

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.
- Intravenous Administration - Although 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* alternative that is non-invasive 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 and 10 mg). The intranasal formulation was a 40 mg/mL supersaturated solution of diazepam in a glycofurol-water cosolvent 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, 5, 10, 15, 20, 30, 45, 60 minutes, and at 1.5, 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) program¹ with a STS approach and maximum likelihood estimation was used.

In the model, the occurrence of the second peak was assumed to take place by 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 (K_a) and the rate constant for loss of drug through external drainage (K_2) 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 (K_3 and K_4 for the 5 mg dose and K_5 and K_6 for the 10 mg dose). This was done to estimate the fractional bioavailability at each phase of absorption for each IN dose.

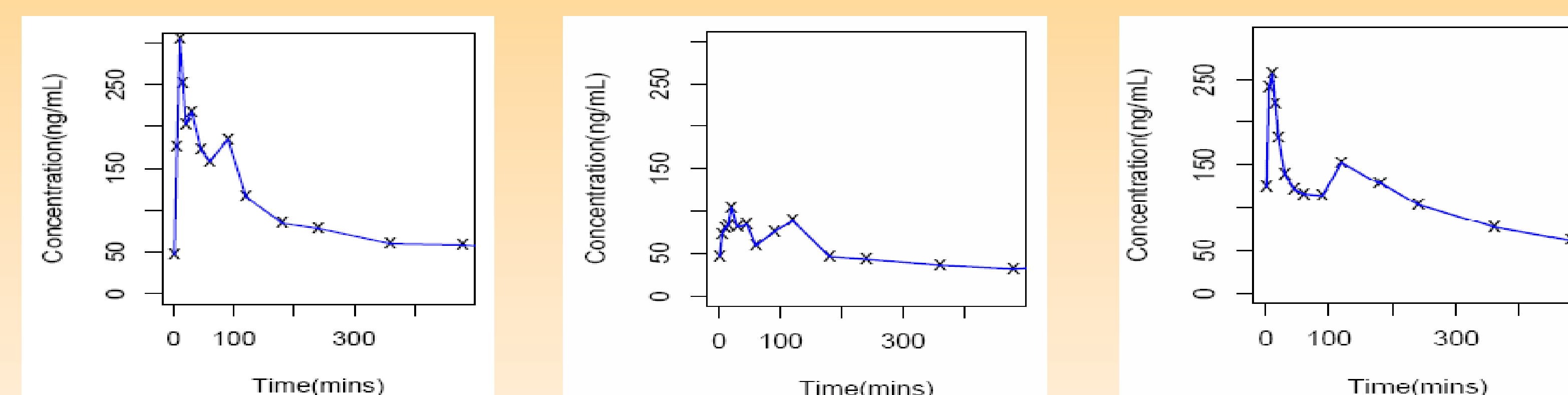


Figure 1. Representative plasma DZP concentrations observed in 3 of the 8 subjects with two phases of absorption.

The fractional bioavailability was estimated using the following equations:

$$5FN = \frac{K_a}{K_a + K_2 + K_3} \quad 5FD = \frac{K_3}{K_a + K_2 + K_3} \quad 5F_{tot} = 5FN + 5FD$$

$$10FN = \frac{K_a}{K_a + K_2 + K_5} \quad 10FD = \frac{K_5}{K_a + K_2 + K_5} \quad 10F_{tot} = 10FN + 10FD$$

where, 5FN, 5FD and 5F_{tot} represent the fractional bioavailability from the early-, delayed-absorption phase and the total bioavailability for the 5 mg dose and 10FN, 10FD and 10F_{tot} represent the fractional bioavailability from the early-, delayed-absorption phase and the total bioavailability for the 10 mg dose.

