Absorption Kinetics of Diazepam after Intranasal Administration
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Objective
- Develop an integrated pharmacokinetic model to characterize double-peak diazepam (DZP) concentration-time curves following intranasal administration, and to estimate the contributions of the early- and late-occurring peaks to systemic exposure of DZP.

Rationale for Intranasal Delivery of DZP for Out-of-Hospital Treatment of Seizure Emergencies
- Initiation of drug at the onset of a seizure emergency improves outcomes and reduces health care costs.
- Typically, treatment is possible outside of medical facilities.
- Intranasal Administration - Although it has a rapid onset of action, administration requires skilled personnel, transport to a medical facility and may cause respiratory depression.
- Intramuscular Administration (IM) - Some anticonvulsants may be given IM, but absorption may be slow and erratic. Further, some caregivers are reluctant to give injections.
- Rectal - Socially unacceptable for many older children and adults.
- Nasal route administration offers convenient and permits self administration by patients or untrained caregivers.

Methods

Study Design
- Eight healthy volunteers were studied using a randomized, single-blind, three-way crossover design. The purpose of the study was to compare the disposition of the commercially available parenteral DZP formulation administered intravenously (IV) at one dose (5 mg) to an investigational intranasal (IN) DZP formulation at two doses (5 mg and 10 mg). The intranasal formulation was a 40 mg/mL supersaturated solution of diazepam in a glycerol-water co-solvent mixture. For the IN administration, a 1 mL syringe was used to instill 0.125 mL into one nostril to deliver the 5 mg dose and into both nostrils for the 10 mg dose.
- Blood for DZP analysis was collected at pre-dose, 0, 1, 3, 5, 10, 15, 20, 30, 45, 60 minutes, and at 1, 2, 3, 4, 6, 8, 10, 24 and 48 hours after dose. DZP concentrations were measured using a validated HPLC method.

Model Building
- Initial visual inspection of the concentration-time data showed the presence of two distinct peaks in most of the subjects at both the intranasal dose levels. (Figure 1)
- The model used took into account a discontinuous absorption in order to describe the concentration-time profiles with two peaks. (Figure 2)
- The model assumes the following:
  - IN DZP dose is absorbed in two portions, an initial rapid phase through the nasal cavity, and the remaining through a delayed absorption compartment.
  - Drug absorption is complete from the delayed absorption compartment.
  - ADAPT V (beta) program with a STS approach and maximum likelihood estimation was used.

In the model, the occurrence of the second peak was assumed to take place through absorption through a delayed transit compartment. The clearance, central and peripheral distribution volumes, and the inter-compartmental rate constants between the central and peripheral compartments were shared among the IN and IV DZP submodels in each subject. The absorption rate constant parameter (Kb) and the rate constant for loss of drug through external drainage (K2) were shared between the two nasal dose models. However, the input and exit rate constants of the transit compartments were estimated separately for each nasal dose (Kd for the 5 mg dose and Kd for the 10 mg dose). This was done to estimate the fractional bioavailability at each phase of absorption for each IN dose.

The fractional bioavailability was estimated using the following equations:

\[ F_5 = \frac{K_a}{K_a + K_3} \]
\[ F_{10} = \frac{K_a}{K_a + K_5} \]

Figure 1. Graphical representation of the integrated pharmacokinetic model for DZP. K1, K2, K3, K4, K5 and K6 = first-order transfer rate constants, Ka = first-order absorption rate constant, K10 = first-order elimination rate constant from central compartment. The estimated values of the rate constants along with their BSV (%CV) are also shown in the figure.

Results
- 6 out of the 8 pharmacokinetic profiles exhibited double peaks, some noticeably sharp and with higher concentrations than the first peak, and in some a delayed blunt peak over a period of time.

Discussion and Conclusions
- The relative standard errors of the estimates of CL and V parameters, and for the secondary parameters such as bioavailability and lag time were all under 30%, and the parameters associated with the nasal absorption processes were typically in the 30-100% range.

The characterization of absorption kinetics is essential in the development of a nasal DZP delivery system, because plasma concentrations vary up to ten-fold after a single oral dose, three-fold after multiple oral doses and several-fold after I.V., I.M., and rectal administration.2,3

References

Figure 2. Graphical representation of the integrated pharmacokinetic model for DZP. K1, K2, K3, K4, K5 and K6 = first-order transfer rate constants, Ka = first-order absorption rate constant, K10 = first-order elimination rate constant from central compartment. The estimated values of the rate constants along with their BSV (CV%) are also shown in the figure.

Figure 3. Model predicted individual fitings. Curves (+) represent the model-predictions and (X) represents the observed concentrations in 15 subjects.

Figure 4. (A) Population model-predicted DZP concentrations versus observed concentrations (ng/mL). (B) Standardized residuals versus model predicted concentrations. (C) Frequency distribution of the weighted residuals.

Table 1. Parameter estimates of final model from ADAPT V. Estimates for rat constant along with their CV’s are listed along with the respective parameters in Figure 2.