Optimizing sedation following major vascular surgery: a double-blind study of midazolam administered by continuous infusion

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A randomized, double-blind study was undertaken to determine the dose requirements, recovery characteristics, and pharmacokinetic variables of midazolam given by continuous infusion for sedation in patients following abdominal aortic surgery. Thirty subjects, 50–75 yr, scheduled to undergo aortic reconstructive surgery, entered the study. Following a nitrous oxide-isoflurane-opioid anaesthetic technique, patients were randomly allocated to receive one of three loading doses (0.03, 0.06 or 0.1 mg · kg⁻¹) and initial infusion rates (0.5, 1.0 or 1.5 µg · kg⁻¹ · min⁻¹) of midazolam, corresponding to groups low (L), moderate (M) and high (H). The infusion of midazolam was adjusted to maintain sedation levels of “3, 4 or 5,” which permitted eye opening in response to either verbal command or a light shoulder tap, using a seven-point scale ranging from “0” (awake, agitated) to “6” (asleep, non-responsive). Ad-

ditionally, morphine was given in increments of 2.0 mg iv prn for analgesia. On the morning after surgery, midazolam was discontinued, and the tracheas were extubated when patients were awake. Blood samples were taken during, and at increasing intervals for 48 hr following discontinuation of the infusion, and analyzed by gas chromatography. The desired level of sedation was maintained during more than 94% of the infusion period in all three groups, with a maximum of three dose adjustments per patient, for treatment which lasted 16.3 ± 0.6 hr. There was, however, an increase in both the infusion rates and mean plasma concentrations from Group L to Group H (P < 0.05), which corresponded to an inverse relationship of morphine requirements during the period of sedation (P < 0.05, Group H vs Group L). Optimal midazolam infusion rates and resulting plasma concentrations at the times the infusions were discontinued (in parentheses) were as follows – Group L: 0.60 ± 0.18 µg · kg⁻¹ · min⁻¹ (76 ± 32 ng · mL⁻¹), Group M: 0.90 ± 0.52 µg · kg⁻¹ · min⁻¹ (133 ± 71 ng · mL⁻¹), and Group H: 1.34 ± 0.69 µg · kg⁻¹ · min⁻¹ (206 ± 106 ng · mL⁻¹). Times to awakening were longer in Group H: 3.1 ± 3.4 hr, than in Group L: 1.1 ± 0.8 h, P < 0.05. Pharmacokinetic variables were found to be dose-independent over the range of infusion rates. Mean values were t_{1/2β} = 4.4 ± 1.5 hr, CL = 5.94 ± 1.69 mL · min⁻¹ · kg⁻¹, Vd = 3.13 ± 1.07 L · kg⁻¹. It is concluded that midazolam, infused between 0.6–0.9 µg · kg⁻¹ · min⁻¹, provides a stable level of sedation, when administered in conjunction with intermittent iv morphine following AAS. This sedation technique, which costs \$1.65 ± 0.73 hr⁻¹ (\$Can), is associated with rapid recovery and minimal side effects.

Key words

ANAESTHESIA: cardiovascular;
HYPNOTICS: benzodiazepines; midazolam;
INTENSIVE CARE: sedation.

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Cette étude randomisée et à double vise à déterminer les doses, les caractéristiques du réveil et les variables pharmacocinétiques du midazolam administré en perfusion continue après une chirurgie aortique abdominale. Trente sujets âgés de 50 à 75 ans programmés pour une chirurgie reconstructive de l'aorte font

partie de l'étude. Après une technique anesthésique protoxyde d'azote-isoflurane-morphinique, les patients sont répartis pour recevoir une de trois doses d'attaque (0,03, 0,06 ou 0,1 $\text{mg} \cdot \text{kg}^{-1}$) avec des vitesses de perfusions initiales (0,5, 1,0 ou 1,5 $\mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$) de midazolam, correspondant aux groupes bas (L), modéré (M) et haut (H). La perfusion de midazolam est réglée de façon à maintenir un niveau de sédation « 3, 4 ou 5 », soit l'ouverture des yeux à un ordre verbal ou une légère percussion de l'épaule, sur une échelle de sept points s'étalant de « 0 » (éveillé, agité) à « 6 » (endormi, sans réponses). En outre, on administre de la morphine à doses progressives de 2,0 mg iv prn pour produire l'analgésie. On discontinue le midazolam le matin qui suit l'intervention, et on extube lorsque le patient est réveillé. Des échantillons de sang sont prélevés pendant la perfusion et à intervalles croissants pour 48 h après l'arrêt de la perfusion et analysés par chromatographie en phase gazeuse. Le niveau voulu de sédation est maintenu pendant plus de 94% de la période de perfusion dans les trois groupes, avec un ajustement maximal de trois doses par patient pour des traitements de $16,3 \pm 0,6$ h. On note toutefois une augmentation à la fois des vitesses de perfusion et des concentrations plasmatiques moyennes du groupe L au groupe H ($P < 0,05$) correspondant à un rapport inversement proportionnel aux besoins de morphine pendant la période de sédation ($P < 0,05$, groupe H versus groupe L). Les vitesses optimales de perfusion et les concentrations plasmatiques consécutives au moment (entre parenthèses) où on arrête les perfusions sont les suivantes: groupe L: $0,6 \pm 0,18 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ ($76 \pm 32 \text{ ng} \cdot \text{mL}^{-1}$), groupe M: $0,90 \pm 0,52 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ ($133 \pm 71 \text{ ng} \cdot \text{mL}^{-1}$), et groupe H: $1,34 \pm 0,69 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ ($206 \pm 106 \text{ ng} \cdot \text{mL}^{-1}$). Les patients du groupe H ($3,1 \pm 3,4$ hr) récupèrent plus lentement que ceux du groupe L ($1,1 \pm 0,8$ h, $P < 0,05$). Les variables pharmacocinétiques dépendent de la dose pour la fourchette des vitesses de perfusion. Les valeurs moyennes sont: $t_{1/2\beta} = 4,4 \pm 1,5$ hr, $\text{CL} = 5,94 \pm 1,69 \text{ mL} \cdot \text{min}^{-1} \cdot \text{kg}^{-1}$, $\text{Vd} = 3,13 \pm 1,07 \text{ L} \cdot \text{kg}^{-1}$. En conclusion, le midazolam perfusé à la vitesse de $0,6 - 0,9 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ procure un niveau stable de sédation lorsqu'il est administré avec des doses intermittentes iv de morphine après une chirurgie de l'aorte abdominale. Cette technique de sédation qui coûte $1,65\$ \pm 0,73 \text{ hr}^{-1}$ (\$Can.) est associée à un réveil rapide et des effets secondaires minimes.

