British Journal of Anaesthesia 1993; 70: 286–292

PHARMACOKINETICS OF FLUMAZENIL AND MIDAZOLAM

R. D. M. JONES, K. CHAN, C. J. ROULSON, A. G. BROWN, I. D. SMITH AND G. H. MYA

SUMMARY

We have studied simultaneously the pharmacokinetics of flumazenil and midazolam in 12 healthy Chinese children, aged 5–9 yr, undergoing circumcision. Two hours before operation each patient received midazolam 0.5 mg kg^{-1} orally for premedication and 0.5 mg kg^{-1} i.v. during induction. Six minutes after cessation of anaesthesia, a bolus of flumazenil 10 μg kg^{-1} was given i.v., followed by an infusion of flumazenil at 5 μg kg^{-1} min^{-1} which was maintained until the child could identify himself. Midazolam data were consistent with a three-compartment model with a mean (SD) elimination half-life of 107 (30) min, total body clearance of 15.4 (3.2) ml min^{-1} kg^{-1} and apparent volume of distribution at steady state of 1.9 (0.6) litre kg^{-1}. Flumazenil data were best interpreted by a mono-exponential function, with a mean terminal elimination half-life of 35.3 (13.8) min, a total plasma clearance of 20.6 (6.9) ml min^{-1} kg^{-1} and apparent volume of distribution at steady state of 1.0 (0.2) litre kg^{-1}. No unchanged midazolam was detected in the 24-h urine sample, but 5.8–13.8% of the flumazenil dose was recovered unchanged. At the time of self identification, 4.5 (1.4) min after flumazenil administration, the mean plasma concentrations of midazolam and flumazenil were 163.1 (43.7) and 29.9 (16.1) ng ml^{-1}, respectively.
(Br. J. Anaesth. 1993; **70**: 286–292)

KEY WORDS

Anaesthesia: paediatric. Antagonists: flumazenil. Hypnotics, benzodiazepines: midazolam. Pharmacokinetics.

Midazolam is a water-soluble benzodiazepine derivative that has been used for premedication and induction of anaesthesia in paediatric patients [1, 2]. Flumazenil is also a benzodiazepine molecule with a high receptor affinity, but almost no intrinsic activity, and has been used effectively to reverse the hypnotic effects of midazolam-induced anaesthesia in children [3]. The disposition of midazolam in children has been studied by several workers [4–6], but the contemporaneous disposition of flumazenil in children has not been reported. This present study was undertaken to measure simultaneously the pharmacokinetics of midazolam and flumazenil and their relationship to psychomotor performance in children in the early postoperative period.

PATIENTS AND METHODS

We studied 12 ASA grade I Chinese children, aged 5–9 yr, undergoing circumcision. The study was approved by the Faculty of Medicine Ethics Committee (The University of Hong Kong) and written, informed consent was obtained from all the parents. Children were excluded from the study if they had a history of asthma or allergies; previous adverse anaesthetic experience; anaesthesia within the previous 1 month; hepatic, renal, respiratory, cardiac or haematological disease; mental retardation or age less than 4 yr. The day before surgery, each child was familiarized with a post-box toy and the completion time of his best performance on seven attempts recorded [3]. On the day of surgery, the patient was premedicated with midazolam 0.5 mg kg^{-1} (maximum dose 15 mg) and atropine 0.02 mg kg^{-1} by mouth 2 h before operation. EMLA emulsion cream 2 g (lignocaine 25 mg g^{-1} and prilocaine 25 mg g^{-1}) was applied to the dorsum of the hand and the contralateral cubital fossa.

On arrival in the operating suite, the children were assessed and recorded as agitated or crying, aware and apparently anxiety-free, drowsy, or asleep but responsive to command [7]. A 23-gauge cannula was inserted into a vein underlying each EMLA-pretreated area. Anaesthesia was induced with alfentanil 5 μg kg^{-1} i.v. followed, 60 s later, by midazolam 0.5 mg kg^{-1} administered over 30 s. Time zero was taken at completion of the midazolam injection. The child was given atracurium 0.5 mg kg^{-1} and the trachea intubated. Anaesthesia was maintained with 67% nitrous oxide and 0.5% isoflurane in oxygen via a Mapleson F breathing system with hand ventilation to an end-tidal carbon dioxide partial pressure of 5 kPa. A caudal injection of 0.25% bupivacaine 0.5 ml kg^{-1} was administered to all patients. Routine monitoring devices included an electrocardiograph, non-invasive arterial pressure recorder, pulse oximeter, capnograph and inspired oxygen concentration (Datex, Cardiocap). At the

R. D. M. JONES*, F.A.N.Z.C.A, F.R.C.ANAES.; C. J. ROULSON, F.R.C.ANAES.; A. G. BROWN, F.R.C.ANAES.; I. D. SMITH, F.R.C.ANAES. (Department of Anaesthesiology); KELVIN CHAN, PH.D., F.R.PHARM.S., F.I.BIOL., F.C.P., F.A.C.B. (Department of Pharmacology); G. H. MYA, F.R.C.S. (EDIN.) (Department of Surgery); University of Hong Kong, Hong Kong. Accepted for Publication: September 23, 1992.

