

Absorption Kinetics of Diazepam After Intranasal Administration

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Objectives: To develop an integrated pharmacokinetic model for diazepam (DZP) that includes an intravenous DZP submodel, and two dose-dependent intranasal absorption submodels, each with two compartments based on physiological and biopharmaceutical considerations to characterize the double-peak concentration-time curves of DZP following intranasal administration, and to also estimate the contributions of the early- and late-occurring peaks to systemic drug exposure.

Methods: The disposition of a commercially available parenteral diazepam administered intravenously (IV, 5 mg) and an investigational intranasal (IN) diazepam formulation at two doses (5 and 10 mg) were compared using a randomized, placebo-controlled, single-blind, three-way crossover design in eight healthy adult volunteers. Each subject received two IN and one IV dose of DZP, and blood samples were collected up to 48 hours after dosing. DZP concentrations were measured using a validated HPLC assay. Plasma concentration-time data of the IV and 2 IN doses were fit simultaneously using ADAPT V (beta) [1]. A two-compartment absorption model with an additional transit compartment and delayed lag time to capture secondary absorption peaks was used to describe the IN data. The proposed model assumes that IN diazepam dose could be absorbed in two portions, initially and rapidly through the nasal cavity, and the remaining through a delayed absorption compartment. The clearance, central and peripheral volumes of distribution, and the intercompartmental 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. The integrated model representing all three submodels is shown in Figure 1.

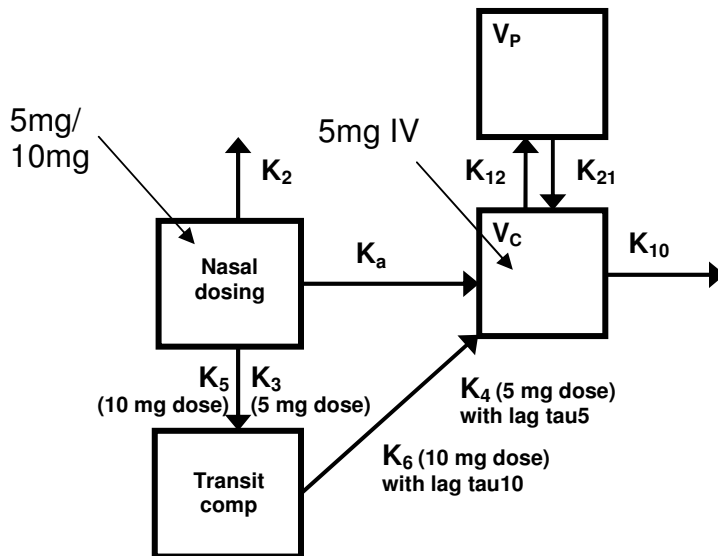


Figure 1. Integrated pharmacokinetic model with IV and two IN submodels.

Results: Based on the individual fits and the goodness of fit plots, the model described the data well, capturing both absorption peaks in most of the subjects (Figure 2). The mean and standard deviation of the shared parameters estimated for the model were: CL_{tot} (0.0144 ± 0.00753 L/min), CL_d (0.1882 ± 0.0688 L/min), V_c

(19.29 ± 3.75 L), and V_p (68.32 ± 39.79 L). The total bioavailability for the 5 mg IN dose was $73 \pm 18\%$, and was partitioned into $42 \pm 12\%$ from the initial absorption phase and $31 \pm 21\%$ at a later time through the delayed-absorption compartment. Similarly the total bioavailability for the 10 mg dose was $70 \pm 19\%$, and partitioned into $43 \pm 14\%$ and $27 \pm 26\%$ representing the contribution of the early- and delayed-absorption phases towards total bioavailability, respectively. The median (range) estimated lag time for the delayed absorption phase for the 5 mg dose was 66 (5, 334) minutes and 104 (36, 296) minutes for the 10 mg dose.

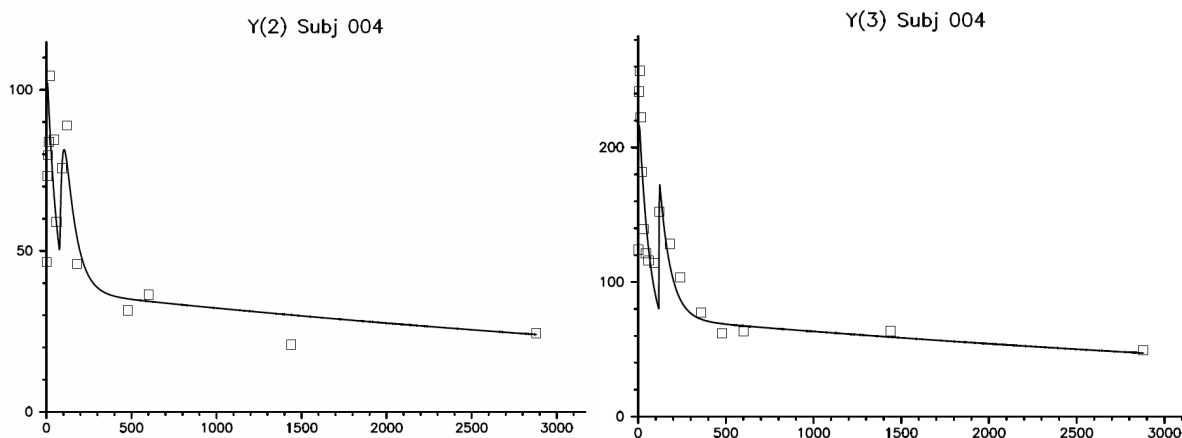


Figure 2. Concentration(ng/mL) – time(minutes) data for 5 mg (Y(2)) and 10 mg (Y(3)) showing the secondary peak being captured by the model.

Conclusions: The inclusion of a transit compartment with lag phase was useful in capturing the double-peak phenomenon in the intranasal concentration-time data. By estimating the contribution of each phase of absorption towards total bioavailability, issues concerning the formulation, delivery device or the method of administration may be explored. Future work will look at the pharmacodynamics of DZP following intranasal delivery.

Reference:

(1). D'Argenio, D.Z. and A. Schumitzky. *ADAPT II User's Guide: Pharmacokinetic / Pharmacodynamic Systems Analysis Software*. Biomedical Simulations Resource, Los Angeles, 1997.