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Absorption of diazepam and lorazepam following intranasal administration

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Summary

The absorption characteristics of diazepam and lorazepam following intranasal administration were determined in order to assess the suitability of this approach for the treatment of status epilepticus in children. Due to the limited aqueous solubility of these drugs, a series of non-ionic surfactants were evaluated for drug solubility and nasal irritation. Cremophor EL (Blagden, U.K.) was selected as the least irritating. The diazepam and lorazepam studies were carried out in 2 and 4 healthy adults, respectively, in cross-over fashion. Diazepam was found to be 84% and 72% absorbed in the two subjects, peak concentration following nasal administration was observed at approximately 1 h and was approximately 27% of that following i.v. administration. Lorazepam bioavailability ranged from 35% to 63%, peak time from 0.5 to 4 h, and peak concentration from 33% to 94% that following i.v. administration (even though the i.v. dose of lorazepam was 1/2 the intranasal dose). Although both drugs are absorbed following intranasal application, this route of administration would appear to have limited potential for the acute treatment of seizures.

Diazepam and lorazepam are well accepted drugs for the treatment of status epilepticus (Homan and Walker, 1983; Leppik et al., 1983). Status epilepticus is a serious and often life-threatening emergency, which requires prompt treatment to minimize mortality as well as reducing neurological sequelae caused by prolonged seizure activity (Oxbury and Whitty, 1971; Meldrum, 1978). Current therapy requires rectal or i.v. administration of drugs to achieve the rapid onset of effect required. In the last decade, the intranasal route of drug administration for systemic effects has received attention due to its convenience and reliability (Freestone and Weinberg, 1976; Parr, 1983; Su, 1986). Intranasal administration of propranolol has been shown to result in drug concentration in blood similar to those observed after i.v. administration (Hussain et al., 1980). Both nasal nicotine solution and intranasal aerosolized insulin have demonstrated efficacy (Russell et al., 1983; Salzman et al., 1985). Given the promise this route of administration seems to hold, this investigation was initiated to determine whether diazepam and lorazepam can be administered intranasally to promptly achieve the therapeutic concentrations required to treat status epilepticus.

Benzodiazepines are poorly water-soluble (diazepam 0.05 mg/ml; lorazepam 0.08 mg/ml). Organic vehicles are therefore necessary for the formulation of nasal drops. A series of non-aque-

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ous solvents apparently acceptable on the basis of toxicity, irritability and carcinogenicity (Spiegel and Noseworthy, 1963; Lewis and Tatken, 1980) were evaluated. Since the volume which can be instilled is limited to about 100 μl for each nostril, a series of solubility tests for diazepam (10 mg) and lorazepam (4 mg) was carried out on these vehicles. Seven non-aqueous vehicles, triacetin, dimethyl sulfoxide, polyethylene glycol 400 (all from Sigma Chemical Co., St. Louis, MO), Cremophor EL (polyoxyethylated castor oil), Lipal-9-LA (laureth-9(polyoxyethylene-9 lauryl ether)) (PVO Research, Boonton, NJ), isopropyl adipate (Union Carbide, New York, NY), and azone 1-dodecylazacycloheptane-2-one (Nelson Laboratories, Irvine, CA) had acceptable solubility (i.e., could deliver the desired dose in < 250 μl solvent). These 7 vehicles were subjectively tested for acceptability by administering 100 μl of each vehicle separately to each nostril of two human subjects at different times. Cremophor EL was quite well tolerated and has been used as a vehicle for parenteral diazepam formulation in Europe. The other 6 vehicles were found to be irritating and unsuitable for intranasal application. Cremophor EL was therefore selected for bioavailability studies.

The subjects were 4 male and one female healthy volunteers, 26–37 years of age, weighing 60–85 kg, and receiving no other medication. The protocols for the two drugs were similar, except that 10 mg diazepam (both i.v. and intranasal) and 2 mg (i.v.)/4 mg (intranasal) lorazepam were administered. The subject received an i.v. dose of 10 mg/2 ml Valium or 2 mg/ml Ativan; and blood samples were obtained serially through a heparin lock. Plasma was stored at $-20\,^{\circ}C$ until analyzed by GC for diazepam (Rutherford, 1977) or lorazepam (Greenblatt et al., 1978). One to two weeks later, the same procedures were repeated except that the drug was administered as nose drops; 10 mg diazepam in 220 μl Cremophor EL or 4 mg lorazepam in 100 μl Cremophor EL. The dose was divided between the two nostrils and was administered with a positive-displacement pipette (SMI) while the subject was supine.

Bioavailability was calculated for each subject from the area under plasma concentration–time curves using standard methods (Gibaldi and Perrier, 1982). Peak time and concentration after intranasal administration were read from the concentration vs time plots. Peak concentration after i.v. administration was estimated by least-square linear regression analysis.

TABLE 1

Intranasal bioavailability of diazepam

Subject	Peak time (h)	Peak conc. (ng/ml)		
		Nasal	i.v. [a]	Bioavailability [b] (%)
1	1.25	110	650	72
2	1.50	240	644	84
Mean	1.38	175	647	78

[a] Estimated by least-square regression.

[b] Estimated from 0–50 h area under the plasma–concentration time curve (see Fig. 1).

