BIOAVAILABILITY OF DIAZEPAM AFTER INTRAVENOUS, ORAL AND RECTAL ADMINISTRATION IN ADULT EPILEPTIC PATIENTS

SORAYA DHILLON¹, JOLYON OXLEY² & ALAN RICHENS¹

¹ Department of Pharmacology and Materia Medica, Welsh National School of Medicine, Heath Park, Cardiff, and

² Chalfont Centre for Epilepsy, Chalfont St Peter, Bucks

1 The absorption of single doses of diazepam in six adult epileptic subjects following intravenous, oral and rectal administration were studied in order to evaluate the usefulness of the latter in emergency situations in the adult.

2 Diazepam tablets (Valium, Roche) and rectal solution (Valium solution for intravenous administration) produced similar peak serum concentrations after delays of 15–90 min.

3 Two suppository formulations showed statistically significant differences in absorption characteristics.

4 Serum diazepam levels above 400 ng ml⁻¹ (suggested to be necessary for a satisfactory anti-convulsant effect) were reached in only a few subjects after rectal doses of 10–20 mg of solution, and then usually after a delay of over 2 h.

Introduction

Intravenous diazepam is the drug of choice for the treatment of prolonged fits or status epilepticus (Browne & Penry, 1973). However intravenous administration is practical only if a physician is available. Absorption of diazepam after intramuscular administration is slow, irregular and dependent on the technique of administration and is therefore unsatisfactory in situations where a rapid effect is required (Hillestad *et al.*, 1974; Gamble *et al.*, 1975). Recent studies on rectal administration of diazepam in solution to children have shown that peak serum concentrations are produced within 10 min in the majority of patients (Agurell *et al.*, 1975; Knudsen, 1977; Dulac *et al.*, 1978). Rectal administration of diazepam suppositories in adults have been shown to result in low peak plasma levels after delays of up to 2 h (Arnold, 1975), suggesting that suppositories cannot be considered to ensure a rapid therapeutic effect. Magnusson *et al.* (1979) investigated the absorption of diazepam solution from Stesolid rectal tubes (Dumex). Low peak serum levels were obtained after 10–20 min, and the bioavailability was reported as incomplete.

We have investigated the absorption of single doses of diazepam in adult epileptic patients following intravenous, oral and rectal administration.

Methods

Nine adult epileptic patients resident at the Chalfont Centre for Epilepsy, Chalfont St Peter, Bucks., England, consented to participate in the study. All patients were on standard antiepileptic drug therapy (Table 1).

The following preparations were used; Valium (Roche) solution for intravenous administration (5 mg/ml); Valium (Roche) 10 mg tablets; diazepam (10 mg) suppositories in a polyethylene glycol base prepared by Dr B. Winsely, John Radcliffe Hospital, Oxford (Suppository A); and Valium (Roche) 10 mg suppositories (Suppository B).

Study 1

The purpose of this study was to determine the absorption profile and bioavailability of diazepam when given orally in tablet form and rectally as a solution.

Six subjects received in a random order and at an interval of at least 2 weeks single 10 mg doses of diazepam by the intravenous, oral and rectal route of administration. The intravenous injection was administered slowly over a 2 min period. Tablets were administered orally following a light breakfast of toast and fruit juice. The rectal solution (Valium

Table 1 Details of patients admitted to trial

Subject	Age (years)	Weight (kg)	Antiepileptic drug therapy (Total daily dose mg)			
1	19	66	CBZ	1200	SV	1000
2	25	64	CBZ	800	P	400
3	35	64	CBZ	1200	SV	500
4	39	67	PRIM	750	SV	500
5	18	54	CBZ	600	SV	1000
6	33	67	CBZ	1000	CZ	4
7	22	65	SV	1200		
8	37	74	CBZ	1200	SV	1000
9	30	76	CBZ	1000	SV	2000

CBZ Carbamazepine, SV sodium valproate, P Phenytoin, PRIM Primidone, CZ Clonazepam

injection 5 mg/ml) was administered with 5 ml syringe attached to a soft polyethylene catheter, which placed the solution approximately 10 cm above the external anal ring. The dead space in the catheter was allowed for.

