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Commentary

Prediction and Potential Impact of Drug Metabolism Disorders

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DESCRIPTION

Drug metabolism is an important aspect of medical practice and pharmacology. Drug metabolism is the metabolic breakdown of drugs by the body, usually by specialized enzymatic systems. Most drugs undergo chemical modification by various body systems to create compounds that are more readily excreted from the body. Drug metabolism plays an important role in determining the pharmacological and toxicological effects of drugs in humans. These chemical changes occur primarily in the liver and are known as biotransformation. However, depending on their chemical structure and the metabolic reactions undergone in the liver, they may be excreted in whole or in part in the urine. Metabolic function within an organism depends on how much its chemical structure differs from the parent compound are determined by metabolism by the host organism which is one of the most important determinants of a drug's pharmacokinetic profile. High metabolic usually leads to low bioavailability and high clearance.

The formation of active or toxic metabolites influences pharmacological and toxicological outcomes. Metabolites are often less active or inactive than the parent drug. The main purpose of drug metabolism is to facilitate drug elimination by increasing the drug's water solubility (hydrophilicity). Incidentally, chemical modifications either decrease or increase the pharmacological activity and/or half-life of drugs. The most extreme example is the metabolic activation of an inactive prodrug to an active drug. However, some biotransformation products (metabolites) may have enhanced activity or exhibit toxic effects. Most drugs must pass through the liver, which is the primary site of drug metabolism. The liver's primary mechanism for metabolizing drugs is through distinct groups of cytochrome P-450 enzymes. The concentration of these cytochrome P-450 enzymes controls the rate of metabolism of many drugs.

Drug metabolism is divided into three stages. In phase, I, enzymes such as cytochrome P450 oxidase introduce reactive or polar groups into xenobiotics. These modified compounds are then attached to polar compounds in a Phase II reaction. These reactions are catalyzed by transferase enzymes such as glutathione-S-transferase. Finally, in phase III, conjugated xenobiotics are further processed before they are recognized by efflux transporters and efflux from the cell. Drug metabolism often converts lipophilic compounds to more readily excreted hydrophilic products. The chemical reactions in a metabolic process are organized into metabolic pathways that transform one chemical into another through a series of steps.

An organism's metabolism allows us to determine which substances are nutritious and useful and which are toxic. For almost all drugs, there is an upper limit to the rate of metabolism in a particular pathway. However, at therapeutic concentrations of most drugs, only a small proportion of the metabolic enzyme sites are typically occupied, and the rate of metabolism increases with drug concentration. Drug metabolism is the biotransformation of drugs in the body so that they are more readily excreted. Most of the metabolic processes involving drugs take place in the liver. This is because the enzymes that make the reaction possible are concentrated in the liver. Drug metabolism rates vary greatly among patients. This affects drug efficacy and toxicity in patients with very high or low metabolic rates. For example, rapid metabolizers degrade drugs very quickly and may not reach therapeutic concentrations of drugs in blood and tissues. In other patients, the drug is metabolized very slowly and accumulates in the bloodstream. The higher the drug concentration in the body, the greater the potential for side effects. Many drugs and other substances in foods and herbal remedies can affect these enzymes and alter the rate at which drugs are metabolized. Drugs act directly on the body, but in most cases, they are broken down by enzymes into many other substances that are excreted from the body.

For many drugs, metabolism occurs in two steps. Phase I reactions involve the formation or cleavage (oxidation, reduction, hydrolysis) of new or modified functional groups. These reactions are not synthetic. Phase II reactions involve conjugation with endogenous substances (e.g., glucuronic acid, sulfate, glycine). These reactions are synthetic. Drug metabolic rate is the rate at which a drug is metabolized after administration. This may vary from person to person for a particular drug due to genetic factors, lifestyle, and medical history.

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