*Address for correspondence: Department of Anaesthesiology, University of Hong Kong, Room 415, Block K, Queen Mary Hospital, Hong Kong.

end of surgery, neuromuscular block was antagonized with neostigmine and atropine, the trachea extubated and ventilation assisted with 100 % oxygen by mask and Mapleson F circuit until spontaneous ventilation had resumed. Six minutes after the administration of neostigmine, a bolus of flumazenil 10 μg kg^{-1} was given followed, 60 s later, by commencement of an infusion of flumazenil 5 μg kg^{-1} which was continued until the child could identify himself.

The duration of anaesthesia and cardiorespiratory data during surgery and recovery were recorded. The dose of flumazenil, time from flumazenil bolus injection to spontaneous eye opening and time until the patient could identify himself were recorded also. The child's mood on awakening was assessed using a structured observation score [8] and systolic arterial pressure, heart rate, ventilatory frequency and modified Steward coma scale [9] were recorded at each blood sampling time after awakening. Any side effects occurring during and after flumazenil administration were noted, as was the time at which any child went back to sleep after eye-opening in recovery. Immediately the patient became co-operative, he was encouraged to complete the post-box toy in the quickest possible time. The child was offered the toy at 10, 30, 60, 120, 180 and 240 min after flumazenil administration and his fastest completion time on a single attempt recorded. At each assessment, a post-box toy completion-time ratio (the postoperative post-box toy completion time/the child's best timed performance on the day before surgery) was calculated.

Blood samples (1.0-ml) were collected into tubes containing lithium–heparin for measurement of the plasma concentration of midazolam immediately before induction of anaesthesia and then at 2, 4, 6, 8, 10, 15, 20, 30 min and immediately before flumazenil was given. Subsequent samples were then taken at 2, 4, 6, 8, 10, 15, 20, 30, 60, 120, 180 and 240 min after flumazenil administration. After operation, a bulked, 24-h urine specimen was collected from each of the patients. Plasma was obtained from blood after centrifugation for 15 min at 3000 *g*. Plasma samples were stored at −20 °C before assay. Flumazenil and midazolam concentrations in plasma and urine samples were measured simultaneously using HPLC with u.v. detection at 220 nm using a programmable photodiode array detector (Waters 994). Flumazenil and midazolam in plasma or urine sample (0.5 ml) and internal standard flurazepam buffered with sodium dihydrogen phosphate 0.1 mol $litre^{-1}$ at pH 9 were extracted into 5 ml of organic solvent mixture (diethyl ether and dichloromethane 60:40 v/v). The organic extract was evaporated to dryness under nitrogen and the residue was re-dissolved in methanol 80 μl and approximately 30 μl of the methanolic concentration was injected into the HPLC system. The mobile phase consisted of 32 % acetonitrile in sodium dihydrogen phosphate buffer 0.04 mol $litre^{-1}$ (containing 0.1 % triethylamine) at pH 7.2. The flow rate was set at 1.5 ml min^{-1}. A C_{18} reversed-phase cartridge column (Nova-pak, Waters) linked to a C_8 pre-column was used and the eluate was measured by a u.v. detector set at 220 nm. The calibration graphs were linear over the ranges 4–200 ng ml^{-1} for flumazenil, 20–1000 ng ml^{-1} for midazolam and 10–500 ng ml^{-1} for both 1-hydroxymidazolam and 4-hydroxymidazolam. The between-batch coefficients of variance for flumazenil 10 ng ml^{-1}, midazolam 50 ng ml^{-1}, 1-hydroxymidazolam 25 ng ml^{-1} and 4-hydroxymidazolam 25 ng ml^{-1} were 4.8 %, 5.6 %, 4.3 % and 4.0 %, respectively. The limit for detection for flumazenil was 4 ng ml^{-1} and for midazolam and its metabolites, 10 ng ml^{-1}. Urine samples were analysed for unchanged drug and metabolites, and for their glucuronides after β-glucuronidase treatment for 18 h at 37 °C. The HPLC assay was found to be specific and selective. During development of the assay procedure, it was established that flumazenil, its carboxylic and demethylated metabolites and midazolam and its hydroxy metabolites did not interact with each other under the conditions stated.

Flumazenil profiles were analysed using the statistical moment theory to obtain pharmacokinetic parameters [10]. Terminal elimination half-life ($T_{\frac{1}{2}}$), areas under plasma concentration–time curves (AUC), and apparent total body clearance (*Cl*) were calculated. Using the trapezoidal rule, the AUC_{120} was calculated from 0 to 120 min; the resident area (t = 120 min to ∞) was calculated as the ratio, C_{120}: elimination rate constant. Plasma clearance was calculated from:

$$Cl_P = \frac{\text{Dose}}{AUC_0^{\infty}} \quad (1)$$

where Cl_P = plasma clearance; AUC_0^{∞} = area under the plasma concentration–time curve. The first order rate constants for the decline of plasma concentration after administration were obtained by linear squares regression of the logarithm of the plasma concentration against time. The steady state volume of distribution was calculated from:

$$V^{ss} = Cl_P \times MRT \quad (2)$$

where V^{ss} = steady state volume of distribution; MRT = mean residence time.

