Anesthesiology
59:390–394, 1983

The Pharmacokinetics of Midazolam in Chronic Renal Failure Patients

H. Ronald Vinik, M.D., J. G. Reves, M.D.,† David J. Greenblatt, M.D.,‡*
Darrell R. Abernethy, M.D., Ph.D.,§ L. R. Smith, M.A.¶

Fifteen patients with chronic renal failure (CRF) were given midazolam 0.2 mg/kg iv over 15 s. All but one lost consciousness in a time ranging from 22–100 s (mean ± SD was 55 ± 26 s) after drug administration. Patients regained consciousness from 6–105 min (mean 53 ± 32) after drug administration. The calculated mean plasma level of midazolam at arousal was 81 ± 47 ng/ml. Pharmacokinetics parameters were determined from midazolam plasma levels measured in 16 consecutive venous blood samples. The pharmacokinetic parameters in CRF patients were compared with those of healthy volunteers matched for age, sex, and body size with the CRF patients. Protein binding was determined by equilibrium dialysis. CRF patients had a significantly higher ($P < 0.005$) plasma-free drug fraction (6.5% ± 0.7) compared with the control patients (3.9% ± 0.1). Total (bound plus unbound) kinetics differed in the two groups: volume of distribution 3.8 ± .3 l/kg in CRF patients *versus* 2.2 ± .2 l/kg in controls ($P < 0.001$), and clearance 11.4 ± 1.6 $ml \cdot min^{-1} \cdot kg^{-1}$ in CRF patients *versus* 6.7 ± 0.9 $ml \cdot min^{-1} \cdot kg^{-1}$ in controls ($P < 0.02$). When kinetic parameters were corrected for protein binding, CRF patients unbound volume of distribution (63.5 ± 6.8 l/kg) and free drug clearance (189 ± 29 $ml \cdot min^{-1} \cdot kg^{-1}$) were not different from the control group's volume of distribution (55.6 ± 5.7 l/kg) and free drug clearance (176 ± 24 $ml \cdot min^{-1} \cdot kg^{-1}$). Midazolam elimination half-life was almost identical in both groups; in CRF it was 4.58 ± 0.75 h and 4.93 ± 1.08 h in healthy controls. Because CRF does not alter the distribution, elimination, or clearance of unbound midazolam, changes in the pharmacodynamic profile of midazolam in CRF patients, if they exist, are more likely due to inherent alterations in drug sensitivity than to pharmacokinetic changes. (Key Words: Anesthetics, intravenous: midazolam. Kidney: failure. Pharmacokinetics: midazolam. Protein: binding.)

MIDAZOLAM MALEATE is a water-soluble (at $pH \leq 4$) benzodiazepine derivative.[1] It has been studied extensively in animals and in humans for premedication, sedation, and induction of anesthesia. The drug has the classic pharmacologic actions of the benzodiazepines including sedative, hypnotic, anticonvulsant, amnestic, and muscle relaxant properties.[1] The pharmacokinetics of midazolam have been studied in normal volunteers and in healthy patients.[2–4] It has a relatively short distribution half-life and elimination half-life, a relatively large volume of distribution, and high plasma clearance. The drug is biotransformed in the liver to hydroxylated metabolites[1] that have considerably less pharmacologic activity than the parent drug. There is minimal renal excretion of the active drug.[5,6]

The pharmacologic characteristics of midazolam (dynamic and kinetic) may make it suitable for use as a sedative/hypnotic in chronic renal failure (CRF) patients. Consequently, a study was designed to evaluate the hypnotic and pharmacokinetic properties of midazolam in patients who have chronic renal failure.

Materials and Methods

Fifteen patients, nine women and six men, with chronic renal failure, undergoing elective creation of arterial venous access procedures, consented to participate in this investigation. Approval by the Institutional Review Board of the University of Alabama in Birmingham was obtained, and all patients gave informed consent. Potential subjects were excluded if they had been dialyzed within 12 h or were likely to be dialyzed in the ensuing 24 h of study. Also, patients who had been maintained on benzodiazepines and those who were sensitive to benzodiazepines were excluded. No attempt was made to control for smoking, ethanol ingestion, or other medications, but a careful drug history was obtained in each patient. Fifteen healthy drug-free volunteers with normal renal function served as a reference group for the pharmacokinetic studies. These subjects were participants in another ongoing study of midazolam pharmacokinetics in relation to old age and overnutrition being performed at Tufts–New England Medical Center. The protocol for the normal volunteer study was reviewed and approved by the Human Investigation Review Committee at Tufts–New England Medical Center, and all subjects gave written informed consent prior to participation. Control subjects were matched as closely as possible with CRF patients for age, sex, and body weight.

