SL05 Predicting Drug Absorption and Disposition Using a Biopharmaceutics Drug Disposition Classification System and Its Use in Deriving QSAR Approaches

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In 2005, Wu and Benet [Pharm. Res., 22:11-23, 2005] noted that a Biopharmaceutics Drug Disposition Classification System (BDDCS) could serve as the basis for predicting the importance of transporters in determining drug bioavailability (F) and disposition. We suggest that BDDCS may be useful in predicting overall drug disposition including: routes of drug elimination; the effects of efflux and absorptive transporters on oral drug absorption; when transporter-enzyme interplay will yield clinically significant effects (e.g., low bioavailability and drug-drug interactions); the direction, mechanism and importance of food effects; and transporter effects on post-absorptive systemic drug concentrations following oral and intravenous dosing. These predictions are supported by a series of studies from our laboratory over the past few years investigating the effect of transporter inhibition and induction on drug metabolism. We reasoned that for highly soluble, highly permeable Class 1 compounds, metabolism would be the major route of elimination and that transporter effects on availability and disposition would be negligible. In contrast for the poorly permeable, highly soluble Class 3 compounds and the poorly permeable, poorly soluble Class 4 compounds, metabolism would only play a minor role in drug elimination. Uptake transporters would be major determinants of F for these poorly permeable drugs and both uptake and efflux transporters could be important for drug elimination. Highly permeable, poorly soluble, extensively metabolized Class 2 compounds constitute the majority of new molecular entities ($\sim 70\%$) and present the most complicated relationship in defining the impact of transporters due to the marked effects of transporter-enzyme interplay. Uptake transporters are unimportant for Class 2 drug bioavailability, but can play a major role in hepatic and renal elimination. Efflux transporters have major effects on bioavailability, metabolism and elimination of Class 2 drugs. It is difficult to accurately characterize drugs in terms of the high permeability criteria, i.e., \geq 90% absorbed. We suggest that extensive metabolism (>70%) may substitute for the high permeability characteristic, and that the BDDCS using elimination criteria may provide predictability in characterizing QSAR related drug disposition profiles for all classes of compounds. Studies from our laboratory utilizing cellular systems, isolated organs, whole animals and humans will be discussed for drugs including: Class 1 compounds verapamil, midazolam and propranolol; Class 2 drugs cyclosporine, sirolimus, tacrolimus, atorvastatin, glyburide, felodipine and warfarin, Class 3 compounds metformin, erythromycin and pravastatin; and the Class 4 drug furosemide, together with inducers and inhibitors of enzymes and transporters. (Supported in part by NIH grants GM61390, GM75900 and unrestricted funds from Amgen, Inc.)