Comparison of Duration of Mechanical Ventilation and Cost Associated with Midazolam and Lorazepam Infusions in Critically Ill Patients

Michael Tierney, Catherine Carter Snell, Pierre Cardinal and Alan Baxter

ABSTRACT

Guidelines were introduced to replace infusions of midazolam with lorazepam for sedation of ventilated ICU patients. We conducted a retrospective study to evaluate the effects of the guidelines. The groups were compared for baseline characteristics and outcome measures which included benzodiazepine dose, benzodiazepine cost and duration of ventilation. There were 90 patients who qualified for entry into the study: 51 received lorazepam and 39 received midazolam. Two patients in the lorazepam group were identified as "outliers" and were excluded. The two groups had similar baseline characteristics. The average lorazepam infusion dose was 1.1 ± 1.5 mg per hour of ventilation compared to 2.1 ± 4.5 mg per hour of ventilation for midazolam. The use of intermittent bolus doses of midazolam for acute sedation was similar in both groups. Benzodiazepine cost per hour of ventilation was $0.33 ± 0.34 for lorazepam versus $0.94 ± 1.9 for midazolam (p=0.14). There was no significant difference in the duration of mechanical ventilation between the two groups. Since implementation of these guidelines, reduced drug expenditures for these two drugs have resulted in cost savings for the hospital. Given our results and a review of the literature, we conclude that lorazepam infusions are a rational choice for sedation of ventilated, critically ill patients.

Key Words: *Cost Savings, Critical Care, Lorazepam, Midazolam*

RÉSUMÉ

On a implanté des lignes directrices sur la substitution des perfusions de midazolam par des perfusions de lorazépam pour la sédation des patients de l'USI sous ventilation artificielle. Nous avons mené une étude rétrospective des conséquences de ces lignes directrices. Les groupes étudiés ont été comparés en termes de caractéristiques initiales et d'indicateurs de résultats qui comprenaient la dose de benzodiazépine, le coût de la benzodiazépine et la durée de la ventilation artificielle. Parmi les 90 patients admissibles à l'étude, 51 ont reçu du lorazépam et 39 du midazolam. Deux patients du groupe lorazépam présentaient des valeurs aberrantes et ont été exclus de l'étude. Les deux groupes avaient des caractéristiques initiales semblables. La dose moyenne de lorazépam perfusé était de 1,1 ± 1,5 mg par heure de ventilation artificielle comparativement à 2,1 ± 4,5 mg pour le midazolam. Le recours à l'administration du midazolam en bolus intermittent pour la sédation immédiate était semblable entre les deux groupes. Le coût de la benzodiazépine par heure de ventilation artificielle était de 0,33 $ ± 0,34 pour le lorazépam, comparativement à 0,94 $ ± 1,9 pour le midazolam (p = 0,14). On n'a observé aucune différence significative dans la durée de la ventilation artificielle entre les deux groupes. Depuis l'implantation de ces lignes directrices, la diminution des dépenses d'achat relatives à ces deux benzodiazépines ont entraîné des réductions de coûts pour l'hôpital. En nous fondant sur ces résultats et l'examen de la documentation, nous concluons que les perfusions de lorazépam représentent un choix judicieux pour la sédation des patients gravement atteints mis sous ventilation artificielle.

Mots clés : *lorazépam, midazolam, soins intensifs, réductions de coûts*

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INTRODUCTION

Benodiazepines are routinely used in critically ill, ventilated patients. The primary indication for sedation of these patients is to facilitate mechanical ventilation by helping the patient tolerate the discomfort of the endotracheal tube and suctioning and preventing "fighting" against the ventilator.[1] Sedation also reduces anxiety and provides comfort to patients who are bedridden for prolonged periods of time, are subject to disruption of their sleep pattern, and receive many procedural and therapeutic interventions. An ideal sedative agent

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would have a rapid onset and short duration of action, be easy to administer, and be inexpensive.

There are three benzodiazepines which are approved in Canada for intravenous administration: diazepam, lorazepam, and midazolam. Although diazepam is inexpensive, administration by continuous infusion is complicated by its poor solubility and limited stability in polyvinyl chloride bags. In addition, diazepam and its major metabolite desmethyldiazepam have long elimination half-lives which may lead to cumulative sedative effects. Midazolam has become the most widely used sedative in ventilated patients[2] because it has a fast onset of action, a relatively short elimination half-life of two hours[3] and can be easily administered via infusion thus facilitating dose titration. Unfortunately, in critically ill patients the elimination half-life and sedative effects of midazolam can be prolonged[4,5,6] and it is relatively expensive; therefore, it may not be the ideal agent for this population.

