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BIOPHARMACEUTICS OF RECTAL ADMINISTRATION OF DRUGS IN MAN IX. COMPARATIVE BIOPHARMACEUTICS OF DIAZEPAM AFTER SINGLE RECTAL, ORAL, INTRAMUSCULAR AND INTRAVENOUS ADMINISTRATION IN MAN

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SUMMARY

Rectal absorption of diazepam was studied in man and compared with intravenous, intramuscular and oral administration. Plasma concentrations of diazepam were measured by means of HPLC analysis after a single dose of 10 mg diazepam in a cross-over study in 9 healthy volunteers.

Plasma concentration–time curves following intravenous administration were described by a tri-exponential function consistent with a three-compartment model system. It was calculated that the drug will not exhibit measurable first pass metabolism.

Comparing the absorption rate constants it appeared that rectal absorption of a solution of diazepam proceeded significantly ($I < 0.05$) more rapidly than absorption after oral and intramuscular administration. Absorption from a macrogol suppository dosage form was rather slow.

The mechanism of the rapid rectal absorption of diazepam from the solute state was discussed. No essential difference in bioavailability was observed between the intramuscular injection, rectal solution and tablets as compared with the intravenous injection. Only for the suppository dosage form was bioavailability calculated to be significantly lower.

INTRODUCTION

The clinical importance of diazepam as an effective anticonvulsant, muscle relaxant, anti-anxiety, sedative and hypnotic drug has led to numerous studies concerning pharmacokinetics and biopharmaceutics in man (Mandelli et al., 1978). Although no simple correlation seems to exist between clinical response and steady-state plasma levels of diazepam (Garattini et al., 1973; Bond et al., 1977; Tansella et al., 1978) many studies did show a correlation between the rate of sedation and the rate of increase of plasma diazepam concentrations (Baird and Hailey, 1972; Bliding, 1974; Kortilla and Linnoila,

1975). If a rapid therapeutic effect is required in a single dose situation (for instance acute convulsive attack phenomena) it is obvious that a rapid absorption from the dosage form used is essential. In this respect it was recently shown in experiments with adult patients that maximal serum concentrations following rectal administration of a solution of diazepam were reached within approximately half an hour (Magnussen et al., 1979). Also rectal administration of a solution of diazepam to children was found to be an alternative route for the acute treatment of convulsive attacks (Agurell et al., 1975; Knudsen, 1977; Langslet et al., 1978; Meberg, et al., 1978; Dulac et al., 1978). However, in none of these studies was the absorption rate of diazepam after rectal dosing accurately characterized and statistically evaluated. In addition, no data were available on pharmacokinetics after rectal administration of diazepam in healthy subjects. Human studies were therefore planned to investigate rectal absorption of diazepam. To establish differences in rate and extent of absorption a comparison was made with the oral, intramuscular and intravenous route of administration.

MATERIALS AND METHODS

Dosage forms

Commercially available diazepam, obtained from Dumex, Copenhagen, Denmark, was used in this study (Stesolid for injection, Stesolid rectal tubes, Stesolid suppositories, Stesolid tablets). All dosage forms contained 10 mg of diazepam.

Human experiments

Nine healthy human subjects, 3 female and 6 male, ranging in age from 18 to 25 years and in body weight from 58 to 70 kg, participated in the cross-over studies at 2-week intervals.

No drugs were taken for two weeks prior to or during the study. The experiments were initiated in the morning after an overnight fast and the volunteers did not take in any food during the first 4 hours of the experiments. They were asked to remain in a sitting position. Diazepam was injected intravenously during 2 min into 9 volunteers. Diazepam was injected intramuscularly into the vastus medialis muscle of the thigh during 2 min into 6 volunteers. The oral dosage form was administered to 7 volunteers. Diazepam (dissolved in 2.5 ml solvent) was administered rectally as micro-enemas into 9 volunteers. Suppositories (1.6 g) were administered to 9 volunteers.

