Quantitative structure–pharmacokinetic relationships for disposition parameters of cephalosporins

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„...also on seeking desirable ADME (absorption, distribution, **metabolism**, excretion) characteristics (Boobis et al., 2002 Kretz and...HyperChem v.5.0/ChemPlus v.1.6 (Hypercube Inc.) and Pallas 2.1 (**Compudrug** Chemistry Ltd). Molecular size was expressed by a variety..."

Abstract

This study explores the utility of quantitative structure–pharmacokinetic relationship models of the disposition parameters: clearance (*CL*), apparent volume of drug distribution (V_{ap}), fractal clearance (CL_f), and fractal volume (v_f), for a series of 23 cephalosporins used in therapeutics. Data for *CL*, V_{ap} and elimination half-life were obtained from literature, whereas CL_f and v_f were calculated from the literature data for *CL* and V_{ap}, respectively. A variety of descriptors expressing acidity/basicity, lipophilicity, molecular size and hydrogen bonding properties were estimated using computer packages. For each pharmacokinetic parameter, projection to latent structures (PLS) was applied to the total dataset. Adequate PLS models, with one principal component, were derived for *CL*, CL_f, V_{ap} and v_f. Identical descriptors were found to be significant for the two clearance as well as for the two volume of distribution terms. *CL* and CL_f expressed similar performance while the predictive performance of v_f was much higher than that of V_{ap}. Multiple linear and non-linear regression models were developed. The regression results were in agreement with the PLS models. The non-linear models were superior to the relevant linear relationships. The worst models found were for V_{ap} (R^2=0.523 and R^2=0.571 for the linear and non-linear model, respectively) and the best models found were for v_f (R^2=0.729 and R^2=0.824 for the linear and non-linear model, respectively).

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