There has been only one published study of the use of lorazepam for sedation of critically ill patients. Pohlman et al[7] reported a randomized comparison of midazolam and lorazepam infusions in medical intensive care unit patients receiving mechanical ventilation. They found no difference between the two agents in the time to return to baseline mental status following discontinuation of the benzodiazepine infusion. However, their small size of 20 patients and the large observed interindividual variation in results limit any conclusions regarding differences between the two agents. Published abstracts describing the use of lorazepam in critically ill patients have provided little additional information.[8,9,10]

Given the large cost differential between lorazepam and midazolam, we introduced clinical guidelines which promoted the use of lorazepam infusions in mechanically ventilated patients. The purpose of this study was to evaluate whether the implementation of these guidelines led to a change in the cost of sedation or duration of mechanical ventilation.

METHODS

Implementation Of Guidelines

In November 1993, clinical guidelines for the use of benzodiazepine sedation (Appendix) were introduced into our ICU, a 16-bed Medical-Surgical Unit. Prior to that time, midazolam infusions at an initial dose of 0.5 mg/h with titration to clinical effect by the bedside nurse, were standard practice. Patients also received intermittent bolus doses of midazolam for short procedures requiring conscious sedation or for rapid sedation of an acutely agitated patient. The guidelines promoted the use of lorazepam by continuous infusion as an equally effective yet less expensive alternative. Due to its faster onset of action, midazolam was still advocated for use by intermittent bolus. Throughout the study period, morphine was the primary narcotic used as an adjunctive analgesic. Morphine dosing was titrated at the discretion of the bedside nurse.

Lorazepam solutions were prepared at a concentration of 0.2 mg/mL in D5W by the ICU nurse just prior to initiation of the infusion and were given a 12-hour expiry time. The infusion was initiated at 1 mg/h and was titrated to the desired level of sedation by the bedside nurse. The maximum recommended dose was 6 mg/h. During weaning from the ventilator, the lorazepam infusion was progressively decreased to 0.25-0.5 mg/h and was discontinued when the patient was extubated.

Design

We conducted a retrospective study to evaluate the effects of implemented guidelines. During the period from August 1993 to August 1994 inclusive, patients who received midazolam or lorazepam infusions in the Intensive Care Unit (ICU) were identified. The decision to use a benzodiazepine infusion was made on clinical grounds by the physician caring for the patient. Patients who received infusions of both agents were excluded. Data were collected by chart review and from the ICU Clinical Database, a computer program which allows for the collection and analysis of selected clinical parameters on all patients admitted to the ICU.

Outcome Measures

Baseline characteristics collected include patient age, sex, duration of mechanical ventilation, ICU admission diagnosis, and APACHE II score. Outcome measures were midazolam and lorazepam infusion doses, midazolam intermittent injection doses, narcotic dosing (standardized as morphine equivalents using a table for conversion of narcotic doses to morphine doses[11] as morphine was the predominant narcotic used), and hours of mechanical ventilation. Benzodiazepine costs per group included both the infusion and bolus doses. Drug cost and dosages are expressed per hour of mechanical ventilation. Benzodiazepine acquisition cost was calculated for each patient using a cost of $0.21 per mg for lorazepam and $0.39 for midazolam.

Statistical Analysis

Data were analyzed using the SPSS® statistical program. Baseline characteristics were compared descriptively. Mean data for outcomes are presented as mean and 95% confidence intervals and were compared using the t-test for independent groups using a Type I error of 0.05. Patients who were ventilated for prolonged periods of time (outliers) were excluded from the analysis to mini-

mize skewing of the results. Outliers were defined based on a duration of mechanical ventilation which exceeded the mean plus two standard deviations as calculated using the data from all patients in the study.

RESULTS

Data were collected for patients who received benzodiazepine infusions from August 1993 to August 1994. During this time there were 106 patients who received benzodiazepine infusions: 51 received lorazepam only, 39 received midazolam only, and 16 received both. Patients who received both infusions were excluded from the analysis. Two patients in the lorazepam group were excluded as they were identified to be outliers with a duration of mechanical ventilation greater than two standard deviations from the mean. These two patients were ventilated for prolonged periods because of severe pulmonary dysfunction and not excessive sedation.

