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PHARMACOKINETICS AND DISPOSITION

Pharmacokinetics of buccal and intranasal lorazepam in healthy adult volunteers

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Abstract
Purpose To investigate the plasma-concentration profile of lorazepam when administered by the intranasal and buccal routes to determine their utility for the treatment of prolonged seizures.
Methods On two occasions separated by at least 7 days washout, 12 healthy adult male volunteers received 2 mg of lorazepam via the intranasal or buccal route. Blood samples were collected at time periods from 0 to 48 h, and pharmacokinetic parameters were determined.
Results Lorazepam was well absorbed from both administration routes; however, there was a more pronounced lag phase with the buccal route and absorption was more rapid from the intranasal route.
Conclusions Intranasal lorazepam has more favourable pharmacokinetics than buccal lorazepam when considering the need for the rapid blood concentrations required for seizure termination. Further clinical evaluation of this route is required.

Keywords Neurology · Pharmacology · Seizures · Children

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Introduction

Prolonged generalised seizures and status epilepticus are a common problem in paediatric practice. Present UK guidelines [1] recommend pharmacological intervention after 5 min of continuous seizure activity on the basis that neuronal damage may begin to occur after this period, and the longer a seizure continues, the less likely it is to stop spontaneously [2]. Since most seizures commence in the community, there is a need for medication that can be administered to convulsing children by parents and caregivers to reliably effect seizure termination.

At present, benzodiazepines form the cornerstone for the initial management of prolonged seizures in children [3]. For a long period of time, diazepam, delivered rectally, has been the treatment of choice for prolonged seizures in the community. More recently, midazolam, administered into the buccal cavity has begun to supersede rectal diazepam, demonstrating superior efficacy in two trials [4, 5] and with greater social acceptability of the route of administration. However, once intravenous administration is possible, lorazepam is the current preferred drug [1] on the basis of a more prolonged duration of action and reduced respiratory depression compared with diazepam or midazolam [3]. The perceived drawback is the requirement for vascular access.

Intranasally administered lorazepam has demonstrated favourable pharmacokinetics [6] and efficacy in children in Malawi and India [7, 8]. However, poor efficacy and nasal

mucosal irritation have been reported in British children following intranasal administration of midazolam [9, 10] leading to a preference for the buccal route. Buccal/sublingual pharmacokinetics and bioavailability of lorazepam have only previously been evaluated using a tablet formulation [11].

The aim of this study was to investigate the plasma concentration profile of lorazepam when administered by the intranasal and buccal routes in healthy adult volunteers in order to determine whether the buccal route might be an appropriate administration route for lorazepam in the management of prolonged seizures in children.

Materials and methods

Subjects

Male healthy volunteers within the age range of 20–35 years were eligible for enrolment in this study. Subjects were excluded from participation based on the presence of any clinically significant disease states, including acute or chronic nasal symptoms and physical abnormalities of the nasal passage. Subjects were also excluded for tobacco use within the past 2 years, or presence of alcohol or substance abuse within the past 5 years by self-report. The study was approved by the Trent Research Ethics Committee (08/H0405/41) and a Clinical Trial Authorisation was approved by the UK Medicines and Healthcare products Regulatory Authority (MHRA).

Study procedures

This was an open-label, randomised, two-way crossover, single dose study with each treatment separated by a washout period of at least 1 week. During each experiment period, subjects were administered the study drug via either the intranasal or buccal route according to a randomisation schedule produced by a statistician outside the investigating team.

Drug administration occurred at approximately 08:00 on each study day. Except for water ad libitum, subjects underwent an overnight fast of at least 8 h. No fluids were allowed 1 h prior to or after dosing, and subjects were kept fasted for at least 1 h after dosing. No medications known to affect lorazepam pharmacokinetics were allowed within 7 days prior to each study period or during any study period.

Vital signs consisting of blood pressure, respiratory rate and pulse rate were measured at selected preset times throughout the study. Adverse events were recorded as they occurred. Venous blood samples (5 ml) were collected at 0 (predose), 5, 15, 30 min and 1, 3, 8, 24 and 48 h after lorazepam administration was completed. The samples were separated into their respective plasma and cell components by a centrifuge. Plasma was stored prior to analysis at approximately −70°C.