All subjects were unpremedicated. Each CRF patient

* Associate Professor of Anesthesiology, University of Alabama Medical Center.

† Professor of Anesthesiology, University of Alabama Medical Center.

‡ Professor of Psychiatry and Medicine, Tufts University School of Medicine and New England Medical Center Hospital.

§ Assistant Professor of Psychiatry and Medicine, Tufts University School of Medicine and New England Medical Center Hospital.

¶ Data Manager, University of Alabama Medical Center.

Received from the Department of Anesthesiology, Clinical Cardiology Computer Center, University of Alabama Medical Center, Birmingham, Alabama, and the Division of Clinical Pharmacology, Tufts University School of Medicine and New England Medical Center Hospital, Boston, Massachusetts. Accepted for publication April 26, 1983.

Address reprint requests to Dr. Vinik: Department of Anesthesiology, The University of Birmingham School of Medicine, University Station, Birmingham, Alabama 35294.

0003-3022/83/1100/0390 $01.05

received 0.2 mg/kg of midazolam over 15 s in a peripheral vein. Multiple (16) blood samples were obtained over the next 24 h from a venous catheter whose tip was either in the right atrium or superior vena cava. Sampling times were 1, 2.5, 6, 15, 30, and 45 min and 1, 1.5, 2, 3, 4, 6, 8, 12, 16, and 24 h after drug administration. The design of the normal volunteer study was slightly different than that in the CRF patients. Volunteers received a single 5-mg intravenous dose of midazolam by continuous intravenous infusion over 10 min. Peripheral venous blood samples (14) were drawn just at the end of the infusion and at the following postinfusion times: 5, 15, 30, and 45 min, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 12, and 24 h. Midazolam plasma levels were determined by gas chromatography using electron capture with a sensitivity of 1–2 ng/ml. The analytical methods have been reported previously in detail.[2,7] Midazolam plasma levels were fitted to a linear sum of exponential terms by weighted iterative nonlinear least squares regression techniques. Squared residual errors were weighted by a factor equal to the reciprocal of the plasma concentration. Coefficients and exponents from the function of best fit were used to calculate the following kinetic parameters of midazolam for each patient: total volume of distribution (V_d) using the area method, elimination half-life ($t_{1/2\beta}$), and total clearance (Cl).[7] The computer-determined functions of best fit were appropriately corrected for the 10-min infusion duration in the control subjects. Plasma protein binding was determined by equilibrium dialysis using 14-C midazolam.[8] Values of V_d and clearance were corrected for the individual differences in protein binding, yielding corresponding values of unbound V_d, and unbound Cl.

Patient observations consisted of determining onset and duration of anesthesia induction. Onset was defined as loss of lid reflex and failure to respond to oral commands. Duration of anesthesia was determined by periodically giving oral commands, and awakening was defined as an appropriate response to command. The heart rate was determined every 5 min from a continuously displayed lead II EKG. Blood pressure (systolic and diastolic) was measured at 5-min intervals using an appropriately sized cuff. Mean blood pressure was calculated from the measured systolic and diastolic values. Respiratory rate was counted at 5-min intervals, and if apnea occurred or if the minute rate fell below 10, respiration was assisted with oxygen by mask. No attempt was made to evaluate pharmacodynamic effects of midazolam in the control subjects.

The plasma level at which consciousness returned was computed in each CRF patient using the fitted pharmacokinetic function to calculate the plasma concentration corresponding to the time when the patient awoke. Pearson correlation coefficients were calculated to determine associations between the pharmacokinetic parameters of total and unbound V_d, Cl, $t_{1/2\beta}$, as well as free fraction against the pharmacodynamic parameters of induction time and sleep time. Pharmacokinetic parameters were compared between groups using a Student's t test. Statistical comparison of HR, RR, and blood pressure was made using analysis of variance accepting a $P < 0.05$ as significant.

Results

The patient characteristics and pharmacokinetic data are presented in Table 1. Control and CRF patients were well matched for age, sex, and body weight. The healthy patients had normal blood chemical values whereas CRF patients had a mean creatinine of 12.8 ± 4.3 (mean ± SD) mg/dl, BUN of 69 ± 22.2 mg/dl, albumin 3.3 ± .61 g/dl, and creatinine clearance of 5.5 ± 4.67 ml/min. Hepatic function studies were normal in both groups of subjects.