Following major vascular surgery, sedative-hypnotic drugs are usually administered in order to provide appropriate sedation, anxiolysis, and diminished motor activity during the period of postoperative mechanical ventilation. Although a variety of medications and techniques has been used for these indications, benzodiazepines and opioid analgesics remain the most commonly used drugs.¹ In a survey of 164 ICU's in the United States, Hansen-Flaschen *et al.* recently reported that lorazepam,

midazolam, and diazepam were the most frequently used benzodiazepines to provide sedation.² In the same survey, it was also demonstrated that sedative-hypnotics are most commonly administered using an intermittent bolus technique. More recently, the trend throughout many ICU's and recovery rooms in both Canada and the United States has been to administer benzodiazepines by continuous infusion, to enhance the quality of postoperative sedation. Advantages provided by a continuous infusion stem from the "peaks and valleys" argument, which suggests that infusion regimens circumvent: (1) transiently high plasma drug concentrations which result from administration of the relatively large bolus doses required of an intermittent technique, and (2) the relatively low plasma drug concentrations that typically occur prior to the administration of the next bolus.³ Accordingly, when appropriately titrated, continuous infusion of a sedative drug should avoid the periods of over-sedation and under-sedation, associated with intermittent bolus administration.

For infusion techniques, midazolam offers several advantages over diazepam, including its compatibility with intravenous solutions, absence of pain at the injection site, and reduced incidence of thrombophlebitis.⁴ Most importantly, midazolam also has the shortest elimination half-life (1.5–3.0 hr) of currently available benzodiazepines, which accounts for less drug cumulation and more rapid recovery following prolonged administration.⁵ Although the use of a continuous infusion of midazolam for ICU sedation has been reported,^{6–10} clinical experience has been relatively limited. Furthermore, there is considerable variability in both dose requirements and pharmacokinetic behaviour of this drug,¹¹ which makes it essential to establish the pharmacokinetic and pharmacodynamic behaviour of midazolam in specific patient populations. For these reasons, a randomized, double-blind dose-finding trial was undertaken, to establish both the infusion requirements and pharmacokinetics of midazolam when administered for sedation during the period of postoperative mechanical ventilation, in patients following aortic reconstructive surgery. In addition, we evaluated the clinical recovery profile following discontinuation of the infusion regimen in this group of older, high-risk subjects.

Methods

Thirty patients scheduled to undergo elective abdominal aortic surgery participated in this study after having given written informed consent to the protocol, which was approved by the institutional Research Ethics Board. Subjects were 50–75 yr of age, and underwent aortobifemoral bypass or tube grafting for either occlusive or aneurysmal disease. Patients with any of the following

characteristics were excluded from the study: known or suspected allergy to midazolam or other benzodiazepines; history of unstable or severe angina; uncontrolled hypertension; chronic congestive heart failure or recent myocardial infarction; an abnormal ECG; clinical or radiographic evidence of chronic obstructive pulmonary disease, hepatic or renal insufficiency (preoperative serum creatinine $> 130 \mu\text{mol} \cdot \text{L}^{-1}$); patients receiving drugs known to interact with benzodiazepines (e.g., cimetidine) within 72 hr of entry into the study, and abnormal weight, defined as a body mass index (weight/height²) either < 20 or $> 30 \text{ kg} \cdot \text{m}^{-2}$.

Anaesthetic technique

Premedication consisted of morphine $0.15 \text{ mg} \cdot \text{kg}^{-1}$ and promethazine $0.3\text{--}0.5 \text{ mg} \cdot \text{kg}^{-1}$ *im* given one hour preoperatively. Induction of anaesthesia was achieved with thiopentone $3\text{--}4 \text{ mg} \cdot \text{kg}^{-1}$, in combination with either fentanyl $4\text{--}5 \mu\text{g} \cdot \text{kg}^{-1}$, alfentanil $20\text{--}40 \mu\text{g} \cdot \text{kg}^{-1}$ or sufentanil $1 \mu\text{g} \cdot \text{kg}^{-1}$, followed by succinylcholine $1.5 \text{ mg} \cdot \text{kg}^{-1}$ *iv*. After tracheal intubation, anaesthesia was maintained with a combination of 70% N_2O in O_2 , and isoflurane, titrated between 0.5–1.5% end-tidal, to maintain systolic blood pressure within 20% of the preoperative ward value. Additional *iv* increments of opioids, to a maximum of $15 \mu\text{g} \cdot \text{kg}^{-1}$, $125 \mu\text{g} \cdot \text{kg}^{-1}$, and $3 \mu\text{g} \cdot \text{kg}^{-1}$ cumulatively for fentanyl, alfentanil and sufentanil respectively, were permitted, while vecuronium was used to provide muscle relaxation. Benzodiazepines were avoided preoperatively and intraoperatively. Finally, combined epidural/general anaesthesia was not used in any patient because of the possible influence of this technique on postoperative sedative and analgesic requirements.

Study protocol

Postoperatively, in all patients, the lungs were mechanically ventilated until the morning of the first postoperative day. Upon emergence from general anaesthesia, subjects were randomly allocated, using a computer-generated randomization schedule, to receive one of three loading doses and initial infusion rates of midazolam, as follows:

Group	Low (L)	Moderate (M)	High (H)
Loading dose ($\text{mg} \cdot \text{kg}^{-1}$)	0.03	0.06	0.1
Initial rate ($\mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$)	0.5	1.0	1.5

Study medication was prepared on the morning of surgery by the Hospital Pharmacy, using a single stock of midazolam supplied by Hoffmann-La Roche. To

TABLE I Sedation scale

0 Agitated
1 Awake
2 Asleep, opens eyes to surroundings
3 Asleep, opens eyes to name
4 Asleep, opens eyes to physical stimulus*
5 Asleep, moves and reacts to physical stimulus*
6 Unconscious and unarousable

*Stimulus = moderate tap on shoulder.

maintain blindness, midazolam was provided in coded 3 ml syringes for bolus doses, in addition to supplying the study medication in one of three concentrations in coded one litre bags of normal saline for infusion, which was then administered on a $\text{ml} \cdot \text{kg}^{-1} \cdot \text{hr}^{-1}$ basis for each patient.