Study 2

The purpose of this study was to determine the absorption profile and bioavailability of the two suppository preparations. These were inserted manually to one digit length above the anal ring. Three of the subjects included in Study 1 had been discharged from the Centre and therefore three further subjects were recruited.

Study 3

The absorption of a larger dose of diazepam solution (20 mg in 4 ml) was compared with the standard dose of 10 mg in three subjects studied previously. Rectal administration of either dosage was given without previous bowel preparation.

The subjects remained supine following each drug administration and no food or drink was allowed for the next 4 h.

Blood samples (5 ml) were taken from the arm not used for the intravenous injection at the following times; prior to drug administration, 2, 5, 10, 20, 30, 60, 90 min and then at 2, 3, 6, 12, 24, 36 and 48 h following intravenous injection. The same sampling sequence was used following oral and rectal administration but excluding the 2 and 5 min samples. Blood samples on day 1 were taken using an indwelling butterfly needle. Serum was frozen and stored at -20°C until analysis.

Serum diazepam concentration was determined by gas liquid chromatography. A Perkin Elmer F33 fitted with an electron capture detector was used. The extraction procedure followed was according to the

method of Rutherford (1977). A coiled glass column 3 m $\times$ 2 mm i.d., was packed with Kovats 3% C87 hydrocarbon on Chromosorb W HC 100–120 mesh. The instrument conditions used were: carrier gas (nitrogen) flow rate 120 ml/min, column temperature 255°C , injection port and detector temperature 300°C .

Analysis of data

The absorption was characterised by the peak serum concentration ($C_{\max}$) and the peak concentration time ($t_{\max}$). The area under the serum concentration time curve (AUC) from $t = 0$ to $t = 36$ h was determined by the trapezoidal rule. The AUC from the last sampling point C_t to infinity C_{∞} was determined by the relationship:

$$\text{AUC}_{C_t}^{C_{\infty}} = \frac{C_t}{\beta}$$

Bioavailability (F) was determined according to the equation:

$$F = \frac{\text{AUC}_{\text{route of administration}}}{\text{AUC}_{\text{intravenous}}} \times \frac{\text{Dose}_{\text{intravenous}}}{\text{Dose}_{\text{route of administration}}} \times 100$$

Statistical analysis was evaluated using Student's *t*-test.

Results

Individual serum diazepam concentration profiles following intravenous, oral and rectal administration of 10 mg diazepam in six subjects are shown in Figure 1. Table 2 compares pharmacokinetic parameters calculated following administration of diazepam orally and rectally. When peak serum concentration ($C_{\max}$) and time to peak ($t_{\max}$) after oral tablets and rectal solution were compared, no statistically significant differences were found. Bioavailability after rectal

Figure 1 Individual serum diazepam concentration profiles in six adult epileptic subjects following administration of diazepam (10 mg) intravenously (●), orally (○) and by rectal solution (▲).

Table 2 Individual peak serum concentration ($C_{\max}$), peak concentration time ($t_{\max}$), area under the serum concentration time curve ($AUC_{0-\infty}$) and calculated bioavailability for six subjects after oral administration of tablets and rectal administration of solution (10 mg dose)

	$C_{\max}$ (ng ml ⁻¹)		$t_{\max}$ (min)		intra- venous	$AUC_{0-\infty}$ ($\mu\text{g l}^{-1}\text{ h}$)		Bioavailability (%)	
	oral	rectal solution	oral	rectal solution		oral	rectal solution	oral	rectal solution
1	280	265	75	20	3843	1831	-†	64	-†
2	300	320	15	60	4648	3214	4362	69	98
3	450	340	25	13	3053	1607	2388	53	78
4	325	215	30	30	2442	2367	2076	97	85
5	350	300	90	60	3926	3251	2419	83	62
6	380	415	50	30	5953	5363	4918	90	83
mean	331	309	48	37				76	81*
s.d.	114.2	68.1	30	20				16.8	13.0

† β not estimated due to an extended absorption profile.* $P < 0.05$.

administration was similar to that after oral administration.