Pharmacokinetic parameters for total (free plus bound) midazolam indicated a significantly higher V'_d and clearance in CRF patients compared with normal subjects. Protein binding was significantly different between groups. The free fraction (FF) was significantly higher (6.5%) in CRF patients than in healthy patients (3.9%). After correction for the individual differences in binding, V_d and Cl for unbound drug were not different between groups. The elimination half-life was similar in both groups, 4.58 ± 0.75 h in CRF patients and 4.93 ± 1.08 h in control patients; however, there was great variability in this and other pharmacokinetic parameters (Fig. 1).

Midazolam (0.2 mg/kg) produced loss of consciousness in all but one CRF patient. The mean time for induction was 55 ± 26 s, ranging from 22 to 100 s. Induction time correlated poorly (r = 0.25) with drug-free fraction. The duration of sleep was 53 ± 32 min ranging from 6 to 105 min. Sleep time was not associated significantly with any of the pharmacokinetic parameters. The arousal threshold blood midazolam level was 81 ± 47 ng/ml (range 21 to 192 ng/ml).

Following midazolam, blood pressure decreased in 10 of 15 patients. Mean blood pressure fell ($P < 0.05$) from control (121 ± 21 to 102 ± 22 mmHg) 20 min after midazolam and returned to control values in 60 min. The heart rate did not change after midazolam administration, and arrhythmias did not occur. Midazolam produced a variety of respiratory changes. Three patients became apneic for 15, 30, and 480 s, and in these patients ventilation was assisted or controlled until spontaneous breathing returned. The mean respiratory rate increased in all patients; the maximum rate was 24 breaths/min at 25 min. A characteristic reaction in all patients was profound relaxation requiring support of the mandible to assure a patent airway; however, attempts to place a nasal or oral airway were resisted by the patients.

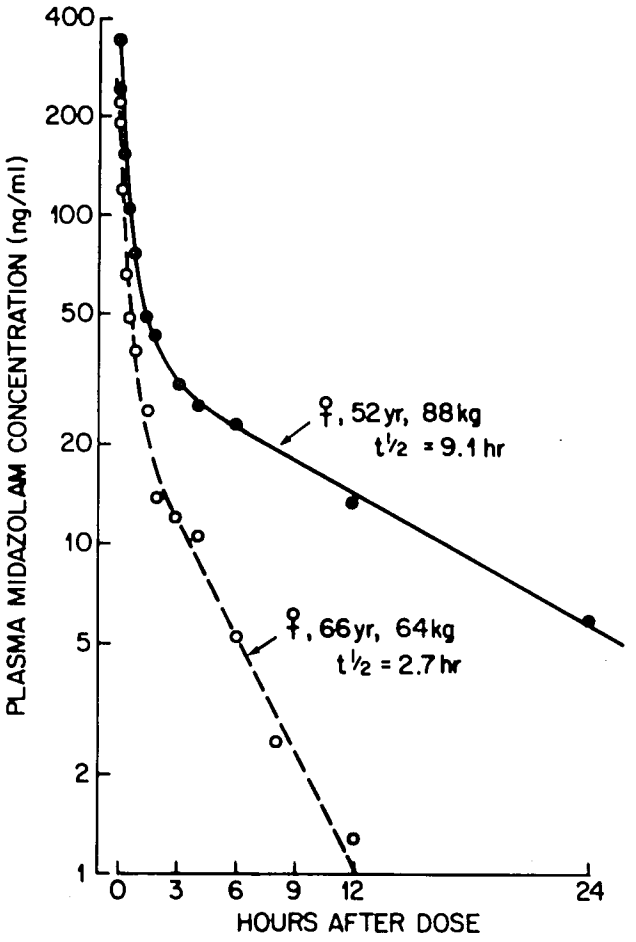

FIG. 1. Plasma midazolam concentrations in two female patients with chronic renal failure. Lines represent pharmacokinetic functions. This illustrates the wide individual variation in midazolam elimination half-life ($t_{1/2}$).

