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A Double-blind, Randomized Comparison of IV Lorazepam versus *Midazolam for Sedation of ICU Patients* via *a Pharmacologic Model*

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Background: **Benzodiazepines, such as lorazepam and midazolam, are frequently administered to surgical intensive care unit (ICU) patients for postoperative sedation. To date, the pharmacology of lorazepam in critically ill patients has not been described. The aim of the current study was to characterize and compare the pharmacokinetics and pharmacodynamics of lorazepam and midazolam administered as continuous intravenous infusions for postoperative sedation of surgical ICU patients.**

Methods: **With Institutional Review Board approval, 24 consenting adult surgical patients were given either lorazepam or midazolam in a double-blind fashion (together with either intravenous fentanyl or epidural morphine for analgesia) through target-controlled intravenous infusions titrated to maintain a moderate level of sedation for 12–72 h postoperatively. Moderate sedation was defined as a Ramsay Sedation Scale score of 3 or 4. Sedation scores were measured, together with benzodiazepine plasma concentrations. Population pharmacokinetic and pharmacodynamic parameters were estimated using nonlinear mixed-effects modeling.**

Results: **A two-compartment model best described the pharmacokinetics of both lorazepam and midazolam. The pharmacodynamic model predicted depth of sedation for both midazolam and lorazepam with 76% accuracy. The estimated sedative potency of lorazepam was twice that of midazolam. The predicted $C_{50,ss}$ (plasma benzodiazepine concentrations where P(Sedation ≥ ss) = 50%) values for midazolam (sedation score [SS] ≥ n, where n = a Ramsay Sedation Score of 2, 3, . . . 6) were 68, 101, 208, 304, and 375 ng/ml. The corresponding predicted $C_{50,ss}$ values for lorazepam were 34, 51, 104, 152, and 188 ng/ml, respectively. Age, fentanyl administration, and the resolving effects of surgery and anesthesia were significant covariates of benzodiazepine sedation. The relative amnestic potency of lorazepam to midazolam was 4 (observed). The predicted emergence times from sedation after a 72-h benzodiazepine infusion for light (SS = 3) and deep (SS = 5) sedation in a typical patient were 3.6 and 14.9 h for midazolam infusions and 11.9 and 31.1 h for lorazepam infusions, respectively.**

Conclusions: **The pharmacology of intravenous infusions of lorazepam differs significantly from that of midazolam in critically ill patients. This results in significant delays in emergence from sedation with lorazepam as compared with midazolam when administered for ICU sedation.**

This article is accompanied by an Editorial View. Please see: Bailey JM: Pharmacokinetic–pharmacodynamic modeling and ICU sedation: Unexplored territories. ANESTHESIOLOGY 2001; 95:281–2.

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PATIENTS undergoing major surgical procedures who require postoperative intubation and mechanical ventilation typically have a significant degree of anxiety and pain.[1] Sedative and analgesic agents are frequently administered to these patients in the intensive care unit (ICU) to prevent the cardiopulmonary and psychological complications associated with pain and anxiety.[2,3] Midazolam and lorazepam are the most commonly used benzodiazepines for ICU sedation.[4] Midazolam is a water-soluble, short-acting benzodiazepine that is rapidly metabolized by the liver *via* the cytochrome P450 enzyme system to active (1- and 4-hydroxymidazolam) and inactive metabolites. The active metabolites of midazolam are subsequently conjugated by hepatic glucuronidation and excreted by the kidneys.[5] Lorazepam is a long-acting benzodiazepine that is metabolized by hepatic glucuronidation to inactive metabolites that are cleared by kidneys.[6]

The pharmacokinetics of midazolam administered as continuous intravenous infusions for sedation in ICU patients differ significantly from the pharmacokinetics of intravenously administered midazolam in healthy individuals.[7–10] To date, the pharmacokinetics of intravenous lorazepam have only been studied in healthy subjects being given single bolus injections or short (*i.e.,* 60 min) infusions of lorazepam.[11–13] Studies of lorazepam in critically ill patients have been limited to assessing the dose–response relationship of lorazepam for ICU sedation.[14,15]

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Lorazepam has recently been advocated as an economic alternative to midazolam for long-term sedation of ICU patients.[16] In the absence of a comprehensive pharmacologic analysis of lorazepam, there are currently no scientifically validated dosing guidelines for the use of lorazepam infusions in the ICU, making it difficult for clinicians to rationally titrate lorazepam in critically ill patients. The purposes of the current study are as follows: (1) to characterize and compare the pharmacokinetic profiles of midazolam and lorazepam in adult surgical ICU patients; (2) to correlate midazolam and lorazepam plasma concentrations with the depth of sedation and the degree of amnesia achieved in these patients; (3) to compare the ease of titration and the recovery profile of the two agents; and (4) to develop rational dosing guidelines for sedation with lorazepam infusions based on the clinical pharmacology of lorazepam in surgical ICU patients.

Materials and Methods

Study Design

After Institutional Review Board (Administrative Panel on Human Subjects in Medical Research, Stanford University School of Medicine, Stanford, CA) approval, written informed consent was obtained from 24 adult patients (age range, 18–85 yr) requiring postoperative intubation and mechanical ventilation in the ICU for up to 72 h after elective surgery at the VA Palo Alto Health Care System (Palo Alto, CA). Individuals were excluded from the study if they had significant hepatic, renal, or neurologic impairment; a recent history of long-term benzodiazepine use or known substance abuse; or a known allergy to either drug. Subjects were given no benzodiazepines within 72 h before the start of the study.

All subjects were prospectively randomly assigned in a double-blinded fashion to be given either midazolam (Versed; Roche Pharmaceuticals, Inc., Nutley, NJ) or lorazepam (Ativan; Wyeth-Ayerst Laboratories, Philadelphia, PA) for postoperative sedation. Midazolam and lorazepam were administered intravenously to all subjects *via* a target-controlled infusion (TCI) to achieve predefined levels of sedation. The TCI device consisted of an 80386-20 laptop computer (Everex, Inc., Fremont, CA), with an MS-DOS operating system (Microsoft, Inc., Redmond, WA) running STANPUMP software,‖ connected *via* serial interface to an intravenous infusion pump (Harvard Pump Model 22; Harvard Apparatus, Inc., South Natick, MA). For the first 13 subjects, STANPUMP targeted plasma study drug concentrations using previously derived pharmacokinetic models for midazolam[17] and lorazepam.[11] In the remaining 11 subjects, STANPUMP targeted plasma study drug concentrations using revised pharmacokinetic models for midazolam and lorazepam derived from the initial 13 subjects to achieve more accurate plasma levels. Postoperative analgesia was provided using either intravenous fentanyl (Sublimaze; Janssen Pharmaceuticals, Inc., Titusville, NJ) administered *via* a TCI (using pharmacokinetic parameters for fentanyl previously described by Shafer *et al.*[18]), or epidural infusions of morphine (Astramorph; AstraZeneca Pharmaceuticals, Westborough, MA) and bupivacaine (Marcaine; Sanofi Winthrop, New York, NY). Intraoperative opioids were limited to intravenous fentanyl (3–5 μg/kg) or epidural morphine (≤10-mg bolus). All other intraoperative anesthetic and therapeutic agents were administered to subjects according to standard anesthetic techniques.

Table 1. Modified Ramsay Sedation Score[19]

SS	Clinical Response
0	Residual neuromuscular blockade present; unable to assess level of sedation
1	Fully awake
2	Drowsy, but awakens spontaneously
3	Asleep, but arouses and responds appropriately to simple verbal commands
4	Asleep, unresponsive to commands, but arouses to shoulder tap or loud verbal stimulus
5	Asleep and only responds to firm facial tap and loud verbal stimulus
6	Asleep and unresponsive to both firm facial tap and loud verbal stimulus

If the subject was restless or agitated, 0.5 was added to the sedation score (SS) to determine the percent of time subjects were agitated.