Plasma concentration–time profiles of midazolam were analysed by the BITRI computer program [11, 12] which utilizes the method of residuals, whereby each curve is fitted with experimental data in terms of a bi-exponential or tri-exponential function. BITRI chooses the best fit such that the logarithms of squared deviation between exponential and computer values are minimized [13]. Distribution and elimination half-lives ($T_{\frac{1}{2}}^{\alpha}$, $T_{\frac{1}{2}}^{\beta}$, $T_{\frac{1}{2}}^{\gamma}$), apparent central volume of distribution (V), apparent volume of distribution at steady state (V^{ss}), apparent volume of distribution in the elimination phase (V^{γ}) and total body clearance (*Cl*) were calculated using standard formulae [10].

RESULTS

After arrival in the operating suite, all children were assessed as awake and appearing calm, but on specific questioning two of the children were frightened of the i.v. cannula and two children expressed fear of

TABLE I. *Patient characteristics, awakening haemodynamics and anaesthetic data in the 12 children (mean (SD) [range])*

Age (yr)	6.5 [5–9]
Weight (kg)	22.0 (6.7) [14–38.5]
Anaesthesia duration (min)	37.4 (8.4) [29–58]
Time from giving flumazenil to eyes open (min)	3.1 (1.1) [1–5]
Time from giving flumazenil to self identification (min)	4.4 (1.4) [2–7]
Mean dose of flumazenil administered ($\mu g\ kg^{-1}$)	27.0 (6.1) [16.8–39.6]
Mean concentration of flumazenil on awakening ($ng\ ml^{-1}$)	29.9 (16.1) [7–62]
Mean concentration of midazolam on awakening ($ng\ ml^{-1}$)	163.1 (43.7) [92–257]
Mean increase in heart rate after flumazenil ($beat\ min^{-1}$)	8.0 (16.2) [−24 to +37]
Mean increase in systolic arterial pressure after flumazenil (mm Hg)	11.5 (17.0) [−8 to +53]
Mean increase in ventilatory frequency after flumazenil (b.p.m.)	4.3 (5.5) [−8 to +10]

postoperative pain. The mean (SD) [range] maximum increase in heart rate (22.3 (24.4) [−28 to 54] $beat\ min^{-1}$) and maximum increase in systolic arterial pressure (27.3 (28.3) [2–108] mm Hg) during the induction period were calculated, but otherwise the induction of anaesthesia was devoid of side effects. The awakening and cardiorespiratory data associated with flumazenil administration are shown in table I. All patients opened their eyes within 5 min of the commencement of flumazenil administration and were able to give their name within a further 2 min. The mean dose of flumazenil administered was 27 (6.1) $\mu g\ kg^{-1}$ and the mean concentration of midazolam on awakening was 163.1 (43.7) $ng\ ml^{-1}$.

Psychomotor testing using the post-box toy completion-time ratio showed that, although the children tested had a faster completion time 3 h after operation compared with their own unpracticed preoperative performance, only one child could match his best preoperative performance 4 h after operation (table II). Fifty percent of the children awoke irritable, crying and refusing to play with the toy and, in total, nine children refused to play on 30 occasions during the 4-h postoperative study period. Although the study group was small, the children who were happy on awakening had the greatest mean midazolam concentrations (181 (62.9) $ng\ ml^{-1}$), those children that were sleepy had the smallest mean flumazenil concentrations (17.3 (7.6) $ng\ ml^{-1}$) and those that were crying had the greatest flumazenil concentrations (37.8 (13.6) $ng\ ml^{-1}$). Six children fell asleep again after giving their name and playing with the post-box toy, but all were awakened easily (table III).

Mean blood concentrations of midazolam and flumazenil declined in all patients (figs 1, 2). Flumazenil was not detectable at 3 h and in seven patients at 2 h. Compartmental analysis of midazolam revealed a three-compartment model with elimination from a central compartment (table IV).

Bulked (0–24 h) urine samples were successfully obtained in 10 of the 12 children. No unchanged midazolam was detected in these samples. A wide variation in the recovery, as a percentage of dose, of the hydroxy metabolites and their glucuronides was observed: 0–0.23% α-hydroxymidazolam, 0.64–13.2% α-hydroxymidazolam glucuronide, 0.03–

TABLE II. *Assessment of the antagonism of midazolam by flumazenil (mean (SD) [range])*

	Toy completion ratio	Mean concn ($ng\ ml^{-1}$)	
		Midazolam	Flumazenil
Pre-induction assessment: aware, apparently anxiety-free ($n = 12$)		47.1 (15.8) [29–83]	0
After flumazenil			
10 min ($n = 7$)	3.7 (1.5) [1.6–6.0]	147 (34.4) [83–197]	32.1 (21.5) [14–97]
20 min ($n = 2$)	2.6 (0.7) [1.9–3.3]	131 (29.7) [72–184]	19.5 (9.5) [8–42]
30 min ($n = 8$)	2.9 (1.2) [1.7–5.7]	120 (27.1) [70–170]	15.7 (9.1) [7–38]
60 min ($n = 5$)	2.3 (1.3) [1.8–4.0]	91 (24.6) [52–138]	10.1 (6.3) [3–23]
120 min ($n = 5$)	2.3 (1.8) [1.8–5.9]	59 (15.4) [40–87]	4.3 (5.6) [0–16]
180 min ($n = 5$)	1.4 (0.7) [1.2–2.3]	41 (9.5) [29–55]	0
240 min ($n = 10$)	1.5 (0.7) [1.1–2.9]	27 (10.6) [15–52]	0