Discussion

The major characteristics that distinguish midazolam from most other benzodiazepines are *p*H-dependent aqueous solubility, rapid onset, short duration, the relatively high metabolic clearance, and its short plasma half-life. In comparing the pharmacokinetics of benzodiazepines, age, sex, and body size must be matched because each of these variables significantly can alter pharmacokinetic parameters.[9-11] The pharmacokinetic properties of midazolam are characterized in young healthy persons of normal body weight by a relatively short elimination half-life of 1.7–2.6 h,[2-4,6] moderately large volume of distribution 1.1–1.7 l/kg,[3-5] and rapid clearance 6.4–8.1 $ml \cdot min^{-1} \cdot kg^{-1}$.[2,4] The clearance of midazolam greatly exceeds the clearance of other benzodiazepines; for example, the clearance of diazepam in healthy young humans ranges from 0.39 to 0.53 $ml \cdot min^{-1} \cdot kg^{-1}$.[10,11]

Renal disease may have important effects on the distribution and clearance of drugs.[12] However, renal disease does not alter markedly the pharmacokinetics of the few benzodiazepines in which it has been studied.[13-17] Midazolam is biotransformed in the liver to form at least three hydroxymetabolites,[1] and because most hepatic drug oxidation is not altered in patients with renal disease,[12] renal disease should have little effect on the hepatic clearance of midazolam. Such is the case with midazolam because unbound drug clearance in CRF patients (189 $ml \cdot min^{-1} \cdot kg^{-1}$) is similar to that in volunteers (176 $ml \cdot min^{-1} \cdot kg^{-1}$). There are differences in pharmacokinetic parameters for total (free plus bound) midazolam in renal failure patients compared with normal controls (table 1), but these differences are attributable to disease-related changes in protein binding. Indeed, the most important pharmacokinetic finding in the present study is that renal disease markedly alters the protein binding of midazolam (free fraction of 93% CRF *vs.* 96% in healthy controls). Renal disease is known to alter protein binding of many drugs,[18,19] including diazepam (93% CRF *vs.* 98% healthy controls).[13] If one corrects for midazolam protein binding, the free drug clearance in CRF patients compared with normal patients and free drug volume of distribution in the two groups are nearly identical. Thus, renal disease does not alter the capacity of the liver to clear the pharmacologically active unbound midazolam.

The pharmacodynamic profile of midazolam observed in the present study must be interpreted with caution. Because we did not concurrently study its dynamic effects in our control patients with normal renal function, we cannot conclude that the cardiovascular, respiratory, and central nervous system effects of midazolam were unique to CRF patients. Nevertheless, induction time (80 ± 8.6 ($\bar{X}$ ± SEM) s) in 10 healthy unpremedicated patients given 0.2 mg/kg midazolam in our previous study[20] was less rapid ($P < 0.05$) than induction time (55 ± 7.0 ($\bar{x}$ ± SEM) s) in the renal failure patients. Because free drug is the active compound, a more rapid hypnotic effect might be related to the larger proportion of free drug in CRF patients (7% *vs.* 4%). Thiopental also has a greater free fraction (28% *vs.* 16%) in CRF patients compared with normal patients.[18] With rapid infusion of midazolam or thiopental in CRF patients, a relatively large fraction of unbound drug may be distributed to the vessel-rich tissues. Thus, the rate of infusion of these drugs during induction of anesthesia may be slowed to minimize the effects of relative overdosage of free drug to the brain, heart, kidneys, and liver.[18]

The mean duration of sleep in our CRF patients was 53 min (range 6–105 min), which is considerably longer than the mean of 4 min (range 3–6 min) reported from a similarly designed study in healthy individuals given 0.15 mg/kg midazolam.[3] It is unlikely that differences in dosage alone explain this discrepancy. The termination of anesthetic effect after a bolus injection generally is

TABLE 1. Midazolam Kinetics in Control Subjects and Patients with Renal Failure

	Mean (±SE) Values for:		
	Controls	Renal Failure	Value of Student's *t*
Characteristics of subjects			
Number	14	14	—
Age (yr)	47.1 (±4.7)	47.4 (±3.9)	0.05 (NS)
Weight (kg)	70.5 (+3.5)	75.1 (+3.4)	0.93 (NS)
Male/female	5/9	5/9	—
Kinetic variables for total (free plus bound) midazolam			
Elimination half-life (h)	4.93 (±1.08)	4.58 (±0.75)	0.26 (NS)
Volume of distribution (l/kg)	2.18 (±.22)	3.79 (±.31)	4.25 ($P < .001$)
Total clearance ($ml \cdot min^{-1} \cdot kg^{-1}$)	6.74 (±.85)	11.40 (±1.55)	2.65 ($P < .02$)
Kinetic variables for unbound midazolam			
Free fraction (percentage unbound)	3.93 (±.12)	6.51 (±.74)	3.46 ($P < .005$)
Unbound volume of distribution (l/kg)	55.6 (±5.7)	63.5 (±6.8)	0.89 (NS)
Unbound clearance ($ml \cdot min^{-1} \cdot kg^{-1}$)	176 (±24)	189 (±27)	0.34 (NS)