Bloodsamples of 8 ml were taken from a forearm vein by means of an intermittent infusion set with reseal injection site (Abbot Butterfly-19, int.) and a three-way stopcock (Pharmaseal K-75a Luer). In the cases of the intravenous injection and rectal micro-enema, bloodsamples were taken 2.5, 5.0, 7.5, 10, 15, 20, 30, 45 and 60 min, 2, 3, 4, 6, 8, 12 and 24 h after administration. In the cases of the intramuscular injection, oral administration and rectal administration of the suppository, bloodsamples were taken 5, 15, 30, 45 and 60 min, 2, 3, 4, 6, 8, 12 and 24 h after administration of the dosage forms. Blood was placed in test tubes containing heparin and plasma was obtained by centrifugation. Plasma was frozen until the time of analysis.

Determination of diazepam and desmethyldiazepam in plasma

Diazepam and N-desmethyldiazepam concentrations in plasma were estimated by high-pressure liquid chromatography as described by Westenberg and De Zeeuw (1976).

Pharmacokinetic analysis and calculations

The absorption rate constant (K_a) was obtained using a non-linear regression analysis of log plasma concentrations vs time (NONLIN). Besides, the absorption was characterized by the peak concentration (C_{max}) and the peak concentration time (t_{max}). The area under the plasma concentration curve (AUC) from t = 0 to t = 24 h was determined by the trapezoidal rule. Relative bioavailability was determined using the partial areas under the curve (0–24 h) according to the equation:

$$F_{rel} = \frac{AUC_{\text{route of administration}}}{AUC_{\text{intravenous}}} \times \frac{Dose_{\text{intravenous}}}{Dose_{\text{route of administration}}}$$

The parameters were determined for each individual and statistical differences were tested by Student's *t*-test ($P < 0.05$, one-sided) for paired data.

RESULTS AND DISCUSSION

Intravenous administration

Plasma concentration–time data following a slow intravenous injection during 2 min of 10 mg diazepam to 9 subjects were obtained (Table 1). It should be noted that administration of single doses of diazepam did not result in significant amounts of the active metabolite N-desmethyldiazepam in plasma (<50 ng/ml). Therefore plasma concentrations of this metabolite were disregarded.

Semi-logarithmic plots of diazepam plasma concentration–time data could satisfactorily be fitted with a tri-exponential function for all 9 subjects. The mean pharmacokinetic parameters are listed in Table 2.

After an extremely rapid initial distribution phase (t = 8.5 min) and a second phase ($t_{1/2}$ = 78 min) a slow elimination phase was observed with a mean terminal half-life of 19.7 h. Since only very small amounts of free diazepam are recovered intact in urine and bile (Kaplan et al., 1973) it is assumed that the drug was completely metabolized: f_m = 1.00 (f_m is the fraction of the dose metabolized).

The ratio of drug concentration in blood to plasma (λ) was reported to be 0.59 for diazepam (Klotz et al., 1976). The following equation was used to estimate the mean liver extraction ratio:

$$E = \frac{f_m \cdot Cl \cdot 1/\lambda}{HBF}$$

where HBF is the hepatic blood flow rate (taken as 1.5 l/min). Cl is the mean total plasma clearance estimated as:

TABLE 1

MEAN (±S.D.) PLASMA CONCENTRATIONS OF DIAZEPAM, ABSORPTION CHARACTERISTICS AND BIOAVAILABILITY AFTER ADMINISTRATION OF VARIOUS DOSAGE FORMS TO HEALTHY VOLUNTEERS. C_{max} AND t_{max} ARE THE MEAN VALUES CALCULATED FROM THE INDIVIDUAL CURVES. THE VALUES, GIVEN IN PARENTHESES, ARE THE COEFFICIENTS OF VARIATION (%)