Postoperatively, subjects were transferred from the operating room directly to the ICU, where they remained intubated and mechanically ventilated and were allowed to regain consciousness. Their depth of sedation was evaluated using a modified version of the Ramsay Sedation Scale (table 1).[19] When subjects had emerged from anesthesia to a sedation score (SS) of 2 or 3, postoperative analgesia was instituted with either an intravenous fentanyl infusion (set to a target plasma concentration of 1.5 ng/ml) or epidural morphine and bupivacaine infusions. Once adequate analgesia was achieved (analgesic medication titrated to a pain-free state), sedation was initiated in a blinded fashion with either a midazolam or lorazepam infusion set to a target plasma concentration of 50 ng/ml. Then the target plasma concentration of the study sedative was titrated up by 25–50 ng/ml every 30 min until SS was equal to 4. If the SS was greater than 4 at any time, the target plasma concentration was decreased by 50% and the subject was observed closely until SS was equal to 3 or 4; then the target plasma concentration was set to the sedative concentration predicted by the STANPUMP program at that time. If a subject became restless, the target plasma concentration of the study sedative was increased by 50 ng/ml or as needed until adequate sedation was achieved. The target

‖ STANPUMP is available on the World Wide Web at: http://pkpharmacodynamic.icon.palo-alto.med.va.gov.

plasma concentration required to sustain an SS of 3 or 4 was maintained for 12–72 h, or as long as sedation was clinically indicated. Both the sedative and fentanyl infusions were stopped when subjects were ready to be weaned from mechanical ventilation. If additional analgesia was required after discontinuation of the fentanyl infusion, small intravenous boluses of morphine (1–2 mg) were administered.

Data Acquisition and Processing

Heart rate, arterial blood pressure (systolic, diastolic, and mean), central venous pressure, and SS were recorded, and arterial blood samples for the benzodiazepine assay were collected from each subject at the following times: (1) at baseline postoperatively before starting the sedative infusion in the ICU; (2) immediately before and at 5, 15, 30, 45, 60, and 120 min after each change in the sedative target plasma concentration; and (3) immediately before and at 5, 15, 30, 45, and 60 min, then at 2, 4, 6, 12, 18, and 24 h after discontinuation of the sedative infusion. Arterial blood samples were collected in 5-ml heparinized glass tubes and immediately placed on ice. Samples were centrifuged at 3,000 rpm for 10 min, and the plasma fraction was separated into polypropylene storage tubes and stored at −20°C until assayed. Plasma benzodiazepine analyses were performed at Stanford University (Stanford, CA) using high-performance liquid chromatography with a limit of quantitation of 16 ng/ml for both the midazolam and lorazepam assays. (A detailed description of the benzodiazepine assay used can be found in Appendix 1 in the Web Enhancement.)

Adequacy of Sedation and Amnesia Assessments

Nurses taking care of each subject were asked at the end of their 8- to 12-h shift to assess the ease of titration of sedation and the adequacy of sedation on a visual analog scale. The investigator (Dr. Geller) completed a similar sedation assessment for each subject within 24 h after discontinuation of the study drug. Both the nurses and the investigator were blinded as to the sedative used in each case. Twenty-four hours after extubation, each subject was asked to complete a questionnaire to assess his or her recall of unpleasant experiences (*e.g.,* pain, anxiety, intubation, mechanical ventilation) during the period of sedation.

Postsedation amnesia was assessed by showing subjects a series of pictures depicting simple objects at different intervals after discontinuation of the study sedative. As soon as a subject was able to initially identify an object, he or she was shown drawings of this object plus additional objects 3, 6, 12, 24, and 36 h later. If subjects recognized a particular object, they were asked at later times if they recalled the drawing shown to them earlier. Once subjects recalled three consecutive drawings previously shown to them, they were no longer considered amnestic. At that point, subjects were shown a composite of drawings and asked to identify what drawings had been shown to them previously. Dundee and George[20] have previously validated this method of recognition and recall testing after administration of benzodiazepines.

Table 2. Demographic Characteristics of Subjects Studied (n = 24)

Parameter	Lorazepam* (n = 14)	Midazolam* (n = 10)	*P* Value†
Age (yr)	74 ± 6	63 ± 10	0.0071
Weight (kg)	85 ± 15	94 ± 47	0.6605
Height (m)	1.76 ± 0.09	1.78 ± 0.11	0.9529
BSA (m^2)	2.04 ± 0.20	2.10 ± 0.43	0.6736
BMI (kg/m^2)	27.07 ± 4.27	29.79 ± 12.73	0.4615
Gender	F = 1; M = 13	M = 10	—
Apache II score‡	10.14 ± 1.61	7.4 ± 2.85	0.0036

* Values are given as mean ± SD unless otherwise indicated. † Analysis of variance F test. ‡ Apache II score measured within 24 h of admission to the intensive care unit.

BSA = body surface area; BMI = body mass index.

Statistical Analyses

Members of the Department of Anesthesia, Stanford University School of Medicine, performed all statistical analyses. Summary results are expressed as mean ± SD unless otherwise noted. *P* values were derived using analysis of variance *F* testing. A value of $P = 0.05$ was considered to be statistically significant in this case. Subjective sedation assessments by subjects being given either lorazepam or midazolam were compared with a chi-square analysis. A value of $P = 0.05$ was considered to be statistically significant.

Multiple nonlinear logistic regression analyses were performed to characterize the pharmacokinetic and pharmacodynamic models for both lorazepam and midazolam. Model performance was assessed both numerically and graphically in both groups. (A detailed summary of the pharmacokinetic and pharmacodynamic analyses can be found in Appendix 2 in the Web Enhancement.) The newly derived pharmacokinetic and pharmacodynamic models for lorazepam and midazolam were integrated to construct dosing regimens and estimate emergence times for light and deep sedation with either agent.

Results

Demographics

Table 2 summarizes the demographics of the 24 subjects enrolled in the study. Ten subjects were given midazolam, and 14 subjects were given lorazepam. All subjects underwent either major vascular, urologic, or general surgical procedures. Both groups were similar in terms of their height, weight, body surface area, and body mass index. The lorazepam subjects were older, on

Table 3. Drug Infusion Data (n = 24)

	Lorazepam* (n = 14)	Midazolam* (n = 10)	*P* Value†
Length of infusion (h)	36.94 ± 30.90	15.02 ± 3.33	0.037
Infusion rate (mg/h)	0.91 ± 0.39	2.54 ± 0.93	< 0.001
Total dose (mg)	31.66 ± 27.39	37.09 ± 13.31	0.569

* Values are given as mean ± SD. † Analysis of variance F test.

average, than the midazolam subjects. Although there was a statistically significant difference in the Apache II scores between the two groups, this difference was not considered to be clinically significant.[21]

Three subjects being given lorazepam developed acute agitation, delirium, tachycardia, and hypertension after discontinuation of the benzodiazepine infusion. This was attributed to acute alcohol withdrawal rather than benzodiazepine withdrawal because all three subjects were subsequently found to have an extensive history of alcohol use preoperatively (which they had denied at the time of enrollment), and all had been given benzodiazepine infusions for less than 48 h. A fourth lorazepam subject had a mechanical failure of the fentanyl drug infusion system during the study. All four of these subjects were replaced in a blinded fashion. When the randomization code was unblinded, all four subjects had been randomly replaced with lorazepam subjects, a finding that was not considered relevant. These four substituted lorazepam subjects were included in the pharmacokinetic analyses but excluded from the pharmacodynamic analyses because their sedation scores were potentially confounded. In one midazolam subject, a failure of the drug infusion system was diagnosed only after the study was closed and unblinded. As a result, this midazolam subject was not replaced and was subsequently excluded from both the pharmacokinetic and pharmacodynamic analyses.