Absorption parameters and bioavailability data following administration of Suppository A and Suppository B are shown in Table 3. Peak serum concentrations were significantly lower and the time to peak significantly longer after Suppository B as compared with Suppository A (Figure 2). In comparison to the solution, peak serum levels were lower and the time to peak longer following both suppository formulations. Bioavailability after the two rectal suppository formulations was similar, but significantly lower than the bioavailability after the rectal solution (Table 2).

Three subjects (1, 2 and 4) received an additional 20 mg dose of diazepam as rectal solution. Individual concentration profiles are shown in Figure 3. Bioavailability after the 20 mg dose in these subjects was

98, 90 and 72% respectively. Peak serum concentrations were less than double those produced by the 10 mg dose. This was due to a slower rate of absorption after the larger dose.

Discussion

The aim of the study was to investigate the absorption of diazepam in adult epileptic patients following rectal administration of various dosage forms in order to evaluate whether this could provide an alternative route of administration in emergency situations. The results show that peak serum concentrations were similar following administration of 10 mg orally in tablet form and the same dose rectally as a solution, although the peak was possibly achieved earlier after

Table 3 Calculated pharmacokinetic parameters after rectal administration of two suppository formulations in six subjects

	$C_{\max}$ (ng ml ⁻¹)		$t_{\max}$ (min)		Bioavailability (%)	
	Suppository A	Suppository B	Suppository A	Suppository B	Suppository A	Suppository B
1	240	150	60	120	72	63
2	325	144	60	480	105	-†
4	165	130	60	120	51	85
7	225	159	90	180	-†	69
8	160	102	120	90	41	35
9	157	103	60	120	65	96
mean	212*	131	75	185*	67	70
s.d.	65.8	24	25	147	24.4	23.3

Level of significance

* $P < 0.05$ * $P < 0.05$ † β not estimated

Figure 2 Serum diazepam concentration profiles (mean values) in six adult epileptic subjects following administration of diazepam (10 mg) intravenously (●) and in suppository form; Suppository A (▲) and Suppository B (○).

rectal solution. Relatively rapid absorption could also be obtained by using suppositories although considerable differences in the absorption characteristics occurred between formulations. Previous studies on diazepam absorption from different suppository bases have shown that erratic and low peak plasma levels are obtained (Schwartz *et al.*, 1966; Arnold, 1975). Although in our study low and delayed peak serum levels were observed after Suppository B (Valium, Roche, the commercially available form), much more satisfactory absorption characteristics were achieved with Suppository A. This is an experimental formulation specifically designed to promote rapid release of the drug from the suppository base. The bioavailability after rectal administration in our subjects was similar to that reported by Moolenaar *et al.* (1980). Much lower values however, have been observed by Magnusson *et al.* (1979). The latter authors suggested that adsorption of diazepam to faecal matter might have accounted for the incomplete bioavailability. With Stesolid rectal tubes (Dumex) the possibility arises that part of the dose might be sucked back into the device on releasing pressure prior to removal from the rectum. In our study and that of Moolenaar *et al.* (1980) a syringe and catheter was used and therefore no such problems were encountered.

No simple correlation exists between clinical response and serum level of diazepam and/or its metabolites. In a recent review (Mandelli *et al.*, 1978) it has been proposed that diazepam has anticonvulsant effects at serum levels above 400 ng ml⁻¹, levels usually reached following a bolus intravenous injection of 10–20 mg. However a definite decrease in

paroxysmal activity in the electroencephalogram was found by Viala *et al.* (1974) in a small number of subjects with serum concentrations of diazepam greater than 250 ng ml⁻¹. In three subjects in whom we administered 20 mg diazepam in solution, peak serum levels between 335–510 ng ml⁻¹ were obtained only after a delay of 1–2 h. This may be unacceptable if the drug is to be used in an emergency situation. However, better definition of the serum concentration required for an anticonvulsant effect is necessary

Figure 3 Individual serum diazepam concentration profiles following rectal administration of diazepam in solution (20 mg) in subjects 1 (●), 2 (○) and 4 (▲).

before the potential efficacy of the route of administration can be judged with certainty.

