Eur J Clin Pharmacol (1989) 37: 161-166

European Journal of Clinical Pharmacology

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Pharmacokinetics of midazolam in patients recovering from cardiac surgery

P. O. Maitre[1], B. Funk[1], C. Crevoisier[3], and H. R. Ha[2]

[1] Department of Anesthesiology and
[2] Division of Clinical Pharmacology and Department of Internal Medicine, University of Basle and
[3] Hoffmann-La Roche & Co Ltd, Basle, Switzerland

Summary. The pharmacokinetics of midazolam has been studied in patients recovering from cardiac surgery, who required sedation for postoperative mechanical ventilation. Twelve males (mean age 64.5 years) with severe heart disease received an infusion of midazolam 15 mg·h^{-1} for 4 h, starting 1 to 3 h post surgery. Multiple blood samples were collected from each patient during the infusion and up to 48-93 h after it. The pharmacokinetic parameters of midazolam were determined using both moment analysis and the program NONMEM.

The average terminal half-life was 10.6 h. The prolonged elimination was mainly due to a decrease in its metabolic clearance (0.25 l·min^{-1}).

The maintenance infusion dose of midazolam in such patients should be reduced. The time to recovery after stopping an infusion depends upon the amount of drug in the body at that time and a simulation of the plasma concentrations after various infusion regimens suggests that recovery will be delayed after prolonged (> 48 h) administration of midazolam to these patients. However, after shorter infusions (< 12 h), redistribution of the drug away from the site of action was still occurring and recovery would be expected to be relatively rapid.

Key words: midazolam; benzodiazepine, pharmacokinetics, biotransformation, surgery, prolonged recovery

Midazolam, the only benzodiazepine water-soluble as a salt, is used as a sedative or hypnotic agent in anaesthesia and intensive care. When given to healthy volunteers or patients, midazolam is regarded as a short acting drug, with an elimination half-life ranging from 2.0 to 3.7 h [1-5]. Disease states and variations in the morphology and physiology of patients have been shown to influence the pharmacokinetics of midazolam; for example, old age and obesity prolong its elimination half-life up to 5.6 and 8.4 h, respectively [3].

Midazolam has much faster elimination than diazepam and does not pain on intravenous injection, and therefore is one of the preferred hypnotics for sedating patients in intensive care units (ICU). Shapiro et al. [6] have shown that a midazolam infusion can provide safe and effective sedation in critically ill patients. Two anecdotal reports by Byatt et al. [7] and by Byrne et al. [8] mentioned a markedly prolonged elimination half-life of midazolam in 8 ICU patients, ranging from 4.3 to 53 h. All but two patients were more than 60 years old, and they all were in poor condition and required mechanical ventilation. A recent study [9] in 17 patients on mechanical ventilation reported a prolonged elimination half-life for midazolam (mean 11.4 h calculated from the reported data), but there was a very wide inter-patient variability in the kinetics of midazolam. The heterogeneity of the diseases of ICU patients, and the large variability between them in the time course of their diseases, makes it difficult to implement a controlled study of the kinetics. As an approach to this problem, recovery from cardiac surgery has here been chosen as an example of a major surgical and metabolic insult and the pharmacokinetics of midazolam has been examined in such patients, selecting those at greatest risk of postoperative complications, i.e. those who might require sedation over a long (> 24 h) period for artificial ventilation.

Materials and methods

Patients were studied after corrective cardiac surgery for multivessel coronary artery disease, severe valvular disease, combined coronary and valvular disease or pending infarction (Table 1). Exclusion criteria were limited to significant preoperative hepatic or

Table 1. Details of the patients and their courses

Patient	Age (years)	Weight (kg)	Surgery	Post surgery clinical course
A	73	75	three vessels CABG	Reoperation for mediastinal bleeding
B	81	57	AVR	Delayed extubation
C	55	71	three vessels CABG	Uneventful
D	63	71	four vessels CABG	Uneventful
E	61	68	single vessel CABG + AVR	Delayed extubation for respiratory complications
F	72	72	single vessel CABG for pending infarct	Resuscitation
G	53	71	four vessels CABG	Uneventful
H	72	86	four vessels CABG	Uneventful
I	57	73	three vessels CABG	Uneventful
K	53	83	four vessels CABG	Intra-aortal balloon counterp.
L	70	80	three vessels CABG	Uneventful
M	64	68	single vessel CABG + AVR	Uneventful
Mean:	64.5	73	AVR = aortic valve replacement	
(SD):	(8.7)	(7.3)	CABG = coronary artery bypass graft	