During the study period, the midazolam infusion was adjusted as often as necessary in order to maintain a sedation level between "3–5" on a modified Ramsay sedation scale,¹³ ranging from "0–6" (Table I). For patients who reached a sedation level in the desired range, the infusion of midazolam was simply continued at the initial rate until the early morning hours (0500–0900 hr) of the first postoperative day. If patients became over-sedated (sedation level = "6"), the midazolam was stopped until the subjects had attained a sedation level of "4," at which time the infusion was re-started at 50% of the initial rate. For patients who were undersedated (either "0," "1" or "2" on the sedation scale), a supplemental bolus of midazolam, equivalent to 50% of the loading dose for that particular group, was given. In addition, the infusion rate was increased by 50% up to a maximum of two increases. The upper permitted rates of infusion were 1.0, 2.0 and $3.0 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ for Groups L, M and H respectively. Importantly, in order to ensure that the level of sedation was maintained in the desired range at all times, infusion rate adjustments were permitted as required throughout the study period.

The time from discontinuation of the infusion and the next 48 hr was considered to be the "post-infusion recovery period." During this time, the tracheas were extubated according to the usual criteria: when the patients were awake (sedation level "0," "1," or "2"), haemodynamically stable, and with evidence of satisfactory pulmonary gas exchange ($\text{PaO}_2 > 80 \text{ mmHg}$ breathing $\text{FiO}_2 = 0.4$; $\text{PaCO}_2 < 50 \text{ mmHg}$) and satisfactory respiratory mechanics (respiratory rate $< 16 \text{ min}^{-1}$, vital capacity $> 15 \text{ ml} \cdot \text{kg}^{-1}$, and maximum negative inspiratory pressure $> 25 \text{ cm H}_2\text{O}$). Sedation scores were recorded, and blood sampling continued during this period, up to the time of discharge from the intensive care unit.

During and after the infusion of midazolam, morphine

was given in 2 mg increments *iv prn* whenever the patient indicated a positive response to the question: "Are you feeling any pain?" There was no upper limit to the amount of morphine which could be administered. For hypertension not associated with pain, treatment consisted of nifedipine 10 mg sublingually q 10–15 min *prn*, or an infusion of nitroglycerine, titrated to maintain systolic blood pressure <160 mmHg. In addition, propranolol was given in 1 mg increments for HR >100 min⁻¹, when the tachycardia was not associated with pain or agitation. Preoperative cardiovascular medications were resumed in the early postoperative period at the discretion of the attending medical staff.

Measurements

The primary efficacy variable in this study was the sedation level (Table I). This scale was designed to quantify the sedation level during the postoperative sedation period with midazolam, and the post-sedation recovery profile. Sedation scores were recorded prior to initiation of the study drug (Time 0) and at decreasing intervals after the start of the infusion. To assess clinical recovery, sedation scores were recorded at the time the midazolam infusion was discontinued (time 0') and at increasing intervals throughout the following 48 hr.

In order to determine the plasma concentrations of midazolam required to achieve and maintain appropriate levels of sedation in this patient population, blood samples were collected in 7 ml lavender-top tubes containing EDTA. Samples were obtained prior to administration of the study drug, then at 30 min, 60 min and q4h until the infusion was stopped. Also, one sample was taken prior to each change in midazolam infusion rate, at the time of discontinuation of the infusion, and at 0.5, 1, 2, 3, 4, 6, 8, 10, 12, 18, 24, 36 and 48 hr following discontinuation of the infusion. Plasma was separated by centrifugation, and specimens were stored at -20°C until assayed. Midazolam plasma concentrations were determined using gas chromatography with electron capture detection (GC-ECD) according to the modified method described by Greenblatt *et al.*¹⁴ The quantitation limit of the assay was 1 ng · ml⁻¹ for midazolam and 2 ng · ml⁻¹ for α -OH-midazolam. Calibration curves of midazolam and α -OH-midazolam were linear from 1 to 256 ng · ml⁻¹ and 2 to 126 ng · ml⁻¹, respectively. Precision of the assay was at 12% in the low concentrations (1 and 2 ng · ml⁻¹), but less than 6% for the higher concentrations. Accuracy was always less than 10%. Alpha-OH-midazolam was assayed in urine following deglucuronidation with β -glucuronidase. Urine sample recovery was 88% and precision and accuracy were less than 7.5%.

Haemodynamic variables, including heart rate (HR), systolic blood pressure (SBP) and pulmonary capillary

wedge pressure (PCWP) were measured directly. Cardiac index (CI) was determined from the average of three values within 20% of each other at end-expiration. These variables were recorded at increasing intervals during and following the infusion of midazolam. In addition, Holter recorders were applied to each patient to provide continuous recordings of leads II and CC5 intraoperatively, and for the first 48 hr postoperatively. The Holter tapes were analyzed using the Marquette 8000T Holter analyzer. Myocardial ischaemia was diagnosed in the presence of reversible horizontal or downsloping ST segment depression >1.0 mV at J + 60 msec, in either ECG lead. Twelve lead ECG's were also obtained daily for three days, and myocardial infarction was diagnosed in the presence of a new Q wave and/or a 5% or greater increase in the MB isoenzyme of creatinine kinase.

Statistical and pharmacokinetic analysis

The time required to achieve optimal sedation in the postoperative period (score of either "3, 4 or 5" on the sedation scale) for each group was calculated, and was used to compare the times to achieve optimal sedation, and the mean dose that produced the desired effect. The product-limit estimates* of the distributions of time for the three groups were compared using the SAS procedures LIFE-TEST. The significance of the differences in mean dose at optimal sedation as tested by one way analysis of variance (ANOVA) using the SAS procedures GLM, and analysis of covariance (ANOCOVA) was also used to evaluate the influence of possible confounding factors. The levels of sedation during and following the infusions of midazolam were compared using repeated measures analysis of variance, to test the overall effects of dose and time. Additionally, comparisons of the three groups were made at each assessment time with t tests, corrected for multiple comparisons.

Pharmacokinetic variables were calculated using non-compartmental analysis.¹² The best log-linear fit to the terminal portion of the individual plasma concentration vs time data curve was determined by linear regression to evaluate the K_{el} (elimination rate constant). The area under the curve (AUC) of concentration in plasma vs time from time zero to infinity was estimated by linear trapezoidal and extrapolation methods; the extrapolated AUC never exceeded 10% of the AUC value. Volume of distribution was determined using the non-compartmental relation $V_d = D/AUC \times K_{el}$, where D was the total dose of midazolam administered. Total clearance (CL) was estimated from the following equation: $CL = D/AUC$. The midazolam concentration at

*Armitage, P, Berry G. Statistical Methods in Research, 2nd ed., Oxford: Blackwell Scientific Publications 1987: 428–9.