TABLE III. *Resedation and mood assessment after administration of flumazenil (mean (SD) [range])*

	Concn on awakening ($ng\ ml^{-1}$)	
	Midazolam	Flumazenil
Resedation after flumazenil (average time 80 (20.6) [60–120] (min)) ($n = 6$)	158.2 (19.5) [133–183]	29.3 (15.0) [7–52]
Toy refusal on awakening ($n = 6$)	139.4 (25.8) [164–92]	25.4 (11.4) [7–42]
Mood on awakening:		
Happy, playful ($n = 3$)	181 (62.9) [103–257]	26.7 (17.9) [14–52]
Calm, drowsy ($n = 3$)	168.7 (25.80) [133–193]	17.3 (7.6) [7–25]
Irritable, crying ($n = 6$)	151.3 (34.5) [92–208]	37.8 (13.60) [62–23]

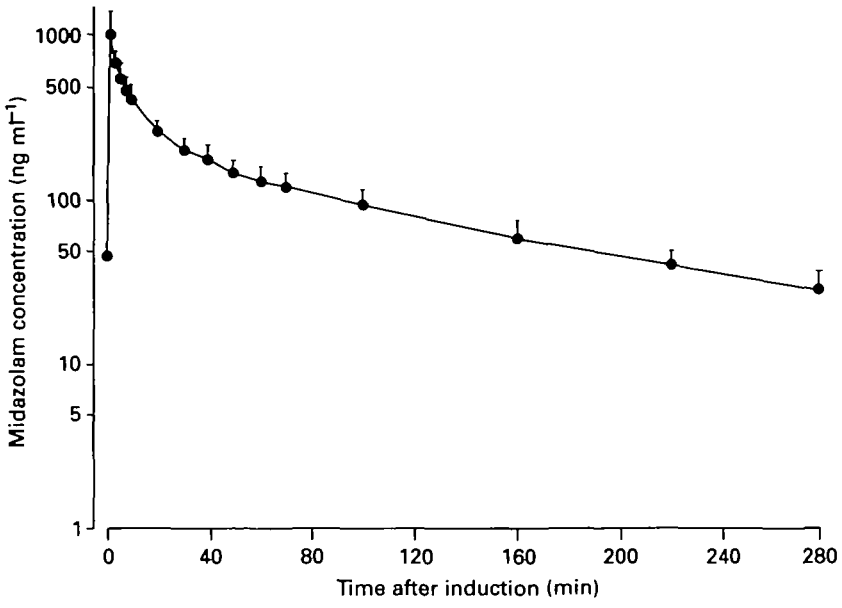

FIG. 1. Mean (SD) serum concentrations of midazolam.

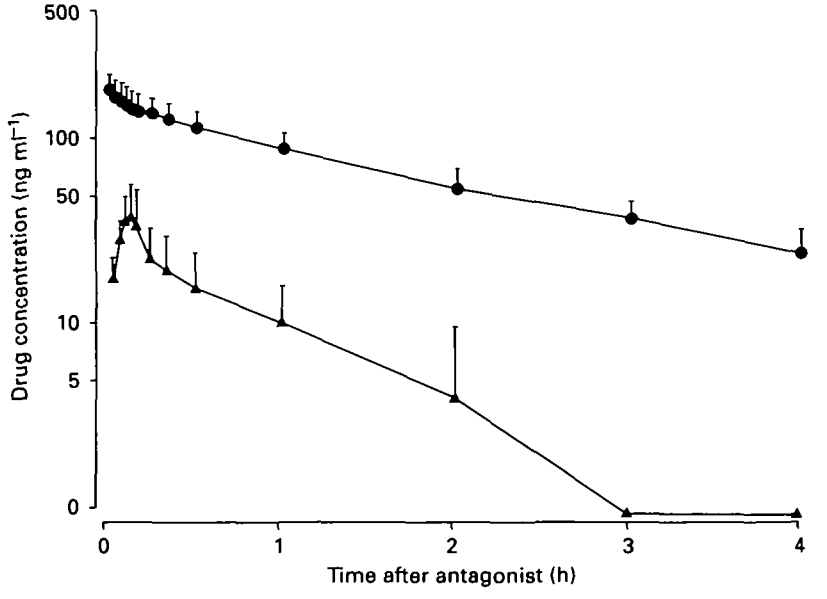

FIG. 2. Simultaneous mean (SD) serum concentrations of flumazenil (▲) and midazolam (●).