Benzodiazepine sedation was initiated in all subjects within 2 h of their arrival to the ICU from the operating room. Four subjects in each group were given postoperative analgesia *via* epidural morphine and bupivicaine, and the remaining subjects were given intravenous fentanyl *via* TCI. No significant hemodynamic differences were observed between the midazolam and lorazepam groups during study drug administration. All subjects had extubation and were discharged from the ICU in stable condition. One subject who developed an increased serum bilirubin level after pancreatic tumor resection died 3 weeks after the end of the study from causes unrelated to the subject's participation in the study.

Table 3 summarizes the study drug infusion profiles for all 24 subjects. There were significant differences in the duration of infusion and the average infusion rates between the two groups. The lorazepam group was given infusions for longer periods, on average (36.9 h), than the midazolam group (15 h). This difference was primarily attributable to three lorazepam subjects who were given lorazepam infusions for greater than 60 h. The average infusion rates for each group were 0.91 and 2.54 mg/h for lorazepam and midazolam, respectively.

Pharmacokinetics and Pharmacodynamics

Twenty-three subjects (9 midazolam subjects and 14 lorazepam subjects) were included in the final pharmacokinetic analyses. Eighteen subjects (nine midazolam subjects and nine lorazepam subjects) were included in the pharmacodynamic and sedation analyses. In addition to excluding the four lorazepam subjects who were initially replaced, a fifth lorazepam subject was also excluded from the pharmacodynamic and sedation analyses because sedation assessments were not interpretable.

The original and revised pharmacokinetic models for lorazepam and midazolam are summarized in table 4. A two-compartment, mixed-effects model best describes the data for both drugs. Including age and weight as covariates into the estimates for central volume of distribution (V_1) and metabolic clearance (Cl_1) significantly improved the performance of the midazolam model. The accuracy of the lorazepam model was not improved with the addition of any covariates. The revised models for both agents differed significantly from the original models, both numerically and in terms of their accuracy in predicting plasma benzodiazepine concentrations. (A detailed comparison of the original and revised pharmacokinetic models for both agents is summarized in Appendix 3 in the Web Enhancement.)

Table 5 summarizes the results of the sequential pharmacodynamic analyses using the naïve pooled data approach (the mixed-effects modeling approach did not adequately describe the pharmacodynamic data). Model H best described the data both numerically (*i.e.,* having the smallest objective function and the highest percentage of correct and close sedation score predictions) and graphically based on the basic model:

$$P(\text{Sedation} \geq \text{ss}) = C^{\gamma}/(C^{\gamma} + C_{50,ss}^{\gamma}) \quad (1)$$

where P(Sedation ≥ ss) = probability of level of sedation ≥ SS (2–6); C = plasma benzodiazepine concentration; $C_{50,ss}$ = plasma benzodiazepine concentration where P(Sedation ≥ ss) = 50%; and γ = slope of probability curve. (For a more complete description of the various pharmacodynamic models tested, see appendix table 1 in the Web Enhancement.)

Model H estimated the potency of lorazepam to be twice that of midazolam, which corresponds to the observed midazolam:lorazepam concentration ratio of 1.8 (table 6). Therefore, estimated $C_{50,ss}$ values (where SS ≥ 2, 3, 4, 5, and 6) for lorazepam are half those of midazolam (34, 51, 104, 152, and 188 ng/ml for lorazepam *vs.* 68, 101, 208, 304, and 375 ng/ml for midazolam, respectively). In the presence of fentanyl, the effective $C_{50,ss}$

Table 4. Original *versus* Revised Pharmacokinetic Models for Lorazepam and Midazolam

Model Parameters	Lorazepam		Midazolam	
	Original[11]	Revised* (n = 14)	Original[17]	Revised* (n = 9)
Volumes (l)				
Central (V_1)	0.46 × wt	40.8 (33%)	33	[1.57 × (63 − age) + 0.322 × (wt − 78) + 33.9] (NA†)
Peripheral (V_2)	0.59 × wt	102 (26%)	[(32.1 × BSA) + 3.32]	131 (26%)
Slow peripheral (V_3)	—	—	365	—
Clearances (l/min)				
Metabolic (Cl_1)	0.001 × wt	0.107 (48%)	[(0.151 × BSA) + 0.0889]	[0.006 × (wt − 78) + 0.296] (47%)
Peripheral (Cl_2)	0.043 × wt	1.86 (NA†)	0.622	0.599 (60%)
Slow peripheral (Cl_3)	—	—	0.264	—
Intraindividual variability (%)	—	11	—	17
Performance measures				
MDWR (%)	−24.38	−2.6	23.56	5.39
MDAWR (%)	28.92	17.27	43.25	22.01

* Revised model parameters listed as values (%CV), where %CV = coefficient of variation as a measure of interindividual variability. † Nonlinear mixed-effects model is unable to calculate %CV for this parameter.

wt = weight (kg); NA = not applicable; BSA = body surface area (m^2); age = age (yr); MDWR = median weighted residual; MDAWR = median absolute weighted residual.

values for both lorazepam and midazolam are decreased by 18% (*i.e.,* all $C_{50,ss}$ values are multiplied by a fentanyl effect parameter of 0.82). This is consistent with the observed effect of fentanyl on benzodiazepine sedation, where subjects being given intravenous fentanyl for analgesia were more deeply sedated at comparable benzodiazepine concentrations than subjects being given epidural analgesia in both groups (fig. 1). The dissipating effects of surgery and anesthesia also reduced the amount of benzodiazepine sedation initially required. This "virtual drug" effect corresponds to an initial plasma midazolam concentration of 159 ng/ml, with an elimination half-life of 12.4 h. Model H predicted that the age of the individual significantly influences the effects of midazolam and lorazepam sedation as well. Within the age range of the population studied, the estimated $C_{50,ss}$ values for both lorazepam and midazolam were decreased by 18% for every 10 yr of age. There was a significant difference in the estimated slopes of the probability curves for lorazepam and midazolam. The slope of the midazolam curves is steeper (*i.e.,* larger γ value) than that of the lorazepam curves, resulting in a faster pre-

Table 5. Pharmacodynamic Parameters Estimated for All Models* (n = 18)

Model Parameters	A	B	C	D	E	F	G	H†
$C_{50,2}$ (ng/ml)	4.3	7.1	25	25	65	67	76	68
$C_{50,3}$ (ng/ml)	11.7	18.2	45	48	98	100	111	101
$C_{50,4}$ (ng/ml)	92	124	131	168	194	195	211	208
$C_{50,5}$ (ng/ml)	282	350	233	323	276	275	292	304
$C_{50,6}$ (ng/ml)	537	636	322	471	335	333	350	375
γ	0.96	1.05	1.96	1.73	3.6	3.7	4.0	—
$\gamma_{Midazolam}$	—	—	—	—	—	—	—	4.5
$\gamma_{Lorazepam}$	—	—	—	—	—	—	—	3.3
Lorazepam potency factor (θ_2)	2	2	2	2	2	2	2	2
Fentanyl effect parameter (θ_3)	—	0.59	—	—	—	—	0.81	0.82
FA	—	—	37	29	—	4.7	—	—
FS	—	—	—	0.64	—	—	—	—
Age effect parameter (θ_4)	—	—	—	—	—	—	—	−0.018
VD (ng/ml)	—	—	—	—	178	171	159	159
K (min^{-1})	—	—	—	—	0.0011	0.0011	0.001	0.0009
Virtual drug half-life (h)	—	—	—	—	10.9	10.9	11.5	12.4
Performance measures								
Objective function	1,533	1,522	1,466	1,456	1,333	1,332	1,312	1,243
Correct predictions‡ (%)	33	38	37	42	41	42	44	49
Close predictions§ (%)	61	65	62	69	71	71	73	76

* Based on the pharmacodynamic model: $P(\text{Sedation} \geq \text{ss}) = C^{\gamma}/(C^{\gamma} + C^{\gamma}_{50,ss})$, where P(Sedation ≥ ss) = probability of level of sedation ≥ SS (2–6); C = plasma benzodiazepine concentration; $C_{50,ss}$ = plasma benzodiazepine concentration where P(Sedation ≥ ss) = 50%; and γ = slope of probability curve. † Model H values listed for a 71-yr-old individual. ‡ Observed SS = predicted SS. § Observed SS = predicted SS ± 1.

