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Discuss factors affecting drug metabolism

Xenobiotic metabolism (from the Greek xenos "stranger" and biotic "related to living beings") is the set of metabolic pathways that modify the chemical structure of xenobiotics, which are compounds foreign to an organism's normal biochemistry, such as any drug or poison. These pathways are a form of biotransformation present in all major groups of organisms, and are considered to be of ancient origin. These reactions often act to detoxify poisonous compounds. The study of drug metabolism is called pharmacokinetics.

***Factors Affecting Drug Metabolism***

***1. Physiological Conditions (age, diet, hormone balance) :***Nutrition can affect the body's response to drugs; conversely, drugs can affect the body's nutrition. Foods can enhance, delay, or decrease drug absorption. ... They can alter metabolism of drugs; eg, high-protein diets can accelerate metabolism of certain drugs by stimulating cytochrome P-450.Aging involves progressive impairments in the functional reserve of multiple organs, which might also affect drug metabolism and pharmacokinetics. In addition, the elderly population will develop multiple diseases and, consequently, often has to take several drugs.

***2. Pathological Conditions (impaired liver or kidney function) :***Liver disease may have complex effects on drug clearance, biotransformation, and pharmacokinetics. Pathogenetic factors include alterations in intestinal absorption, plasma protein binding, hepatic extraction ratio, liver blood flow, portal-systemic shunting, biliary excretion, enterohepatic circulation, and renal clearance. Sometimes alterations increase levels of bioavailable drug, causing normal drug doses to have toxic effects.

***3. Genetic Factors (species/strain difference, sex, ethnic polymorphism, individual differences) :***Genetic variation (polymorphism) accounts for some of the variability in the effect of drugs. With N-acetyltransferases (involved in Phase II reactions), individual variation creates a group of people who acetylate slowly (slow acetylators) and those who acetylate quickly. This variation may have dramatic consequences, as the slow acetylators are more prone to dose-dependent toxicity.

***4. Drug-drug Interactions (enzyme inhibition, enzyme induction) :***

Mechanisms of Drug Actions by Enzyme Inhibition:

a) Direct Enzyme Inhibition:

Although activation of enzymes may be exploited therapeutically, most effects are produced by enzyme inhibition. Inhibition caused by drugs may be either reversible or irreversible. A reversible situation occurs when an equilibrium can be established between the enzyme and the inhibitory drug. A competitive inhibition occurs when the drug, as "mimic" of the normal substrate competes with the normal substrate for the active site on the enzyme. Concentration effects are important for competitive inhibition.

In noncompetitive inhibition, the drug combines with an enzyme, at a different site other than the active site. The normal substrate can not displace the drug from this site and can not interact with the active either since the shape of the enzyme has been altered.

Among the many types of drugs that act as enzyme inhibitors the following may be included: antibiotics, acetylchlolinesterase agents, certain antidepressants such as monoamine oxidase inhibitors and some diuretics.

b) Antimetabolites:

Metabolites are any substances used or produced by biochemical reactions. A drug which possesses a remarkably close chemical similarity (mimic) to the normal metabolite is called an antimetabolite.

The antimetabolite enters a normal synthetic reaction by "fooling" an enzyme and producing a counterfeit metabolite. The counterfeit metabolite inhibits another enzyme or is an unusable fraudulent end product which cannot be utilized by the cell for growth or reproduction. Such antimetabolites have been used as antibacterial or anticancer agents.

Enzyme induction refers to an increase in the rate of hepatic metabolism, mediated by increased transcription of mRNA encoding the genes for drug metabolizing enzymes. This leads to a decrease in the concentrations of drugs metabolized by the same enzyme.

***5. Stereochemistry (substrate stereoselectivity, product stereoselectivity, regioselectivity):***

The pharmacokinetics of many chiral drugs are stereoselective. ... Stereochemistry influences not only the disposition and activity of the parent drug but also the nature and potential pharmacological activity of the metabolites formed.