1.12% 4-hydroxymidazolam and 0.01–1.15% 4-hydroxymidazolam glucuronide. One child was an extensive hydroxylator, having a high recovery of hydroxy metabolites and the glucuronide (denoted by the greater values). Unchanged flumazenil was recovered in all the urine samples, ranging from 5.84% to 13.8% (mean 9.07 (SD 2.96)) of the dose administered. The demethylated metabolite, desmethylflumazenil, was detected but was not measurable by our HPLC method because its analytical peak was too close to the solvent front of the chromatogram. The carboxylic acid metabolite of flumazenil was not resolved by our present HPLC method. The child demonstrating extensive hydroxylation of midazolam also excreted the largest amount of unchanged flumazenil in the urine (13.8%); however, his other pharmacokinetic and pharmacodynamic data were unremarkable.

DISCUSSION

The clinical pharmacokinetics of drugs in anaesthetic practice may be influenced by the mutual pharmacokinetic interactions of drug distribution, metabolism and excretion. In their studies in healthy volunteers, Breimer and co-workerd observed that flumazenil and midazolam at repeated therapeutic doses did not show any cumulation or saturation kinetics [14]. Therefore it is unlikely, in this present clinical study, that pharmacokinetic interaction occurred when midazolam and flumazenil were administered together. In all our Chinese children, clearance of midazolam from the plasma may be described best by a tri-exponential function; however, other workers have described a bi-exponential decline in plasma midazolam concentrations [1, 4, 5]. This may be explained by our 2-min sampling interval during

TABLE IV. *Pharmacokinetic findings in the 12 children. Volumes of distribution at steady state* (V^{ss}) *and equilibrium* (V^{γ}), *volume of the central compartment* (V), *total body clearance* (Cl), *half-lives of the three phases* ($T_{\frac{1}{2}}^{\alpha}$, $T_{\frac{1}{2}}^{\beta}$, $T_{\frac{1}{2}}^{\gamma}$) *and rate constants (mean (SD) [range])*

	Midazolam	Flumazenil
V^{ss} (litre)	41.1 (18.9) [21.5–93.7]	21.0 (7.1) [10.3–32.7]
(litre kg^{-1})	1.87 (0.57) [1.15–2.93]	1.0 (0.2) [0.7–1.6]
V^{γ} (litre)	48.8 (22.2) [25.2–106.5]	20.5 (6.7) [9.8–31.2]
(litre kg^{-1})	2.2 (0.7) [1.2–3.3]	0.9 (0.2) [0.7–1.6]
V (litre)	7.2 (5.6) [1.8–23.3]	
(litre kg^{-1})	0.31 (0.17) [0 09–0.73]	
Cl (litre min^{-1})	344 (150) [199–736]	469.83 (239.52) [136.27–963.17]
(ml min^{-1} kg^{-1})	15.37 (3.16) [11.02–23.00]	20.57 (6.92) [7.29–30.85]
Terminal $T_{\frac{1}{2}}$	101.7 (31.9) [59.7–179.4]	35.3 (13.8) [21.5–75.5]
$T_{\frac{1}{2}}^{\alpha}$ (min)	2.55 (1.37) [0.84–5.00]	
$T_{\frac{1}{2}}^{\beta}$ (min)	16.1 (6.8) [3.9–26.0]	
$T_{\frac{1}{2}}^{\gamma}$ (min)	107.0 (30.2) [65.0–189.0]	
k_{31} (h^{-1})	1.03 (0.37) [0.55–1.84]	
k_{10} (h^{-1})	3.53 (1.74) [1.76–7.06]	
k_{13} (h^{-1})	4.5 (3.83) [0.89–14.20]	
k_{12} (h^{-1})	8.17 (6.93) [1.49–24.38]	
k_{21} (h^{-1})	8 30 (5.52) [3.49–23.67]	
$k_{31}:k_{10}$	0.35 (0.18) [0.12–0.75]	
$k_{12}:k_{21}$	1.14 (0.80) [0.06–3.00]	

the initial distribution phase and our measurement of plasma concentrations for nearly 300 min compared with shorter sampling times in other studies. The kinetics of i.v. midazolam were superimposed on a "background" concentration of the oral midazolam premedication. This was considered valid if, within the constraints of clinical practice, it is assumed that first order kinetics existed. Our midazolam pharmacokinetic data show a mean $T_{\frac{1}{2}}^{\gamma}$ of 107 min, total body clearance of 15 ml kg^{-1} min^{-1} and an apparent central volume of distribution of 0.3 litre kg^{-1}. The smaller central volume of distribution and higher clearance in our subjects should have resulted in a rapid initial and subsequent distribution half-lives; however, our mean terminal elimination half-life data are intermediate when compared with other studies [1, 15, 16]. This may be explained by the different fat distribution in Chinese children, the differing anaesthetic techniques used and the age-related variation in metabolism of benzodiazepines which undergo oxidation as their main metabolic pathway of elimination [17]. The mean (SD) ratio of $k_{12}:k_{21}$ was 1.14 (0.8), suggesting a rapid distribution of the i.v. midazolam from the central plasma compartment to the shallow compartment, and the mean ratio of $k_{31}:k_{10}$ was 0.35 (0.18), suggesting a slow return from the deep fat and muscle compartments before elimination.