FA = additive fentanyl effect; FS = synergistic fentanyl–benzodiazepine effect; VD = virtual drug effect parameter; K = VD elimination rate constant.

Table 6. Observed Benzodiazepine Plasma Concentrations (SS = 2–5)

SS	Lorazepam (n = 9)*	Midazolam (n = 9)*	M/L
2	32.2 (6–80)	52.3 (6–139)	1.6
3	47.6 (31–117)	79.3 (1–214)	1.7
4	62.2 (25–118)	119 (36–262)	1.9
5	61.9 (27–108)	116.8 (70–232)	1.9
			1.8 ± 0.15†

* Values are given in ng/ml as median (range). † Average observed midazolam:lorazepam concentration ratio (M/L; mean ± SD).
SS = sedation score.

dicted onset and offset of sedation with midazolam than with lorazepam at equipotent concentrations (fig. 2).

Adequacy of Sedation and Amnesia

Subjects in both groups were effectively sedated throughout the study with minimal agitation (< 1%). However, there were significant differences in the observed sedation patterns between lorazepam and midazolam subjects (table 7). The number of initial titrations required to achieve optimal sedation (SS = 3 or 4) were similar in both groups, although the median time to achieve this level of sedation was much longer in the lorazepam group (335 min) than in the midazolam group (5.5 min). This difference is attributable in part to study

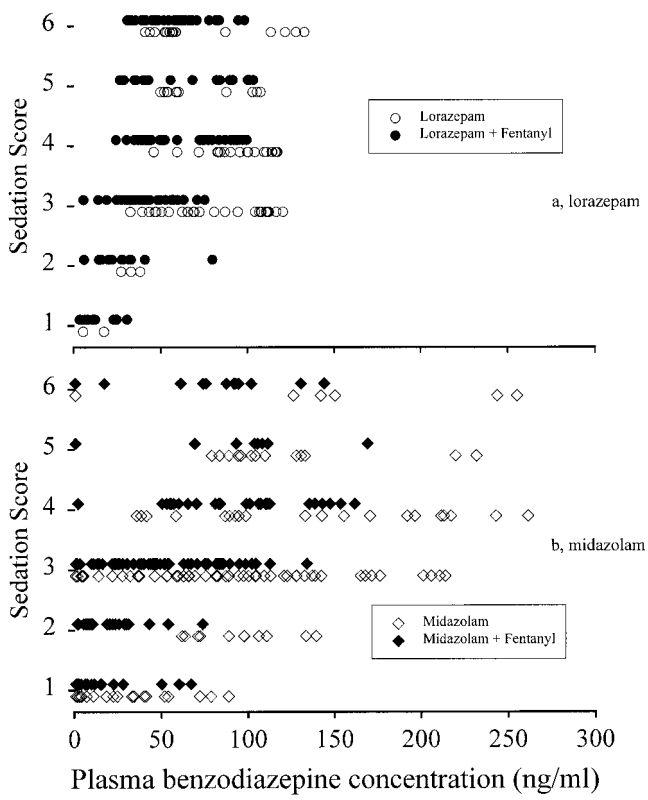

Fig. 1. Sedation score *versus* measured plasma benzodiazepine concentrations for lorazepam (*A*) and midazolam (*B*) in the presence and absence of intravenous fentanyl.

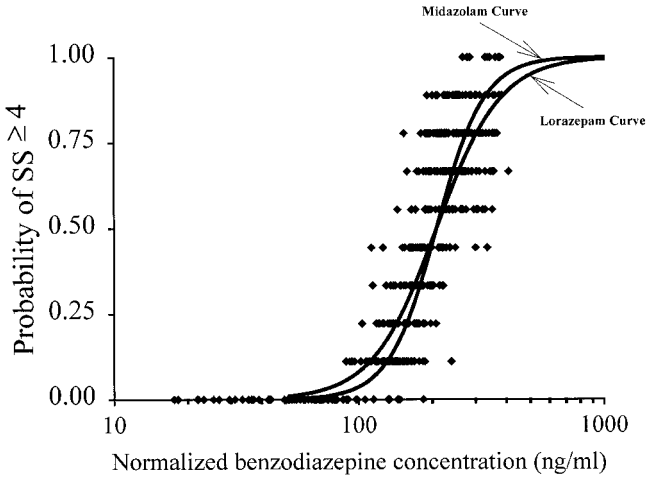

Fig. 2. Midazolam and lorazepam probability curves for sedation score (SS) ≥ 4 *versus* normalized plasma benzodiazepine concentration for model H. Normalized plasma benzodiazepine concentrations are based on the predicted plasma benzodiazepine concentrations derived from the population pharmacokinetic model, which are then normalized by their respective $C_{50,ss}$ and virtual drug concentration values.

design. To preserve study blinding, both midazolam and lorazepam were administered to subjects with an initial target plasma concentration of 50 ng/ml, which was increased every 30 min as needed to achieve SS = 4. At this initial target concentration, in the presence of fentanyl or resolving sedative effects of surgery and anesthesia, lorazepam subjects tended to be initially oversedated, requiring subsequent decreases in the target plasma benzodiazepine concentration and delaying the time required to achieve optimal sedation. During the maintenance period of sedation, subjects in the lorazepam group were optimally sedated (SS = 3 or 4) only 49% of the time *versus* 69% of the time for midazolam subjects (fig. 3). Lorazepam subjects were more deeply sedated (*i.e.,* SS = 5 or 6) more often (47%) than midazolam subjects (22%). These depth of sedation differences between lorazepam and midazolam subjects were statistically and clinically significant ($P = 0.0001$). There were also significant differences in emergence times between the two groups after discontinuation of the benzodiazepine infusion (table 7). Lorazepam subjects emerged from sedation more slowly and had extubation much later than midazolam subjects (*i.e.,* 8.7 *vs.* 3 h and 21.2 *vs.* 5.4 h , respectively). Nurses caring for subjects and blinded to the study drug administered found both drugs to be comparable in terms of ease of titration and adequacy of sedation (table 7). In contrast, the investigator, who was also blinded to the study drug, thought that midazolam was easier to titrate and provided more adequate sedation than lorazepam.

