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Population Pharmacokinetics of Midazolam Administered by Target Controlled Infusion for Sedation following Coronary Artery Bypass Grafting

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Background: **Midazolam is commonly used for short-term postoperative sedation of patients undergoing cardiac surgery. The purpose of this multicenter study was to characterize the pharmacokinetics and intersubject variability of midazolam in patients undergoing coronary artery bypass grafting.**

Methods: **With institutional review board approval, 90 consenting patients undergoing coronary artery bypass grafting were enrolled at three study centers. All subjects received sufentanil and midazolam *via* target-controlled infusions. After operation, midazolam was titrated to maintain deep sedation for at least 2 h. It was then titrated downward to decrease sedation for a minimum of 4 h more and was discontinued before tracheal extubation. Arterial blood samples were taken throughout the study and were assayed for midazolam and 1-hydroxymidazolam. Midazolam population pharmacokinetic parameters were estimated using NONMEM. Cross-validation was used to estimate the performance of the model.**

Results: **The pharmacokinetics of midazolam were best described by a simple three-compartment mammillary model. Typical pharmacokinetic parameters were V_1 = 32.2 l, V_2 = 53 l, V_3 = 245 l, Cl_1 = 0.43 l/min, Cl_2 = 0.56 l/min, and Cl_3 = 0.39 l/min. The calculated elimination half-life was 15 h. The median absolute prediction error was 25%, with a bias of 1.4%. The performance in the cross-validation was similar. Midazolam metabolites were clinically insignificant in all patients.**

Conclusions: **The intersubject variability and predictability of the three-compartment pharmacokinetic model are similar to those of other intravenous anesthetic drugs. This multicenter study did not confirm previous studies of exceptionally large variability of midazolam pharmacokinetics when used for sedation in intensive care settings. (Key words: Anxiolytics; continuous infusion; nonlinear regression; population modeling; surgical intensive care unit.)**

POSTOPERATIVE sedation often is necessary for patients whose tracheas remain intubated and whose lungs are mechanically ventilated in the surgical intensive care unit (ICU) after coronary artery bypass grafting (CABG). Inadequate sedation of such patients during the immediate postoperative period may lead to increased cardiopulmonary and metabolic demands, resulting in hypertension, tachycardia, arrhythmia, coronary ischemia, tachypnea, and hyperventilation.[1,2] Midazolam is a water-soluble benzodiazepine commonly administered to surgical ICU patients for postoperative sedation.[3] After a single intravenous bolus injection, midazolam rapidly crosses the blood–brain barrier with an onset of drug effect within 2 to 2.5 min after typical sedative doses.[4] Midazolam is metabolized by the hepatic cytochrome P450 (CYP3A4) system to active and inactive metabolites.[5] The principal metabolite of midazolam, 1-hydroxymidazolam, is almost as equipotent as the parent compound.[6] It is rapidly conjugated to 1-hydroxymidazo-

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lam glucuronide and subsequently cleared by the kidneys. This glucuronide metabolite has substantial pharmacologic activity in large amounts, as may be the case in ICU patients with renal insufficiency who are receiving continuous infusions of midazolam for extended periods.[7] The other pharmacologically active metabolite of midazolam, 4-hydroxymidazolam, is not formed in detectable concentrations after intravenous dosing of midazolam in healthy volunteers.[6]

The pharmacokinetics of midazolam have been well defined after short-term infusions or intermittent bolus injections for sedation in healthy volunteers.[6,8–12] These studies show that midazolam is rapidly cleared from the blood with an elimination half-life of 1.5 to 3.5 h, resulting in a rapid offset of sedation.[6,10] Studies of midazolam infusions in critically ill patients in the ICU have indicated that the pharmacokinetic parameters of midazolam vary significantly in this population, with elimination half-lives of 1.5 to 50 h.[13–19] Altered pharmacokinetic behavior has been implicated as resulting in accumulation of midazolam, its active metabolites in critically ill patients, or both, leading to prolonged sedation of these patients after midazolam is discontinued.[20–23]

The current study was an effort to develop a quantitative model of midazolam pharmacokinetics and pharmacodynamics that may improve the accuracy of midazolam administration to critically ill patients by accounting for the wide intersubject variability reported for midazolam in this population. The study was limited to a specific patient population well represented in ICUs: postoperative CABG patients. This article focuses on the pharmacokinetic analysis; its goal is to provide the most accurate pharmacokinetic model possible with contemporary pharmacokinetic tools to develop well-supported dosage guidelines and to provide parameters for incorporation into pharmacokinetically based infusion devices.

The pharmacodynamic analysis is presented in a companion article.[24] The development of clinical dosing guidelines necessitates understanding of pharmacokinetics and pharmacodynamics. Therefore, we placed the dosing guidelines developed from this study in the second manuscript, after the pharmacokinetic and pharmacodynamic models were developed.

Materials and Methods

Study Design

After we received institutional review board approval, we obtained written informed consent from 90 adult patients (≥ 35 yr) who required mechanical ventilation in the surgical ICU for a minimum of 6 h after elective CABG surgery. Equal numbers of patients were recruited at three centers: Duke University Medical Center (Duke); Emory University Medical Center (Emory); and the Palo Alto VA Health Care System (PAVA). The patients all had a left ventricular ejection fraction of more than 25% before operation and were hemodynamically stable before and after surgery. The baseline creatinine concentration was 1.2 mg/dl (range, 0.5 to 2.4 mg/dl). Preoperative medication included aspirin (n = 20), calcium blockers (n = 23), heparin (n = 19), β-blockers (n = 30), insulin (n = 12), and nitrates (n = 31). Excluded from the study were patients with neurologic disorders, tracheostomy, severe liver or renal disease, intraoperative complications, a history of recent drug abuse or long-term benzodiazepine use, a history of allergy to benzodiazepines, and those undergoing cardiac procedures in addition to CABG.

