no cyanosis, change in breath sounds, or hemodynamic instability. If the pulse oximeter had not been in use, the case could easily have proceeded to the point of anesthetic disaster before any sign of trouble was detected.

In summary, we have described a case of accidental bronchial insertion of an esophageal stethoscope, resulting in hypoxemia which was discovered in a timely fashion through the use of pulse oximetry. We recommend a heightened awareness of the possibility of misplacement of esophageal probes and suggest that the use of pulse oximetry may have been life-saving in this case.

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The Pharmacokinetics of Rectal Midazolam for Premedication in Children

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Midazolam, a short-acting, water-soluble benzodiazepine with a short elimination half-life in adults,[1,2] has been recommended as an intramuscular preanesthetic sedative in children.[3] Rectal administration of benzodiazepines may offer similar sedation and relief of anxiety without the discomfort and fear associated with intramuscular injections in children.[4] Thus, we sought to determine whether a rectal solution of midazolam could be used in children and to characterize the pharmacokinetics of midazolam following rectal administration.

METHODS

Sixteen healthy children (ASA I), ranging in age from 3 to 9 yr and undergoing minor genitourinary surgery, were studied. The protocol was approved by our Human Ethics Committee and informed consent was obtained from the parents. All the children were premedicated with midazolam 0.3 mg/kg diluted in 5 ml of saline solution and administered per rectum. Sedation was evaluated using two criteria: the child's behavior and the acceptance of both the mask and anesthetic vapors. Behavior was evaluated by the same investigator. It was rated by one of the following five categories: 1) agitated; 2) awake but with spontaneous body movements; 3) calm and motionless; 4) drowsy; and 5) asleep. Acceptance of the mask at induction of anesthesia was assessed 30 min after midazolam administration by the same investigator. Anesthesia was induced with halothane, nitrous oxide, and oxygen.

Plasma concentration time course of midazolam following rectal administration was studied in nine of the children. Venous blood samples (2 ml) were drawn 3, 5, 10, 15, 20, 30, 60, 90, 120, 180, 240, and 300 min after rectal administration. Plasma was separated by centrifugation and stored at −20° C until analyzed. Plasma concentrations were determined by gas-liquid chromatography with electron capture detection.[5] This method has a sensitivity of 2.0 ng/ml and a coefficient of variation of 2.8–4% at the plasma concentrations studied. The main metabolite of midazolam, α-hydroxymidazolam, is not detected by the assay. Midazolam plasma concentration decay curve was analyzed by a nonlinear least-squares regression technique. Pharmacokinetic parameters were determined from the coefficients and exponents obtained by analysis of the plasma concentrations. They included maximum plasma concentration (Cp_{max}), time to Cp_{max} (t_{max}), terminal half-life ($T_{1/2\beta}$), and apparent clearance (Cl). The area under the plasma concentration time curve (AUC_0^∞, $\int_0^\infty c.dt$) was calculated by the trapezoidal rule and the unknown area to infinity calculated from the slope β and the last measured midazolam plasma concentration. The mean residence time (MRT) was determined by noncompartmental techniques[6] and calculated as the ratio:

$$MRT = \frac{AUMC}{AUC} = \frac{\int_0^\infty c.t.dt}{\int_0^\infty c.dt}$$

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TABLE 1. Modification of Behavior after Rectal Administration of Midazolam in Children (n = 16)

Patient Behavior	Time (min)			
	0	10	20	30
Agitated	6	—	—	—
Awake	5	4	2	2
Calm	5	7	7	7
Drowsy	—	5	7	7
Asleep	—	—	—	—

The area under the moment curve (AUMC) was estimated by a method similar to that used for AUC. All the results are expressed as mean ± SD.

RESULTS

The mean age of the children was 4.8 ± 1.6 yr. Modifications of the children's behavior after midazolam administration are summarized in table 1. The level of sedation was comparable 20 and 30 min after midazolam. Acceptance of the mask and anesthetic vapors was judged satisfactory (child unafraid of the mask and cooperative) in all the children 30 min after midazolam. No changes in respiratory rate were observed. Figure 1 shows the plasma concentration decay curve following rectal administration. The pharmacokinetic parameters after midazolam administration are summarized in table 2. Midazolam was rapidly absorbed by the rectal route and the Cp_{max} was reached 16 min after the end of administration. $T_{1/2}\beta$ was 106 ± 29 min and the MRT was 134 ± 32 min. Cl was 795 ± 300 ml/min.

DISCUSSION

Midazolam is an effective drug for premedication in both adults[7] and children.[3] Rita *et al.*[3] demonstrated that im midazolam allayed children's anxiety and allowed smooth induction of anesthesia. We elected to study rectal administration of midazolam because injections can be responsible for psychologic stress in children.

