to a lesser extent 6 mg) were administered more frequently in the 3 mg cohort compared to the 2 mg cohort. Comparatively, the 2 mg cohort was more frequently administered 2 mg doses compared to the 3 mg cohort

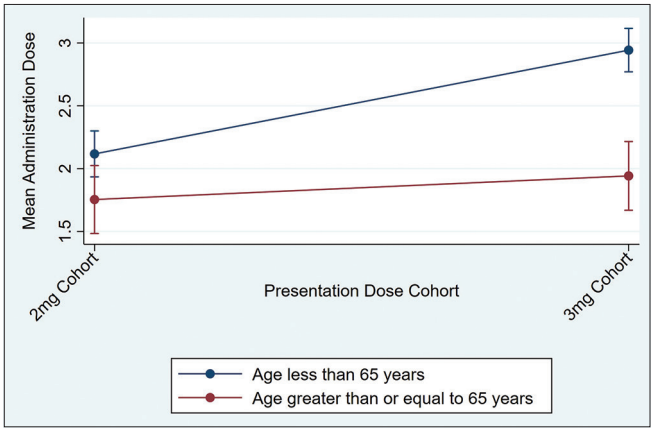

Figure 2: Interaction effect of presentation dose and age on administration dose. Source: Original. This figure illustrates the interaction effect between presentation dose and age. The mean midazolam administration doses for patients less than 65 years of age and those greater than or equal to 65 years of age are plotted for patients within each presentation dose cohort. For those greater than or equal to age 65 years, there is no statistically significant effect of presentation dose on administration dose (red line). However, for patients less than 65 years of age, those in the 3 mg presentation dose cohort were administered significantly higher midazolam doses than those in the 2 mg cohort (blue line). Error bars denote standard error

barrier to get additional medication. For example, a patient in the 2 mg presentation dose cohort may not have been given a dose higher than 2 mg because the clinician did not feel it was worth the effort to have an additional unit dose of the drug dispensed. Although the study was not designed to evaluate how such a phenomenon could either be exploited or counteracted for the benefit of patient care, one could envision how a healthcare system could benefit from these findings. If a healthcare system wishes to alter drug dosing, a change in the presentation dose has the possibility to influence physician administration behavior.

Although it may be disheartening that an anesthesia provider's dosing decisions can be manipulated by the dispensing dose, our results suggest that clinicians are not increasing their administration doses in all situations. We found that the effect of presentation dose on administration dose differed as a function of age, as evidenced by the significant interaction effect in the regression model. Specifically, we found that the association between presentation dose and administration dose was present for patients less than 65 years of age but was absent for those greater than 65 years of age. This suggests that while anesthesia providers are being influenced by the effect of the presentation dose, it is being tempered by the clinical characteristics of the patient. Although the effect of presentation dose on administration dose for those greater than 65 years of age was not statistically significant, given the study's power, the confidence interval for this estimate was wide enough such that we cannot exclude the possibility that there is a smaller effect.

As this is an observational study, there is always the potential that residual confounding can affect the association between the primary predictor and the outcome. Several of the covariates that were considered as possible confounders including age, gender, and ASA classification were not associated with the primary predictor, and in sensitivity analysis did not qualitatively affect the nature of the association. Because there was a small association between weight and presentation dose cohort, weight was included in the regression model to adjust for confounding. There may exist other variables that could confound the association, but because the decision to change the compounding pharmacy was unrelated to any other known policy changes, we did not expect the characteristics of the 2 mg and 3 mg presentation dose cohorts to be substantively different. Furthermore, the magnitude of the association is so large that it is unlikely that residual confounding could be responsible for the entirety of the observed effect.

Although this study was not powered to detect differences in adverse outcomes between the two dispensing dose cohorts, there were no reportable differences in major adverse outcomes such as reintubation or prolonged emergence from anesthesia. Given the retrospective nature of the study, however, we cannot exclude whether there were differences in minor adverse outcomes such as prolonged stay in the Post Anesthesia Care Unit or increased post-operative sedation between the two cohorts as such data were not recorded. The results strongly suggest, however, that when there is no definitive dosing protocol, a change in the presentation dose of midazolam influences administration behavior.

Although we were able to show the presence of this effect with respect to administration of midazolam in the peri-operative period, further studies examining whether changes in the presentation doses of other drugs can induce similar changes in the administration doses are warranted. Future studies that prospectively measure various post-operative outcome measures would be helpful in determining the effect of changes in administration behavior on clinically relevant outcomes. In addition, the findings of this study highlight the importance of choosing the dosage presentation of drugs for an anesthesia formulary.

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Conflicts of interest

There are no conflicts of interest.

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