Midazolam (Versed; Roche Pharmaceuticals, Nutley, NJ) and sufentanil (Sufenta; Janssen, Titusville, NJ) were administered intravenously to all patients during and after operation by target-controlled infusion (TCI). The TCI device consisted of an 80386-20 Tempo laptop computer (Everex, Fremont, CA) connected to an infusion pump (Harvard Pump 22; Harvard Apparatus, South Natick, MA) through a serial interface and running MS-DOS software (Microsoft, Redmond, WA). The software program used to run the TCI was either STANPUMP (PAVA and Emory)‡‡ or CACI II (Duke),[25] reflecting institutional experience with each device. Data from Bührer *et al.*[26] and Hudson *et al.*[27] were used in the pharmacokinetic algorithms of these software programs for midazolam and sufentanil, respectively. The internal algorithms of the STANPUMP and CACI programs were identical, resulting in identical infusion profiles with each system.

All patients followed a standardized perioperative anesthetic and invasive monitoring protocol. They were administered lorazepam (0.5 to 2 mg orally) and methadone (5 to 10 mg orally) 1 h before surgery. Intravenous midazolam (0.5 to 1 mg, to a total of 5 mg) was administered by TCI as necessary during insertion of invasive monitors. Anesthesia was induced with midazolam *via* TCI using a target plasma concentration of 150 ng/ml.

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

Table 1. The Ramsay Sedation Score

Score	Description
0	Patient paralyzed, unable to assess level of sedation
1	Patient anxious, agitated, or restless
2	Patient cooperative, oriented, and tranquil
3	Patient sedated but responds to commands
4	Patient asleep but responds to glabellar tap
5	Patient asleep but responds to nail bed pressure (no response to glabellar tap)
6	Patient asleep, no response to nail bed pressure

With loss of the eyelid reflex, 0.1 mg/kg vecuronium was administered for muscle relaxation, and a sufentanil infusion was started *via* TCI, with a target plasma concentration of 1–2 ng/ml. The target plasma concentration for midazolam was maintained throughout the operation at 75–150 ng/ml. During cardiopulmonary bypass, the sufentanil target plasma concentration was decreased to 0.5 to 1 ng/ml; after cardiopulmonary bypass, it was further decreased to 0.3 to 0.6 ng/ml. Maintenance muscle relaxation was provided by intermittent intravenous boluses of vecuronium to a total dose of 0.2 mg/kg for the operation. Supplemental anesthesia was provided with isoflurane or enflurane, up to 1%, as necessary. The TCIs of sufentanil and midazolam were suspended at the end of the surgery. Within the ranges listed, the actual dose of the drugs administered was at the discretion of the attending anesthesiologist.

When patients arrived in the ICU, the sufentanil infusion was restarted at a target plasma concentration of 0.15 ng/ml. If additional analgesia was necessary, intravenous boluses of sufentanil (0.25 μg/kg) were administered as needed with the TCI system. Meanwhile, the patients were allowed to regain consciousness, and their sedation score was evaluated using a modified version of the Ramsay sedation scale (table 1).[28] When they emerged from anesthesia with a sedation score of 5 or less, the midazolam TCI infusion was restarted at an initial target plasma concentration of 50 ng/ml. The target plasma concentration of midazolam was then titrated up by 25–50 ng/ml every 15 min as necessary to reach and maintain a sedation score of 5. If a sedation score of 6 was assessed, the target plasma concentration was decreased by 25–50 ng/ml every 30 min until a sedation score of 5 was again achieved. The target plasma concentration necessary to sustain a sedation score of 5 was maintained for at least 2 h, after which the target plasma concentration was decreased as clinically indicated by 25–50 ng/ml every 30 min to maintain a sedation score of 3 or 4. Midazolam infusions were continued after operation for a minimum of 6 h in all patients. Midazolam and sufentanil infusions were discontinued at some time before tracheal extubation at the discretion of the investigator.

Data Acquisition and Processing

Heart rate, arterial blood pressure (systolic, diastolic, and mean), central venous pressure, pulmonary artery pressure (systolic, diastolic, and mean), and sedation scores were measured, and arterial blood samples for midazolam assay were collected in each patient at the following times: (1) at baseline after operation before restarting the midazolam infusion in the ICU; (2) just before any change in the midazolam target plasma concentration; (3) at 5, 15, 30, 45, 60, and 120 min during each target concentration; (4) just before the midazolam infusion was discontinued; and (5) at 5, 15, 30, 45, and 60 min and then at 2, 4, 6, 12, 18, 24 h after the midazolam infusion was discontinued. Arterial blood samples were collected in 7-ml heparinized glass tubes and immediately placed on ice. Samples were then centrifuged at 2,000 rpm for 15 min, after which the plasma fraction was separated into polypropylene storage tubes and stored at −10°C until assay. Plasma midazolam analyses were performed at Tufts University (Boston, MA) using gas chromatography and mass spectroscopy detection.[29] This method simultaneously measures plasma concentrations of midazolam (coefficient of variation, 4.7%) and 1-hydroxymidazolam (coefficient of variation, 7.2%). The limits of quantitation were 3 ng/ml for midazolam and 10 ng/ml for 1-hydroxymidazolam.

Pharmacokinetic Analyses

NONMEM (University of California, San Francisco, CA),§§ a nonlinear regression program, was used to analyze the data. Two different approaches were used to estimate the population kinetics: Naïve pooled and mixed-effect modeling (MEM). The naïve pooled approach involves pooling the data from all patients and determining a single set of pharmacokinetic parameters that best describe this pooled data set. This technique does not differentiate between interindividual and intraindividual variability. The MEM approach is computationally more complex in that it estimates not only the structural pharmacokinetic parameters that describe the data set, but also the interindividual and intraindividual variability of the pharmacokinetic parameters.