Where NS = not significant at the $P < 0.05$ level.

considered to be a result of distribution of the drug to tissues other than the brain.[21] In the case of midazolam, which has a short distribution phase and relatively large volume of distribution,[2] this is also a likely explanation for the relatively short duration of action in healthy patients. Because of differences in administration and sampling of midazolam, we cannot compare the distribution half-times and initial volumes of distributions in the groups of the present investigation. However, the unbound volume of distributions are the same in both groups, suggesting similar unbound (active) drug distributions. It is likely that if differences exist in sleep time, they are due to inherent alterations in drug sensitivity of CRF patients. The wide variation in individual sleep times is impossible to explain; however, it is interesting that there was also a wide range (21–192 ng/ml) in awakening blood levels. Variability in response among individuals is characteristic of benzodiazepines.

The respiratory depressant effect of midazolam has been well documented.[22,23] Most reports indicate transient periods of apnea during the induction sequence. However, patients with chronic lung disease are at greater risk for CO_2 retention and hypoxia.[24] Patients with CRF are also susceptible to the respiratory depressant effects of induction doses of midazolam, demonstrating transitory apnea and need for airway support in many cases. Because chronic renal failure patients have a decreased oxygen carrying capacity because of anemia, hypoxia is poorly tolerated. This study demonstrated the potential for midazolam to produce mechanical and presumably central respiratory depression.

Cardiovascular changes produced by midazolam in doses sufficient for sedation or anesthesia are modest. Induction in normal patients is associated most commonly with a slight decrease in systemic blood pressure and modest heart rate increase. These changes are usually within 25% of their starting values[22,25–26] and are of minimal clinical importance. In patients with ischemic heart disease, systemic blood pressure is decreased but the cardiac index is maintained.[27,28] In the CRF patients, statistically significant decreases in blood pressure were evident but were gradual and did not require support other than temporary increase in fluid administration. Heart rate was not changed and there were no arrhythmias.

In summary, midazolam is a rapid-acting and effective sedative hypnotic for patients with chronic renal disease. It is safe in the dosage (0.2 mg/kg) we employed if precautions are taken to maintain the airway and assist ventilation. Chronic renal failure patients have unimportant hemodynamic changes after midazolam, but they may

remain unconscious for a longer time than other patients. Because renal disease does not change the free drug clearance (liver biotransformation), there appears to be no need to modify the total dose on pharmacokinetic grounds; however, renal patients may be more susceptible to the sedative hypnotic effects of midazolam. Also, because a greater proportion of the drug is unbound in CRF patients, it may be prudent to reduce the rate of midazolam infusion in these patients. We conclude that midazolam should be titrated for the desired effect in patients with chronic renal disease, realizing that although the body does not clear midazolam differently in renal failure, the drug may have greater central nervous system effects in these patients.

The authors are grateful for the collaboration and assistance of Ann Locniskar, Marcia Divoll, Jerold S. Harmatz, and Dr. Lawrence J. Moschitto.

