Absorption of clonazepam after intranasal and buccal administration

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Serum concentrations of clonazepam after intranasal, buccal and intravenous administration were compared in a cross-over study in seven healthy male volunteers. Each subject received a 1.0 mg dose of clonazepam intranasally and buccally and 0.5 mg intravenously. A C_{max} of 6.3 ± 1.0 ng ml^{-1} (mean; ± s.d.) was measured 17.5 min (median) (range 15–20 min) after intranasal administration. A second peak (4.6 ± 1.3 ng ml^{-1}) caused by oral absorption was seen after 1.7 h (range 0.7–3.0 h). After buccal administration a C_{max} of 6.0 ± 3.0 ng ml^{-1} was measured after 50 min (range 30–90 min) with a second peak of 6.5 ± 2.5 ng ml^{-1} after 3.0 h (range 2.0–4.0 h). Two minutes after i.v. injection of 0.5 mg clonazepam the serum concentration was 27 ± 18 ng ml^{-1}. It is concluded that intranasal clonazepam is an alternative to buccal administration. However, the C_{max} of clonazepam after intranasal administration is not high enough to recommend the intranasal route as an alternative to intravenous injection.

Keywords clonazepam absorption intranasal buccal pharmacokinetics

Introduction

For adequate treatment of status epilepticus or serial seizures with clonazepam, the rapid attainment of effective concentrations is necessary and, consequently, intravenous injection is generally the route of choice.

In several institutions in The Netherlands buccal administration of clonazepam is used in mentally retarded children with serial seizures [1]. However, accurate buccal clonazepam dosing is difficult in patients with convulsions and hypersalivation. In these situations intranasal administration may be an alternative. Intranasal administration is also more convenient than rectal administration. We have developed a clonazepam solution for intranasal administration. The nasal formulation for clonazepam contains dimethyl-β-cyclodextrin (DMβCD) as a solubilizer and absorption enhancer. Cyclodextrins are biocompatible polymers, able to form inclusion complexes with drugs. Clonazepam is virtually water insoluble. However, stable aqueous solutions can be prepared with DMβCD [2]. The aim of this study was to compare serum concentrations of clonazepam after intranasal, buccal and intravenous administration.

Methods

Subjects and protocol

The study involved seven healthy male volunteers aged 26 to 58 years, weighing from 69 to 82 kg. All were healthy and took no other medication. The protocol was approved by the local Ethics Committee and all volunteers gave written informed consent.

Intranasal clonazepam (5 mg ml^{-1}) was prepared by dissolving clonazepam (Bufa, The Netherlands) together with dimethyl-β-cyclodextrin (Avebe, The Netherlands) in a molar ratio of 1:8 in 96% v/v ethanol. The solvent was evaporated and the residue redissolved in 0.9% w/v saline. The pH was adjusted to 3.0. The intranasal spray device was a unit-dose pump (Pfeiffer GmbH, Germany).

The subjects participated in three test sessions at 2 week intervals. During the sessions they received a 1.0 mg dose of intranasal or buccal clonazepam or 0.5 mg clonazepam intravenously. Each intranasal dose was administered in one spray of 0.1 ml in both nostrils. Clonazepam was administered buccally by rubbing 0.4 ml of a 2.5 mg ml^{-1} solution (Rivotril® oral solution, Roche, The Netherlands) into the

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buccal mucous membrane. After administration the volunteer was instructed not to swallow the solution for as long as possible and not to speak for 1 h. Clonazepam (Rivotril® injection, Roche, The Netherlands) was injected into a forearm vein at a dose of 0.5 mg over 2 min. The medication was given after an overnight fast. Two hours after administration a normal diet was resumed.

Venous blood samples were taken at 0, 2, 5, 10, 15, 20, 30, 40, 60, 90 min, 2, 3, 4, 6, 8 and 24 h after dosing. The serum samples were stored at −20° C until analysis.

Drug analysis

To 0.5 ml serum were added 100 µl water, 50 µl desmethyldiazepam in ethanol 96% (2.5 µg ml^{-1}, internal standard) and 200 µl borax buffer solution 0.04 mol l^{-1} (pH 9.0), and the mixture was extracted with dichloromethane. The organic phase was separated and evaporated to dryness. The residue was dissolved in mobile phase and injected onto the column.

The h.p.l.c. system consisted of a Waters-Millipore 486 tunable absorbance detector, a 510 injector, a U6K pump and a Spectra Physics Data jet integrator for determination of peak heights. The column (30 cm × 3.9 mm i.d.) was packed with µ-Bondapak C18 (Waters-Millipore, The Netherlands). The mobile phase (pH 3.6) consisted of a mixture of acetonitrile, methanol and phosphate buffer solution 6 mmol l^{-1} (180 + 200 + 500). The flow rate was 2.0 ml min^{-1}. U.v. detection was at 210 nm. Calibration curves were linear ($r > 0.999$) up to 50 ng ml^{-1}. The limit of determination was 2 ng ml^{-1} at which concentration the intra-run coefficient of variation was 16%. The inter-run coefficient of variation was 10% for a 4 ng ml^{-1} solution.