renal dysfunction, or allergy to benzodiazepines. After institutional approval, 12 male patients undergoing open heart surgery gave informed consent to the study. The patients received 5 to 15 mg diazepam or 15 to 50 mg oxazepam on the preceding evening and were premedicated before surgery with i.m. morphine and scopolamine. Anaesthesia was induced with thiopental, etomidate or fentanyl, and then maintained with fentanyl. Diazepam, enflurane, nitrous oxide or droperidol were also used occasionally as adjuvants to anaesthesia. Muscle relaxation was maintained with pancuronium. After cardiopulmonary bypass, a continuous infusion of nitroglycerine was started and was maintained throughout the study period. After the operation had been completed, the patients were brought to the intensive care unit (ICU) and were artificially ventilated overnight. Haemodynamic stability was maintained by titrating sympathomimetic drugs (dopamine or adrenaline), vasodilators (nitroglycerine and sodium nitroprusside) and volume replacement.

One to 3 h after arrival in the ICU, the patients required sedation to tolerate the endotracheal tube and an i.v. infusion of midazolam 15 $mg \cdot h^{-1}$ was given for 4 h. Patients requiring more sedation after the standard infusion of midazolam were given morphine i.v. The dose of midazolam (60 mg in 4 h) received is equivalent to the total dose normally administered over 24 to 36 h for sedation. This relatively large dose permitted accurate characterisation of the elimination phase by making drug detectable for a longer period of time.

Cardiac output was measured before and at the end of the infusion of midazolam, and then approximately every 12 h. Each measurement was performed in triplicate by the thermodilution technique, and the mean value is reported. A blank blood sample was obtained before starting the infusion for determination of midazolam protein binding and to verify that the plasma did not contain any midazolam. During the infusion of midazolam, blood samples were collected in heparinized tubes every 30 to 60 min. After discontinuation of the infusion, sampling was performed at logarithmically spaced time intervals for the first 12 h, and then approximately every 12 h until 48 to 93 h post infusion. After centrifugation, plasma was kept at $-20°C$ until assayed.

Plasma for the protein binding analysis was obtained from the predose samples. Total plasma concentrations of midazolam in the range 923–995 $ng \cdot ml^{-1}$ were achieved by adding small amounts of midazolam in isotonic phosphate buffer (Sørensen pH = 7.4) to the plasma samples. The specific radioactivity of ^{14}C-midazolam was 75.64 $\mu Ci \cdot mg^{-1}$ and the radiochemical purity was 97%. Plasma protein binding was determined in duplicate by equilibrium dialysis using Dianorm Teflon dialysis cells (Diachema Inc., Switzerland) and Union Carbide Corporation cellulose tubing (presoaked in buffer) with a molecular weight cutoff of 8000 Da. Spiked plasma samples of 900 µl were dialyzed for 4 h against an equal volume of isotonic phosphate buffer at 37° C. Aliquots from both sides of the membrane were removed and assayed for midazolam by liquid scinitillation counting.

The plasma concentration of midazolam was measured by gas liquid chromatography with electron capture detection, after extraction with n-hexane, evaporation of the n-hexane and solution in butyl acetate [10]. The lower limit of determination was 1 $ng \cdot ml^{-1}$. Each measurement was performed in duplicate and the average value is reported. The method is quite specific for midazolam, and any concomitant drugs that the patients received were shown not to interfere with the assay, especially not diazepam and its metabolites.