References

1. Pieri L, Schaffner R, Scherschlicht R, Polc P, Sepinwall J, Davidson A, Mohler H, Cumin R, Da Prada M, Burkard WP, Keller HH, Muller RKM, Gerold M, Pieri M, Cook L, Haefely W: Pharmacology of midazolam. Arzneimittelforsch 31:2180–2201, 1981
2. Greenblatt DJ, Locniskar A, Ochs HR, Lauven PM: Automated gas chromatography for studies of midazolam pharmacokinetics. ANESTHESIOLOGY 55:176–179, 1981
3. Brown CR, Sarnquist FH, Canup CA, Pedley TA: Clinical, electroencephalographic, and pharmacokinetic studies of a water-soluble benzodiazepine, midazolam maleate. ANESTHESIOLOGY 50:467–470, 1979
4. Smith MT, Eadie MJ, Brophy TO: The pharmacokinetics of midazolam in man. Eur J Clin Pharmacol 19:271–278, 1981
5. Vree TB, Baars AM, Booij LHD, Driessen JJ: Simultaneous determination and pharmacokinetics of midazolam and its hydroxymetabolites in plasma and urine of man and dog by means of high-performance liquid chromatography. Arzneimittelforsch 31:2215–2219, 1981
6. Allonen H, Ziegler G, Klotz U: Midazolam kinetics. Clin Pharmacol Ther 30:653–661, 1981
7. Greenblat DJ, Pheifer HJ, Ochs HR, Franke K, MacLaughlin DS, Smith TW, Koch-Weser J: Pharmacokinetics of quinidine in humans after intravenous, intramuscular, and oral administration. J Pharmacol Exp Ther 202:365–378, 1977
8. Moschitto LJ, Greenblatt DJ: Concentration independent plasma protein binding of benzodiazepines. J Pharm Pharmacol: In press
9. Klotz U, Avant GR, Hoyumpa A, Schenker S, Wilkinson GR: The effects of age and liver disease on the disposition and elimination of diazepam in adult man. J Clin Invest 55:347–359, 1975
10. Greenblatt DJ, Allen MD, Harmatz JS, Shader RI: Diazepam disposition determinants. Clin Pharmacol Ther 27:301–312, 1980
11. MacLeod SM, Giles HG, Bengert B, Liu FF, Sellers EM: Age- and gender-related differences in diazepam pharmacokinetics. J Clin Pharmacol 19:15–19, 1979
12. Reidenberg MM: The biotransformation of drugs in renal failure. Am J Med 62:482–485, 1977
13. Ochs HR, Greenblatt DJ, Kaschel HJ, Klehr W, Divoll M, Abernethy DR: Diazepam kinetics in patients with renal insufficiency or hyperthyroidism. Br J Clin Pharmacol 12:829–832, 1981
14. Kangas L, Kanto J, Forsstrom, Iisalo E: The protein binding of diazepam and N-demethyldiazepam in patients with poor renal function. Clin Nephrol 5:114–118, 1976
15. Verbeeck R, Tjandramaga TB, Verberckmoes R, DeSchepper PJ: Biotransformation and excretion of lorazepam in patients with chronic renal failure. Br J Clin Pharmacol 3:1033–1039, 1976
16. Alvan G, Odar-Cederlof I.: The pharmacokinetic profile of oxazepam. Acta Psychiatr Scand 274:47–55, 1978
17. Kampf D, Huempel M, Lerche U, Kessel M: Effects of uremia and hemodialysis on lormetazepam disposition. Clin Pharmacol Ther 30:77–85, 1981
18. Burch PG, Stanski DR: Decreased protein binding and thiopental kinetics. Clin Pharmacol Ther 32:212–217, 1982
19. Reidenberg MM: The binding of drugs to plasma proteins from patients with poor renal function. Clin Pharmacokinet 1:121–125, 1976
20. Reves JG, Corssen G, Holcomb C: Comparison of two benzodiazepines for anaesthesia induction: Midazolam and diazepam. Can Anaesth Soc J 25:211–214, 1978
21. Saidman LJ: Uptake, distribution and elimination of barbiturates, Anesthetic Uptake and Action. Edited by Eger EI II. Baltimore, Williams and Wilkins, 1974, pp 264–284
22. Forster A, Gardaz JP, Suter PM, Gemperle M: I.V. midazolam as an induction agent for anaesthesia: A study in volunteers. Br J Anaesth 52:907–911, 1980
23. Forster A, Gardaz JP, Suter PM, Gemperle M: Respiratory depression by midazolam and diazepam. ANESTHESIOLOGY 53:494–497, 1980
24. Southorn P, Rehder K, Didier EP: Midazolam sedation and respiratory mechanics in man. ANESTHESIOLOGY 55:A367, 1981
25. Fragen RJ, Gahl F, Caldwell N: A water-soluble benzodiazepine. RO 21-3981, for induction of anesthesia. ANESTHESIOLOGY 49:41–43, 1978
26. Conner JT, Katz RL, Pagano RR, Graham CW: RO 21-3981 for intravenous surgical premedication and induction of anesthesia. Anesth Analg 57:1–5, 1978
27. Reves JG, Samuelson PN, Lewis S: Midazolam maleate induction in patients with ischaemic heart disease: Haemodynamic observations. Can Anaesth Soc J 26:402–409, 1979
28. Samuelson PN, Reves JG, Kouchoukos NT, Smith LR, Dolw KM: Hemodynamic responses to anesthetic induction with midazolam or diazepam in patients with ischemic heart disease. Anesth Analg 60:802–809, 1981