The results for diazepam are shown in Table 1 and data from a representative subject are shown in Fig. 1. Peak time following intranasal administration of diazepam was comparable in both subjects; the mean value was 1.38 h. Peak concentration following i.v. administration was similar in the two subjects, with a mean value of 647 ng/ml. On the other hand, peak concentration following intranasal administration differed substantially between subjects with values of 110 ng/ml and 240 ng/ml in the two individuals.

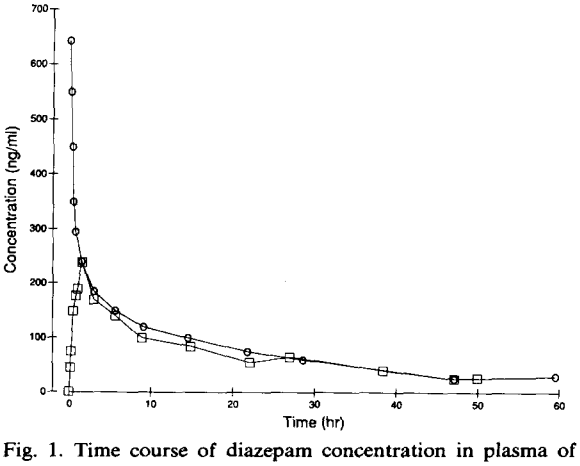

Fig. 1. Time course of diazepam concentration in plasma of subject 1 following i.v. (○) and intranasal (□) administration.

TABLE 2

Intranasal bioavailability of lorazepam

Subject	Peak time (h)	Peak conc. (ng/ml)		
		Nasal	i.v. [a]	Bioavailability (%)
3	4.0	15.5	46.2	35
4	0.5	27.5	29.4	63
5	2.0	15.8	24.3	56
6	2.5	15.8	31.2	51
Mean	2.25	18.7	32.7	51
S.D.	1.44	5.90	9.42	11.9

[a] Estimated by least-square regression.

The peak concentration and peak time for diazepam after intranasal administration are quite comparable to those found after 10 mg rectal suppository (Moolenaar et al., 1980), about 200 ng/ml and 1.5 h respectively. When 10 mg diazepam was administered as a rectal solution (Moolenaar et al., 1980), the peak concentration (290 ng/ml) was observed at 0.25 h and the concentration was approximately constant from the time of the peak to 3 h. Absorption from rectal solution achieved higher concentrations more quickly than we observed following intranasal administration.

The results for lorazepam are shown in Table 2, and data from a representative subject in Fig. 2. The mean peak time of lorazepam concentration

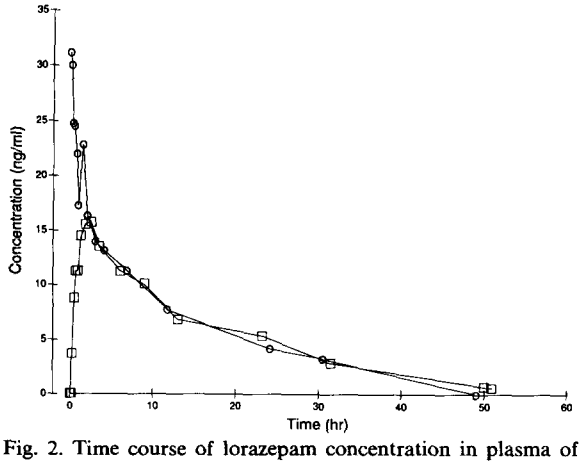

Fig. 2. Time course of lorazepam concentration in plasma of subject 6 following i.v. (○) and intranasal (□) administration.

in plasma of the 4 subjects following intranasal administration was 2.25 h, but varied from 0.5 to 4 h. Mean peak concentration was 18.7 ng/ml following intranasal administration and 32.7 ng/ml following i.v. administration. In one subject (number 4), peak concentration was comparable following intranasal and i.v. administration. This subject also had the shortest peak time, 0.5 h. Bioavailability ranged from 35% to 63% with a mean of 51%. The peak concentration (20.7 mg/ml) and time (2.2 h) reported by Greenblatt et al. (1982) for sublingual administration is similar to that observed here for intranasal administration.

The mean peak time for intranasal diazepam absorption is shorter than for lorazepam, 1.38 h vs. 2.25–3 h, and the extent of absorption is greater for diazepam, the more lipophilic drug. The rate of intranasal absorption of both drugs is rather slow for the treatment of a medical emergency such as status epilepticus. It is generally recognized that the high peak concentration following i.v. administration of benzodiazepine is essential for action. It may be possible to improve the intranasal absorption of benzodiazepines through the use of another solvent, use of a cosolvent, or use of an aerosol to maximize contact of the solution with the biological barrier, although the poor aqueous solubility of these drugs is likely to limit the success of this route. Due to the poor aqueous solubility of the benzodiazepines, the surfactant Cremophor was used neat in this study, and may have promoted absorption through the undesirable effect of disrupting the mucosal barrier (mild irritation was observed in some subjects). It appears that there is little room between the poor aqueous solubility of these compounds and the potential for solvent irritation (and toxicity, not addressed in this study) to achieve a satisfactory formulation.

Although diazepam and lorazepam cross the nasal mucosa and are absorbed into the systemic circulation, absorption is rather slow and peak concentration is low relative to that found after i.v. administration. It would appear that this route of administration may be of limited utility for benzodiazepines in the treatment of status epilepticus where rapid onset of effect is essential.

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