	i.v. injection (10 mg) (n = 9)	Rectal solution (10 mg) (n = 9)	Suppository (10 mg) (n = 9)	Tablet (10 mg) (n = 7)	i.m. injection (10 mg) (n = 6)
Plasma concentration (ng/ml)					
t: 2.5 (min)	564 ± 156 (27.7)	11 ± 4 (36.4)			
5.0	623 ± 131 (21.0)	130 ± 46 (35.4)	–	0.2 ± 0.6 (300)	48 ± 64 (133.3)
7.5	592 ± 128 (21.6)	226 ± 68 (30.0)			
10	542 ± 123 (22.7)	289 ± 76 (26.3)			
15	516 ± 105 (20.3)	297 ± 90 (30.3)	51 ± 20 (39.2)	94 ± 185 (196)	167 ± 136 (81.4)
20	472 ± 100 (21.2)	294 ± 75 (25.5)			
30	416 ± 88 (21.1)	282 ± 60 (21.3)	160 ± 51 (31.9)	239 ± 175 (73.2)	279 ± 195 (69.9)
45	379 ± 89 (23.5)	290 ± 63 (21.7)	220 ± 42 (19.1)	301 ± 114 (37.9)	319 ± 180 (56.4)
60	347 ± 90 (25.9)	262 ± 57 (21.7)	249 ± 52 (20.9)	325 ± 66 (20.3)	320 ± 141 (44.1)
2 (h)	268 ± 83 (30.9)	260 ± 59 (22.7)	254 ± 69 (27.1)	309 ± 65 (21.0)	296 ± 59 (19.9)
3	216 ± 73 (33.8)	206 ± 78 (37.8)	222 ± 66 (29.7)	223 ± 73 (32.7)	229 ± 68 (29.7)
4	195 ± 53 (27.1)	201 ± 47 (23.4)	201 ± 59 (29.3)	204 ± 61 (29.9)	200 ± 61 (30.5)
6	138 ± 65 (47.1)	166 ± 37 (22.3)	156 ± 59 (37.8)	166 ± 57 (34.3)	176 ± 52 (29.5)
8	145 ± 50 (34.5)	145 ± 42 (28.9)	126 ± 64 (50.8)	141 ± 46 (32.6)	132 ± 70 (53.0)
12	120 ± 35 (29.1)	134 ± 42 (31.3)	133 ± 51 (38.3)	130 ± 36 (27.7)	148 ± 51 (34.4)
24	73 ± 24 (32.9)	95 ± 31 (32.6)	76 ± 35 (46.0)	81 ± 18 (22.2)	81 ± 31 (38.3)
K_a (h^{-1})		17.5 ± 8.1 (46.3)	2.1 ± 1.1 (52.4)	8.2 ± 9.8 (119.5)	1.7 ± 0.8 (47.1)
C_{max} (ng/ml)	650 ± 104 (16.0)	369 ± 58 (15.7)	272 ± 41 (15.1)	383 ± 102 (26.6)	375 ± 79 (21.1)
t_{max} (min)	6 ± 5 (83.3)	17 ± 6 (35.3)	82 ± 20 (24.4)	52 ± 40 (76.9)	95 ± 39 (41.1)
AUC_{0-24} ($ng\ ml^{-1}\ hr$)	3498 ± 615 (17.6)	3584 ± 498 (13.9)	2958 ± 472 (15.9)	3474 ± 542 (15.6)	3633 ± 672 (18.5)
F_{0-24} (%)	100	102	84	99	104

TABLE 2

MEAN (±S.D.) PHARMACOKINETIC PARAMETERS OF DIAZEPAM AFTER INTRAVENOUS ADMINISTRATION OF DIAZEPAM TO 9 HEALTHY VOLUNTEERS, ACCORDING TO A 3-COMPARTMENT OPEN MODEL WITH ELIMINATION FROM THE CENTRAL COMPARTMENT. THE VALUES, GIVEN IN PARENTHESES, ARE THE COEFFICIENTS OF VARIATION (%)

