A MECHANISTIC APPROACH FOR THE EVALUATION OF PHARMACOKINETIC DRUG-DRUG INTERACTIONS

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Pharmacokinetic drug-drug interactions, the ability of one drug to alter the absorption, distribution, metabolism, and elimination of co-administered drugs, can lead to serious clinical consequences. It is therefore necessary to avoid developing drugs with drug-drug interaction potential. As it would be impossible to evaluate the possible interactions among all existing drugs, a mechanistic approach is proposed. The central dogma of the mechanistic approach is the evaluation of the potential interaction of a drug with key drug metabolizing enzymes. The following key experiments are proposed for the evaluation of the drug-drug interaction potential of a drug or drug candidate: 1. Determination of key drug metabolizing enzyme pathways via the identification of metabolites and the evaluation of the effect of specific inhibitors (e.g. CYP inhibitors) on metabolism. Understanding the major drug metabolizing enzyme pathway will allow one to predict drug-interactions with existing drugs which are known inhibitors or inducers of drug-metabolizing enzymes. 2. Evaluation of inhibitory potential for drug metabolizing enzymes. If a drug inhibits a certain drug metabolizing enzyme, it may inhibit other drugs that are substrates of the enzyme. 3. Evaluation of induction potential for drug metabolizing enzymes. A drug that induces a drug metabolizing enzyme may enhance the metabolic elimination of other drugs which are substrates of the induced enzyme. The key enzymes to be studied are cytochrome P450s, phase II conjugating enzymes, and transporters. The most useful experimental systems are in vitro human hepatic systems, especially human hepatocytes.
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