TABLE II Patient characteristics

Group	L (n = 10)	M (n = 10)	H (n = 10)	Mean
Age (yr)	64.1 ± 8.4	68.6 ± 7.4	70.2 ± 5.6	67.6 ± 7.1
Sex (M/F)	5/5	9/1*	7/3	21/9
Weight (kg)	69 ± 8	77 ± 10	75 ± 14	74 ± 11
ASA class (II/III)	1/9	0/10	0/10	1/29
Aneurysmal/occlusive	5/5	7/3	6/4	18/12
SBP (mmHg)	135 ± 19	129 ± 14	138 ± 21	134 ± 18
Creatinine ($\mu\text{mol} \cdot \text{L}^{-1}$)	92 ± 17	113 ± 16	116 ± 32	107 ± 22

L = low infusion rate; M = moderate infusion rate; H = high infusion rate; SBP = preoperative systolic blood pressure (ward value).

TABLE III Midazolam infusion characteristics

Group	L (n = 10)	M (n = 10)	H (n = 10)	Mean
Duration of infusion (hr)	16.8 ± 0.4	16.3 ± 0.5	15.6 ± 0.6	16.2 ± 0.5
Rate adjustments (n)	0.6 ± 0.5 (0-2)	0.7 ± 0.5 (0-3)	0.5 ± 0.5 (0-3)	0.6 ± 0.5 (0-3)
Maintenance infusion rate ($\mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$)	0.6 ± 0.2	0.9 ± 0.5	1.3 ± 0.7	0.9 ± 0.5
Midazolam $C_{\text{end inf}}$ ($\text{ng} \cdot \text{mL}^{-1}$)	76 ± 32 (32-140)	133 ± 71 (43-247)	206 ± 106* (97-468)	138 ± 69 (32-468)
Time at sedation level 3, 4, or 5 (%)	95.2	94.9	94.4	94.8
Morphine requirements (mg)	42.9 ± 11.4	34.0 ± 22.5	18.0 ± 8.5*	31.6 ± 14.1
Duration of ventilation (hr)	24.5 ± 3.1	23.6 ± 1.5	22.1 ± 2.7	23.4 ± 2.4
Time to awakening (hr)	1.1 ± 0.8 (0.5-3.0)	1.6 ± 1.2 (0.5-4.0)	3.1 ± 3.4* (0.5-12.0)	1.9 ± 1.8 (0.5-12.0)

*Different from Group L, $P < 0.05$.

The maintenance infusion rates (mean rates during the period of sedation) for each group, and corresponding plasma concentrations of midazolam, are presented. Infusion rates were adjusted as required in order to achieve and maintain a sedation score of "3, 4 or 5" (Table I) during the period of postoperative mechanical ventilation. Morphine requirements specify mean cumulative doses of morphine during the period of sedation only. Ranges, where applicable, are presented in parentheses. $C_{\text{end inf}}$ = concentration at the end of infusion.

the end of the infusion $C_{\text{end inf}}$ was also reported. The α -OH-midazolam urine recovery (F_u) was calculated from the ratio: $F_u = (A_0/\text{Dose}) \times 100$, where A_0 = the amount of α -OH midazolam found in the urine.

Finally, demographic data, major outcomes and adverse events were compared using Fisher's exact test (SAS/FREQ) for those events with adequate frequency of occurrence. Data are presented as mean $\pm$ SD in the text, figures and tables, and statistical significance was assumed when $P < 0.05$.

Results

Patient population

The important characteristics of the study population are presented in Table II. Except for a greater proportion of men than women in Group M ($P < 0.05$), the demographics were similar for the three groups. Because of an unequal sex distribution, sex was entered as a covariate in a comparison of the three dose groups with re-

spect to the optimal midazolam infusion rate, but was not found to correlate with this outcome measure ($P > 0.10$). Therefore, sex was not considered further in the analysis of midazolam dose requirements. The proportion of patients receiving nitrates, β -adrenergic blocking drugs and calcium-channel blocking drugs, was similar in the three groups.

The mean age of the study population was 67.6 ± 7.1 yr, and all patients were ASA class III, except for one patient in Group M who was ASA class II. Intraoperatively, two patients received a tube graft, and the remaining 28 subjects received a bifurcated graft, anastomosed to either the iliac or common femoral arteries. There were no major complications during surgery which lasted an average of 2.6 ± 0.6 hr (range 1.7–4.3 hr).

Midazolam infusion requirements

The characteristics of the midazolam infusion regimens for the three groups, and the midazolam plasma concentrations, are presented in Table III, and Figures 1

FIGURE 1 The midazolam infusion rates for the three groups are presented (mean $\pm$ SD). In all groups, the infusion rate was adjusted, as required, to maintain a sedation level of "3, 4 or 5," on the 7-point sedation scale, while morphine was administered 2 mg *iv prn* for analgesia.

and 2 (left panels). Midazolam was administered for an average of 16.8 ± 0.4 , 16.3 ± 0.5 , and 15.6 ± 0.6 hr in Groups L, M and H respectively ($P = \text{NS}$). However, during this time, infusion requirements for the three groups varied considerably. The mean midazolam infusion rates and resulting plasma concentrations (in parentheses) were as follows – Group L: $0.60 \pm 0.18 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ ($76 \pm 32 \text{ ng} \cdot \text{ml}^{-1}$), Group M: $0.90 \pm 0.52 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ ($133 \pm 71 \text{ ng} \cdot \text{ml}^{-1}$), and Group H: $1.34 \pm 0.69 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ ($206 \pm 106 \text{ ng} \cdot \text{ml}^{-1}$). At the moment when sedation levels had stabilized, the mean infusion rate of midazolam was higher in Group H than in Group L ($P = 0.003$). Interestingly, the amount of morphine administered to provide analgesia was inversely related to the midazolam requirements. During the period of sedation, patients in Group L received an average of 42.9 ± 11.4 mg of morphine, compared with an average of 34.0 ± 22.5 mg of morphine in Group M, and 18.0 ± 8.5 mg in Group H ($P < 0.05$, L different from H).

Despite the observed differences in infusion requirements, in all three groups, patients were optimally sedated (sedation level 3–5) about 95% of the time (Table III). During the remaining 5% of the infusion period, the sedation scores were low in Group L (either "1" or "2"), whereas sedation scores in Group H were high ("6"). Furthermore, the proportion of patients requiring dose adjustments in each of the three groups did not differ significantly. Upward adjustments were required in 50%, 20%, and 10% of groups L, M and H, respectively, in contrast to the proportion of patients who required

Sedation Level vs Midazolam Concentration

FIGURE 2 The measured sedation levels and corresponding midazolam plasma concentrations during the periods of sedation and recovery are presented. After the first two hours, stable levels of sedation were maintained during the period of infusion in all three groups, but at higher midazolam plasma concentrations in Group H than in Group L. This was associated with a delayed early recovery time in Group H.

downward adjustments (10%, 50% and 40%, for groups L, M and H respectively). No subject required more than three adjustments in the infusion rate of midazolam during the period of postoperative sedation.