Dose	10.0 mg diazepam intravenously		
Number	9		
Age (years)	21	± 4	(19.0)
Weight (kg)	67	± 14	(20.9)
A (ng/ml)	299	± 38	(12.7)
α (h^{-1})	4.85	± 0.71	(14.6)
B (ng/ml)	304	± 37	(12.2)
β (h^{-1})	0.53	± 0.12	(22.6)
C (ng/ml)	175	± 34	(19.4)
γ (h^{-1})	0.035	± 0.007	(20.0)
$t_{1/2}$ (α) (h)	0.24	± 0.039	(27.8)
$t_{1/2}$ (β) (h)	1.3	± 0.17	(13.1)
$t_{1/2}$ (γ) (h)	19.7	± 6.8	(34.5)
Cl_{tot} (ml/min)	29.4	± 8	(27.2)

$$Cl = \frac{\text{Dose}}{A \cdot \alpha^{-1} + B \cdot \beta^{-1} + C \cdot \gamma^{-1}} \text{ (ml. min}^{-1}\text{)}$$

It can be calculated that the mean per cent liver extraction was maximally 0.033 indicating that the drug will not exhibit measurable first-pass liver metabolism. This was confirmed by the bioavailability studies following oral and rectal administration.

Oral administration

Seven subjects of the group of volunteers participated in this study. Plasma concentration–time data of diazepam following oral administration of 10 mg were obtained (Table 1).

Diazepam was rapidly absorbed from the tablets: the mean peak plasma concentration (C_{max}) of 383 ng/ml was reached within 60 min. However, as can be observed from Table 3, there was a considerable variation in the individual absorption rate constants. This is in agreement with results of Garattini et al. (1973) and Gamble et al. (1973) reporting an interindividual variability in plasma diazepam concentrations up to 30-fold after a single oral dose of 15 mg.

Using the area under the plasma level curve as an index of the extent of absorption it can be concluded that absorption was essentially complete 24 h after oral administration (Table 1). As discussed earlier, no measurable first-pass effect can be expected. The mean overall elimination rate constant after oral administration was 0.036 h^{-1} (Table 3), which corresponds well with the value obtained following intravenous administration of the drug under study (Table 1).

TABLE 3

INDIVIDUAL ABSORPTION AND ELIMINATION RATE CONSTANTS AFTER ADMINISTRATION OF THE VARIOUS DOSAGE FORMS TO 9 VOLUNTEERS

Subject	1	2	3	4	5	6	7	8	9	Mean ± S.D.	Variation coefficient
Oral											
K_a (h^{-1})	0.77	15.3	26.0	11.3	1.42	1.55	1.06			8.2 ± 9.8	119%
K_{el} (h^{-1})	0.034	0.039	0.044	0.026	0.028	0.037	0.031			0.034 ± 0.006	19%
Intramuscular											
K_a (h^{-1})	0.68	0.78	1.00	3.67	2.87	1.09				1.7 ± 1.3	76%
K_{el} (h^{-1})	0.037	0.023	0.045	0.041	0.083	0.076				0.051 ± 0.023	45%
Rectal solution											
K_a (h^{-1})	21.0	29.2	25.7	19.3	21.1	12.8	3.7	16.6	8.5	17.5 ± 8.1	46%
K_{el} (h^{-1})	0.031	0.038	0.037	0.027	0.042	0.034	0.031	0.038	0.037	0.035 ± 0.005	14%
Suppository											
K_a (h^{-1})	2.0	1.4	2.5	2.9	4.6	1.1	1.8	2.1	1.0	2.1 ± 1.1	52%
K_{el} (h^{-1})	0.056	0.024	0.026	0.029	0.029	0.034	0.039	0.031	0.037	0.034 ± 0.009	26%

Intramuscular administration

Six subjects of the group of volunteers participated in this study. Plasma concentration–time data of diazepam following a slow intramuscular injection during 2 min of 10 mg of diazepam in the vastus medialis muscle of the thigh were obtained (Table 1). Absorption from the intramuscular site was rather slow: the mean peak level of 375 ng/ml was reached after 95 min. However, no significant ($P < 0.05$) difference in absorption rate constants was calculated between the oral and intramuscular route of administration. In addition the variation coefficient was observed to be lower for the intramuscular route (Table 3). Bioavailability after this route was found to be essentially complete. Conflicting data concerning diazepam kinetics following intramuscular administration of the drug have been reported. Sedative effect and rate of absorption after intramuscular injection were reported to be superior to oral administration (Kortilla and Linnola, 1975; Baird and Hailey, 1973). On the other hand, most studies concluded the opposite in case of diazepam (McCaughey and Dundee, 1972; Hillestad et al., 1974; Mandelli, 1978; Bank-Mikkelsen et al., 1978).