The pharmacokinetic characteristics of midazolam in each patient were determined using two different approaches. Noncompartmental moment analysis was first used to assess the individual pharmacokinetics in each patient. The area under the curve of the measured concentration of midazolam vs time (AUC) and the area under the first moment curve (AUMC) were calculated by numerical integration using the trapezoidal rule. Three pharmacokinetic parameters were obtained: the elimination clearance (CL_e), mean residence time (MRT) and apparent volume of distribution of midazolam at steady state (V_z). The nonlinear regression program NONMEM[1] was used to obtain average pharmacokinetic parameters for the group of patients. This program concurrently analyzes pooled data from different patients. It estimates the average value of the pharmacokinetic parameters for the group, and also calculates the variability of the pharmacokinetic parameters between patients. NONMEM is traditionally used to analyze observational data when there are few data points per patient. Despite the fact that there were sufficient data points to determine the pharmacokinetic parameters in each patient by conventional curve fitting, it was decided to use NONMEM because a relationship between cardiac output and pharmacokinetic parameters was being sought, and it was more convenient to do so with the library of programs in NONMEM than with other conventional curve fitting programs. Using NONMEM, the data were fitted to a 2-compartment and then to

[1] Beal SL, Sheiner LB (1980) NONMEM Users Guide. Division of Clinical Pharmacology, University of California, San Francisco

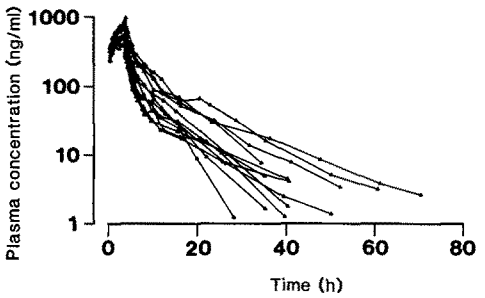

Fig. 1. Midazolam plasma concentration-time profile during and after infusion of midazolam 15 $mg \cdot h^{-1}$ for 4 h

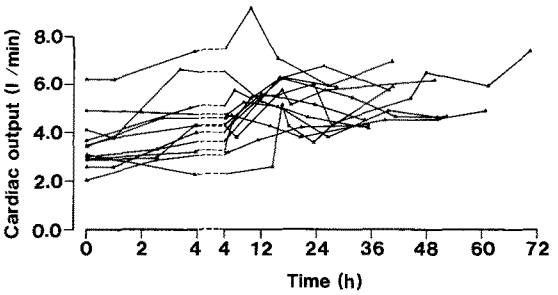

Fig. 2. Time course of postoperative cardiac output in the group of 12 patients. The time scale has been expanded for the first 4 h, i.e. during infusion of midazolam

a 3-compartment open model with elimination from the central compartment. Linear pharmacokinetics were assumed (i.e. the pharmacokinetic parameters are assumed to be independent of the concentration). Further assumptions regarding the NONMEM model have been described by Sheiner [11]. The following parameters were estimated by the regression program for the 3-compartment model: elimination clearance (CL_e), fast distribution clearance, slow distribution clearance, and the volumes of the three compartments. For the 2-compartment model, the parameters were CL_e, distribution clearance and volume of the central and peripheral compartments. To choose whether the 2 or 3 compartment model was more appropriate, the following criteria were considered: the difference in the log likelihood value (asymptotic chi square distribution), which is supplied by NONMEM, the standard error of the parameters, and the plots of the residuals. Correlations were sought between body weight or cardiac output and the pharmacokinetics of midazolam by entering various models in the NONMEM program, which describe the effect of body weight or cardiac output on the initial volume of distribution, the fast distribution clearance and the elimination clearance. The same criteria as above were used to determine whether entering those individual factors in the pharmacokinetic model would help to account for pharmacokinetic variability between patients.

Results

Details of the 12 patients are shown in Table 1. No major intra-operative complications were reported, and all patients were brought uneventfully to the ICU. The postoperative complications are reported in Table 1.

For each patient, an average of 20 blood samples (range 18 to 23) was taken for assay of midazolam. In 9 patients, the midazolam concentration was below the determination limit ($<1\ ng \cdot ml^{-1}$) before the end of the study period. The plasma concentration-time profiles for the 12 patients are shown in Fig. 1. This figure is not intended to show the detail of each individual concentration-time profile, but rather to show the average tendency, as well as inter-patient variability in the pharmacokinetics of midazolam in this group.

The time course of the cardiac output in the 12 patients is depicted in Fig. 2. Although the protocol was not designed for a specific study of the effect of midazolam on haemodynamics, it can be seen that on average the cardiac output was stable during the infusion of midazolam, despite the high plasma midazolam concentration obtained (Fig. 2).

The individual pharmacokinetic parameters obtained using moment analysis are shown in Table 2. On average, the fraction AUC (0-t)/AUC was 0.98; this fraction close to 1.0 reflects the fact that many late blood samples were obtained during the elimination phase, which permitted precise characterisation of the pharmacokinetics in the patients.