Analysis of recovery

Upon discontinuation of midazolam, a relatively rapid decline in the level of sedation was observed in all groups (Figure 2, upper right panel). However, the early recovery phase was prolonged in Group H, as reflected by higher sedation scores at 1, 2 and 3 hr post-infusion, compared with either Group L or Group M ($P = 0.03$). This difference in sedation scores correlated with longer times to awakening in Group H (3.1 ± 3.4 hr), compared with the times to awakening (spontaneous eye opening) in either Group L (1.1 ± 0.8 hr) or Group M (1.6 ± 1.2 hr), $P < 0.05$. All patients attained a sedation level of either "1 or 2" by the third hour post-infusion, except for one patient in Group H who did not attain a sedation level of "1" for 12 hr. Interestingly, mean midazolam plasma concentrations exhibited a near-linear response over the range of sedation from 1–5, although considerable inter-individual variability was also demonstrated (Figure 3).

Midazolam pharmacokinetics

In each group, a rapid decrease in midazolam concentration was observed in the first hour following termination of the infusion, primarily reflecting the process

FIGURE 3 Midazolam plasma concentrations are plotted according to the level of sedation during the post-sedation (recovery) period. Triangles represent individual data points, and open circles represent the mean midazolam concentration at each level of sedation. A near-linear response is observed over the range of sedation from 1–5, but considerable inter-individual variability is also demonstrated. Data in parentheses reflect the number of observations at each level of sedation.

of redistribution. Plasma decay curves for representative patients from each of the three groups, and corresponding α -OH-midazolam concentrations, are shown in Figure 4. Pharmacokinetic variables are presented in Table IV. Although there was an increase in $C_{end\ inf}$ from Group L to Group H ($P < 0.05$), pharmacokinetic variables were dose-independent over the range of infusion rates, as reflected by similarity of clearance the rates, volumes of distribution, and elimination half-lives in the three groups. In this patient population, whose mean age was 67.6 ± 7.1 yr, the mean pharmacokinetic values were $CL = 5.94 \pm 1.69$ $\text{ml} \cdot \text{min}^{-1} \cdot \text{min}^{-1}$, $V_d = 3.13 \pm 1.07$ $\text{l} \cdot \text{kg}^{-1}$, and $t_{1/2\beta} = 6.3 \pm 2.2$ hr. The urinary fraction of midazolam excreted as α -OH-midazolam was $34 \pm 12\%$.

Midazolam and α -OH Midazolam Plasma Concentrations

FIGURE 4 Midazolam plasma decay curves, and corresponding α -OH midazolam concentrations for representative patients from Groups L, M and H are displayed.

Haemodynamic and electrocardiographic (Holter) response

Heart rate and SBP during and following the infusion of midazolam are displayed in Figure 5. In response to the loading dose of midazolam, a transient decrease in SBP occurred in Groups M and H. Mean SBP values 15 min after beginning the infusion were 159 ± 19 , 127 ± 27 , and 125 ± 31 mmHg for Groups L, M and H respectively. Importantly, the observed decrease in SBP occurred within the normal physiological range, because patients tended to be hypertensive just prior to administration of the loading dose of midazolam, and in no patient did SBP decrease below 90 mmHg. Postoperative hypertension (SBP > 160 mmHg) was observed in 60% of patients, and normalized to < 160 mmHg in all instances with either nifedipine and/or nitroglycerin. In order to maintain $HR < 100$ min^{-1} , propranolol was administered to patients in all three groups (average dose per patient = 1.1 ± 0.4 , 2.2 ± 3.2 and 1.0 ± 0.2 mg during the period of sedation for Groups L, M and H, respectively; $P = \text{NS}$). Overall, stability of both HR and SBP was maintained throughout the study period, and there were no significant between-group differences in either PCWP or CO measurements.

Analysis of electrocardiographic records (Holter) demonstrated no differences between groups with respect to the number of patients who developed either myocardial ischaemia, ventricular ectopy, or runs of ventricular ectopy. Therefore, the Holter data for the three groups were combined (Table V). The number of patients who developed postoperative myocardial ischaemia (25%) was no greater than the number who developed ischaemia either the preoperatively (19%) or intraoperatively (27%).

TABLE IV Midazolam pharmacokinetic variables

Group	L (n = 10)	M (n = 10)	H (n = 10)	Mean
C _{end inf} (ng · ml ⁻¹)	76.1 ± 31.6	132.7 ± 70.5	206.6 ± 106.2*	138.4 ± 69.4
CL (ml · min ⁻¹ · kg ⁻¹)	6.32 ± 1.77	5.91 ± 1.55	5.70 ± 1.78	5.94 ± 1.69
Vd (L · kg ⁻¹)	3.31 ± 1.17	2.97 ± 0.42	3.12 ± 1.61	3.13 ± 1.07
t _{1/2β} (hr)	6.2 ± 1.7	6.2 ± 1.8	6.5 ± 3.0	6.3 ± 2.2
Fu	0.37 ± 0.09	0.36 ± 0.15	0.31 ± 0.12	0.34 ± 0.12

*Different from L; *P* < 0.05.

C_{end inf} = concentration at end of infusion; CL = total clearance; Vd = volume of distribution; t_{1/2β} = elimination half-life; Fu = urine fraction of midazolam excreted as α-OH-midazolam.

Post-Operative Heart Rate & Blood Pressure
(Mean ± S.D.)

FIGURE 5 SBP and HR during the period of sedation. Apart from a modest decrease in SBP in response to the loading dose of midazolam, stability of both variables was maintained in all three groups.

TABLE V Postoperative outcomes (n = 30)

Parameter	Incidence
Myocardial ischaemia	
- Preoperative (n)	4 (19%)
- Intraoperative (n)	7 (27%)
- Postoperative (n)	7 (25%)
Myocardial infarction (n)	1 (3%)
Congestive heart failure (n)	0
Respiratory failure (n)	1 (3%)
Renal failure (n)	0
Death (n)	0

Patient outcome

The only adverse event during the recovery period which may have been attributable to the study medication was confusion. Two subjects in Group M were confused during the recovery period, one for two days, and the other for seven days. Interestingly, the second patient was also noted intraoperatively to have macroscopic evidence of

TABLE VI Post-sedation recovery profiles

Group	L (n = 10)	M (n = 10)	H (n = 10)
Duration of ICU stay (hr)	72.3 ± 14.3	62.4 ± 5.4	55.1 ± 3.4
Recall of ventilator (n)	10*	5	5
Hallucinations (n)	0	2 (20%)	2 (20%)
Postoperative confusion (n)	0	2 (20%)	1 (10%)
Overall satisfaction in ICU (P/T/U)	0/9/1	3/7/0	3/5/2

*Different from Groups M and H, *P* < 0.05.