§§Beal SL, Sheiner LB: NONMEM User's Guide. San Francisco, University of California, San Francisco, 1979

The parameters of two- and three-compartment mammillary models were fitted to the data using both the naïve pooled and MEM approaches. The pharmacokinetic parameters estimated included volumes (central compartment [V_1], rapid redistribution compartment [V_2], and slow redistribution compartment [V_3]) and clearances (metabolic [Cl_1], rapid redistribution [Cl_2], and slow redistribution [Cl_3]). To compare the results from the different approaches, the weighted residuals (WR) were used as the primary measure of goodness of fit:

$$WR = (Y - \hat{Y})/\hat{Y}$$

where Y = the measured concentration and $\hat{Y}$ = the model prediction.

The median WR (MDWR) was used as an estimate of model bias:

$$MDWR = \text{median}\{WR_1, WR_2, WR_3, \ldots, WR_n\}$$

where n = the total number of observations in the study.

The median absolute weighted residual (MDAWR) was used as an estimate of model precision:

$$MDAWR = \text{median}\{|WR1|, |WR_2|, |WR_3|, \ldots, |WR_n|\}$$

where n = the total number of observations in the study.

NONMEM minimizes an objective function in performing nonlinear regression analysis. A model with a smaller objective function offers an improvement in the goodness of fit; decreases of 8 or more per added model compartment are considered significant at $P < 0.05$ on the chi-square distribution. The intraindividual variability was calculated using a constant coefficient of variation (CV) model. The interindividual variability was estimated in the MEM approach using a log-normal distribution model. The performance of the models was assessed graphically using residual error plots. The measured-over-predicted concentration values (mathematically equivalent to the WRs plus 1) were plotted on a log scale progressively for each model; the model with the best fit was in turn graphically compared with the performance of the models described by Bührer *et al.*,[26] Maitre *et al.*,[30] and Greenblatt *et al.*[10] for midazolam.

Covariate analysis was also performed using NONMEM. The influence of height, weight, age, body surface area (BSA), and body mass index (BMI) were evaluated sequentially in the pharmacokinetic model to determine whether the overall accuracy of the model could be improved with the addition of one or more of these covariates. The accuracy of each covariate model was evaluated using the goodness-of-fit measures, as described before.

Cross-validation provides an estimate of the ability of the model to predict new observations. Our cross-validation analysis is described in appendix 1.

We calculated the 20%, 50%, and 80% plasma decrement curves for midazolam based on the pharmacokinetics estimated in this study and those reported by Bührer *et al.*[26] The 50% plasma decrement curve corresponds to the "context-sensitive half-time" described by Hughes.[31] In addition, 20% and 80% decrement curves are calculated to show how increasing the depth of midazolam drug effect (and thus the percentage decrease necessary for emergence) can prolong recovery.

Results

All 90 patients enrolled in the protocol survived the surgery and recovery and were discharged from the

Table 2. Demographic Characteristics of Studied Subjects (n = 63)

	Duke	Emory	PAVA	$P < 0.01$*
Number of subjects studied	19	22	22	—
Age (yr)	60 ± 8	64 ± 7	67 ± 7	NS
Weight (kg)	86 ± 15	84 ± 14	87 ± 15	NS
Height (m)	1.70 ± 0.07	1.76 ± 0.09	1.78 ± 0.07	NS
BSA (m^2)	1.97 ± 0.18	1.99 ± 0.18	2.05 ± 0.19	NS
BMI ($kg \cdot m^{-2}$)	29.47 ± 5.02	27.15 ± 4.50	27.18 ± 3.70	NS
Gender	F = 5; M = 14	F = 2; M = 20	F = 0; M = 22	—
Duration of midazolam infusion (h)	8.11 ± 1.66	10.21 ± 1.67	11.61 ± 2.99	S
Total midazolam dose (mg)	28.74 ± 6.31	33.38 ± 7.99	48.35 ± 11.81	S

Values are mean ± SD.

F = female; M = male; PAVA = Palo Alto VA; BSA = body surface area; BMI = body mass index.

* Using ANOVA: NS = no statistically significant difference between the three centers; S = statistically significant difference between the three centers.

Table 3. Pharmacokinetics Parameters for the Simple Models

Parameter	Different Kinetic Sets			
	Greenblatt[10]	Bührer[26]	Maitre[30]	Present Study
Estimated parameters				
Volumes (l)				
V_1	29.6	3.3	10.3	32.2 (58)
V_2	99.4	17.56	27.8	53 (16)
V_3	—	96.76	65.5	245 (71)
Clearances ($l \cdot min^{-1}$)				
Cl_1	0.34	0.54	0.25	0.43 (40)
Cl_2	0.99	2.01	0.38	0.56 (56)
Cl_3	—	0.83	0.11	0.39 (68)
Derived parameters				
V_{ss} (l)	129	117.7	103.6	330.2
Fractional coefficients (unitless)				
A	0.845	0.93	0.89	0.88
B	0.155	0.056	0.088	0.090
C	—	0.013	0.018	0.032
Exponents (min^{-1})				
α	0.053	1.097	0.080	0.048
β	0.002	0.047	0.006	0.006
γ	—	0.0031	0.0011	0.0007
Rate constants (min^{-1})				
k10	0.011	0.16	0.024	0.013
k12	0.034	0.609	0.037	0.017
k13	—	0.252	0.011	0.012
k21	0.010	0.114	0.014	0.011
k31	—	0.0085	0.0017	0.0016
Half-lives (min)				
α	13.09	0.632	8.70	14.33
β	319.8	14.8	108.50	113.63
γ	—	225	633.00	905.088
Performance measures				
MDWR (%)	−37.11	−0.39	−47.82	1.39
MDAWR (%)	40.89	25.80	49.33	25.33
Objective function	9554.63	9941.36	9538.39	9204.20

Values in parentheses are coefficients of variation (CV) on the calculated parameter.