Dose administration

A standard 2.0 mg dose of lorazepam (4 mg/ml ampoule, Ativan, Wyeth, UK) was used for all routes of administration. Subjects remained recumbent at a 20–40° angle for 1 h following each administration. A mucosal atomisation device (Wolfe Tory Medical, Salt Lake City, UT, USA) was used to deliver the dose for both routes. For intranasal administration, a single spray of lorazepam (500 μl) was administered to the lateral nasal wall of the right nostril. Subjects were not allowed to blow their nose or sniff and swallow for 10 min following administration in an attempt to limit initial absorption to the nasal mucosa. For buccal administration, a single spray of lorazepam (500 μl) was administered into the buccal cavity. Subjects were not allowed to swallow for 10 min after administration.

Assay of samples

Lorazepam was assayed by high pressure liquid chromatography (HPLC)-tandem mass spectrometry (LC-MS/MS) using an Agilent 1200 series HPLC and 6410B mass spectrometer. After addition of lorazepam D4 as internal standard, lorazepam was extracted from 0.5 ml plasma at pH 10 into chloroform. The chloroform extract was dried down under nitrogen and reconstituted in mobile phase prior to analysis on the LC-MS/MS system. Liquid chromatography analysis was performed using a ZORBAX C18 column, and tandem mass spectrometry analysis was performed using the following transitions: lorazepam 321–275 as quantifier and 321–229 as qualifier and lorazepam-d4 325–279. The assay was calibrated over the range 0–100 ng/ml using dilutions of a stock 1 mg/ml lorazepam standard provided by LCG Standards. The lower limit of quantification of the method was 1 ng/ml. The between-batch coefficients of variation of the method determined at concentrations of 2.5, 10 and 20 ng/ml were 9.1, 5.1 and 5.2% respectively.

Pharmacokinetic analysis

All pharmacokinetic and statistical analyses were conducted using WinNonLin (version 6.1, Pharsight). Time to maximum (Tmax) plasma concentration and maximum plasma concentration (Cmax) were taken from the observed concentration-time profile. Standard PK parameters [area under the concentration versus time curve from time 0 to the last quantifiable time point (AUC_{0-t}), area under the concentration versus time curve from time 0 extrapolated to time infinity ($AUC_{0-\infty}$), plasma clearance (CL/F), terminal

phase volume of distribution (Vz/F) and terminal half-life ($t_{½}$)] were calculated using standard methods. All plasma concentrations reported as missing or below the lower limit of quantification were excluded from the analysis. For calculating the terminal half life at least three of the last data points were used, and the r^2 was greater than 0.90.

Results

A total of 12 volunteers completed all study periods. The samples taken following intranasal administration in subjects 1, 2 and 4 were not analysed due to laboratory error. The age of subjects ranged from 20 to 35 years, with a mean of 28 years. The mean (SD) weight of the 12 subjects was 81.6 (14.3) kg.

No significant adverse events occurred throughout the two study periods. Overall, drowsiness/sleepiness was the most commonly reported effect. Adverse events associated specifically with the intranasal route included a bad taste and a burning sensation in the nose; no sneezing or coughing was observed. No specific adverse events were associated with the buccal route. No clinically significant vital sign changes were observed during the study, and no subject became oversedated.

The mean pharmacokinetic parameters for the buccal and intranasal routes of administration are listed in Table 1. There was a more pronounced lag phase with the buccal route compared to the intranasal route (2.6 vs. 0.6 min respectively). Absorption was also more rapid with the intranasal route with a shorter Tmax (104 vs. 160 min) and a higher Cmax (16.4 vs. 14.4 ng/ml). The buccal:intranasal ratio of $AUC_{0\text{-}t}$ (1.10) and $AUC_{0\text{-}\infty}$ (1.12) suggests that buccal lorazepam is slightly more bioavailable than intranasal lorazepam. The mean terminal half-life was 18.6 and 14.9 h for the buccal and intranasal routes respectively.

The mean lorazepam concentration-time profiles from 0 to 60 min and 0 to 48 h are shown in Fig. 1. The profiles appear very similar from 3 to 48 h however important differences exist in the initial time period following administration. Mean lorazepam absorption is more rapid from the intranasal route; in particular, there is a significant difference in the rate of absorption between the two routes of administration at 5 and 10 min. The mean profiles suggest that overall bioavailability may be slightly greater with the buccal formulation.