Flumazenil pharmacokinetic data were best interpreted by non-compartmental analysis, because of the bolus and infusion administration regimen used in this study. The mean plasma concentrations of the drug after the infusion appeared to decline bi-exponentially (fig. 2), although this was not observed in several patients whose drug concentrations declined almost mono-exponentially in a manner similar to that described in adults [18, 19]. The present HPLC assay was not sufficiently sensitive to measure flumazenil in plasma in these patients 120 min after dose administration. The terminal elimination half-life of flumazenil may therefore be underestimated. Nevertheless, the kinetic data were derived using statistical moment analysis which takes into account the total dose administered. V^{ss} in our children was about half that reported in adults, clearance values were similar, and the flumazenil terminal half-life was 35 min in children compared with reported values of 60–77 min in adults [18, 20, 21]. Both flumazenil and midazolam are water soluble drugs at low pH, but at physiological pH the imidazole ring forming part of the midazolam structure closes and lipid solubility is enhanced [22]. V^{ss} and V^{γ} for flumazenil were approximately 50 % those of midazolam, reflecting the latter drug's wider distribution and greater lipid solubility within the body. This is endorsed by the low $k_{31}:k_{10}$ ratio for midazolam and the absence of unchanged midazolam in the urine, implying that the slow release of the drug from the deep fat compartment enables complete metabolism by the liver before elimination [17, 23]. The clearance of flumazenil from the plasma was more rapid compared with midazolam and unchanged flumazenil was recovered in the urine. Flumazenil attains equilibration rapidly in the central compartment, is only slightly bound to plasma proteins compared with midazolam and it is likely that more of the drug remains in the plasma compartment for a longer time because its lipid solubility is less than that of midazolam at physiological pH [18]. The small volume of distribution and high clearance of flumazenil resulted in a terminal half-life which was 33 % of the terminal half-life of midazolam in our children. Flumazenil concentrations in the plasma were minimal at 2 h and not detectable by our method of analysis at 3 h. The mean dose of flumazenil administered to our children to attain awakening (27 μg kg^{-1}) was similar to that given by Klotz, Ziegler and Reimann (approx. 35 μg kg^{-1}) to adults [18] and our measured concentrations of flumazenil at awakening were greater than the steady state values used by Breimer and colleagues in adults to antagonize a single i.v. dose of midazolam (approx. 0.25–0.75 mg kg^{-1}) [14].

Two hours after oral administration of midazolam,

all of the children arrived in the operating suite awake, co-operative and apparently anxiety-free, but on specific questioning 30% of the children expressed some fear. Their mean (SD) midazolam concentration was 47 (15.8) ng ml^{-1} (fig. 1) which is close to the lower range of concentrations at which sedative effects are seen in adult intensive care patients [24–27], but considerably less than the amnesic threshold reported by Persson, Nilsson and Hartvig [28]. Each benzodiazepine has its own plasma decay curve and pattern of threshold concentrations [27]. The anxiolytic effect of midazolam occurs at smaller serum concentrations that those required for sedation and therefore most of the children were calm on arrival in the operating suite [22]. To achieve a hypnotic effect with midazolam in adults, a plasma concentration of 300–500 ng ml^{-1} is required [29, 30]. Children require a rapid, pleasant, smooth induction of anaesthesia, but the variability in clinical response to a given dose of midazolam requires either that a large dose is administered, or that an opioid (in this study, alfentanil) is also given to ensure these favourable characteristics [31]. In all the children the induction was smooth, rapid and without incident, but the peak measured mean plasma midazolam concentration at 2 min was 1000 ng ml^{-1}, which declined to values less than 300 ng ml^{-1} at 20 min (fig. 1). At the time of antagonist administration, the children's mean plasma concentration of midazolam (180 ng ml^{-1}) (fig. 2) was at the adult mid-range sedative concentration. However, 50% of the children awoke crying and refused to play with the post-box toy, implying a mild inverse agonistic effect which was also reported by other workers, in adults [32, 33]. Interestingly, these children also had the greatest mean serum concentrations of flumazenil on awakening. These findings are in contrast with our previous experience. Following flumazenil administration to children undergoing the same surgical procedure, but using a spontaneously breathing anaesthetic technique with halothane, only 20% of the children refused the toy or cried on awakening [3]. The halothane-supplemented children awoke more slowly, but were given a smaller mean dose of antagonist (0.024 mg kg^{-1}). This is in accord with the findings of Geller and colleagues, who demonstrated that flumazenil improved the quality of emergence from anaesthesia in patients given halothane anaesthesia without benzodiazepines [34]. Our children who were happy and co-operative on awakening had greater serum concentrations of midazolam compared with the children who were irritable, crying and refused to play with the post-box toy. Moreover, the children who were drowsy on awakening had a smaller mean serum concentration of flumazenil (table III). The sample size was too small for any statistical comparison; however, the data were blind and lend credence to pharmacokinetic–pharmacodynamic model of midazolam plasma concentration and effects which is currently being developed by other workers [14].