MDWR = median weighted residual; MDAWR = median absolute weighted residual.

hospital in satisfactory condition. Approximately 70% of patients required inotropic support either in the operating room or the ICU. Renal failure developed in none. None required additional sedatives during the midazolam study.

Of the 90 patients enrolled in the study, 27 were excluded for the following reasons: plasma midazolam samples could not be assayed because of interfering peaks for 12 patients; the computer files documenting the drug infusion schemes were not available for six patients; and the drug infusion schemes for nine patients

Table 4. Pharmacokinetics Parameters for MEM Three-compartment BSA-adjusted Model

Parameter	Estimate	CV (%)
Estimated parameters		
V_1 (l)	33	60
V_2 (l)	3.32 + BSA × 32.1	24
V_3 (l)	365	85
Cl_1 ($l \cdot min^{-1}$)	0.0889 + BSA × 0.151	40
Cl_2 ($l \cdot min^{-1}$)	0.622	49
Cl_3 ($l \cdot min^{-1}$)	0.264	55
Performance measures		
MDWR (%)	−0.08	
MDAWR (%)	24.26	
Objective function	9182.68	

MEM = mixed-effects model; CV = coefficient of variation; BSA = body surface area; MDWR = median weighted residual; MDAWR = median absolute weighted residual.

||||Youngs EJ, Wada DR, Verotta D, Shafer SL: Comparison of pooled-data and population approaches when the structural model is misspecified. Proceedings of the 1996 Western Multi-conference 1996:154–8

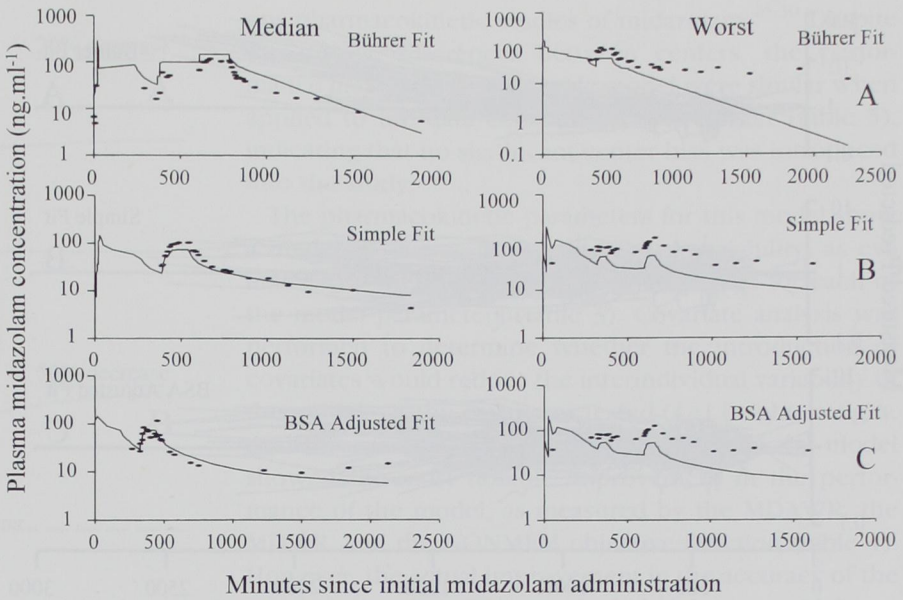

Fig. 1. Plasma midazolam concentration over time for the median and worst performances of (*A*) the Bührer *et al.*[26] model, (*B*) the newly derived simple model, and (*C*) the newly derived body surface area–adjusted model. The solid circles represent measured midazolam concentrations; the solid lines represent the concentrations predicted by the population models.

did not match the plasma concentration profiles, indicating serious technical problems. From a total of 1,708 midazolam plasma samples collected from the 63 evaluable patients, 27 samples (1.6%) were excluded from the final analysis. These 27 observations were excluded either on the basis of physiologic impossibility (*e.g.*, a large increase in the measured midazolam concentration as a single observation when no additional drug had been given) or because of the potential for introducing bias (*e.g.*, observed values in the terminal elimination phase *after* previous plasma concentrations decreased below the limits of detection of the assay). Table 2 shows the demographics and the midazolam infusion characteristics for the 63 patients included in the pharmacokinetic analysis. The number of samples included in the analysis was 1,681.

The addition of a third compartment resulted in notable improvements in the objective function, precision, and bias estimates and smoother residual error plots in both MEM and naïve pooled analyses. Therefore, a three-compartment model was chosen over a two-compartment model. Although previous studies suggest that naïve pooled analyses can perform at least as well and sometimes better than MEM analysis in estimating pharmacokinetic parameters,[32] both techniques described the data from this study with comparable accuracy. Because the MEM model also provided estimates of the interindividual variability, it was selected over the naïve pooled model in this study. The parameters of the three-compartment MEM model are shown in the last column of table 3. Values in parentheses are the standard deviations of these calculated parameters in the log domain, which are approximately equal to the CVs for the volumes and clearances, and reflect the interindividual variability of these parameters. Table 3 also shows the pharmacokinetic parameters derived for midazolam in three previous studies. The first set of results is from the study by Greenblatt *et al.*[10] in healthy volunteers. The second set of pharmacokinetic parameters is from the study conducted by Bührer *et al.*[26] in healthy volunteers; these are the pharmacokinetic parameters initially used in the TCI in this study. The third column lists the pharmacokinetic parameters for midazolam estimated from the study of patients after CABG surgery by Maitre *et al.*[30]

Height, weight, age, BSA, and BMI were introduced sequentially into the simple three-compartment model as covariates in an attempt to improve the quality of the fit and to account for part of the observed interindividual variability. The accuracy of the model was improved most notably with the addition of BSA, which was lin-

Table 5. MDWR and MDAWR of the Simple Model for Different Centers

	Duke	Emory	PAVA
MDWR (%)	−6.99	8.88	4.56
MDAWR (%)	27.78	19.15	30.42

MDWR = median weighted residual; MDAWR = median absolute weighted residual; PAVA = Palo Alto VA.