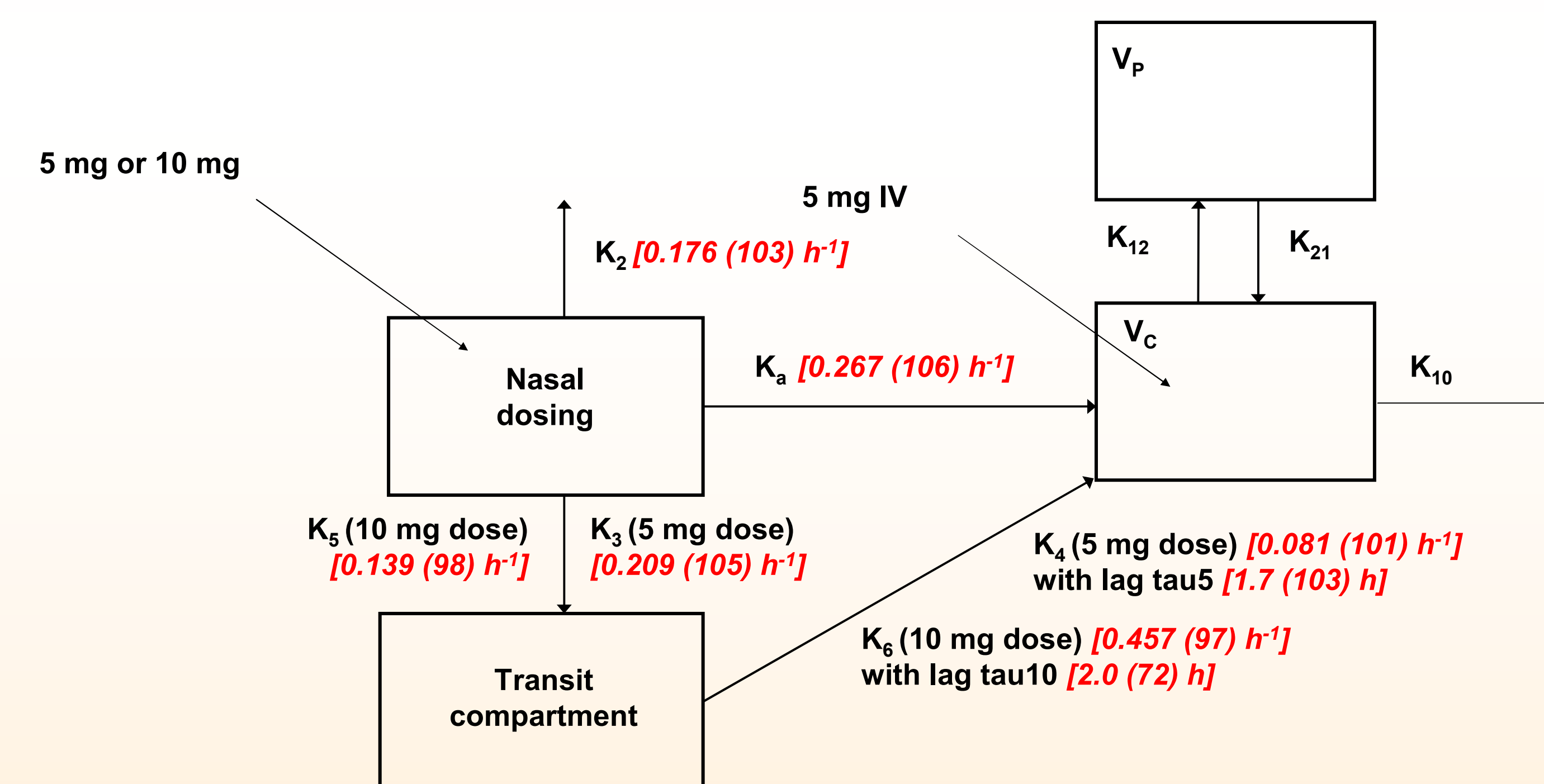


Figure 2. Graphical representation of the integrated pharmacokinetic model for DZP. K_{12} , K_{21} , K_3 , K_4 , K_5 and K_6 = first-order transfer rate constants, K_a = first-order absorption rate constant, K_{10} = first-order elimination rate constant from central compartment. The estimated values 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.

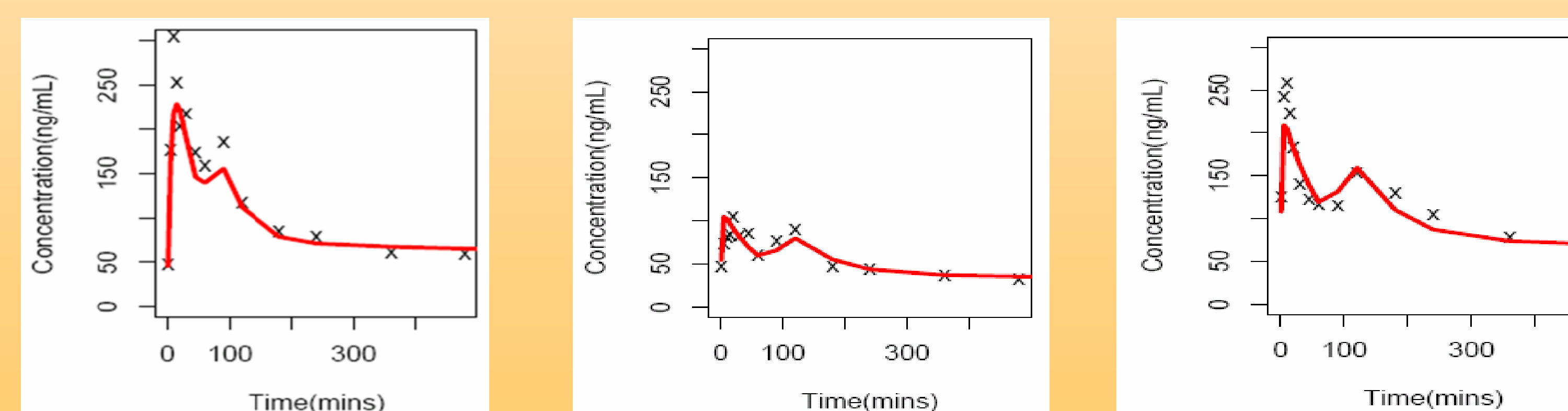


Figure 3. Model predicted individual fittings. Curves (—) represent the model-predictions and (X) represents the observed concentrations in 3 subjects.