When using NONMEM, the 3-compartment model was preferred over the 2-compartment model to describe the midazolam plasma concentration-time course (chi square: $p < 0.005$). As normalization of the parameters for body weight did not improve the fit the reported results are not weight-normalized. No relationship was found between cardiac

Table 2. Moment analysis: Pharmacokinetic parameters of midazolam

Patient	Fraction AUC (0-t)/AUC	MRT (h)	CL_e (l/min)	V_z (l)
A	0.99	8.17	0.18	90.5
B	0.99	4.76	0.34	96.1
C	0.99	3.50	0.37	77.2
D	0.92	6.38	0.20	77.6
E	0.99	7.84	0.20	93.6
F	0.99	5.34	0.19	61.8
G	0.99	2.52	0.30	45.8
H	0.99	4.54	0.42	113.5
I	0.96	5.80	0.34	119.3
K	0.97	4.88	0.39	113.1
L	0.97	5.83	0.44	153.8
M	0.99	4.57	0.28	77.0
Mean:	0.98	5.34	0.30	93.3
(SD):	(0.02)	(1.55)	(0.09)	(27.7)
CV:		29%	30%	30%
Mean using a log transformation:		5.10	0.29	89.0

CV - coefficient of variation calculated as SD*100/mean. It indicates interindividual variability of the pharmacokinetic parameters

Table 3. NONMEM estimates of pharmacokinetic parameters of midazolam

Parameters estimated by NONMEM	Average estimated value for the group of patients (SEM)[a]	Inter-individual variability (coeff. of variation)
Total body clearance	0.25 (0.018) l·min^{-1}	36%
Fast distribution clearance	0.38 (0.052) l·min^{-1}	39%
Slow distribution clearance	0.11 (0.015) l·min^{-1}	8%
Initial volume of distribution	10.3 (1.66) l	29%
Volume of 2nd compartment	27.8 (2.57) l	33%
Volume of 3rd compartment	65.5 (6.65) l	37%
Residual intra-individual variability	11% (coeff. of variation)	
Derived values		
Volume of distribution at steady-state	103.6 l	
Terminal elimination half-life	10.6 h	

[a] SEM represent the uncertainty in the estimation by NONMEM of the average values of the parameters in the 12 patients

output and pharmacokinetics. The average pharmacokinetic estimates for the patients obtained with NONMEM are displayed in Table 3. From those estimates, an average elimination half-life of 10.6 h was calculated. For each parameter, NONMEM provided an estimate of the variability of the pharmacokinetic parameters between patients (Note: it is unusual in a NONMEM analysis to obtain an estimate of the interindividual variability for each parameters, especially when the number of patients is not large, but this was possible here probably because of the large number of data per patient).

The protein binding of midazolam was within normal limits for all patients (mean percentage bound to plasma protein (SD): 97.43 (0.47)%) when compared to previously published values [3, 12].

Discussion

The NONMEM model implicitly assumed a log-normal distribution of pharmacokinetic parameters in the population, so the pharmacokinetic parameter values in Table 3 must be compared with those in Table 2 using the same distribution. The comparison shows that the metabolic clearance estimated by NONMEM (0.25 l·min^{-1}) was slightly smaller than the average value obtained by moment analysis (0.29 l·min^{-1}). The difference might be due to the different statistical models used by each method. In particular, NONMEM uses a more sophisticated statistical model, taking into account both inter-patient variability in the pharmacokinetic parameters and the intraindividual variability. Variability in CL between patients was 36% and 30% (coefficients of variation) when estimated using NONMEM and moment analysis, respectively. These figures are in accordance with inter-individual variability in the clearance of other drugs [13, 14]. Finally, there is a moderately good agreement for average V_z obtained using either NONMEM (103.6 l) or moment analysis (89.0 l). Inter-patient variability in V_z was 30%.