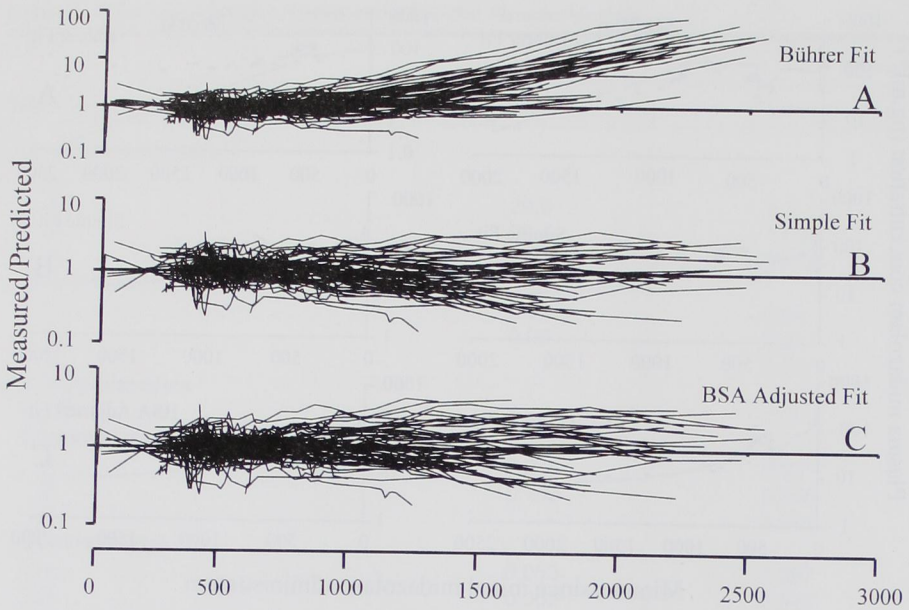

Fig. 2. The residual error plots expressed as measured/predicted plasma midazolam concentrations over time, for (*A*) the Bührer *et al.*[26] model, (*B*) the newly derived simple model, and (*C*) the newly derived body surface area–adjusted model. The error (Y) scale for the Bührer *et al.*[26] results is 10 times greater than the Y scale in plots B and C.

early correlated with V_2 and Cl_1, as listed in table 4. Compared with the simple model with no covariates, adding BSA as a covariate improved MDWR from 1.39 to −0.08 even though MDAWR was unchanged at approximately 25%. The objective function also improved significantly by 21 points.

Figure 1A shows the median and worst performances of the Bührer model that were programmed into the TCI device. Figures 1B and 1C represent the median and worst performances of the simple and the BSA-adjusted models derived from this study, respectively. These fits were selected according to individual MDAWRs for each model. This figure suggests that in individual patients, the newly derived pharmacokinetic parameters describe the data better than the original Bührer pharmacokinetic parameters for midazolam. The corresponding residual error plots for these three models are shown in figure 2. It can be seen from figure 2A that during the first 12 h, the infusion rates calculated from Bührer's kinetics achieved the target plasma concentrations with reasonable accuracy. During the postinfusion phase, however, the measured concentration was consistently higher than the predicted concentration, with the error increasing progressively. The newly derived pharmacokinetic parameters from both the simple and the BSA-adjusted models for midazolam describe the data more accurately than the Bührer model during both the infusion and the postinfusion phases.

The performance of the simple model at all three centers was unbiased. The variability was smallest at Emory and largest at PAVA. Table 5 summarizes the accuracy and bias of the simple model for each of the study centers.

Cross-validation analysis was performed on both derived models and is described in appendix 1.

Plasma levels of the 1-hydroxymidazolam metabolite were measured simultaneously with the parent compound in all samples. 1-Hydroxymidazolam levels were above the detection limit in seven persons and were at most only 20% of the corresponding concentration of the parent compound. Furthermore, the concentrations of 1-hydroxymidazolam were not detectable during the postinfusion phase in any of these patients.

Figure 3 shows the 20%, 50%, and 80% plasma decrement times for midazolam based on the pharmacokinetics determined in this study and those of Bührer *et al.*[26] As will be seen in a companion manuscript,[24] the midazolam concentrations must typically decrease by at least 50% for patients to awaken from adequate sedation. Figure 3 suggests that a 50% decrease will require 1 to 2 h for infusions of less than 12 h in duration. After 12 h, the time necessary for a 50% decrease in concentration increases to 3 h for a 24-h infusion and to 4 h for a 36-h infusion. If patients are maintained at a very deep level of sedation, so an 80% decrease in plasma concentration is necessary for emergence, then after an infusion of 24 h patients may not awaken until 20 h after the infusion is discontinued (fig. 3C).