Figures 4A and B compare the relative amnestic effects of lorazepam to midazolam in the subjects studied. Figure 4A demonstrates that the observed amnestic effect of lorazepam was significantly greater than that of midazo-

Table 7. Observed Benzodiazepine Sedation Patterns (n = 18)

	Lorazepam (n = 9)	Midazolam (n = 9)	*P* Value*
Onset of sedation			
No. of titrations required to initially achieve SS = 3–4	1.8 ± 0.97	1.2 ± 0.44	NA
Time to initially achieve SS = 3–4 (min)	Median: 335 (range: 5.05–613)	Median: 5.5 (range: 4.93–65.02)	NA
Emergence from sedation			
Elapsed time from the end of infusion to SS = 2 (h)	8.71 ± 5.97	3.02 ± 2.58	0.013
Elapsed time from the end of infusion to extubation (h)	21.24 ± 15.92	5.36 ± 2.35	0.005
Plasma drug concentration at extubation time (ng/ml)	17.39 ± 12.72	38.21 ± 28.88	0.011
Nursing sedation assessments			
Ease of titrations†	75.77 ± 4.40	77.73 ± 4.41	0.469
Adequacy of sedation‡	82.58 ± 2.95	84.07 ± 2.82	0.309
Investigator sedation assessments			
Ease of titrations†	60.63 ± 7.37	82.67 ± 5.90	0.032
Adequacy of sedation‡	70.56 ± 7.70	91.11 ± 1.90	0.020

Values are given as mean ± SD unless otherwise noted.

* Analysis of variance F test. † Visual Analog Scale ranging from 0–100, where 0 = extremely difficult to titrate, 100 = extremely easy to titrate. ‡ Visual Analog Scale ranging from 0–100, where 0 = totally inadequate, 100 = perfectly adequate.

SS = sedation score; NA = not applicable because apparent differences were influenced by study design (see text).

lam throughout the postinfusion period. At 24 h after infusion, the amnestic effect of midazolam had resolved in all subjects, whereas approximately 50% of the lorazepam subjects continued to exhibit impaired recall; at 36 h after infusion, 30% of the lorazepam group still demonstrated impaired recall. Figure 4B shows the relationship between the incidence of recall and plasma benzodiazepine concentrations. The observed $C_{50,ss}$ values for lorazepam and midazolam-induced amnesia were approximately 6 and 25 ng/ml, respectively, giving lorazepam a relative amnestic potency of 4 compared with midazolam. There were no significant differences in the subjective recall assessments by subjects, and the majority of subjects in both groups had no unpleasant recall of their experiences in the ICU.

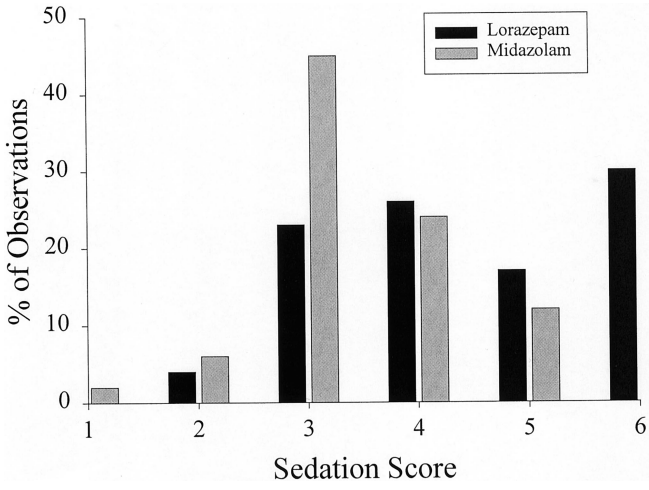

Fig. 3. Incidence of a sedation score of 1–6 in lorazepam and midazolam subjects during the benzodiazepine infusion period.

Discussion

Both midazolam and lorazepam are commonly administered as continuous intravenous infusions for sedation of intubated ICU patients. Although the pharmacology of intravenous midazolam infusions for ICU sedation has been well characterized, the pharmacology of lorazepam infusions in this setting has not been previously established. The lack of pharmacologic data for intravenous lorazepam infusions in critically ill patients has made it difficult to adequately compare the sedative effects of lorazepam and midazolam infusions or to create valid dosing guidelines for lorazepam in these patients. The results of the current study demonstrate that there are substantial pharmacokinetic and pharmacodynamic differences between midazolam and lorazepam which have significant clinical and drug dosing implications in ICU patients.

Pharmacokinetics

The pharmacokinetics of midazolam in the current study were best described by a two-compartment model with age and weight as covariates on V_1 and weight as a covariate on Cl_1 (table 4). The midazolam model described the data with minimal bias and a high degree of accuracy, although there was significant interindividual variability, especially during the postinfusion phase (see appendix figures 1A, 1B, 2A, and 2B in the Web Enhancement). This variability is probably attributable to the greater variability in age and weight in the midazolam group, as reflected by their influence as covariates in the pharmacokinetic model derived for midazolam. The values derived for V_1, Cl_1, and peripheral clearance (Cl_2) for midazolam in the current study were similar to those of

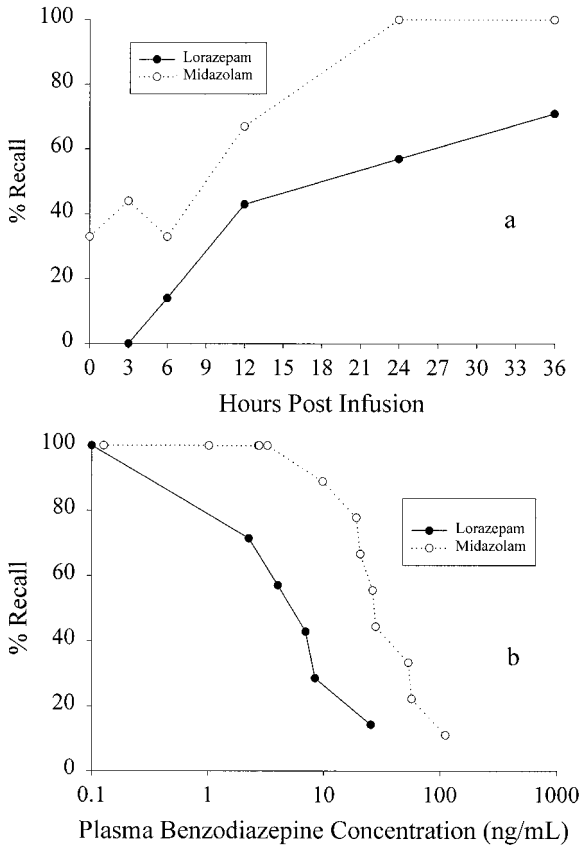

Fig. 4. Incidence of lorazepam and midazolam subjects recalling an object (*A*) *versus* time during the postinfusion period and (*B*) *versus* plasma benzodiazepine concentration.

the model of Zomorodi *et al.*[17] for midazolam used in the initial phase of the current study (see appendix table 2 in the Web Enhancement). The presence of a large third peripheral compartment in the model of Zomorodi *et al.*,[17] which is absent from the midazolam model derived in the current study, is most likely the result of differences in study populations, drug dosing, and study design. In the trial of Zomorodi *et al.*,[17] subjects were given larger doses of midazolam than were subjects in the current study (*i.e.,* 48.4 *vs.* 37 mg), and part of the dose was administered intraoperatively during cardiopulmonary bypass surgery. The effect of cardiopulmonary bypass on midazolam kinetics is to increase the V_1 and decrease the Cl_1, as a result of hemodilution, alterations in protein binding, and decreases in liver blood flow during cardiopulmonary bypass surgery.[22–24]