The discrepancies in these studies are probably related to the variation in injection site and injection technique used (Gamble et al., 1975). It is important to mention that although rate and extent of absorption might be similar when comparing oral and intramuscular administration of diazepam, 5 out of 6 volunteers reported pain at the diazepam injection site.

Rectal administration

Micro-enemas

Plasma concentration–time data following rectal administration of a solution (2.5 ml) of 10 mg diazepam to 9 subjects were obtained (Table 1). Diazepam was very rapidly absorbed from the rectum lumen: the mean peak plasma concentration of 369 ng/ml was reached after 17 min. Comparing the absorption constants, it appeared that absorption proceeds significantly ($P < 0.05$) more rapidly with this administration than after oral and intramuscular administration (Table 3). No significant ($P < 0.05$) difference in the elimination rate constant was observed after the rectal and intravenous routes of administration. Since the $AUC_{0\text{-}24}$ was essentially the same for both routes of administration it is clear that the bioavailability after administration of the rectal solution is complete. Our results are in contrast with a rectal study of Magnussen et al. (1979) who found incomplete bioavailability (50 ± 17%).

These authors suggested that adsorption of diazepam to fecal matter, or rectal loss of the dosage form might account for this incomplete absorption. Another possibility suggested by the authors was that incomplete bioavailability was possibly due to the fact that the experiments were done in patients, who received ergot alkaloids rectally for a long period of time preceding to the diazepam administration.

Although it is generally assumed that the applicability of rectal solutions is limited due to the irritating character of the solvent, it is of importance to note that no discomfort was reported by any of the volunteers. This is probably related to the small volume (2.5 ml) used. In experiments done with a larger volume (up to 10 ml) the solvent was found

to be somewhat more irritating for the volunteers (Moolenaar et al., 1980).

The mechanism of the rapid rectal absorption of diazepam from the solute state has been uncertain until now. It is obvious that the solvent used favours the driving force for absorption, due to complete dissolution of diazepam. In this respect it can be mentioned that an aqueous suspension of diazepam in 10 ml of water did not give rise to significant amounts of diazepam in plasma. On the other hand, it might be possible that the permeability of the epithelial cells of the rectal mucosa is increased or rectal blood supply is improved, due to components of the solvent used, such as alcohol and propyleneglycol. Further studies have been initiated to test this hypothesis.

Suppositories

Plasma concentration–time data following rectal administration of macrogol suppositories containing 10 mg of diazepam to 9 subjects were obtained (Table 1). Comparing the rectal solution and the suppository dosage forms, it appeared that absorption from the suppository was rather slow: the mean peak level of 272 ng/ml was reached only after 82 min. The mean C_{max} value was significantly ($P < 0.05$) lower than after administration of the other dosage forms. These results are in good agreement with the rectal study of Kortilla et al. (1976) using polyethyleneglycol suppositories with diazepam: in this study t_{max} was 90 min and C_{max} was 245 ng/ml. Comparing the absorption rate constant it appeared that absorption proceeded significantly ($P < 0.05$) slower via this administration than after administration of the micro-enema and the tablet. However, no significant ($P < 0.05$) difference in absorption rate constant was found comparing the intramuscular injection and the suppository dosage form. Bioavailability 24 h after administration was rather complete (84%). Yet this value was calculated to be significantly ($P < 0.05$) lower compared with the other dosage forms.

These experiments confirm the conclusion of others (Schwartz et al., 1966; Arnold, 1975; Agurell et al., 1975; Knudsen, 1977) that absorption of diazepam from suppositories can not be considered as an optimal method to ensure a rapid therapeutic action.