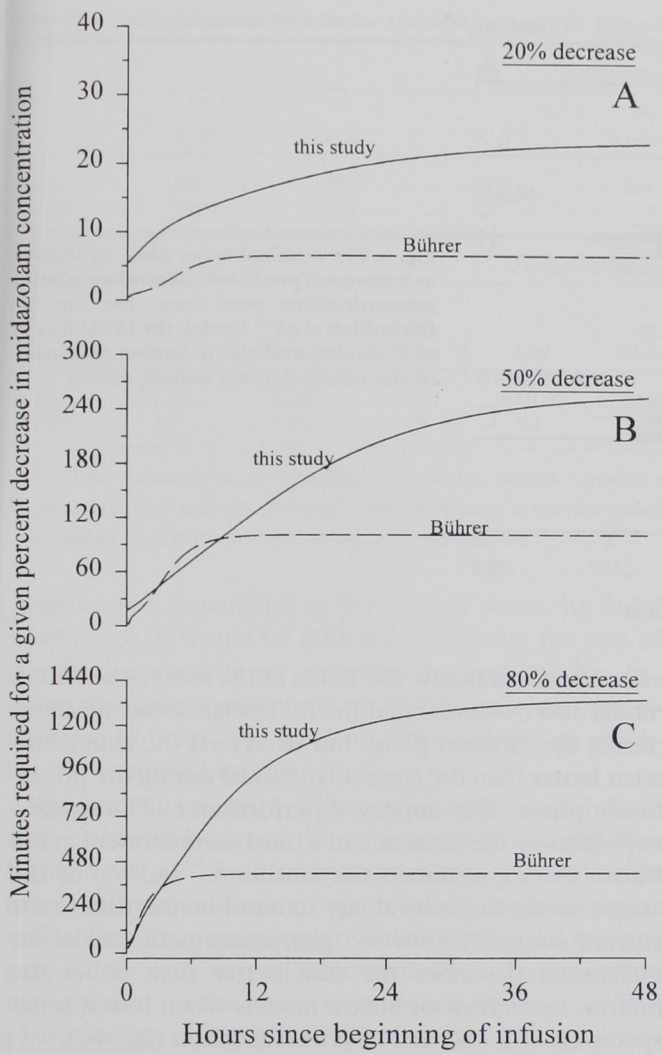

Fig. 3. The context-sensitive recovery times for midazolam using the Bührer *et al.*[26] kinetic model (dashed line) and the newly derived simple model (solid line) for (*A*) 20%, (*B*) 50%, and (*C*) 80% decrease in plasma midazolam concentration after the midazolam infusion is discontinued.

Discussion

The demographics of the patients studied were similar for all three study sites (table 2). Those studied at PAVA received higher average doses of midazolam (48 mg) than did patients studied at either Emory or Duke (33 mg and 29 mg, respectively). Duke patients received the shortest duration of midazolam infusion (8 h, from the start of infusion in the operating room) compared with Emory and PAVA subjects (10 h and 12 h, respectively).

The pooled data collected in this study were best described by a simple three-compartment mammillary model; this is in agreement with the results from previous pharmacokinetic studies of midazolam.[26,30] Despite the dosing differences between centers, the performance measures of this simple model were similar when applied to the data collected at each center (table 5), indicating that no significant center bias was introduced into the study.

The pharmacokinetic parameters for this model show a moderate degree of interindividual variability, as evidenced by the relatively large CVs obtained for each of the model parameters (table 3). Covariate analysis was performed to determine whether the introduction of covariates would reduce the interindividual variability of the model. Of the covariates tested (*i.e.*, height, weight, age, BSA, and BMI), the addition of BSA to the model showed the most notable improvement in the performance of the model, as measured by the MDAWR, the MDWR, and the NONMEM objective function (table 4). However, the actual improvement in the accuracy of the estimations when BSA was included in the model was trivial, as seen in figures 2B and 2C. Furthermore, there was no improvement in the CVs of the calculated volumes and clearances. These findings suggest that the addition of BSA as a model covariate does not improve the ability of the model to predict drug concentrations in individual patients. This is shown in figures 1B and 1C.

Both the simple and the BSA-adjusted models were tested using cross-validation (described in the appendix). This enabled us to estimate the prospective performance of both models during clinical conditions identical to those in this study. The results of the cross-validation analysis did not confirm the superior performance of the BSA-adjusted model over the simple model. On this basis, despite the intuitive appeal of adjusting volumes and clearances to BSA (or some other measure of size), such adjustment was not supported in this study. We concluded that the simple three-compartment model was likely to outperform the BSA-adjusted model in prospective tests.

The individual midazolam pharmacokinetic parameters estimated in the current study differ considerably from the pharmacokinetic parameters of Bührer *et al.*[26] that we used to administer midazolam (table 3). In comparing the MDWR and MDAWR in table 3, the Bührer model appears to perform in a similar manner as the newly derived three-compartment model. However, this reflects similar performance during the infusion, when most of our samples were gathered. During this portion of the study, the concentrations are heavily determined by metabolic clearance (Cl_1), and clearance of the pharmacokinetics of Bührer *et al.*[26] (0.54 l/min) is similar to