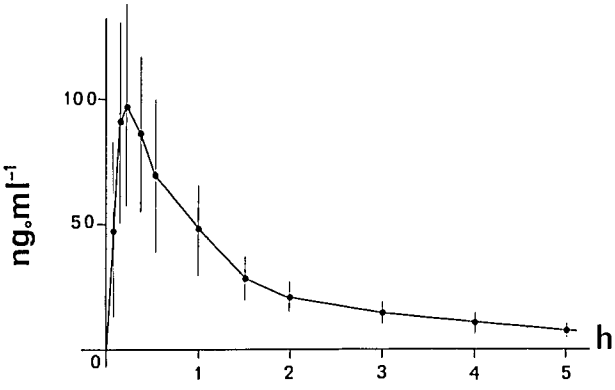

FIG. 1. Plasma concentration decay curve in children after rectal administration of midazolam, 0.3 mg/kg (mean ± SD).

The degree of sedation 20–30 min after rectal administration of midazolam is sufficient for smooth induction of anesthesia *via* mask with halothane and nitrous oxide. Like the other benzodiazepines (diazepam[4] and flunitrazepam[8]), midazolam is rapidly absorbed by the rectal route. The maximum plasma level of drug was attained between 9 and 29 min after administration. The mean midazolam t_{max} by the rectal route (16 min) is almost similar to that previously reported for flunitrazepam (15 min)[8] in children after rectal administration or diazepam, the peak being reached within 20 min in children.[9] The mean Cp_{max} reached 100 ng/ml, a level sufficient for sedation and hypnotic effect.[1,10] In all the children the Cp_{max} was higher than 40 ng/ml, which would be the "threshold" level for sedation.[1] Twenty min after rectal administration, midazolam plasma concentrations were close to the Cp_{max}, which could explain the sedation obtained in approximately 20 min. Thirty minutes after midazolam ad-

TABLE 2. Pharmacokinetic Parameters of Each Child

Patient Number	Weight (kg)	Cp_{max} (ng·ml^{-1})	t_{max} (min)	MRT (min)	$T_{1/2}\beta$ (min)	AUC ng·ml^{-1}·min	Cl ml·min^{-1}
1	19	50	15	113	77	5,244	1,086
2	16	124	9	140	124	9,600	500
3	18.5	196.5	11	100	81	11,220	492
4	25	73	20	133	91	9,360	802
5	21	183	10	130	115	11,640	542
6	20	77	29	130	89	9,300	645
7	18.5	45.5	23	149	111	3,960	1,400
8	18.0	58	21	208	170	6,246	865
9	12.5	80	9	104	94	4,866	822
Mean	18.7	98.6	16	134	106	7,937	795
SD	3.4	56.6	7	32	29	2,883	300

See "Methods" for abbreviations.

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ministration, the plasma levels were lower than after 10 min but good induction conditions persisted, particularly acceptance of the mask. This could be due to the appearance of the main metabolite of midazolam, α-hydroxymidazolam, which was not detected by the assay. Moreover, there is a closer correlation between drug concentration and clinical effect when midazolam plus α-hydroxymidazolam plasma concentration are considered.[10]

The mean value for the elimination half-life is comparable to the values reported in adults after iv[1] or oral administration.[1,11] In children, the elimination half-life of midazolam is markedly shorter than that of diazepam, which is close to 18 h.[12] Flunitrazepam's elimination half-life has not been determined after rectal administration in children, but elimination half-life is about 12 h in children following iv injection.[13] Rapid elimination of midazolam is explained by an important and rapid degradation by hepatic enzymes; thus, unchanged midazolam in the urine is negligible.[14] As most maturational changes occur within the first year of life, hepatic metabolism in children between 3 and 9 yr is close to that in adults. This could explain the short elimination half-life observed in these children. Variability of kinetic data is usual with benzodiazepines and has already been observed with midazolam in adults.[1,15] In this study it could be partly due to interindividual variations in rectal absorption.[4]

After rectal administration, midazolam may be absorbed by the superior hemorrhoidal veins that lead to the portal circulation. Because midazolam undergoes first-pass hepatic extraction,[1] we decided to use 0.3 mg/kg for rectal administration. The bioavailability of midazolam was less than 50% after enteral administration.[1,10] After an oral dose of 7.5 mg, the systemic availability averaged 30%, whereas 80–100% of midazolam was absorbed after im administration.[16]

In conclusion, midazolam is effectively and rapidly absorbed by the rectal route, which can replace the im injection. Because the elimination half-life is much shorter than that of diazepam or flunitrazepam in children, prolonged sedative effects are less likely.

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