THERAPEUTIC CONSIDERATIONS

If diazepam is to be administered for anticonvulsive purposes, absorption rate may be of great importance. Although intravenous administration of diazepam is the most rapid way to suppress convulsions, other routes of administration may be valuable when intravenous administration is inconvenient, for instance, because of the development of thrombophlebitis (in our study 3 of the 9 adult volunteers), or because of technical difficulties (status epilepticus), or can not be realized within a short period of time (dependent on doctor's arrival). The mean plasma concentration data of diazepam following 2 h after administration of the various dosage forms were plotted in Fig. 1.

As discussed earlier, no simple correlation exists between clinical response and plasma levels of diazepam. Yet our results may indicate that only for the micro-enema absorption of diazepam is absorption sufficiently rapid to be an alternative route of administration in case of acute convulsive attack phenomena, as compared with intravenous administration. In this respect it should be considered that, in view of anticonvulsant plasma levels of 400–500 ng/ml (Mandelli et al., 1978), a dose of 20 mg diazepam may be required for adult patients.

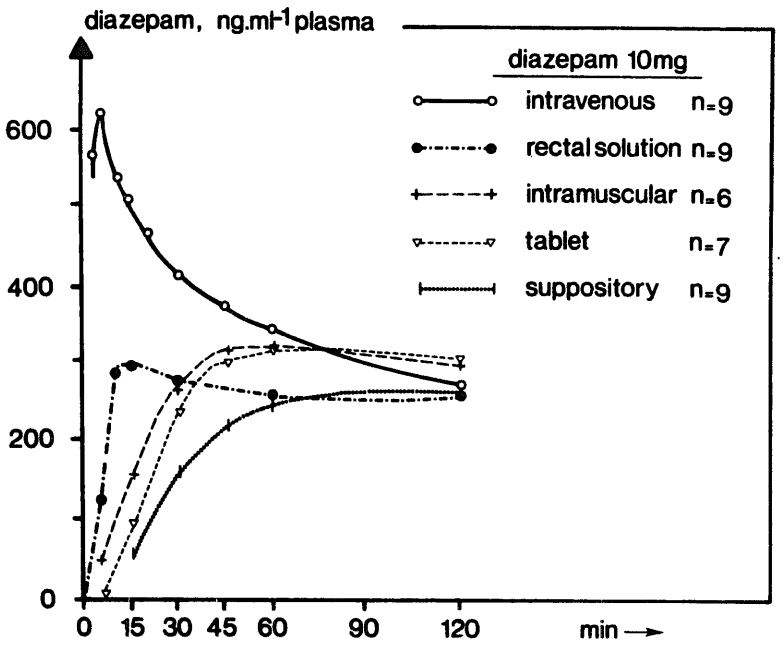

Fig. 1. Mean plasma concentrations of diazepam on linear scale after single intravenous, intramuscular, oral and rectal administration of 10 mg diazepam in different dosage forms, to healthy human subjects.

Although absorption after oral and intramuscular administration may be complete, the rate of uptake cannot compete with that of application of the rectal solution of diazepam. In this respect it is important to emphasize that suppositories do not provide an optimal dosage form for rectal administration of diazepam in single-dose treatment.

CONCLUSIONS

From intravenous data it is concluded that a 3-compartment model is necessary to describe the pharmacokinetic pattern of diazepam in man. Our measurements of the mean per cent liver extraction indicate that no distinct first-pass metabolism of diazepam will occur. After oral administration of diazepam in tablet form, absorption is rather fast and complete. However, a considerable variation in the individual absorption rate constants can be expected. After intramuscular administration of diazepam in solution form, absorption is rather slow. However, no difference in bioavailability occurs, as compared with intravenous administration.

After rectal administration of diazepam in solution form, absorption is extremely rapid. Absorption proceeds significantly ($P < 0.05$) more rapidly than after oral and intramuscular administration of diazepam. Bioavailability after administration of the rectal solution is essentially complete. For the suppository dosage form, absorption is rather slow and incomplete 24 h after administration.

From a therapeutic view-point it is concluded that in single-dose therapy with diaze-

pam, if a rapid therapeutic effect is required, only rectal administration of diazepam in solution form may be looked upon as an alternative route of administration for routine medication.

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