The pharmacokinetic parameters of midazolam reported here differ markedly from previously published values. The elimination that observed in our patients ($t_{1/2}$ elimination = 10.6 h) was much longer than the value reported by Harper et al. [1] ($t_{1/2}$ = 4.6 h) in patients of similar age after cardiac surgery. Two reasons may account for the discrepancy:

More seriously ill patients were studied here, since the protocol excluded patients with uncomplicated single coronary artery disease. The subjects were more likely, therefore, to have postoperative complications and to require prolonged ventilation. Indeed, 5 patients had postoperative complications, of whom 3 remained intubated longer than 24 h. This population was investigated because such critically ill patients are most likely to require prolonged ventilation and sedation. Although not stated explicitly in the study by Harper et al., their patients might have been in a better condition than ours. Physiological-pharmacokinetic interactions induced by disease are expected to be more prominent in patients with a more severe illness, and this could account for the longer elimination half-life in the present group.

(2) As pointed out by Jusko [15], a common problem in pharmacokinetics is incomplete measurement of drug washout from the body, caused either by premature termination of sample collection or by analytical limitations. In the study by Harper et al., [1] the sampling time was limited to 12 h, and under those conditions their value for elimination half-life (4.6 h) is likely to be an underestimate. A larger dose of midazolam was administered here, which gave measurable plasma concentrations of the drug for a longer period, and extensive samples were collected during the elimination phase, up to 48–93 h post infusion. This is reflected by the high average AUC (0-t)/AUC ratio (0.98; Table 2) and means that the pharmacokinetics could accurately be characterised. The result confirms the findings of Byatt et al. [7] and of Byrne et al. [8] that the elimination of midazolam

can be prolonged in certain categories of ICU patients. However, no patient in our group approached the very long half-life (53.3 h) observed by Byrne in a 71 year-old artificially ventilated man. Finally, the mean $t_{1/2}$ elimination (11.4 h) calculated from the recent data of Oldenhof et al. [9] obtained in patients on mechanical ventilation is very close to the present value (10.6 h).

Elimination half-life is a function of the rate of elimination of the drug (described by clearance), and of the volume of distribution. In the literature, the values reported for V_z (apparent volume of distribution at steady-state) in volunteers and patients undergoing minor surgery vary between 0.7 and 1.60 $l \cdot kg^{-1}$ [1, 4, 5]. Normalizing, for the sake of comparison, the V_z by body weight gives a mean value of 1.27 $l \cdot kg^{-1}$ (moment analysis) or 1.41 $l \cdot kg^{-1}$ (NONMEM) for the present patients. Harper et al. [1] reported a very similar value (1.39 $l \cdot kg^{-1}$) for their patients receiving midazolam after cardiac surgery. The mean V_z calculated from the data of Oldenhof et al. [9] was 1.66 $l \cdot kg^{-1}$. The metabolic clearance observed here (0.25–0.30 $l \cdot min^{-1}$) was similar to that calculated from Oldenhof's data (0.33 $l \cdot min^{-1}$; 9) and was less than the clearance reported in young subjects (0.38–0.93 $l \cdot min^{-1}$; 1–5) but compares well with values reported for elderly subjects (0.28–0.43 $l \cdot min^{-1}$; 1, 3). The high volume of distribution and smaller clearance found in cardiac surgery and intensive care patients explains why the elimination of midazolam in those patients is slower than in young, healthy subjects. As midazolam has a hepatic extraction ratio in the intermediate range (30–70%), the reduced metabolic clearance could be due either to a reduction in liver blood flow, or in enzymatic activity (intrinsic clearance), or in both. The low midazolam clearance in this study contrasts with the higher metabolic clearance (0.45 $l \cdot min^{-1}$) found by Westphal eta l. [16] in 9 patients recovering from cardiac surgery and receiving an infusion of midazolam (2 $mg \cdot h^{-1}$ for 8 h). Westphal et al. [16] stated that their calculated value for clearance was based upon the assumption that steady state was obtained during the infusion of midazolam. From the elimination half-lives reported by Harper et al. [1] and by Oldenhof et al. [9], and from our results, it is very likely that the patients in Westphal's study were not at steady-state, and their study design was inadequate for accurate estimation of midazolam clearance.