The post-sedation recovery profiles are presented. Overall satisfaction of the experience in the intensive care unit was rated for each patient, based on subjective experience, as being either pleasant (P), tolerable (T), or unpleasant (U).

cirrhosis, despite normal preoperative liver functions tests. One patient in Group H remained confused for a day after discontinuing the midazolam, whereas no patient in Group L was confused postoperatively.

One person in Group L experienced a sequence of complications, beginning with postoperative bleeding. This was treated with large amounts of blood and crystalloid. After extubation, the patient developed respiratory failure, and required further ventilation for an additional four days, during which time he experienced a non-transmural myocardial infarction, from which he recovered. No other patient sustained a myocardial infarction, and there were no deaths or other serious adverse outcomes (Table V).

Finally, to provide subjective evaluation of their postoperative experience, each patient was asked to respond to a questionnaire, after leaving ICU, but before discharge from hospital. The main findings are presented in Table VI. All patients in Group L recalled being connected to a ventilator postoperatively, whereas only 50% of the patients in Groups M and H had this recollection (*P* < 0.05). Two patients in Group M and two patients in Group H also described having experienced hallucinations postoperatively, whereas no patient in Group L described such events. Despite the known stresses of the ICU environment, 87% of the patients in this study rated their ICU experience as being pleasant or tolerable.

Discussion

Recent surveys indicate that a variety of medications and techniques are used to provide sedation and analgesia in the ICU.^{1,2} Ideally, the medication should be water-soluble, and capable of providing both hypnosis and anxiolysis, while producing minimal side effects. Additionally, the drug must be characterized by a relatively rapid onset of action and short recovery time, and be cost-effective. Midazolam has many of these attributes, and may be the most suitable of currently available benzodiazepines for administration by continuous infusion for ICU sedation. Although a number of studies support the use of midazolam for ICU sedation in both adult and paediatric patients, observations of a relatively wide inter-patient variability¹² suggest the need to investigate the dose requirements and pharmacokinetic behaviour of this drug in specific patient populations. This randomized, double-blind trial was therefore undertaken to establish infusion requirements, pharmacokinetics, and recovery characteristics of midazolam, when administered for prolonged sedation in vascular patients following aortic reconstructive surgery.

In order to establish the most efficient dosing regimen necessary to achieve and maintain the desired level of postoperative sedation, patients were randomized to receive one of three loading doses and initial infusion rates of midazolam. We observed an increase in both the infusion requirements and mean plasma concentrations, from Group L to Group H ($P < 0.05$). Maintenance infusion rates of 0.60 ± 0.18 , 0.90 ± 0.52 , and $1.34 \pm 0.69 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ resulted in plasma concentrations of 76 ± 31 , 132 ± 71 , and $207 \pm 106 \text{ ng} \cdot \text{ml}^{-1}$ respectively, for low, moderate and high rates of infusion. Not surprisingly, these concentration differences affected the times to awakening post-infusion, which were shortest in Group L ($1.1 \pm 0.8 \text{ hr}$), and longest in Group H ($3.1 \pm 3.4 \text{ hr}$), $P < 0.05$.

The importance of the observed inter-group differences in midazolam serum concentrations at similar levels of sedation, can best be explained by the inverse relationship of morphine dose vs midazolam infusion rate. The greater morphine requirement in Group L may have been a direct result of the treatment (i.e., the initial midazolam dose), and probably influenced the sedation outcomes. Indeed, synergy for the hypnotic effects of benzodiazepine-opioid combinations has been demonstrated in both animal studies¹⁵ and in humans.¹⁶ Although the observed differences in morphine requirements preclude the prediction of infusion rates which would have been necessary if opioid administration had been standardized for each group, the method used in this study reflects a more rational approach to good clinical care, i.e., *prn*, rather than fixed doses of analgesic medications. Whether opioids are ad-

ministered by intermittent bolus injection or continuous infusion to provide analgesia in the post-surgical patient, the important principle is to adjust the dose to individual patient requirements.

From the foregoing, recommendations regarding the optimal infusion rate of midazolam for postoperative sedation in vascular patients must take into consideration the longer times to awakening associated with higher infusion rates, and the greater morphine requirements with lower infusion rates. Balancing these factors, it is reasonable to recommend a loading dose of midazolam of $0.03\text{--}0.06 \text{ mg} \cdot \text{kg}^{-1}$, followed by an initial infusion rate between $0.6\text{--}0.9 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$, corresponding to mean plasma concentrations of $76 \pm 32\text{--}133 \pm 71 \text{ ng} \cdot \text{ml}^{-1}$ in this patient population. The infusion rate should be adjusted, as required, to maintain the desired level of sedation. Using this regimen, the average morphine requirement is $1.5\text{--}2.0 \text{ mg} \cdot \text{hr}^{-1}$.

Other investigators have demonstrated the efficacy of midazolam administered by continuous infusion in the ICU setting, but with reported infusion requirements varying as much as ten-fold. In one recent study, Oldenhof *et al.* reported midazolam infusion requirements varying between $0.4\text{--}3.5 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$, in a series of 17 patients undergoing mechanical pulmonary ventilation in a general intensive care unit.¹² Although all subjects were adequately sedated, the disparity of infusion requirements was considerable. This can probably be explained by the large range in age of their study population (32–85 yr). Not unexpectedly, it was found that age had an inverse correlation with the final infusion rate of midazolam ($P < 0.001$). In our study, where the range of ages was considerably smaller (51–75 yr), and where the medical status of the patients was more uniform, midazolam infusion requirements varied to a lesser extent.