Flumazenil is distributed into the brain within minutes of i.v. administration and attains brain concentrations which are greater than those in plasma, but then is cleared rapidly from the brain and excreted [21]. The clinical effect of flumazenil is dependent on the dose of midazolam, dose of flumazenil, pharmacokinetics of both drugs and the timing of antagonist administration. Despite being fully awake, the children who were willing to perform the post-box toy test demonstrated mild residual psychomotor impairment for the first 2 h after operation. At 4 h, all of the children tested performed close to their best, practised, unmedicated preoperative attempt. The sensitivity of our assay did not permit measurement of plasma flumazenil concentrations at 3 h, but the mean midazolam concentrations in our children at that time were in the adult anxiolytic range. The resedation in six of our patients was presumably caused by residual midazolam hypnotic effects being relatively unopposed by flumazenil (table III). These children went back to sleep approximately 80 min after initial awakening, but were roused easily, albeit crying and irritable and similar to the "normal" small child who is awoken abruptly. The awakening mean plasma concentration of midazolam in the resedated children was less than the awakening mean midazolam concentrations in the happy or sleepy children, suggesting that midazolam was redistributed more rapidly to the deep compartment in these children, resulting in later sedation when the midazolam returned to the central compartment and, furthermore, that resedation *per se* was not the result of rapid redistribution of flumazenil from the central compartment.

A smooth induction of anaesthesia with midazolam in children is achieved with large plasma concentrations of midazolam and at the expense of prolonged sedative and anxiolytic effects which are apparent with smaller concentrations of midazolam. Flumazenil antagonized the hypnotic effects of midazolam rapidly and effectively and the pharmacokinetic disposition of flumazenil in children was similar to that defined in adults [18]. Relative plasma concentrations of agonist and antagonist seem to determine the quality of emergence from anaesthesia. A mild inverse agonistic effect of flumazenil has been reported in adults and may also occur in children with large plasma concentrations of flumazenil [33].

ACKNOWLEDGEMENTS

We thank F. Hoffmann-La Roche & Co. Ltd, Basle, Switzerland for supplying the agents used, and Mr Andy Lai and Miss Shirley Tsang for their technical assistance.

REFERENCES

1. Tolia V, Brennan S, Aravid MK, Kauffman RE. Pharmacokinetic and pharmacodynamic study of midazolam in children during esophagogastroduodenoscopy. *Journal of Pediatrics* 1991; **119**: 467–471.
2. Feld LH, Negus JB, White PF. Oral midazolam preanesthetic medication in pediatric outpatients. *Anesthesiology* 1990; **73**: 931–834.
3. Jones RDM, Lawson AD, Andrew LJ, Gunawardene WMS, Bacon-Shone J. Antagonism of the hypnotic effect of midazolam in children: a randomized, double blind study of placebo and flumazenil administered after midazolam-induced anaesthesia. *British Journal of Anaesthesia* 1991; **66**: 660–666.