Understanding the dose-effect relationship is a primary concern for any drug treatment. Knowledge of the pharmacokinetics of midazolam in present patients only permits prediction of the average plasma concentration-time course of the drug in given dose

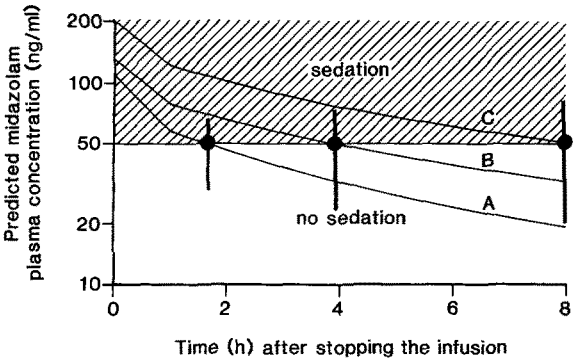

Fig. 3. Simulation, using the average pharmacokinetic parameters in Table 3, of the plasma concentration-time decay after infusion of midazolam 2 $mg \cdot h^{-1}$ for 12 h *(Curve A)*, 2 $mg \cdot h^{-1}$ for 48 h *(Curve B)* and 3 $mg \cdot h^{-1}$ for 48 h *(Curve C)*. Assuming that the sedative effects of midazolam disappear at < 50 $ng \cdot ml^{-1}$, recovery would be rapid after a moderate amount of midazolam given for a relatively short period, but long term sedation with the same rate of infusion or a higher rate, would result in prolonged recovery. The large variability in midazolam pharmacokinetics, limits our ability to predict the time course of drug concentrations, as shown by the standard deviation of the predicted concentrations *(thick vertical lines)*

regimen. There is, however, a direct relationship between the plasma concentration of midazolam and the intensity of sedation. Therefore, knowledge of the plasma concentration-time course helps in predicting the time course and intensity of the sedative effect. There is no consensus as to the recommended plasma concentration of midazolam for sedation of patients requiring mechanical ventilation. Differences in patient sensitivity, as well as the concomitant administration of opiates for pain relief, may account for wide variation in the "sedative" concentration of midazolam. Results from Oldenhof et al. [9] and extrapolation from studies in healthy volunteers [5, 17] suggest that "sedation" (defined as an arousable state, slurred speech, long reaction time and dyskinesia) is achieved at plasma midazolam concentrations between 100 and 250 $ng \cdot ml^{-1}$. Assuming that midazolam 100 $ng \cdot ml^{-1}$ will achieve adequate sedation in mechanically ventilated patients, and assuming that tolerance to the drug does not develop over time, the average pharmacokinetic parameters in Table 3 suggest that a continuous infusion of midazolam at the rate of 1–3 $mg \cdot h^{-1}$ will result in adequate sedation at steady state. Allonen et al. [5] and Crevoisier et al. [17] showed that the sedative effect of midazolam disappeared when the plasma concentration fell below 50 $ng \cdot ml^{-1}$. Considering 100 $ng \cdot ml^{-1}$ and 50 $ng \cdot ml^{-1}$ as adequate concentrations of midazolam to obtain, respectively, sedation or alertness, and using the pharmacokinetic parameters in Table 3, it is possible to calculate the time to recovery after various dosing schemes of

midazolam. The example presented in Fig. 3 shows that, on average, recovery can be expected as early as 90 min after discontinuing a 12 h infusion of midazolam at 2 $mg \cdot h^{-1}$, and 4 h after stopping a 48 h infusion at the same rate. If a higher infusion rate were used (3 $mg \cdot h^{-1}$ for 48 h), then recovery would be prolonged up to 8 h. It must be noted, however, that the large variability in midazolam pharmacokinetics observed in the present patients limits our ability to predict accurately the time course of plasma midazolam concentrations (and the effect of midazolam), as shown by the large standard deviation of the predicted concentrations in Fig. 3.

The clinical implication of the results are threefold. (1) The relatively low metabolic clearance found in these patients suggests that the maintenance infusion rate of midazolam in them should be reduced. An infusion rate of 2 $mg \cdot h^{-1}$ (1–3 $mg \cdot h^{-1}$) is probably adequate to achieve a "sedative" concentration of midazolam at steady-state. (2) The time to recovery after discontinuation of the midazolam infusion depends on the amount of drug in the body at the time the infusion is stopped. Patients recovering from cardiac surgery will awaken rapidly after a relatively brief (12 h) midazolam infusion. However, if sedation is needed over a prolonged period, then recovery will be delayed. (3) Although the required concentration of midazolam for sedating ventilated patients has not been firmly established, the slower elimination of midazolam observed here, as well as the large variability between patients in pharmacokinetic parameters suggest that, in selected cases, measuring plasma midazolam concentrations in patients receiving a prolonged infusion (> 48 h) might help to avoid surprisingly long recovery times after administration of the drug has ceased.