An additional point to take into account is whether after rectal administration serum diazepam levels rise fast enough to produce an adequate concentration of the drug within the brain. Following intravenous administration a considerable fraction of the dose is presented to the brain almost immediately and these initial high levels may be critical for the anticonvulsant effect. Subsequent redistribution of the drug can lead to a rapid loss of anticonvulsant effect. If the drug is absorbed slowly in the first place, adequate brain concentrations may never be reached. However it is of interest that in children rectal instillation of diazepam solution (0.7 mg kg^{-1}) can produce peak serum levels of up to $1 \mu\text{g ml}^{-1}$ within 10–20 min

(Knudsen, 1977) and is effective in the treatment of febrile convulsions (Knudsen, 1979). But in view of the age dependent differences in drug absorption these observations may not necessarily be valid for an adult population. Clinical studies need to be initiated to establish whether diazepam rectal solution in adults could be considered as an alternative to the intravenous route of administration in the treatment of fits.

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References

- AGURELL, S., BERLIN, A., FERNGREN, H. & HELLSTRÖM, B. (1975). Plasma levels of diazepam after parenteral and rectal administration in children. *Epilepsia*, **16**, 277–283.
- ARNOLD, E. (1975). A simple method for determining diazepam and its major metabolites in biological fluids: application in bioavailability studies. *Acta. Pharmac. Tox.*, **36**, 335–352.
- BROWNE, T. & PENRY, K. (1973). Benzodiazepines in the treatment of epilepsy. *Epilepsia*, **14**, 277–310.
- DULAC, O., AICARDI, J., REY, E. & OLIVE, G. (1978). Blood levels of diazepam after single rectal administration in infants and children. *J. Pediat.*, **93**, 1039–1041.
- GAMBLE, J.A.S., DUNDEE, J.W. & ASSAF, R.A.E. (1975). Plasma diazepam levels after single dose oral and intramuscular administration. *Anaesthesia*, **30**, 164–169.
- HILLESTAD, L., HANSEN, T., MELSON, H. & DRIVENESS, A. (1974). Diazepam metabolism in normal man: I Serum concentration and clinical effects after intravenous, intramuscular and oral administration. *Clin. Pharmac. Ther.*, **16**, 479–484.
- KNUDSEN, F.U. (1977). Plasma-diazepam in infants after rectal administration in solution and by suppository. *Acta Paediat. Scand.*, **66**, 563–567.
- KNUDSEN, F.U. (1979). Rectal administration of diazepam in solution in the acute treatment of convulsions in infants and children. *Arch. Dis. Child.*, **54**, 855–857.
- MAGNUSSON, I., OXLUND, H.R.W., ALSBIRK, K.E. & ARNOLD, E. (1979). Absorption of diazepam in man following rectal and parenteral administration. *Acta Pharmac. Tox.*, **45**, 87–90.
- MANDELLI, M., TOGNONI, G. & GARATTINI, S. (1978). Clinical pharmacokinetics of diazepam. *Clin. Pharmacokin.*, **3**, 72–91.
- MOOLENAAR, F., BAKKER, S., VISSER, J., HUIZINGA, T. (1980). Biopharmaceutics of rectal administration of drugs in man IX. Comparative biopharmaceutics of diazepam after single rectal, oral, intramuscular and intravenous administration in man. *Int. J. Pharmaceut.*, **5**, 127–137.
- RUTHERFORD, D.M. (1977). Rapid micromethod for the measurement of diazepam and desmethyldiazepam in blood plasma by gas liquid chromatography. *J. Chromatog.*, **137**, 439–448.
- SCHWARTZ, D.E., VECCHI, M., RONCO, A. & KAISER, K. (1966). Blood levels after administration of diazepam in various forms. *Arzneim-Forsch.*, **16**, 1109–1110.
- VIALA, A., CANO, J.P., DRAVET, C., PASSINARI, C.A. & ROGER, J. (1971). Blood levels of diazepam (Valium®) and N-desmethyldiazepam in the epileptic child. *Psychiatr. Neurol. Neurochir.*, **74**, 153–158.

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