Intranasal Administration of Diazepam Aiming at the Treatment of Acute Seizures: Clinical Trials in Healthy Volunteers

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Intranasal administration of diazepam may be a practical alternative to the conventional acute medication of seizures, such as status epilepticus. Nine healthy students participated in an open crossover study on intranasal *versus* intravenous administration of diazepam (2 mg). Blood samples were collected, pharmacodynamic tests were performed, and the volunteers filled out questionnaire. Peak concentration was achieved after 18±11 min and the bioavailability was 50.4±23.3%. A pharmacodynamic effect was observed after about 5 min, but the dose, even for i.v. administration, was too low to generate a strong measurable effect. The results indicate that intranasally administered diazepam may be an effective alternative to i.v. administration in relief of seizures, *e.g.* in an acute situation when a physician or nurse is not available on location.

Key words intranasal administration; diazepam; volunteers; bioavailability

Treatment of epileptic seizures should be controlled without causing adverse reactions and in such a way that it promotes a good quality of life. The preferred drugs for the treatment of epileptic seizures are diazepam or clonazepam intravenously (i.v.), followed by phenytoin or phenobarbital.[1,2] These drugs are effective for hospitalized or institutionalized patients. They are, however, not applicable to patients living at home with their families, because i.v. administration of these drugs to a patient in seizure requires skilled personnel and an acute care facility, since the treatment may be associated with hypotension, cardiac dysrhythmias or central nervous system depression.

Rectal administration of diazepam as a clysma is an alternative in pediatric therapy. Parents and other caregivers may easily be trained to give these drugs rectally. Such therapy, however, is not that convenient in adults, though clinical trials show that this treatment results in less psychological, sociological and financial stress for the family, including reduced hospitalizations, and it improves the quality of life.[3—5] In a study by Kriel *et al.*[3] it was shown that rectal administration of diazepam was effective in controlling seizures in 85% of the patients and improved quality of life in 58% of the patients.

The intranasal administration of drugs may be an alternative to the rectal delivery. Drugs are absorbed rapidly from the nasal cavity, due to the highly vascularized nasal tissue and the relatively leaky epithelium. This rapid absorption is a benefit for acute medication. The absorption should also be fast, since drugs that are not absorbed within 10—30 min are cleared down to the nasopharynx and swallowed, due to the mucociliary clearance mechanism.[6]

A non-toxic intranasal delivery system for water-insoluble substances, such as benzodiazepines, has been developed.[7,8] When a clinically relevant dose of diazepam and clonazepam was administered to rabbits, both peak concentration and the pharmacodynamic response were achieved within 5 and 3 1/2 min, respectively.[9] The aim of the present study is to compare the pharmacokinetic and pharmacodynamic parameters after intranasal and intravenous administration of di-

MATERIALS AND METHODS

Diazepam was kindly provided by Lyfjaverslun Islands (Reykjavik, Iceland), polyethylene glycol 200 by Union Carbide (Charleston, U.S.A.) and glycofurolum 75 by Hofman-la Roche (Basle, Switzerland). The intranasal diazepam formulation (20 mg/ml) consisted of a mixture 5% glycofurol in polyethylene glycol 200. The subjects received 100 μl into one nostril. For comparison, a commercial intravenous diazepam formulation was used (Stesolid®, Dumex-Alpharma A/S, Copenhagen, Denmark).

The protocol was an open crossover trial, approved by the local ethics committee and the National Health Authorities of Iceland and the State Committee on Pharmaceuticals. Nine healthy volunteers, between 20—30 years old (weighing 58—80 kg), were chosen among 20 caucasian students who applied for participation, on the basis of normal liver and kidney function and no sign of a cold within the last two weeks prior to the first experimental day. They could not use any drugs that may interact with diazepam nor sedatives such as tranquilizers or alcohol, 3 d prior and during the experiment. Blood samples were withdrawn at time 0, 2, 5, 10, 30, 105, 300 min after administration. The serum diazepam concentration was measured by means of a fluorescence polarization immunoassay (FPIA) from Abbott A/S (Copenhagen, Denmark). Prior to and 30 min after application, the nasal mucous membranes in both nostrils were inspected by an evaluator, and the volunteers were asked to note all adverse reactions at 1, 10 and 30 min after the administration. After 0, 5, 30 and 90 min, the subjects were tested for some pharmacological tests (short time memory, catching, vigilance, concentration and tension) and recorded by the investigators. Short time memory was measured by reading 10 single numbers with a fixed speed followed by allowing the participants to repeat the numbers. The number of right numbers was recorded. Catching was measured by asking the participants to catch a pencil dropping 1.5 m from above. Vigilance, concentration and tension were based on a questionnaire.

Standard methods were used to calculate the pharmacoki-

for all subjects. The area-under-the-curve (AUC) was calculated using the trapezoidal method, the time to t_{max} was read from the plasma concentration profiles F_{total} was calculated as the percent of AUC_{nasal} over $AUC_{i.v.}$. Standard statistical techniques were used throughout the study. For the evaluation of significance, one way ANOVA was used.