The pharmacokinetics of lorazepam in the current study were also described by a two-compartment model, albeit without covariates. This revised model for lorazepam described the data with much less bias and a higher degree of accuracy than the original model for lorazepam derived by Greenblatt *et al.*[11] (table 4). The pharmacokinetic parameters estimated for lorazepam in the current study differed significantly from those described by Greenblatt *et al.*[11] (see appendix table 2 in the Web Enhancement). Both models for lorazepam are two-compartment models with similar estimates for the central V_1 and the Cl_1, but the peripheral volume of clearance (V_2) estimated in the current study was 2.5 times larger and the estimated Cl_2 was 40% less than estimated by Greenblatt *et al.*[11] The larger estimated V_2 is most likely attributable to the larger doses of lorazepam administered to subjects in the current study than in the study by Greenblatt *et al.*[11] (*i.e.,* 31.7 *vs.* 2–4 mg). Larger lorazepam doses allow for a more accurate estimate of V_2 (and hence the total volume of distribution) because plasma lorazepam concentrations remain above the limits of detection of the lorazepam assay for longer periods after decreases in the lorazepam infusion rate. The slower Cl_2 estimated for lorazepam in the current study may be explained by differences in tissue blood flow and protein binding of lorazepam between healthy and critically ill patients. The larger V_1, together with the slower Cl_2 estimated for lorazepam, results in a much longer elimination half-life for lorazepam (952 min) than predicted by model of Greenblatt *et al.*[11] (736 min). As a result of these model differences, the model of Greenblatt *et al.*[11] tends to overestimate lorazepam plasma levels during the infusion period and underestimate them during the postinfusion period compared with the revised lorazepam model (see appendix figures 1C, 1D, 2C, and 2D in the Web Enhancement).

The results of the current study demonstrate significant pharmacokinetic differences between lorazepam and midazolam. Lorazepam has a larger estimated V_1 and a smaller estimated V_2 than midazolam, although the total volume of distribution is similar for both agents (see appendix table 2 in the Web Enhancement). This difference may be explained by the greater lipid solubility of midazolam, with greater redistribution into peripheral tissues compared with lorazepam.[6] This may also account for the slower Cl_2 of midazolam. The estimated Cl_1 for midazolam is 2.5 times the estimated Cl_1 of lorazepam. This may be explained by differences in the hepatic metabolism of these two drugs; the hepatic glucuronidation of lorazepam occurs much more slowly than the oxidative hydroxylation of midazolam by the cytochrome P450 enzyme system in the liver.[25,26] The slower metabolic clearance of lorazepam accounts for its longer elimination half-life as compared with midazolam (*i.e.,* 952 min for lorazepam *vs.* 572 min for midazolam). These pharmacokinetic differences account for some of the differences in the observed onset and offset of sedation between these two agents.

Pharmacodynamics

The pharmacodynamics of lorazepam and midazolam sedation were best described by Model H, which accounts for differences in potency and onset and offset times of sedation between the two agents. Model H also includes the effects of age, fentanyl administration, and residual effects of surgery and anesthesia on benzodiaz-

epine sedation (table 5). This model predicts with 76% accuracy that an approximate level of sedation would result from a corresponding benzodiazepine plasma concentration at steady state. The model also predicts that the potency of lorazepam is twice that of midazolam. This is consistent with the average observed midazolam: lorazepam concentration ratio of 1.8 (table 6) and the differences in the observed lorazepam and midazolam concentrations at the time of extubation (17.39 ng/ml for lorazepam *vs.* 38.21 ng/ml for midazolam; table 7). Previously, the potency ratio for lorazepam to midazolam had not been described in critically ill patients. Model H also accounts for the more rapid onset and offset of sedation with midazolam than with lorazepam, which is independent of their pharmacokinetic differences. This is reflected in the larger γ value for midazolam (table 5) which represents a steeper probability curve and a more rapid transition between different levels of sedation for midazolam than for lorazepam as the benzodiazepine concentration varies over time (fig. 2).

Age was found to be a significant covariate of benzodiazepine sedation in the current study independent of its effects on pharmacokinetics. Older subjects required much lower benzodiazepine plasma concentrations to achieve comparable levels of sedation as compared with younger patients. This is consistent with the clinical observation that elderly patients appear to be more sensitive to the effects of benzodiazepines. Although most of the subjects in the current study were greater than 60 yr of age, there appeared to be an inverse linear relationship between age and $C_{50,ss}$ across the spectrum of sedation, with an 18% decrease in the benzodiazepine $C_{50,ss}$ value for each additional 10 yr of age. It is important not to extrapolate this result to much younger individuals, whose age is not reflected in the current study population. Otherwise, one might conclude that a 30-yr-old patient would require $3 \times 18\%$, or 54%, higher benzodiazepine levels than a 60-yr-old individual to achieve similar levels of sedation.

The model predicts that the estimated $C_{50,ss}$ values for both agents are decreased by 18% in the presence of fentanyl, which is consistent with the study observation that subjects being given intravenous fentanyl in both groups were sedated at much lower plasma benzodiazepine concentrations (fig. 1). This also accounts for the fact that the observed plasma benzodiazepine concentrations at SS = 2–5 (table 6) were less than the predicted $C_{50,ss}$ values at each level of sedation (table 5). The measured benzodiazepine plasma concentrations included subjects being given intravenous fentanyl in both groups, whereas the $C_{50,ss}$ values estimated by the model are independent of the effects of fentanyl. Because fentanyl levels were not measured in the current study, the effect of fentanyl in this model is a binary all-or-none effect. This may be attributable to the inaccuracy of using predicted rather than measured fentanyl concentrations in determining the model. The pharmacokinetic model used to administer fentanyl to subjects in the current study was derived from a different patient population[18] (*i.e,* healthy individuals being given short-term fentanyl infusions) and may not accurately predict fentanyl concentrations in our subjects. As an alternative, the fentanyl concentration-effect curve may be sufficiently steep that the effect of fentanyl on sedation is an all-or-none binary phenomenon.

Model H also accounts for the synergistic effect between benzodiazepine sedation and the resolving sedative effects of surgery and anesthesia during the immediate postoperative period. This "virtual drug" effect was described in a previous pharmacodynamic model for midazolam in patients undergoing coronary artery bypass grafting who were being given midazolam for postoperative sedation.[27] In the present study, the virtual drug effect has an initial sedative effect equivalent to a midazolam plasma concentration of 159 ng/ml, which decreases exponentially over time with an elimination half-life of 12.4 h (table 5). The model predicts that after approximately 37 h (*i.e.,* three virtual drug half-lives), the virtual drug effect on sedation is minimal and the sedative effects of benzodiazepines remain relatively constant, assuming steady-state fentanyl requirements.

Dosing Regimens for Benzodiazepine Sedation

By integrating the derived pharmacokinetic and pharmacodynamic models for lorazepam and midazolam, we can simulate continuous intravenous infusions of midazolam or lorazepam in similar patients and predict the resulting patterns of sedation and emergence with a high degree of accuracy. Tables 8 and 9 summarize midazolam and lorazepam sedation regimens required for postoperative sedation of a 71-yr-old, 70-kg male ICU patient. These are based on constant-rate infusion regimens adjusted over time to maintain either light (SS = 3) or deep (S = 5) levels of sedation with or without intravenous infusions of fentanyl (*i.e.,* $\leq$ 200 μg/h) for analgesia. The benzodiazepine concentrations used to define depth of sedation and emergence in each case are based on the modes (*i.e.,* peaks) of the probability curves for discrete sedation scores (*i.e.,* SS = 1, 2, 3, . . .6) rather than the estimated $C_{50,ss}$ values because the distribution of the discrete probability curves are asymmetric, making the modes a more accurate prediction of sedation than the $C_{50,ss}$ values (fig. 5). Bolus doses and subsequent infusion rates for each benzodiazepine regimen are listed for infusions lasting up to 72 h, at which point near–steady-state infusion rates and emergence times have been achieved for each regimen, assuming that constant levels of sedation are maintained. Emergence time from sedation is defined as the time it takes for the patient to emerge to SS = 2 after discontinuation of the benzodiazepine infusion. At this level of sedation, a patient is easily arousable and able to follow commands and may be potentially extubated if appropriate. The