Discussion

To our knowledge this is the first study to compare the pharmacokinetic parameters of lorazepam following buccal and intranasal administration and demonstrates that lorazepam is more rapidly absorbed from the nasal than the buccal mucosa. Rapid absorption is likely to be important during the management of acute seizures [3].

The absorption values obtained for the intranasal route are broadly equivalent to values obtained from the literature using a similar dose (Table 1). The intravenous formulation was chosen as it is widely available and has been used in two clinical trials in children [7, 8]. Wermeling et al. [6] and Lau and Slattery [12] used liquid preparations of lorazepam specifically formulated for intranasal use, not presently available in the UK. These contained a much higher

Table 1 Pharmacokinetic parameters of lorazepam

Study	Present study		Wermeling et al. [6]	Lau and Slattery [12]	Greenblatt et al. [11]
No. of participants	12	9	11	5	10
Dose (mg)	2	2	2	4	2
Route	Buccal	Intranasal	Intranasal	Intranasal	Sublingual
Tlag (min)	2.6 (2.7)	0.6 (1.6)	NR	NR	14.9 (3.5)[c]
Tmax (min)	160.9 (46.9)	104.7 (74.8)	30[a] (15–120)[b]	135 (30–240)[b]	135
Cmax (ng/ml)	14.4 (3.3)	16.4 (5.5)	21.4 (24.3)	18.7 (5.9)	20.7
$AUC_{0\text{-}t}$ (min·ng/ml)	16,694 (3,638)	15,640 (3,330)	17,280 (1,524)	NR	NR
$AUC_{0\text{-}\infty}$ (min·ng/ml)	19,307 (4,210)	17,437 (4,436)	23,610 (2,280)	NR	NR
Half-life (min)	1,116 (567)	896 (217)	1,098 (1,698)	NR	864 (60)[c]
CL/F (mL/min)	107.9 (22.3)	121.2 (29.7)	NR	NR	NR
Vz/F (L)	170.6 (86.6)	153.3 (42.1)	140.1 (16.8)	NR	NR

Tlag Time between administration and detectable plasma levels, *Tmax* time to maximum plasma concentrations, *Cmax* maximum plasma concentration, *AUC* area under curve, *CL/F* plasma clearance, *Vz/F* terminal phase volume of distribution, *NR* not reported

Values are presented as mean (SD)
except [a] median; [b] range; [c] standard error