RESULTS AND DISCUSSION

Intranasal administration of diazepam resulted in a rapid absorption of the drug. Peak concentration was achieved after about 18±11 min (5 out of 9 had t_{max}=10 min), providing 32.9±21.6% of the concentration, compared to the serum concentration obtained 10 min after an intravenous injection (Fig. 1, Table 1). The rate of absorption (k_{abs}) was found to be 0.43±0.19 min^{-1}. The most important time (clinically) for a successful treatment of seizure are the first 10 min. When this study was compared with other studies in the literature, 32.9±21.6% concentration is achieved after 10 min, compared with 12—27% in other studies after 10 min[10—13] and 46.5±19.1% after 30 min. The dose was kept at minimum (only 2 mg), since this study was the first clinical trial for this formulation. Sampling of plasma was only carried out over a 5 h period because the treatment of seizures is an acute treatment. Apparent half-life for diazepam was about 16 h since its terminal half-life ranges over 24 h. A six-fold increase in the dose should be possible using these vehicles, although the solubility of benzodiazepines is very low. The results indicate that clinically relevant amounts of diazepam can be absorbed within 10 min after the administration. This form for administration has the advantage that problems such as respiratory depression, *etc.* associated with intravenous injection are eliminated, providing a safer delivery system.

Several studies have been conducted where benzodiazepines have been administered intranasally to animals and humans. The most common is midazolam, administered in the form of undiluted parenteral solution for inducing sedation in children.[14—19] These studies show solely pharmacodynamic data but not clinical pharmacokinetic information. Few pharmacokinetic studies have been performed where plasma concentration profiles are presented. Time to maximal plasma concentration was between 12—15 min in those studies (except for one, where t_{max} was 83 min),[10] and the concentration around 15 min was about 12—27%, relative to an i.v. dose. Studies on rectal administration of diazepam show that 12 min onset time is sufficient for improving quality of life and effective in controlling seizures in the majority of patients, suffering from multiple seizures.[2]

Even after i.v. administration, the pharmacological effects were small, due to the low dose used. However, some effects were measured. Table 2 shows a summary of the pharmacodynamic responses after the administration. Intravenously administered diazepam was effective in decreasing the ability to concentrate and decreased vigilance, but the effect was not strong due to the low dose administered.

Intranasally administered diazepam, however, was effective in decreasing tension and the ability to memorize (short-time memory). The onset of effect on short-time memory was rapid and significantly different after nasal application as compared to the intravenous group, indicating that some of the diazepam may have been transported directly from the nasal cavity to the brain through the olfactory area.[20]

No signs of irritation were seen on the nasal mucosa, except for one volunteer who had a minor redness 30 min after the administration. The majority of subjects felt some irritation immediately after the administration. Thirty minutes later, however, all subjects had no or only minor sense of irritation. Eight out of nine participants would prefer nasally to intravenously administered diazepam for the treatment of acute seizures in themselves or in their child. It may be concluded that intranasal delivery of diazepam may be an alternative to i.v. and rectal treatment of acute seizures.

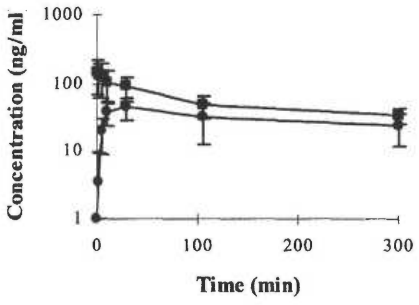

Fig. 1. Plasma Concentration–Time Profile (±S.D.) for Diazepam after Intranasal (●) and Intravenous (■) Administration of 2 mg Diazepam to Healthy Human Volunteers

Table 1. Kinetic Parameters of Diazepam in Humans after Single Administration (2 mg) Intranasally and Intravenously

Parameter	Intravenous	Intranasal
Dose (mg)	2	2
k_{abs} (min^{-1})	—	0.43±0.19
k_e (h^{-1})	0.064±0.017	0.189±0.077
$t_{1/2}$ (h) (apparent)	14.4±7.0	17.8±15.5
t_{max} (min)	—	18±11
C_{max} (ng/ml)	—	39±17
$AUC_{0-30\,min}$ (ng·min/ml)	2,972±980	1,095±412
F_{total} (%)	—	50.4±23.3

Table 2. The Onset of Individual Pharmacodynamic Tests, after Single Intranasal or Intravenous Administration of Diazepam (2 mg) to Healthy Volunteers.

Test	Intravenous onset (min)	Intranasal onset (min)	Significance (p)	Comments
Decreased ability to concentrate	5	5	No	
Decreased vigilance	5	5—30	0.1	Stronger effect after i.v.
Decreased tension	30	30	0.17	Stronger effect after i.n.
Decreased ability to memorise	5—30	5	0.05	Stronger effect after i.n.
Decreased ability to catch	No effect	No effect	No	

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