Table 8. Representative Dosing Guidelines for Continuous Intravenous Infusions of Midazolam for Intensive Care Unit Sedation*

	Initial Bolus (mg)	Midazolam Infusion Duration (h)							
		0	1	3	6	12	24	48	72
Light sedation (SS = 3)									
Midazolam infusion alone	0								
Midazolam infusion rate (mg/h)		0	0.2	1.2	1.7	2.0	2.1	2.1	2.1
Emergence time† (h)		10.3	9.4	7.8	6.4	5.1	4.2	3.7	3.6
Midazolam + fentanyl infusions	0								
Midazolam infusion rate (mg/h)		0	0.0	0.3	1.1	1.5	1.7	1.7	1.8
Emergence time† (h)		13.5	12.5	10.6	8.2	5.8	4.4	3.7	3.6
Deep sedation (SS = 5)									
Midazolam infusion alone	3.4								
Midazolam infusion rate (mg/h)		8.5	7.6	5.8	5.1	4.9	4.9	5.0	5.0
Emergence time† (h)		11.4	12.8	14.4	15.3	15.6	15.4	15.0	14.9
Midazolam + fentanyl infusions	2.2								
Midazolam infusion rate (mg/h)		5.8	5.3	4.4	4.0	4.0	4.0	4.1	4.1
Emergence time† (h)		14.2	14.9	15.7	16.1	16.0	15.5	15.0	14.9

* For a 71-yr-old, 70-kg man receiving postoperative sedation with midazolam ± intravenous fentanyl (≤ 200 μg/h) for analgesia. † Emergence time = time (h) for sedation score (SS) = 2.

emergence times listed at each point in time represent the predicted emergence time if the benzodiazepine infusion were discontinued at that moment. The infusion regimens that include fentanyl assume that the fentanyl infusions are started immediately upon admission to the ICU and are continued after discontinuation of the benzodiazepine infusion for postoperative analgesia.

The predicted emergence times from different benzodiazepine sedation regimens differ considerably, depending on the depth of sedation maintained, the duration of infusion, and the agent used. For the first 24 h postoperatively, the residual sedative effects of surgery and anesthesia heavily influence the emergence time. As a consequence of this virtual drug effect, initial boluses of benzodiazepines are not required for light sedation, and the start of the benzodiazepine infusion may be delayed for 2–3 h postoperatively, until the patient emerges from anesthesia and surgery. To maintain deep levels of sedation, initial bolus doses of benzodiazepines are required, with higher benzodiazepine infusion rates for the first 3–6 h postoperatively to induce and maintain deep levels of sedation. By 12–24 h, the virtual drug effect has diminished and the benzodiazepine levels have increased to the point that steady-state benzodiazepine infusion rates are achieved for both agents. By 36 h, the virtual drug effect has essentially resolved and emergence time from sedation primarily becomes a function of declining benzodiazepine levels.

The rate at which benzodiazepine plasma levels decrease after discontinuation of the infusion is a function of the benzodiazepine pharmacokinetics, the duration of the infusion, and the benzodiazepine level at the time the infusion is terminated. Figure 6 shows the predicted time required for lorazepam and midazolam plasma con-

Table 9. Representative Dosing Guidelines for Continuous Intravenous Infusions of Lorazepam for Intensive Care Unit Sedation*

	Initial Bolus (mg)	Lorazepam Infusion Duration (h)							
		0	1	3	6	12	24	48	72
Light sedation (SS = 3)									
Lorazepam infusion alone	0								
Lorazepam infusion rate (mg/h)		0	0.2	0.6	0.6	0.5	0.5	0.5	0.5
Emergence time† (h)		10.2	9.3	8.5	8.8	9.6	10.7	11.7	11.9
Lorazepam + fentanyl infusions	0								
Lorazepam infusion rate (mg/h)		0	0.0	0.2	0.5	0.5	0.4	0.4	0.4
Emergence time† (h)		13.6	12.6	10.7	9.0	9.5	10.8	11.9	12.2
Deep sedation (SS = 5)									
Lorazepam infusion alone	3.6								
Lorazepam infusion rate (mg/h)		6.4	3.3	1.4	1.2	1.2	1.1	1.1	1.1
Emergence time† (h)		15.6	22.6	26.4	27.5	28.7	30.0	30.9	31.1
Lorazepam + fentanyl infusions	2.4								
Lorazepam infusion rate (mg/h)		4.4	2.4	1.1	1.0	1.0	0.9	0.9	0.9
Emergence time† (h)		17.5	22.8	25.9	27.1	28.5	30.1	31.2	31.5

* For a 71-yr-old, 70-kg man receiving postoperative sedation with lorazepam ± intravenous fentanyl (≤ 200 μg/h) for analgesia. † Emergence time = time (h) for sedation score (SS) = 2.

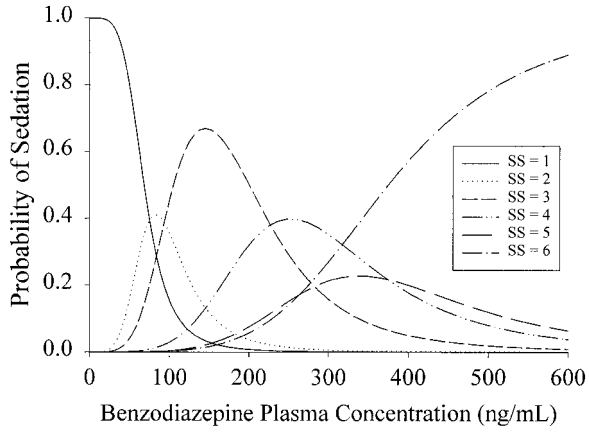

Fig. 5. Probability curves for discrete sedation scores (SS = 1, 2, 3, . . . 6).

centrations to decrease by 43 and 75% as a function of the infusion duration at steady-state sedation. A 43% decrease in benzodiazepine levels would be required for patients to emerge from light sedation (*i.e.,* SS = 3 → 2), while a 75% decrease would be required for them to emerge from deep sedation (*i.e.,* SS = 5 → 2). The predicted emergence time from sedation with lorazepam is much longer than that of midazolam, regardless of the infusion duration or depth of sedation. In this example, emergence time from light sedation with midazolam infusions lasting longer than 12 h is 3–5 h *versus* an emergence time of 10–12 h for light sedation with lorazepam infusions of similar duration (tables 8 and 9). Patients who are deeply sedated with either agent have much greater emergence times, even with short-term (*i.e.,* < 24 h) benzodiazepine infusions. In this example, emergence time from deep sedation with midazolam infusions lasting longer than 12 h is approximately 15 h *versus* an emergence time of approximately 30 h after deep sedation with lorazepam for comparable periods. Figure 7 compares the emergence times from light and deep sedation after a 72-h TCI of either midazolam or lorazepam. These results are consistent with the predicted emergence times listed in tables 8 and 9 for constant-rate infusions, as well as the emergence times observed in the current study. The average observed emergence time from light to moderate sedation (*i.e.,* SS = 3 or 4 → 2) was 3 h in the midazolam group and 9 h in the lorazepam group (table 7).