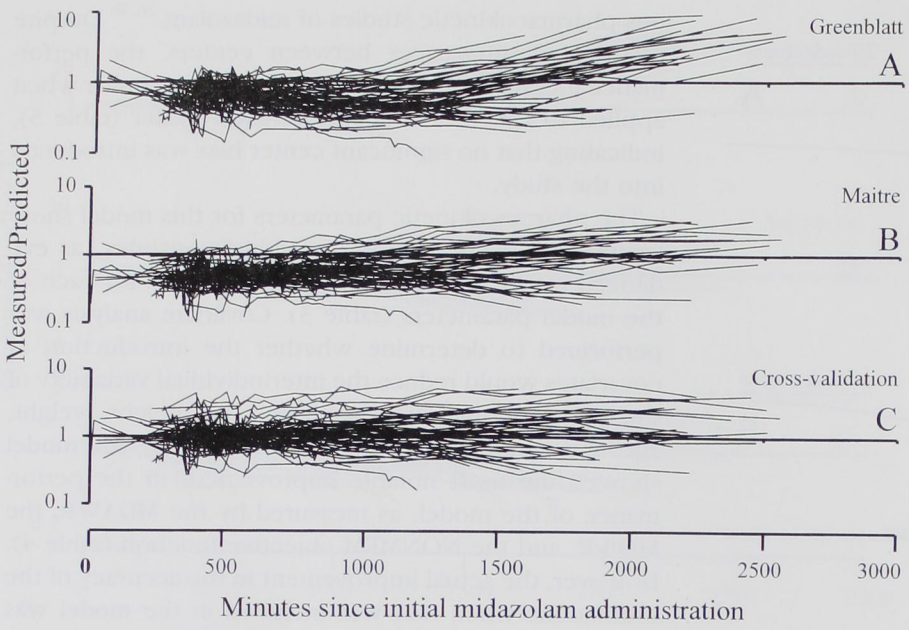

Fig. 4. The residual error plots expressed as measured/predicted midazolam plasma concentrations over time, for the (*A*) Greenblatt *et al.*[10] model, the (*B*) Maitre *et al.*[30] model, and the (*C*) cross-validation of the newly derived simple model.

that in our patients (0.43 l/min), which may account for the similar median errors. The plasma concentration plots for individual patients (figs. 1A and 1B) and the residual error plots for all patients (figs. 2A and 2B) show that the newly derived pharmacokinetic model outperforms the Bührer pharmacokinetic model uniformly in the postinfusion phase. The superior performance of the revised model is reflected in the lower objective function obtained for the revised model compared with the Bührer model (table 3).

The pharmacokinetic parameters for midazolam derived from the current study differ markedly from those obtained by Greenblatt *et al.*[10] and Maitre *et al.*[30] (table 3). The volumes and clearances from each of these models were tested against the data collected from the current study to compare their performance to the existing model. The Greenblatt and Maitre models proved to be more biased and less precise, as evident by the higher MDWR, MDAWR, and objective function values. The residual error plots in figure 4 graphically compare the performance of the Greenblatt and Maitre models to the cross-validation of the existing model. The Greenblatt model generally overestimated the midazolam plasma concentrations during the infusion phase and underestimated them during the postinfusion phase. This is most likely explained by the absence of a third compartment in the Greenblatt model. Because the subjects in the Greenblatt *et al.*[10] study received much smaller doses of midazolam (*i.e.*, 5 mg), the contribution of the third compartment to the model occurred at concentrations below the limits of the assay. The Maitre model also overestimated the midazolam concentrations during the infusion phase but described the data somewhat better than the Greenblatt model during the postinfusion phase. This improved performance is most likely explained by the presence of a third compartment in the Maitre model, although the smaller V_3 and V_{ss} of the Maitre model limits its ability to describe the data in the current study. The revised pharmacokinetic model for midazolam describes the data better than either the Bührer, Greenblatt or Maitre models when tested retrospectively (fig. 2B) and in cross-validation (fig. 4C).

The differences observed between the volumes and the clearances derived in this study and those obtained in the Bührer *et al.*[26], Greenblatt *et al.*,[10] and Maitre *et al.*[30] studies are most likely explained by differences in the study populations, drug dosing, and study design. In the Bührer *et al.*[26] study, patients were much younger (mean age, 38 yr) and healthier than those in the current study. The patients in the Bührer *et al.*[26] study also received much smaller intravenous doses of midazolam during a shorter period (*i.e.*, 3.75 to 25 mg, with an average dose of 13 mg, administered over 3–5 min), thereby potentially influencing the estimates of both the volumes and the clearances obtained in this study. Although the volume and clearance estimates from the Greenblatt *et al.*[10] study shown in table 3 were derived from older patients (mean age, 68 yr), the intravenous dose administered to these patients was substantially less (*i.e.*, 2.5 to 5 mg as a single bolus injection) than the dose

Table 6. Cross-validation Results for the Simple and the BSA-adjusted Models

	Cross-validation Results for the Simple Model							
	V_1 (l)	V_2 (l)	V_3 (l)	CL_1 ($l \cdot min^{-1}$)	CL_2 ($l \cdot min^{-1}$)	CL_3 ($l \cdot min^{-1}$)	MDWR (%)	MDAWR (%)
Mean	30.2	55.8	278	0.411	0.667	0.276	−1.5	25.5
CV (%)	12	23	27	7	16	10	13*	23

	Cross-validation Results for the BSA-adjusted Model									
	V_1 (l)	V_2 Intercept	V_2 *vs.* BSA Slope	V_3 (l)	CL_1 Intercept	CL_1 *vs.* BSA Slope	Cl_2 ($l \cdot min^{-1}$)	Cl_3 ($l \cdot min^{-1}$)	MDWR (%)	MDAWR (%)
Mean	31.34	4.05	36.01	646.3	0.149	0.123	0.739	0.302	6.58	26.53
CV (%)	14	119	17	54	89	21	15	27	20*	42

BSA = body surface area; CV = coefficient of variation; MDWR = median weighted residual; MDAWR = median absolute weighted residual.

Values are as mean and CVs of the estimated parameters in the nine groups with the respective MDWR and MDAWRs of the excluded groups.

* The quoted value is the standard deviation (SD) on MDWR.

administered to patients in the current study. At these small doses, it would be difficult to estimate the size of the third compartment and the terminal half-life, because the drug concentrations would be expected to decrease to below the levels of detection before reaching the terminal log-linear phase.

