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Pharmacokinetic Modeling of Valsartan in Dog following a Single Oral Administration

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Abstract : Valsartan is a potent and highly selective antagonist of the angiotensin II type 1 receptor, and is widely used for the treatment of hypertension. The aim of this study was to investigate the pharmacokinetic properties of the valsartan in dogs following oral administration of a single dose using quantitative modeling approaches. Forty beagle dogs were randomly divided into two group. Group A (n=20) was administered a single oral dose of valsartan 80 mg (Diovan® 80 mg), and group B (n=20) was administered a single oral dose of valsartan 160 mg (Diovan® 160 mg) in the morning after an overnight fast. Blood samples were collected into heparinized tubes before and at 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 12 and 24 h following oral administration. The plasma concentrations of the valsartan were determined using LC-MS/MS. Non-compartmental pharmacokinetic analyses were performed using WinNonlin Standard Edition software, and modeling approaches were performed using maximum-likelihood estimation via the expectation maximization (MLEM) algorithm with sampling using ADAPT 5 software. After a single dose of valsartan 80 mg, the mean value of maximum concentration (Cmax) was 2.68 ± 1.17 μg/mL at 1.83 ± 1.27 h. The area under the plasma concentration-versus-time curve from time zero to the last measurable concentration (AUC24h) value was 13.21 ± 6.88 μg·h/mL. After dosing with valsartan 160 mg, the mean Cmax was 4.13 ± 1.49 μg/mL at 1.80 ± 1.53 h, the AUC24h was 26.02 ± 12.07 μg·h/mL. The Cmax and AUC values increased in proportion to the increment in valsartan dose, while the pharmacokinetic parameters of elimination rate constant, half-life, apparent of total clearance, and apparent of volume of distribution were not significantly different between the doses. Valsartan pharmacokinetic analysis fits a one-compartment model with first-order absorption and elimination following a single dose of valsartan 80 mg and 160 mg. In addition, high inter-individual variability was identified in the absorption rate constant. In conclusion, valsartan displays the dose-dependent pharmacokinetics in dogs, and Subsequent quantitative modeling approaches provided detailed pharmacokinetic information of valsartan. The current findings provide useful information in dogs that will aid future development of improved formulations or fixed-dose combinations.

Keywords : dose-dependent, modeling, pharmacokinetics, valsartan
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