The synergistic sedative effect of fentanyl with benzodiazepine sedation results in reduced benzodiazepine requirements and infusion rates. Fentanyl may also affect emergence time, although this influence is not reflected in the simulated infusion regimens (tables 8 and 9) because the fentanyl infusions were continued after termination of the benzodiazepine infusion. Discontinuing the fentanyl infusion concurrently with the benzodiazepine infusion shortens the maximum emergence time for both agents (*i.e.,* from 15 h to 12 h after deep sedation

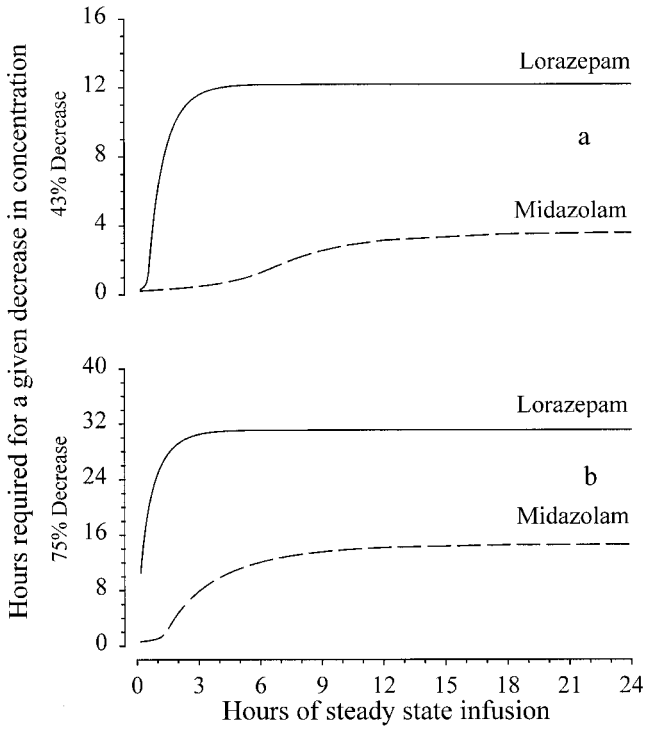

Fig. 6. Predicted time required for (*A*) a 43% decrease and (*B*) a 75% decrease in plasma benzodiazepine concentration as a function of the duration of the benzodiazepine infusion. This corresponds to the benzodiazepine concentration change required to emerge from light and deep sedation, respectively.

with midazolam and from 31 h to 26 h after deep sedation with lorazepam).

These emergence times from sedation with midazolam and lorazepam are in contrast to the sedation emergence times observed in previous studies comparing midazolam and lorazepam infusions in ICU patients. In the study reported by Pohlman *et al.*,[15] subjects being given midazolam infusions took *longer* to emerge from sedation than lorazepam subjects (*i.e.,* 30.3 h for midazolam *vs.* 4.4 h for lorazepam).[15] The longer midazolam emergence times observed by Pohlman *et al.*[15] are probably related to the relatively larger drug doses administered in the midazolam group. In that study, the average total dose of midazolam administered was 23 *versus* 5 mg/kg in the lorazepam group. In the absence of measured plasma benzodiazepine concentrations or any attempt to construct a pharmacokinetic–pharmacodynamic model to compensate for study bias, it is difficult to conclude that midazolam and lorazepam subjects in the study reported by Pohlman *et al.*[15] were comparably sedated. Thus, it is impossible to compare emergence times between the two groups in the current study.

Sedative versus *Amnestic Effects of Midazolam and Lorazepam*

There were significant differences between the observed amnestic potency of midazolam and lorazepam in the current study that could not be explained by their

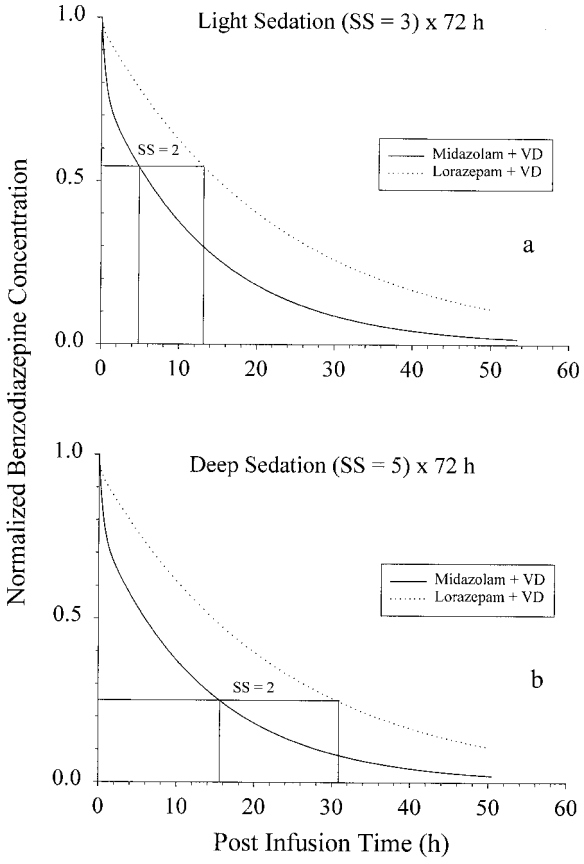

Fig. 7. Predicted emergence times after (*A*) light (SS = 3) and (*B*) deep (SS = 5) sedation with target-controlled infusions of either midazolam or lorazepam for 72 h. VD = virtual drug effect.

sedative effects alone. The amnestic potency of lorazepam to midazolam was 4 (fig. 4), compared with a sedative potency of 2 (table 5). The greater amnestic potency of lorazepam, together with its longer duration of action, resulted in significant delays in the resolution of amnesia in the lorazepam group (> 36 h) compared with the midazolam group (< 24 h). This has clinically significant implications for management of patients after their lorazepam infusion has been discontinued; although patients are awake and are able to follow commands, they might not be able remember relevant conversations and events for several days.

Subjective assessments by the subjects studied and the nurses caring for them showed that the quality of sedation and anxiolysis achieved with lorazepam and midazolam were similar in the current study (table 7). This is consistent with the results of the study of Cernaianu *et al.*,[14] who reported that nurses caring for ICU patients who were sedated with either lorazepam or midazolam infusions found that the quality of sedation was similar for both agents. The blinded investigator in the current study thought it was easier to titrate midazolam infusions to a desired level of sedation than lorazepam infusions. This is, perhaps, explained by the study design, which required a greater number of initial titrations (made primarily by the investigator) in the lorazepam group to achieve optimal sedation.

Conclusion

Both lorazepam and midazolam are safe and effective sedative agents when administered as continuous intravenous infusions for postoperative sedation of surgical ICU patients. The results of the current study demonstrate that there are significant differences in the clinical pharmacology of lorazepam and midazolam, which have significant clinical implications in these patients. Lorazepam is more potent and has a longer duration of action than midazolam. The longer duration of sedative effect may lead to significant delays in extubation and discharge of ICU patients who have been given even short-term infusions of lorazepam for sedation.

Maintaining patients at deep levels of sedation with either agent may delay emergence from sedation, extubation, and ICU discharge. Surgical ICU patients initially have lower benzodiazepine requirements because of the residual sedative effects of surgery and anesthesia. This effect is negligible beyond the first postoperative day. Administering fentanyl infusions for analgesia in conjunction with benzodiazepines reduces the amount of benzodiazepine sedation required and hastens the emergence from sedation in patients when the two drugs are discontinued simultaneously.

The current study demonstrates that mathematical models derived from critically ill patients can be used to accurately predict benzodiazepine plasma concentrations and resulting sedation levels over time in these patients. This enables us to develop rational dosing guidelines for postoperative sedation of surgical ICU patients with either agent, taking into account the synergistic sedative effects of resolving anesthesia and intravenous fentanyl administered for postoperative analgesia. This minimizes the effect of study design and differences in drug administration regimens in interpreting the observed differences between two study groups.

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