As depicted in Table I, the two groups were well matched for baseline characteristics. Table II presents the outcome measures for each group. Theaverage infusion dose was approximately twice as high in the midazolam group (p=0.04) presumably because of the greater potency of lorazepam. The use of intermittent bolus doses of midazolam was similar in both groups representing approximately 13% of the total midazolam dose in the midazolam group. There was no significant difference in the amount of narcotics received by patients in the two groups (p=0.35). There was no significant duration in the duration of ventilation between the two groups which averaged between six and seven days in both groups (p=0.77). Benzodiazepine costs in the lorazepam group were approximately one-third that of the midazolam group although this difference was not statistically significant (p=0.14).

Table I: Comparison Of Baseline Characteristics Of Patients

	Midazolam n=39	Lorazepam n=51
Age (years)*	56 ± 20	56 ± 19
Sex (% male)	61	75
APACHE II Score*	21.2 ± 7.1	21.9 ± 7.8
Duration of Ventilation (%)		
<24 hours	20	18
24-72 hours	20	33
>72 hours	60	49
Reason for Admission (%)		
Post-Operative	25	20
Trauma	15	16
Sepsis	7	10
Miscellaneous	53	54

*Mean ± SD

Table II: Comparison of Outcome Measures (Mean) in the Midazolam (n=39) and Lorazepam (n=49) Groups

	Midazolam Mean	95% CI	Lorazepam Mean	95% CI	p Value
Infusion Dose (mg/h)	2.1	0.71-3.53	1.1	0.66-1.50	0.04
Midazolam Bolus Doses (mg/h)	0.27	0.13-0.41	0.23	0.15-0.31	0.60
Morphine Equivalent Dose (mg/h)	2.48	0.65-4.37	1.65	1.07-2.23	0.35
Benzodiazepine Cost ($/h)	0.94	0.34-1.54	0.33	0.24-0.42	0.14
Duration of Ventilation (h)	148	93-203	159	112-206	0.77

DISCUSSION

The implementation of clinical guidelines promoting the use of lorazepam infusion for sedation in ventilated patients resulted in cost savings without a change in the duration of ventilation. Although we could not detect a statistically significant difference in benzodiazepine cost per hour of ventilation, using pharmacy inventory purchases for midazolam and lorazepam during the study period we found that implementation of the guidelines was associated with a reduction in annualized expenditures of $28,792. These results support our belief that lorazepam is a more cost effective agent than midazolam for sedation of critically ill patients.

Midazolam has become the preferred benzodiazepine for sedation of critically ill patients due to its fast onset of action and short elimination half-life after bolus injection. A short elimination half-life should translate into a relatively rapid reversal of sedation upon discontinuation of the drug. In mechanically ventilated patients, this should facilitate weaning from the ventilator. Despite the differences in published elimination half-lives between midazolam (two hours) and lorazepam (10-20 hours),[3] we found no difference in the duration of ventilation in the lorazepam and midazolam groups. Possible explanations for this include the following:

1. The difference in half-life between midazolam and lorazepam is too small to result in clinically significant differences in duration of action.
2. The half-life of midazolam in intensive care patients has been reported to be much longer than in healthy volunteers and is similar to lorazepam. In 17 intensive care patients, Oldendorf et al reported widely variable midazolam half-lives with only one patient having a half-life of less than two hours, while six patients had half-lives of greater than 10

hours.[4] The awakening time after termination of midazolam infusion was greater than 10 hours in 10 of 16 instances. This prolonged half-life of midazolam in critically ill patients may be due to reduced hepatic metabolism or to a larger volume of distribution.[5,6] Although the pharmacokinetics of lorazepam have not been characterized in critically ill patients, one might expect less variability as the main route of elimination of lorazepam is hepatic glucuronidation, a reaction which is well preserved in patient with significant liver disease.[3] Therefore, the elimination of midazolam may be similar to lorazepam in critically ill patients which would explain the lack of difference in duration of ventilation seen in our patients.