In another recent study, Teasdale *et al.* reported infusion requirements of midazolam following coronary artery bypass graft (CABG) surgery.¹⁷ This group found that the mean rate of infusion required to maintain a sedation score of "3–5" was $0.23 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ in their surgical population. This resulted in a time to awakening of 2.5 hr (median) and time to extubation of 4.4 hr following discontinuation of the infusion (mean duration $14.8 \pm 0.6 \text{ hr}$). The 95% confidence interval of the infusion requirements reported in their study ($0.21\text{--}0.31 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$) suggests a relatively small range of infusion requirements following CABG, compared with infusion requirements in a more heterogeneous group of ICU patients.¹¹ Interestingly, a three-fold difference in steady-state infusion requirements of midazolam appears to exist when comparing CABG and vascular surgery patients, despite the similar ages of these surgical populations (45–72 yr in the Teasdale study vs 51–75 yr in the current

study). Differences in infusion requirements can most likely be accounted for by the influence of the different anaesthetic techniques (high-dose fentanyl in the Teasdale study and moderate-dose opioid/inhalational anaesthesia in the current study), and also the influence of cardiopulmonary bypass on drug disposition and pharmacokinetic behaviour.^{18,19}

A second major objective of this study was to determine the pharmacokinetic behaviour of midazolam in vascular surgery patients. Such data are necessary for establishing multiexponential models which better characterize recovery profiles following discontinuation of infusions for specified durations.²⁰ Midazolam is eliminated primarily through hepatic biotransformation, via hydroxylation and subsequent conjugation with glucuronic acid.^{5,21} The major metabolite is α -OH midazolam, which is formed in the liver by cytochrome P-450 III A4.²² Alpha-OH midazolam has an elimination half-life of 45 min in healthy volunteers,³ but exerts little activity *in vivo* because of its relatively high rate of protein binding. The moderately high extraction ratio of midazolam by the liver (30–70%)²⁴ implies that its metabolic clearance depends on both liver perfusion and enzyme activity (intrinsic clearance). As hepatic blood flow decreases during general anaesthesia and surgery, it might have been anticipated that clearance rates would be lower in our study population. However, clearance rates in the current study were similar to those observed in healthy volunteers,²⁴ suggesting negligible influence on hepatic blood flow. In contrast, the volume of distribution is increased by three- to four-fold, which may account for the prolonged elimination half-life of midazolam in vascular surgery patients, compared with young healthy individuals (6.3 ± 2.2 hr vs 2.3 ± 0.4 hr, respectively). When making such comparisons, it must be appreciated that derived pharmacokinetic variables depend on the type of models used, the dose, and the sampling schedule. Interestingly, proportional increases in V_d and $t_{1/2\beta}$ have also been demonstrated for the opioid analgesics alfentanil and sufentanil, in patients undergoing aortic reconstructive surgery.^{25,26}

Despite the prolonged elimination half-life, when appropriately adjusted, infusion of midazolam is characterized by a relatively rapid recovery time following AAS (awakening = 1.9 ± 1.8 hr after an average of 16 hr of administration). The favourable recovery profile can best be explained by the relatively short context-sensitive half-time of this drug (i.e., the time required for a 50% decrease in plasma concentration following termination of an infusion of specified duration, the so-called "context").²⁷ Hughes *et al.* have suggested that context-sensitive half-times are a useful clinical descriptor of post-infusion central compartment kinetics. From their phar-

macokinetic models, the context-sensitive half-times of midazolam associated with infusions of three hours, eight hours, and at steady-state, are approximately 60, 80, and 82 min, respectively.²⁷ Although the manual method of administration used in our study did not produce fixed drug levels, relative stability of midazolam concentrations was maintained in all three groups during the period of sedation. Upon discontinuation of the infusion, the time required for a 50% decrease in plasma concentration was 2.8 ± 1.0 hr, reflecting the combination of redistribution and elimination processes.

This study incorporated a follow-up questionnaire to evaluate post-sedation recovery profiles. It is noteworthy that all patients in the low-dose group recalled that their lungs were mechanically ventilated at some time, whereas only 50% of patients who received the moderate and higher infusion rates of midazolam recalled the ventilator. The amnesic effect of benzodiazepines are well documented, and may be very desirable in the stressful environment of the ICU. It is conceivable, however, that infusion rates of midazolam which would ensure amnesia in a higher proportion of patients, would also result in excessive levels of sedation, and could lead to prolonged recovery times. Overall, four patients (13%) experienced hallucinations during their ICU stay, and 10% were transiently confused following the infusion. It is possible that these events were associated with the infusion of midazolam, but other factors related to the ICU environment may be implicated as well. When taking into consideration the fact that up to 30% of ICU patients show some psychopathology,²⁸ and that inadequate sedation is frequently associated with a feeling of helplessness and physical impairment,²⁹ the results of the current study are most favourable.

One possible limitation of this study is the use of a sedation scale as a primary efficacy variable. This is due in part to the subjectivity of the measurement, and because of ambiguity as to whether sedation scales assess the degree of calmness, somnolence or both.³⁰ In fact, it has been suggested that the use of the term "sedation" has come into such casual use that it has become jargon.³¹ The problem may arise from the failure of clinicians to distinguish between analgesic, hypnotic, and anxiolytic effects of centrally acting drugs such as the benzodiazepines and opioid analgesics. In general, sedation scales are either objective scores (as used in this study), or linear subjective visual analogue (VAS) scales, with opposites at each end of the scale. As with most investigations, the sedation scale in this study was used to assess the degree of somnolence (or drowsiness) using a modified Ramsay scale.¹³ To avoid an excessive number of adjustments in the rate of infusion, the end point of sedation was accepted over a relatively wide range (from "asleep,

opens eyes to name," to "moves and reacts to physical stimuli," corresponding to sedation levels of 3, 4 or 5). Despite the limitations of the measurement, the sedation scale provides a simple and effective method of determining appropriate infusion requirements of midazolam for postoperative sedation. Furthermore, this scale is relevant in the clinical setting as well, and has recently been adopted by our Recovery Room and ICU personnel.

Finally, pharmacoeconomic considerations deserve comment. To analyze this aspect, the costs of the sedation regimens were compared on a patient-by-patient basis, using the acquisition cost of midazolam in 1993 Canadian dollars (midazolam 10 ml vials, concentration 5 mg · ml⁻¹). The acquisition costs, per patient, for overnight sedation with midazolam were \$16.09 ± 5.27 (Group L), \$27.31 ± 14.74 (Group M) and \$36.86 ± 15.92 (Group H). This represented an average hourly cost of \$1.65 ± 0.73, in order to provide continuous sedation with midazolam in this patient population. On balance, such costs are relatively modest, when taking into consideration the total cost of ICU care, and the potential cost-savings associated with reduced recovery times following prolonged sedation. However, it is up to the individual practitioner to evaluate these cost data, especially in view of the fact that less expensive but longer-acting benzodiazepines may prolong ICU stay, whereas more rapidly-acting sedatives such as propofol are generally more expensive.³² Clearly, cost-benefit studies comparing different sedative-hypnotics, as well as many other medications used in the ICU setting, will be the focus of considerable future research.