We cannot explain the differences in volume and clearance estimates between the current study and and that by Maitre *et al.*[30] Both subject groups were comparable in age and weight. Both groups received similar doses of midazolam for postoperative sedation after CABG surgery. There were several differences in study design that may account for the observed differences in results. The pharmacokinetic analysis of the Maitre *et al.*[30] study was based on a smaller number of patients (*i.e.*, 12 *vs.* 63 patients) and fewer plasma samples (240 samples *vs.* 1,681 samples). In addition, the patients included in the Maitre *et al.*[30] study were all from the same institution, whereas the current study included patients from three different centers. Traditional zero-order infusion systems were used to administer midazolam to patients in the Maitre *et al.*[30] study, whereas a TCI system was used to administer the drug in the current study. Gustafsson *et al.*[33] have shown that administering drugs using standard infusion pump systems results in less predictable plasma concentrations and less accurate histories of drug administration, which can introduce significant errors into pharmacokinetic analyses. The midazolam infusion in the Maitre *et al.*[30] study was also not initiated until the patients arrived in the ICU; in the current study, some of the midazolam was administered during operation and could have been absorbed by the cardiopulmonary bypass system, thereby reducing plasma concentrations and increasing estimates for V_2 and V_3. If this were the case, we would have expected that the performance of the model in the Maitre *et al.*[30] study in describing our observations would be worse during the early stages of the infusion and then improve progressively with subsequent drug administration. This is not evident from the residual error plots. Regardless of the explanation for the observed differences, the midazolam pharmacokinetics reported by Maitre *et al.*[30] do not accurately describe the observations from the current multicenter study.

We did not try to estimate the effects of surgery, anesthesia, or cardiopulmonary bypass on midazolam pharmacokinetics. At two centers, midazolam levels were drawn during surgery, so the pharmacokinetic model incorporates some intraoperative observations. The midazolam concentration was sampled intensively when patients arrived in the ICU. The early time course of midazolam concentration at arrival in the ICU mostly reflects the disposition of midazolam administered during operation. Therefore, although few intraoperative samples were gathered, the pharmacokinetic model incorporates the pharmacokinetics of intraoperatively administered midazolam, as observed in the postoperative recovery period.

Context-sensitive recovery times are more meaningful parameters to consider than half-lives when drugs are infused. They are useful descriptors of postinfusion central compartment kinetics.[31] The pharmacokinetics of the new model predict recovery similar to that for the Bührer pharmacokinetics for infusions less than 6 h, but beyond this time they predict much slower recovery.

In conclusion, midazolam is commonly administered to patients for postoperative sedation after CABG surgery to prevent agitation and cardiopulmonary instability. The pharmacokinetics of midazolam in patients undergoing CABG who receive continuous infusions differ from the pharmacokinetics in healthy patients who receive small doses of midazolam for brief periods. Despite the number of patients studied (n = 63) and the multicenter design, the volumes and clearances for midazolam were more homogeneous among our study population than we expected based on the many reports of high variability.[13,17–19] This may reflect the relatively homogeneous physical status of patients requiring CABG surgery compared with other patients who require intensive care for critical, multiple-organ illnesses. A simple three-compartment model (with no covariates) predicted the plasma midazolam concentrations after CABG surgery with a median absolute error of 26% in the cross-validation. The addition of physiologic covariates to the model did not improve the model's performance in cross-validation.

Understanding the pharmacokinetics of midazolam after CABG surgery and estimating the predictive ability of pharmacokinetic models may promote the development of rational dosing guidelines for titrating midazolam in this patient population. Appropriate dosing can be expected to provide adequate levels of sedation, reduce the incidence of cardiopulmonary depression associated with excessive sedation, and speed the recovery of normal mental status after the midazolam infusion is discontinued.

Appendix 1

The cross-validation analysis included the following steps: (1) the entire sample studied was divided randomly into nine smaller groups of seven patients each; (2) one group was excluded and the model was fit to the remaining patients to estimate the structural parameters; and (3) the structural parameters were then used to predict the observations in the excluded group and estimates of MDWR and MDAWR were thus obtained. Because the excluded group's data were not used to develop the model, the MDWR and MDAWR parameters are nearly unbiased estimates of the predictive ability of the model. Steps 2 and 3 were performed in turn for each group. Although cross-validation is not a truly prospective validation, it is an established method to estimate model performance during identical experimental conditions.[34]

Cross-validation analysis was performed with the newly derived parameters of both the simple and the BSA-adjusted three-compartment models using MEM analysis. The entire population was divided randomly into nine groups of seven patients (groups A–I), and cross-validation was performed as described before. The first two rows of table 6 show the results for the simple model and the last two rows are for the BSA-adjusted model. The values shown are the mean and CVs of the estimated parameters in the nine groups together with the respective MDWR and MDAWRs in the excluded groups.

In the simple model, the mean estimates of the pharmacokinetic parameters in the cross-validation analysis closely resembled those of the simple model. In addition, the CVs of these mean volume and clearance estimates obtained from the cross-validation analysis were less than 30%, suggesting that the simple model derived from the current study is likely to perform well in truly prospective trials during similar conditions. The absolute magnitude of the predictive bias (MDWR) of the simple model increased slightly, as expected, from 1.39% to 1.5% in the cross-validation, whereas the predictive precision (MDAWR) remained constant at approximately 25% (compare tables 5 and 6).

In contrast to the simple model, the cross-validation analysis of the BSA-adjusted model shows a greater variability in the parameter estimates between groups. The CVs for these parameters ranged from 14% for V_1 to 120% for the V_2 intercept, indicating considerable uncertainty in the parameter estimates. In addition, the predictive bias of the BSA-adjusted model increased from −0.08% to 6.58%, and the predictive precision decreased by 2% with cross-validation analysis (compare tables 4 and 6). The mean MDAWR for the cross-validation analysis (26.5%) is greater than that calculated from the original MEM fit (24.3%) and is also greater than that calculated in the cross-validation of the simple model (25.5%).

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