Biotransformations in Drug Metabolism

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1 DRUG METABOLISM IN DRUG DEVELOPMENT AND DRUG THERAPY

The major function of drug metabolism is to facilitate removal of compounds from the organism, thereby preventing unwanted accumulation of foreign compounds or of potentially toxic levels of endogenous compounds. This physiological function of metabolism is quantified using two pharmacokinetic terms, *bioavailability* and *clearance*. Bioavailability indicates the percentage of administered drug that reaches the systemic circulation, and is indicated by percent absorbed minus pre-systemic metabolism. Clearance indicates the rate of removal of the drug from the systemic circulation, and is indicated by the rates of post-systemic metabolism and excretion. Bioavailability and clearance combine to affect the total drug exposure which is usually quantified by *area under the concentration-versus-time curve* (AUC). These relationships are clarified in Fig. 1.

In addition to clearance, metabolism can affect the spectrum of consequences of drug action including both the desired therapeutic effects and undesired effects. During the early stages of drug development, metabolism-based strategies allow scientists to improve the pharmacokinetic properties of a lead compound by blocking or inserting sites of facile metabolism. During the clinical studies and post-marketing stages, metabolism data can be used to promote safe use of a drug, including dosing adjustments or warnings about drug–drug interactions. The most common fate of metabolism is the formation of *inactive products*—metabolites having no physiological effect (desired or undesired). In the case of inactive products, the rate of clearance would be equal to the loss of parent drug. If the drug is converted to inactive metabolites pre-systemically or too quickly for the desired action, then analogues can be developed with these sites of metabolism blocked, thereby slowing metabolic clearance. A second possible fate of drug metabolism is the formation of *active metabolites*—those having the desired activity to an extent similar to (or greater than) the parent drug. In the case of active metabolites (called "prodrugs" under certain circumstances), clearance of all active

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