Data analysis

Values of AUC(0,2 h) were calculated using a combination of the linear- and log-trapezoidal methods. The highest observed concentration and the corresponding sampling time were defined as C_{max} and t_{max}, respectively.

Differences in pharmacokinetic variables were examined using the Student's *t*-test for paired data. Data are reported as mean ± s.d. To assess the statistical significance of the difference between the administration routes the 95% CI for the mean difference was calculated.

Results

Mean serum concentrations of clonazepam after intravenous, intranasal and buccal administration are shown in Figure 1. After intravenous administration the concentrations declined over the first 10–15 min such that after 20 to 40 min they were similar to the peak values after buccal and intranasal administration. After 2 h no significant differences in serum drug concentrations were observed between the different routes of administration. All participants completed the study. Intravenous data for one subject were excluded from analysis because of extravasation during the injection. Serum drug concentrations after buccal administration to another subject could not be measured because of chromatographic interference.

Values of C_{max} and t_{max} are shown in Table 1.

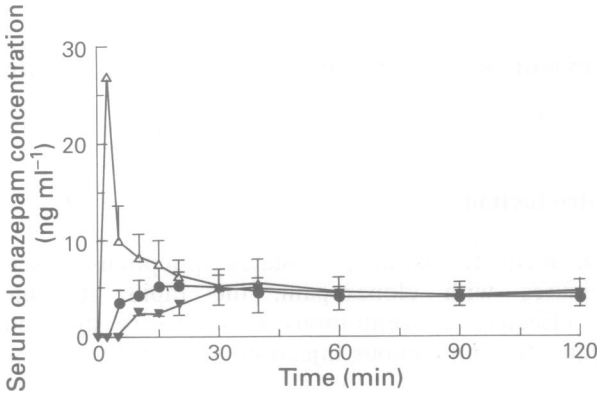

Figure 1 Mean (± s.d.) serum clonazepam concentrations after intravenous (0.5 mg, △), buccal (1.0 mg, ▼) and intranasal (1.0 mg, ●) administration of clonazepam.

Table 1 C_{max} and t_{max} values following the administration of 0.5 mg clonazepam intravenously and 1.0 mg bucally and intranasally to seven healthy male volunteers

	Intranasal				*Buccal*				*Intravenous*	
Subject	$C_{max,1}$ *(ng* ml^{-1}*)*	$t_{max,1}$ *(min)*	$C_{max,2}$ *(ng* ml^{-1}*)*	$t_{max,2}$ *(h)*	$C_{max,1}$ *(ng* ml^{-1}*)*	$t_{max,1}$ *(min)*	$C_{max,2}$ *(ng* ml^{-1}*)*	$t_{max,2}$ *(h)*	C *(ng* ml^{-1}*)*	t *(min)*
1			5.5	2.0	4	40	9	3.0	5	2
2	6.0	20	4.5	2.0	3	30	6	2.0	*	*
3	4.5	20	3.0	1.0	9	40			50	2
4	7.0	20	3.5	3.0	9	40	4	4.0	15	2
5	6.5	15	5.0	1.5	7	60			20	2
6	7.5	15	7.0	0.7	3	90			45	2
7	6.5	15	4.0	2.0	†	†	†	†	25	2
Mean	6.3	17.5	4.6	1.7	6.0	50	6.5	3.0	27	2.0
± s.d.	1.0		1.3		3.0		2.5		18	
Range		15–20		0.7–3.0		30–90		2.0–4.0		

*No data because of extravasation.
†No data because of analytical interference.

Initial peak drug concentrations were reached significantly faster after intranasal compared with buccal administration ($P < 0.05$; 95% CI for the mean difference: 1.3 to 66.7 min). The differences in these maximum concentrations after intranasal (6.3 ± 1.0 ng ml^{-1}) and buccal (6.0 ± 3.0 ng ml^{-1}) administration did not reach statistical significance ($P > 0.5$; 95% CI for the mean difference : −4.4 to +4.6 ng ml^{-1}).

After intravenous administration of 0.5 mg drug the mean AUC(0,2 h) was 11 ± 3 ng ml^{-1} h. Relative, dose-normalised AUC(0,2 h) values after buccal and intranasal administration were 0.41 and 0.45, respectively.

Discussion

After both intranasal and buccal administration of clonazepam two peak serum drug concentrations were obtained in six of seven and three of six subjects, respectively. The first peak was presumed to reflect initial rapid mucosal absorption and the second was a consequence of oral absorption.

The usual intravenous administered dose of clonazepam is at least 1.0 mg. However, a dose of 0.5 mg was used in this study for safety reasons. In studies in patients with status epilepticus therapeutic benefit was associated with serum clonazepam concentrations ranging from 13 to 90 ng ml^{-1} [3]. A therapeutic concentration threshold of 18 ng ml^{-1} has been suggested [4]. However, after buccal and intranasal administration of 1.0 mg clonazepam, concentrations above 18 ng ml^{-1} were not observed in this study.

Therefore we conclude that, although intranasal clonazepam (1.0 mg) is an alternative to buccal administration in patients with serial seizures, initial serum drug concentrations are too low to recommend its use as an alternative to intravenous injection in patients with status epilepticus.

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(*Received 2 August 1994, accepted 24 November 1994*)