In summary, continuous infusion of midazolam is efficacious for providing conscious sedation for mechanically ventilated patients following AAS. Upon emergence from anaesthesia, we recommend administration of a loading dose 0.03–0.06 mg · kg⁻¹, followed by an initial infusion rate between 0.6–0.9 µg · kg⁻¹ · min⁻¹. The infusion rate should be titrated as required to maintain the desired level of sedation. Higher infusion rates are associated with a decrease in opioid requirements, but also result in delayed times to awakening.

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References

- 1 Merriman HM. The techniques used to sedate ventilated patients: a survey of methods used in 34 ICUs in Great Britain. *Intensive Care Med* 1981; 7: 217–24.
- 2 Hansen-Flaschen JH, Brazinsky S, Basile C, Lanken PN. Use of sedating drugs and neuromuscular blocking agents in patients requiring mechanical ventilation for respiratory failure. *JAMA* 1991; 266: 2870–5.
- 3 Jacobs JR, Reves JG, Glass PSA. Rationale and technique for continuous infusions in anesthesia. *Int Anesthesiol Clin* 1991; 29: 23–38.
- 4 Bellantuono C, Reggi V, Tognoni G, Garattini S. Benzodiazepines: clinical pharmacology and therapeutic uses. *Drugs* 1980; 19: 195–219.
- 5 Reves JG, Fragen RJ, Vinik HR, Greenblatt DJ. Midazolam: pharmacology and uses. *Anesthesiology* 1985; 62: 310–24.
- 6 Driessen JJ, Dirksen MSC, Rutten JMJ, Santman F, van Egmond J, Vree TB. Continuous infusion of midazolam during anaesthesia and postoperative sedation after maxillo-facial surgery. *Acta Anaesthesiol Scand* 1989; 33: 116–21.
- 7 Mathews HML, Carson IW, Collier PS, et al. Midazolam sedation following open heart surgery. *Br J Anaesth* 1987; 59: 557–60.
- 8 Michalk S, Moncorge C, Fichelle A, et al. Midazolam infusion for basal sedation in intensive care: absence of accumulation. *Intensive Care Med* 1988; 15: 37–41.
- 9 Booker PD, Beechey A, Lloyd-Thomas AR. Sedation of children requiring artificial ventilation using an infusion of midazolam. *Br J Anaesth* 1986; 58: 1104–8.
- 10 Silvasi DL, Rosen DA, Rosen KR. Continuous intravenous midazolam infusion for sedation in the pediatric intensive care unit. *Anesth Analg* 1988; 67: 286–8.
- 11 Oldenhof H, de Jong M, Steenhoek A, Janknegt R. Clinical pharmacokinetics of midazolam in intensive care patients; a wide interpatient variability? *Clin Pharmacol Ther* 1988; 43: 263–9.
- 12 Gibaldi D, Perrier D. *Pharmacokinetics*, 2nd ed., New York: Marcel Dekker Inc., 1982.
- 13 Ramsay MAE, Savege TM, Simpson BJR, Goodwin R. Controlled sedation with alphaxalone-alphadolone. *BMJ* 1974; 2: 656–9.
- 14 Greenblatt DJ, Locniskar A, Ochs HR, Lauven PM. Automated gas chromatography for studies of midazolam pharmacokinetics. *Anesthesiology* 1981; 55: 176–9.
- 15 Kissin I, Brown PT, Bradley EL Jr. Morphine and fentanyl anesthetic interactions with diazepam: relative antagonism in rats. *Anesth Analg* 1990; 71: 236–41.

- 16 Kissin I, Vinik HR, Castillo R, Bradley EL Jr. Alfentanil potentiates midazolam-induced unconsciousness in subanalgesic doses. *Anesth Analg* 1990; 71: 65–9.
- 17 Teasdale SJ, Karski JM, Carroll JA, *et al.* Continuous intravenous midazolam infusion for post CABG sedation in the ICU-dose finding study. *Can J Anaesth* 1993; 40: A31.
- 18 Buylaert WA, Herregods LL, Mortier EP, Bogaert MG. Cardiopulmonary bypass and the pharmacokinetics of drugs. *Clin Pharmacokinet* 1989; 17: 10–26.
- 19 Kanto J, Himberg JJ, Heikkilä A, Arola M, Jalonen J, Laaksonen V. Midazolam kinetics before, during and after cardiopulmonary bypass surgery. *Int J Clin Pharm Res* 1985; 2: 123–6.
- 20 Shafer SL, Stanski DR. Improving the clinical utility of anesthetic drug pharmacokinetics (Editorial). *Anesthesiology* 1992; 76: 327–30.
- 21 Dundee JW, Halliday NJ, Harper KW, Brogden RN. Midazolam. A review of its pharmacological properties and therapeutic use. *Drugs* 1984; 28: 519–43.
- 22 Kronbach T, Mathys D, Umeno M, Gonzalez FJ, Meyer UA. Oxidation of midazolam and triazolam by human liver cytochrome P450III_{A4}. *Mol Pharmacol* 1989; 36: 89–96.
- 23 Heizmann P, Eckert M, Ziegler WH. Pharmacokinetics and bioavailability of midazolam in man. *Br J Clin Pharmacol* 1983; 16: 43S–49S.
- 24 Kanto JH. Midazolam: the first water-soluble benzodiazepine. Pharmacology, pharmacokinetics and efficacy in insomnia and anesthesia. *Pharmacotherapy* 1985; 5: 138–54.
- 25 Hudson RJ, Thomson IR, Burgess PM, Rosenbloom M. Alfentanil pharmacokinetics in patients undergoing abdominal aortic surgery. *Can J Anaesth* 1991; 38: 61–7.
- 26 Hudson RJ, Bergstrom RJ, Thomson IR, Sabourin MA, Rosenbloom M, Strunin L. Pharmacokinetics of sufentanil in patients undergoing abdominal aortic surgery. *Anesthesiology* 1989; 70: 426–31.
- 27 Hughes MA, Glass PSA, Jacobs JR. Context-sensitive half-time in multicompartment pharmacokinetic models for intravenous anesthetic drugs. *Anesthesiology* 1992; 76: 334–41.
- 28 Kornfield DS, Zimberg S, Malm JR. Psychiatric complications of open-heart surgery. *N Engl J Med* 1965; 273: 287–92.
- 29 Miller-Jones CMH, Williams JH. Sedation for ventilation. A retrospective study of fifty patients. *Anaesthesia* 1980; 35: 1104–7.
- 30 Wansbrough SR, White PF. Sedation scales: measures of calmness or somnolence? *Anesth Analg* 1993; 76: 219–21.
- 31 Eger EI II. A glossary of anesthetic jargon. *Anesth Analg* 1989; 68: 740–3.
- 32 Johnstone RE, Martinec CL. Costs of anesthesia. *Anesth Analg* 1993; 76: 840–8.