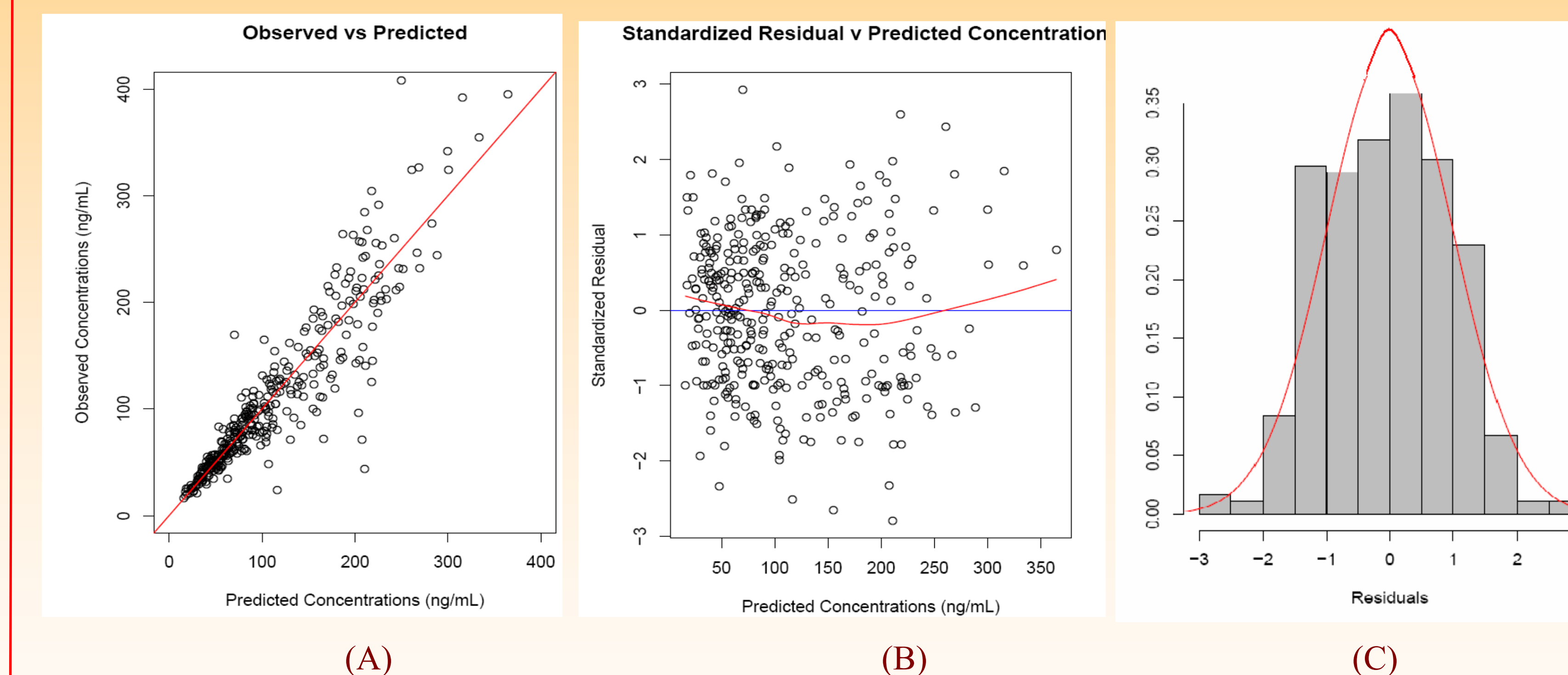


Figure 4.: (A) Population model-predicted DZP concentrations versus observed concentrations (ng/mL), (B) Standardized residuals versus model predicted concentrations (C) Frequency distribution of the weighted residuals.

Parameter	Estimate (BSV %CV)	Parameter	Estimate (BSV %CV)
CL _{tot} (L/h)	0.84 (52)	5FD (%)	31 (67)
CL _d (L/h)	11.28 (36)	5F _{tot} (%)	73 (24)
V _c (L)	19.29 (19)	10FN (%)	43 (33)
V _p (L)	68.32 (59)	10FD (%)	27 (95)
5FN (%)	42 (29)	10F _{tot} (%)	70 (26)

- 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.

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

Discussion and Conclusions

- 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}
- The estimates for total bioavailability (73 and 70%) are similar for both the 5 mg and 10 mg doses, with approximately the same fractions being absorbed at the early- and delayed-absorption phases.
- The estimated lag times for initiation of delayed absorption, 1.7 h and 2 h, suggests that approximately 40% of the bioavailable dose after intranasal administration of the 5 mg and 10 mg is available systemically nearly 2 hours after dosing. Considering that ideal treatment of seizure emergencies requires both rapid onset and preferably, sustained action; the fact that a significant portion of the drug is being absorbed at a later time may offer clinical advantages.
- Future studies will assess the pharmacodynamics of IN DZP to understand the effect of biphasic absorption on blood levels required to treat seizure emergencies. The present model may be useful in determining appropriate sampling schedules to elucidate double peaks and also in dealing with issues concerned with optimization of the formulation, delivery device or the method of administration.

References

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