4. Salonen M, Kanto J, Iisalo E, Himberg JJ. Midazolam as an induction agent in children. A pharmacokinetic and clinical study. *Anesthesia and Analgesia* 1987; **66**: 625–628.
5. Payne K, Mattheyse FJ, Liebenberg D, Dawes T. The pharmacokinetics of midazolam in paediatric patients. *European Journal of Clinical Pharmacology* 1989; **37**: 267–272.
6. Rey E, Delaunay L, Pons G, Murat L, Richard MO, Saint-Maurice C, Olive G. Pharmacokinetics of midazolam in children: comparative study of intranasal and intravenous administration. *European Journal of Clinical Pharmacology* 1991; **41**: 355–357.
7. Jones RDM, Kapoor SC, Warren SJ, Moffat C, Merridew CG, MacKillop A, Hui PW. Effect of premedication on arterial blood gases prior to cardiac surgery. *Anaesthesia and Intensive Care* 1990; **18**: 15–21.
8. Krane EJ, Jacobson LE, Lynn AM, Parrot C, Tyler DC. Caudal morphine for postoperative analgesia in children: A comparison with caudal bupivacaine and intravenous morphine. *Anesthesia and Analgesia* 1987; **66**: 647–653.
9. Robertson GS, MacGregor DM, Jones CJ. Evaluation of doxapram for arousal from general anaesthesia in outpatients. *British Journal of Anaesthesia* 1977; **49**: 133–139.
10. Gibaldi M, Perrier D. Pharmacokinetics. In: Swarbrick J, ed. *Drugs and the Pharmaceutical Sciences*, Vol. 15. New York: Marcel Dekker, 1982; 271–318.
11. Jones RDM, Chan K, Andrew LJ. Pharmacokinetics of propofol in children. *British Journal of Anaesthesia* 1990; **65**: 661–667.
12. Chan K, Tse J, Jennings F, Orme ML'E. Disposition of pethidine in man under acidic urinary pH3. A comparison of pharmacokinetics among Caucasians, Chinese and Indian subjects. *Methods and Findings in Experimental and Clinical Pharmacology* 1987; **9**: 243–250.
13. Boxenbaum HC, Riegelman S, Elashoff RM. Statistical estimation in pharmacokinetics. *Journal of Pharmacokinetics and Biopharmaceutics* 1974; 2: 123–148.
14. Breimer LTM, Burm AGL, Danhof M, Hennis PJ, Vletter AA, de Voogt J-WH, Spierdijk J, Bovill JG. Pharmacokinetic–pharmacodynamic modelling of the interaction between flumazenil and midazolam in volunteers by aperiodic EEG analysis. *Clinical Pharmacokinetics* 1991; **20**: 497–508.
15. Clausen TG, Wolff J, Hansen PB, Larsen F, Rasmussen SN, Dixon JF, Crevoisier C. Pharmacokinetics of midazolam and α-hydroxy-midazolam after rectal and intravenous administration. *British Journal of Clinical Pharmacology* 1988; **25**: 458–463.
16. Pentikainen PJ, Valisalmi L, Himberg JJ, Crevoisier C. Pharmacokinetics of midazolam following intravenous and oral administration in patients with chronic liver disease and in healthy subjects. *Journal of Clinical Pharmacology* 1989; **29**: 272–277.
17. Greenblatt DJ, Abernethy DR, Locniskar A, Harmatz JS, Limjuco RA, Shader RI. Effect of age, gender and obesity on midazolam kinetics. *Anesthesiology* 1984; **61**: 27–35.
18. Klotz U, Ziegler G, Reimann IW. Pharmacokinetics of the selective benzodiazepine antagonist Ro 15-1788 in man. *European Journal of Clinical Pharmacology* 1984; **27**: 115–117.
19. Klotz U, Kanto J. Pharmacokinetics and clinical use of flumazenil (Ro 15-1788). *Clinical Pharmacokinetics* 1988; **14**: 1–12.
20. Breimer LTM, Hennis PJ, Burm AGL, Danhof M, Bovill JG, Spierdijk J, Vletter AA. Pharmacokinetics and EEG effects of flumazenil in volunteers. *Clinical Pharmacokinetics* 1991; **20**: 491–496.
21. Geller E, Halpern P. Benzodiazepine antagonists. In: Lebowitz PW, ed. *Recovery from Anesthesia*. Boston: Little, Brown and Co., 1991; 69–81.
22. Nilsson A. Pharmacokinetics of benzodiazepines and their antagonists. In: White PF, ed. *Kinetics of Anaesthetic Drugs in Clinical Anaesthesiology*. London: Baillière–Tindall, 1991; 615–634.
23. Wills RJ, Khoo K-C, Soni PP, Patel IH. Increased volume of distribution prolongs midazolam half-life. *British Journal of Clinical Pharmacology* 1990; **29**: 269–272.
24. Michalk S, Moncorge C, Fichelle A, Farinotti R, Desmonts JM. Long term midazolam infusion for basal sedation in intensive care: a clinical and pharmacokinetic study. *Anesthesiology* 1986; **65**: A66.
25. Westphal LM, Cheng EY, White PF, Sladen RN, Rosenthal MH, Sung M-L. Use of midazolam infusion for sedation following cardiac surgery. *Anesthesiology* 1987; **67**: 257–262.
26. Maitre PO, Funk B, Crevoisier C, Ha HR. Pharmacokinetics of midazolam in patients recovering from cardiac surgery. *European Journal of Clinical Pharmacology* 1989; **37**: 161–166.
27. Reves JG. Benzodiazepines. In: Prys-Roberts C, Hug CC, eds. *Pharmacokinetics of Anesthesia*. Oxford: Blackwell, 1984; 157–186.
28. Persson MP, Nilsson A, Hartvig P. Relation of sedation and amnesia to plasma concentrations of midazolam in surgical patients. *Clinical Pharmacology and Therapeutics* 1988; **43**: 324–331.
29. Lauven PM, Schwilden H, Stoeckel H, Greenblatt DJ. The effects of a benzodiazepine antagonist Ro 15-1788 in the presence of stable concentrations of midazolam. *Anesthesiology* 1985; **63**: 61–64.
30. Persson MP, Nilsson A, Hartvig P, Tamsen A. Pharmacokinetics of midazolam in total intravenous anaesthesia. *British Journal of Anaesthesia* 1987; **59**: 548–556.
31. Kissin I, Vinik HR, Castillo R, Bradley EL. Alfentanil potentiates midazolam-induced unconsciousness in subanalgesic doses. *Anesthesia and Analgesia* 1990; **71**: 65–69.
32. Chiolero RL, Ravussin P, Chassot PG, Neff R, Freeman J. Ro 15-1788 for rapid recovery after craniotomy. *Anesthesiology* 1986; **65**: A466.
33. Higgitt D, Lader M, Fonagy P. The effects of the benzodiazepine antagonist Ro 15-1788 on psychophysiological performance and subjective measures in normal subjects. *Psychopharmacology* 1986; **89**: 395–403.
34. Geller E, Weinbroum A, Halpern P, Nevo Y, Rudick V. Flumazenil, the specific benzodiazepine receptor antagonist (Ro 15-1788), affects recovery from halothane anesthesia. *Anesthesiology* 1987; **67**: A422.