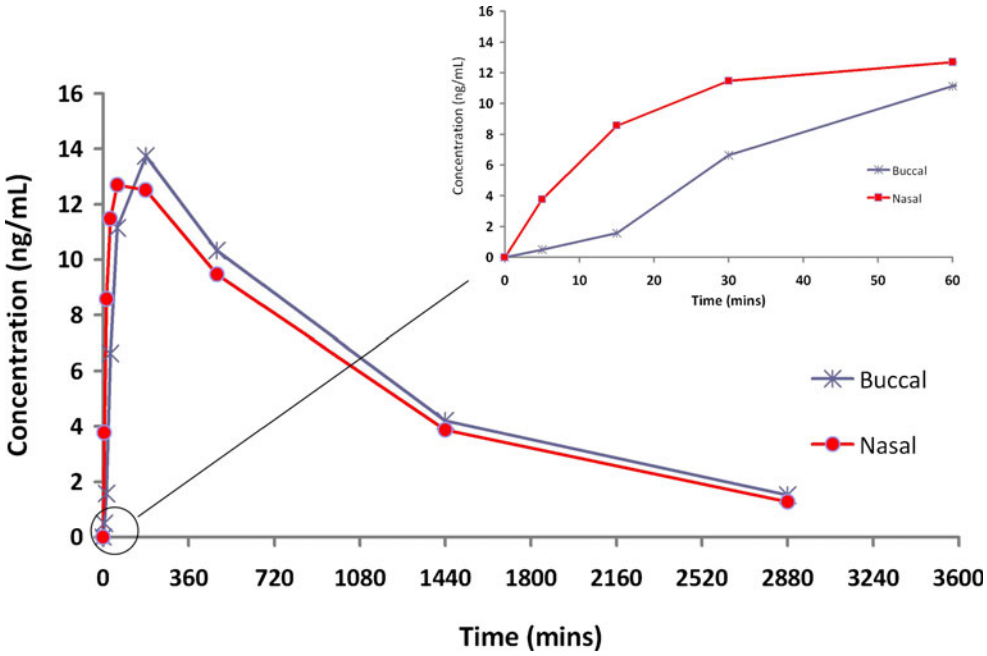

Fig. 1 Plasma concentration-time profile of intranasal and buccal lorazepam

concentration of lorazepam than the intravenous formulation. The buccal route of administration has not previously been studied with a liquid formulation. Greenblatt et al. [11] used a specially formulated sublingual tablet and recognised that Cmax and Tmax might be improved using a preparation of lorazepam that was more easily absorbed, since the in vitro dissolution rate of the tablet was reported as 84% in 1 h. The median Tmax of the present study was 180.5 min for the buccal route suggesting that using the liquid intravenous formulation does not appear to facilitate more rapid absorption, though the lag time to absorption is improved. Lorazepam is a highly permeable drug, but it has poor aqueous solubility, which significantly affects the rate of absorption. Further study of the buccal absorption of different formulations is warranted.

Midazolam, administered via the buccal route, has now gained wide acceptance as the treatment of choice for prolonged seizures in children in the absence of vascular access [3]. Midazolam shows much more favourable transmucosal pharmacokinetics than lorazepam, with a median Tmax of 30 min for the buccal route [13] and a mean Tmax of 14 min for the intranasal route [14].

There is difficulty in defining minimum plasma concentrations of benzodiazepines at which the majority of seizures will terminate. No published data exist for midazolam, while for lorazepam, a plasma concentration of 20–30 μg/l improved seizure control in patients with intractable partial seizures [15], though generalising from this situation to the acute prolonged seizure is likely to be fraught. Absorption characteristics provide essential data regarding the relative utility of each of the routes and provide a starting point from which to estimate potential doses.

Extrapolating results directly from the present study in healthy volunteers to the clinical situation of a convulsing patient is further complicated by underlying pathology. Inflammation of the nasal mucosa may enhance or detract from absorption via this route, and seizure aetiology and duration influence response to benzodiazepines [3]. However, evaluation of the comparative performance of a formulation delivered by alternative routes is best conducted, from a scientific, clinical and ethical perspective, in a healthy adult volunteer population, a position supported by current European Medicines Agency (EMA) and Food and Drug Administration (FDA) recommendations.

There is little published experience of the use of either intranasal or buccal lorazepam for the treatment of prolonged seizures in either adults or children. Intranasal lorazepam has been demonstrated to be an effective, safe, non-invasive treatment for prolonged seizures in children in Malawi, using a dose of 100 μg/kg in an open randomised trial comparing it with intramuscular paraldehyde [7]. In a more recent study in India, intranasal lorazepam was not found to be inferior to intravenous lorazepam in effecting seizure termination within 10 min [8]. Reports of the use of buccal lorazepam are limited to a case series reporting the use of sublingual lorazepam (dose 50–150 μg/kg) in tablet form to effectively treat acute serial seizures in 10 children [16]. In spite of this buccal lorazepam appears to be recommended for use in acute seizures by at least one recently published textbook [17]. A trial comparing intravenous, intranasal and buccal lorazepam was terminated early [18] because an interim analysis showed the buccal arm of the study to be 30% less effective in stopping seizures within 10 min compared with the IV dose. This observation is corroborated by the absorption

parameters derived for buccal lorazepam in our study and underlines the need to undertake pharmacokinetic studies to evaluate formulation and novel delivery routes prior to evaluating them in the clinical situation.

The results from the present study suggest that the intranasal administration route leads to a significantly faster detectable concentration of lorazepam in plasma than the buccal route, with a shorter Tlag and Tmax, making it a more suitable route for the termination of prolonged seizures. Our findings suggest that intranasal, rather than buccal, lorazepam is likely to be more appropriate for the management of children with acute seizures. Consideration must also be given to the particular formulation used—the intravenous preparation contains the excipients benzyl alcohol and propylene glycol. The exposure of small children to these chemicals has been the subject of some concern [19], and they may irritate the intranasal mucosa. These concerns are mitigated, however, by the fact that the dose used in prolonged seizure termination is small and potentially repeated only once, thereby limiting cumulative exposure. It is clear that clinical studies of both the efficacy and toxicity of intranasal lorazepam in children are required before it can be accepted as standard therapy.

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Competing interests None.

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