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Drug Elimination

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Definition/Introduction

Drug elimination is the sum of the processes of removing an administered drug from the body. In the pharmacokinetic ADME scheme (absorption, distribution, metabolism, and excretion) it is frequently conside encompass both metabolism and excretion. Hydrophobic drugs, to be excreted, must undergo metabolic moc making them more polar. Hydrophilic drugs, on the other hand, can undergo excretion directly, without the ne metabolic changes to their molecular structures.

Although many sites of metabolism and excretion exist, the chief organ of metabolism is the liver, while the c primarily tasked with excretion is the kidney. Any significant dysfunction in either organ can result in the accumulation of the drug or its metabolites in toxic concentrations.

A variety of other factors impacts elimination — intrinsic drug properties, such as polarity, size, or pH. Also, factors include genetic variation among individuals, disease states affecting other organs, and pathways invol the way the drug distributes through the body, such as first-pass metabolism.

Issues of Concern

Drug elimination is the removal of an administered drug from the body. It is accomplished in two ways, eithe excretion of an unmetabolized drug in its intact form or by metabolic biotransformation followed by excretio excretion is primarily carried out by the kidneys, other organ systems are involved as well. Similarly, the live primary site of biotransformation, yet extrahepatic metabolism takes place in a variety of organ systems affec multiple drugs.

Given the multiple organ systems and the variety of metabolic transformations present, drug elimination can significant degree of complexity. Hydrophilic drugs are typically directly excreted by the kidneys, while the hydrophobic drugs undergo biotransformation before excretion. The purpose here is twofold – biotransformat serves to both detoxify the exogenous substances as well as to increase their hydrophilicity, ensuring their eli via the kidneys.

Two broad metabolic pathways of hepatic drug transformation exist. Phase I is the direct modification of the molecule, whereas phase II entails conjugation of the target to a polar molecule of low molecular weight. Pha prepares the drug to enter phase II, but single-phase metabolism also exists.[1][2]

Phase I involves oxidation, reduction, and hydrolysis of the exogenous molecule. These reactions are accomp by hepatic microsomal enzymes, which reside in the smooth endoplasmic reticulum of the hepatocytes. Best l among them is the cytochrome P450 system, whose enzymes are predominantly involved in oxidative metabo Within the cytochrome P450 family (CYP), the enzyme responsible for the metabolism of more than 50% of drugs is the CYP3A4. Its activity encompasses various classes of medications, including opioids, immunosuppressants, antihistamines, and benzodiazepines. The enzymes can also be induced and inhibited b

variety of substances they interact with, including pharmaceuticals. The increase in metabolic activity with C induction results in diminished activity of drugs targeted by that particular isoform. Conversely, CYP inhibiti result in increased drug plasma concentration, potentially leading to toxicity. The CYP3A4 is induced by phe phenobarbital, and St. John's wart, while diltiazem, erythromycin, and grapefruit inhibit it. Caution is therefo necessary when administering CYP3A4-metabolized drugs in the presence of any of the inhibitors or inducer

Phase II consists of covalent bonding of polar groups to nonpolar molecules to render them water-soluble and renal or biliary excretion. Target molecules enter phase II directly or via initial processing through phase I. A of polar adjuncts is transferred, including amino acids, glucuronic acid, glutathione, acetate, and sulfate. Glucuronidation is one of the major pathways of phase II biotransformation. The UDP-glucuronosyltransfera (UGT) enzyme family performs this activity. Typically, glucuronide derivatives possess less or no activity of original drug, but in some cases, pharmacologically active compounds result. Morphine-6-glucuronide is a ph metabolite of morphine with significant analgesic activity. As with the CYP enzymes, inducers, and inhibitor phase II, enzymes exist and may influence the efficacy of drugs that rely on conjugation before excretion.

The first-pass effect is a feature of hepatic metabolism that also plays a role in the elimination of multiple dru the enteric consumed drugs are exposed directly to the liver via the portal vein, where they undergo biotransf before entering the systemic circulation. This activity reduces the bioavailability and needs to be factored into dose administered to the patient. Intravenously administered drugs are not subject to the first-pass effect.

Extrahepatic drug metabolism takes place in the GI tract, kidneys, lungs, plasma, and skin.

Renal excretion completes the process of elimination that begins in the liver. Polar drugs or their metabolites filtered in the kidneys and typically do not undergo reabsorption.[5] They subsequently get excreted in the uri Urinary pH has a significant impact on excretion, as drug ionization changes depending on the alkaline or aci environment. Increased excretion occurs with weakly acidic drugs in basic urine, and weakly basic drugs in a urine.

Excretion in the bile is another significant form of drug elimination. The liver can actively secrete ionized dr a molecular weight greater than 300 g/mol into bile, from where they reach the digestive tract and are either eliminated in feces or reabsorbed as part of the enterohepatic cycle.

Other pathways of excretion include the lungs, breast milk, sweat, saliva, and tears.[6][7][8][9]

Clinical Significance

Hepatic diseases, such as liver cirrhosis, affect drugs eliminated via the liver. Compromise of phase I and II m pathways will lead to increased half-lives of long-acting drugs, contributing to toxicity. The decline in plasm in the setting of liver disease can lead to an increase in unbound drug fraction in plasma. As liver disease inc severity, the dose of a drug must be reduced to obtain the same effect. Changes in liver perfusion can also affe metabolism of drugs. States of decreased blood flow to the liver, such as shock, hypovolemia, or hypotension lead to a decline in metabolic rate.

Renal disorders, such as chronic kidney disease, can reduce renal function hindering drug excretion. As kidne function declines with age, drug excretion becomes less efficient, and dosing adjustments may be needed. Ot direct renal dysfunction, pathologies that impact renal blood flow or urine flow can affect drug elimination as Examples of such disorders are congestive heart failure, liver disease, and pathologies affecting antidiuretic h release.[10]

Nursing, Allied Health, and Interprofessional Team Interventions

Aging patients experience a decline in both liver and kidney function. The Beers Criteria have been develope allow for risk stratification in the older population and are useful when dosing medications in individuals ove years of age. Similarly, administration of drugs to patients affected by liver or kidney disease or exhibiting

pathologies that may impact those organs must take dose adjustments into account. All drug package inserts c specific concerns regarding renal and hepatic dosing which the healthcare team needs to be aware of for their [11]

Nursing, Allied Health, and Interprofessional Team Monitoring

When taking care of patients with hepatic or renal disease or conditions affecting those organs, nurses must c the fact that drug elimination may be affected. Drug doses may require reduction, and some drugs may requir discontinuation. If the administration of a particular drug is absolutely necessary, careful monitoring for adve effects is of the essence. In patients unaffected by liver or kidney pathology, the plasma concentration of drug vancomycin or phenytoin still needs monitoring to ensure they remain in the therapeutic window.[12]

Continuing Education / Review Questions

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