Acknowledgements. The work was supported in part by grants from the Swiss National Science Foundation and Hoffmann-La Roche, Basel. The authors wish to thank Dr. K. Skarvan and Prof. D. A. Thomson for their help, Dr. M. Buehrer and Prof. D. R. Stanski for reviewing the manuscript, and the cardio-thoracic surgeons of the Kantonsspital Basel Stadt for allowing to study their patients.

References

1. Harper KW, Collier PS, Dundee JW, Elliott P, Halliday NJ, Lowry KG (1985) Age and nature of operation influence the pharmacokinetics of midazolam. Br J Anaesth 57: 866–871
2. Greenblatt DJ, Locniskar A, Ochs HR, Lauven PM (1981) Automated gas chromatography for studies of midazolam pharmacokinetics. Anesthesiology 55: 176–179
3. Greenblatt DJ, Abernethy DR, Locniskar A, Harmatz JS, Limjuco RA, Shader RI (1984) Effect of age, gender, and obesity on midazolam kinetics. Anesthesiology 61: 27–35
4. Smith MT, Eadie MJ, O'Rourke T (1981) The pharmacokinetics of midazolam in man. Eur J Clin Pharmacol 19: 271–278
5. Allonen H, Ziegler G, Klotz U (1981) Midazolam kinetics. Clin Pharmacol Ther 30: 653–661
6. Shapiro JM, Westphal LM, White PF, Sladen RN, Rosenthal MH (1986) Midazolam infusion for sedation in the intensive care unit: Effect on adrenal function. Anesthesiology 64: 394–398
7. Byatt CM, Lewis LD, Dawling S; Cochrane GM (1984) Accumulation of midazolam after repeated dosage in patients receiving mechanical ventilation in an intensive care unit. Br Med J 289: 799–800
8. Byrne AJ, Yeoman PM, Mace P (1984) Accumulation of midazolam in patients receiving mechanical ventilation [letter]. Br Med J 289: 1309
9. Oldenhof H, de Jong M, Steenhoek A, Janknegt R (1988) Clinical pharmacokinetics of midazolam in intensive care patients, a wide interpatient variability? Clin Pharmacol Ther 43: 263–269
10. Ha HR, Funk B, Maitre PO, Zbinden AM, Follath F, Thomson DA (1988) Measurement of midazolam in plasma from hospitalized patients as measured by gas liquid chromatography with electron capture detection. Clin Chem 34: 676–679
11. Sheiner LB, Rosenberg B, Melmon K (1972) Modelling of individual pharmacokinetics for computer aided dosage. Comput Biomed Res 5: 441–459
12. Kanto JH (1985) Midazolam the first water-soluble benzodiazepine. Pharmacotherapy 5: 138–155
13. Vozeh S, Katz G, Steiner V, Follath F (1982) Population pharmacokinetic parameters in patients treated with oral mexiletine. Eur J Clin Pharmacol 23: 445–451
14. Maitre PO, Vozeh S, Heykants J, Thomson DA, Stanski DR (1987) Population pharmacokinetics of alfentanil: The average dose-plasma concentration relationship and interindividual variability in patients. Anesthesiology 66: 3–12
15. Jusko WJ (1986) Guidelines for collection and analysis of pharmacokinetic data. In: Evans WE, Schentag JJ, Jusko WJ (eds) Applied pharmacokinetics. Applied Therapeutics Inc, San Francisco, pp 9–54
16. Westphal LM, Cheng EY, White PF, Sladen RN, Rosenthal MH, Sung ML (1987) Use of midazolam infusion for sedation following cardiac surgery. Anesthesiology 67: 257–262
17. Crevoisier C, Ziegler WH, Eckert M, Heizmann P (1983) Relationship between plasma concentration and effect of midazolam after oral and intravenous administration. Br J Clin Pharmacol 16: 51S–61S

Received: June 30, 1988
accepted in revised form: February 23, 1989

Dr. P. O. Maitre
Department of Anesthesiology and Intensive Care
Inselspital
CH-3010 Berne, Switzerland