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Opinion Article

Potential Effect of First-Pass Metabolism in Fasting and Chronic Alcohol Consumption Conditions

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DESCRIPTION

First-pass metabolism, also known as systemic metabolism, refers to the metabolic transformations that occur in the liver or intestinal wall following oral administration of drugs or other xenobiotics. The first-pass effect is the phenomenon in which a drug is metabolized at a specific site in the body, resulting in a decrease in the concentration of active drug when it reaches its site of action or systemic circulation. This process can significantly affect the bioavailability, efficacy, and safety of drugs, as well as the interpretation of pharmacokinetic and pharmacodynamic data. The liver is the major site of first-pass metabolism, due to its high metabolic capacity and the fact that it receives the blood supply from the gastrointestinal tract through the portal vein. The intestinal wall can also contribute to first-pass metabolism, particularly for compounds that are substrates for intestinal enzymes or undergo significant presystemic extraction. The main mechanisms of first-pass metabolism include oxidation, reduction, hydrolysis, and conjugation reactions. The enzymes responsible for these reactions include Cytochrome P450 (CYP) enzymes, UDP-Glucuronosyltransferases (UGTs), Sulfotransferases (SULTs), Carboxylesterases, and others.

CYP enzymes are the most studied and important group of enzymes involved in drug metabolism. There are several isoforms of CYP enzymes, with CYP3A4 being the most abundant and responsible for the metabolism of about half of all drugs on the market. CYP enzymes can either activate or deactivate drugs, depending on the specific substrate and the reaction involved. For example, CYP3A4 can convert the antihypertensive drug verapamil to an inactive metabolite, while it can convert the immunosuppressant cyclosporine to an active metabolite. UGTs and SULTs are responsible for the conjugation of drugs with glucuronic acid or sulfate, respectively. This conjugation reaction usually leads to the formation of more hydrophilic and less lipophilic metabolites that are more easily eliminated in urine or bile. Carboxylesterases can hydrolyze ester-containing drugs, while other enzymes such as aldehyde oxidase and Flavin-Containing Monooxygenase (FMO) can catalyze other oxidation or reduction reactions.

The extent and degree of first-pass metabolism can vary widely among different drugs and individuals, depending on factors such as drug dose, formulation, route of administration, genetic polymorphisms, and drug-drug interactions. For example, some drugs such as propranolol and morphine undergo extensive first-pass metabolism, resulting in low bioavailability and high inter-individual variability. In contrast, some drugs such as diazepam and midazolam undergo minimal first-pass metabolism, resulting in high bioavailability and predictable pharmacokinetics. Drug interactions can also affect first-pass metabolism, either by inducing or inhibiting the activity of specific enzymes. For example, the antibiotic rifampicin can induce CYP3A4 activity, leading to increased metabolism and decreased efficacy of drugs such as cyclosporine and tacrolimus. On the other hand, the antifungal drug ketoconazole can inhibit CYP3A4 activity, leading to decreased metabolism and increased toxicity of drugs such as midazolam and simvastatin.

The implications of first-pass metabolism for drug development and clinical practice are significant. In drug development, first-pass metabolism can affect the selection of drug candidates, the design of drug formulations, and the prediction of drug-drug interactions. For example, drugs that undergo extensive first-pass metabolism may require alternative routes of administration, such as intravenous infusion or transdermal patch. Drugs that are substrates for specific enzymes may require co-administration with enzyme inhibitors or inducers to achieve the desired pharmacological effect. In clinical practice, first-pass metabolism can affect the dosing, efficacy, and safety of drugs. For example, drugs that undergo extensive first-pass metabolism may require higher doses or more frequent.

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antifungal drug ketoconazole can inhibit CYP3A4 activity, leading to decreased metabolism and increased toxicity of drugs such as midazolam and simvastatin. Drugs subject to first-pass metabolism include morphine, buprenorphine, diazepam, and midazolam. The process of first-pass metabolism is available pharmacologically. Drug bioavailability decreases in proportion to the proportion of the initial dose that is converted to inactive metabolites by liver enzymes. Notable drugs that experience significant first-pass effects are buprenorphine, chlorpromazine, cimetidine, diazepam, ethanol (alcohol), imipramine, insulin, lidocaine, midazolam, morphine, pethidine, propranolol, and Tetrahydrocannabinol (THC).