Research and Reviews: Drug Delivery

Absorption, Distribution, Metabolism, and Elimination of Drug Metabolism

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Commentary

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DESCRIPTION

The study of drug metabolism or biotransformation is vitally important to our understanding of the time course of drugs in the body, the structuring of dosage regimens, the pharmacology and toxicology of drug metabolites, and the interactions of multivalent drug combinations. Hydrophobicity is an important chemical characteristic of most drug molecules, because the probabilities of both good oral absorption and interactions with molecular targets tend to increase as hydrophobicity increases. Unfortunately, the probability of efficient renal or biliary excretion of drugs from the body diminishes as hydrophobicity increases. Thus, the metabolism or biotransformation of hydrophobic drug molecules to more hydrophilic molecules is a very important factor in the elimination of drugs from the body. Although the enzymes that mediate drug metabolism are found in many tissues, it is within the liver and the epithelial cells of the upper portion of the intestines where most drug metabolism occurs. For a drug that is subject to biotransformation, if it is administered by intravenous infusion, then the liver is likely to be the major site for biotransformation.

On the other hand, it is possible that the same drug administered orally will be subject to biotransformation both in the intestine during absorption and in the liver as well. The role of biotransformation on drug action was recognized as early as the mid-nineteenth century, however the scientific interest in drug metabolism grew exponentially after the discovery by Axelrod and Estabrook and coworkers that the liver red pigment described by Garfinkel and

Klingenberg performed the function of hepatic drug-metabolizing oxido-reductases.

Drug metabolism is the phase of biochemical transformation of the drug. It is highly variable among drugs and depends on biological conditions. The metabolism phase is absent for the few drugs that are not transformed. Biotransformations may involve one or more successive reactions:

- Phase 1 transformations (reactions of functionalization) involve the creation of a functional group or the modification of an existing one by oxidation, reduction, or hydrolysis.
- Phase 2 transformations (reactions of conjugation) couple a drug or a metabolite to an endogenous conjugating molecule such as glucuronic acid, sulfuric acid, acetic acid, glutathione, etc.

From a physicochemical point of view, drug metabolism is expected to yield metabolites of lower lipophilicity relative to the parent drug, e.g., by adding an ionisable group. As a result, metabolites are often excreted faster than the parent drug, but there are exceptions. From a pharmacological point of view, it is essential to check the pharmacodynamics consequences of these metabolic reactions. Often but far from always, biotransformation involves inactivation or detoxification. Activation concerns pro-drugs, but also active compounds (drugs) giving rise to active metabolites. The latter may exhibit a PK profile different from that of the parent drug, and/or a qualitatively different activity.

Some enzymes involved in metabolism present a genetic polymorphism, which separates populations of patients according to their phenotypes. This is the field of pharmacogenetics. Independently of any pathological state, individuals who are very fast or poor metabolizers need to be identified and have their dosages adjusted. Specific monitoring must also be applied for drugs with a low therapeutic index resulting in a low safety margin due to relatively vicinal effective and toxic doses.