3. There is not a well established relationship between the half-life and duration of action of benzodiazepines.[3]
4. Our sample size may be inadequate to detect a clinically significant difference in duration of ventilation. Given the large variability in the duration of ventilation (as represented by the wide confidence intervals), future studies should either enroll large numbers of patients or patients should be selected or stratified according to anticipated duration on ventilation.

Our results are consistent with other recent reports on the use of lorazepam for sedation of critically ill patients. In the studies by Pohlman et al[7] and Krosner et al[8], patients in the lorazepam group required approximately half the dose of those in the midazolam group (4.1 vs 2.5 mg/h). Our findings combined with other reports[7-10] support the efficacy and safety of lorazepam compared to midazolam in critically ill patients.

Since the initiation of our study, there has been a study questioning the stability of lorazepam prepared for infusion.[12] Lorazepam 0.1 mg/mL in D5W in polyvinyl chloride bags is reported to be stable for eight hours but with significant loss of activity (16%) by 24 hours after admixture. We continue to use an expiry time of 12 hours as we believe that any lost drug is not significant given that the dose is titrated to a clinically measurable endpoint.

There are limitations to the interpretation of the results of our study. This was not a randomized, blinded, controlled trial but represents our experience with the implementation of clinical guidelines for sedation in ICU patients. The lack of randomization and blinding introduces the possibility of selection bias in including patients into this study. We did not measure patient comfort but doses were titrated to effect and all patients had bolus doses of intermittent midazolam prescribed. The fact that there was no difference in the use of midazolam boluses between the two groups supports our belief that patients in both groups were titrated to similar levels of sedation. Retrospectively, we reviewed the charts of patients in our study to determine if there were differences in the two groups in pre-admission use of benzodiazepines or ethanol abuse and the use of neuromuscular blocks during ICU admission. Although it is difficult to extract such data from a chart review, especially on the first two parameters, no obvious differences were found.

Our choice of lorazepam as the preferred benzodiazepine sedative was made on an understanding of the pharmacodynamic and pharmacokinetic characteristics and costs of the available parenteral benzodiazepines. We believe our selection of lorazepam is supported by the results of our study as well as those of others. A properly controlled randomized study is required to determine if one drug has clinical advantages over the other. In the absence of such data we believe that lorazepam infusion is a rational choice for sedation of ventilated ICU patients.

In conclusion, the development and implementation of clinical guidelines for benzodiazepine sedation in our ICU has resulted in no demonstrable change in patient care but has been associated with a reduction in benzodiazepine expenditures.

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Appendix: Benzodiazepine Sedation In The ICU

Goal of Sedation
The objective with the use of benzodiazepines is to titrate the dose such that the patient is calm and relaxed while still being either awake or lightly asleep (i.e., easily roused from sleep).

Initiation of Sedation
Sedation should be initiated with an IV bolus of benzodiazepine (diazepam, lorazepam, midazolam). The choice of agent depends on the desired onset of action. Midazolam has a rapid onset of action with adequate sedation achieved within 1-2 minutes. In single doses, they have similar duration of action although diazepam can accumulate with repeated doses. Lorazepam has an onset of action of 5-15 minutes and may not be suitable when rapid sedation is required. Doses are as follows:
Lorazepam - 1 to 3 mg at a rate not exceeding 2 mg/min;
Midazolam - 2 to 7 mg at a rate of 1 mg/min.
With all agents, the lower end of the dosing range should be used for elderly, debilitated and/or non-ventilated patients.

Maintenance of Sedation
IV infusions of lorazepem are used to maintain sedation. Initiate at 1-2 mg/h but occasional patients will require dose titration up to 6 mg/h. Once the patient is adequately sedated, the dose should be titrated down to the minimum required to achieve the desired level of sedation. When the patient is being weaned from the ventilator, the dose of lorazepam should be progressively weaned down to 0.25-0.5 mg/h. When the patient is extubated, the infusion may be stopped (if not already discontinued) and reversal of sedation will generally take 4-8 hours.

Adjunctive Agents
Midazolam may be used for sedation prior to short procedures requiring conscious sedation or for rapid sedation of an agitated patient. Midazolam infusions are rarely indicated, expensive and must be approved by the ICU attending.
Morphine is given by continuous IV infusion (supplemented with intermittent IV injections) to maintain adequate analgesia.
Haloperidol may be used to control agitation in patients not responding to maximum doses of lorazepam. The dose range is 0.5-10 mg q4-6h.