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A REVIEW ON: PHARMACOKINETIC AND DRUG DISPOSITION

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Abstract

A significant factor in both health and sickness is the billions of microorganisms that comprise the gut microbiome. Xenobiotics—drugs that are taken orally, in particular—interact directly with the gut microbiota to be broken down into metabolic products. Additionally, the metabolizing enzyme machinery of the host is affected indirectly by microbial metabolites such bile acids, which interact with nuclear receptors to affect drug disposition and pharmacokinetics. Understanding a drug's fate, or its disposition (absorption, distribution, metabolism, and excretion—abbreviated ADME) and pharmacokinetics—the mathematical depiction of these processes' rates and concentration-time relationships—is essential to pharmaceutical research and development. These investigations are essential for defining conditions for safe and effective use in patients, supporting safety assessment, and helping to find and choose new chemical entities. They are especially useful in bridging the gap between animal research and human situations. With an emphasis on the importance of this information for a thorough comprehension of a drug's mechanisms of action and toxicity, this presentation aims to give an overview of the life cycle of a medication in the body of an animal.

Keywords: Xenobiotics; human and animal exposure; predictive value.

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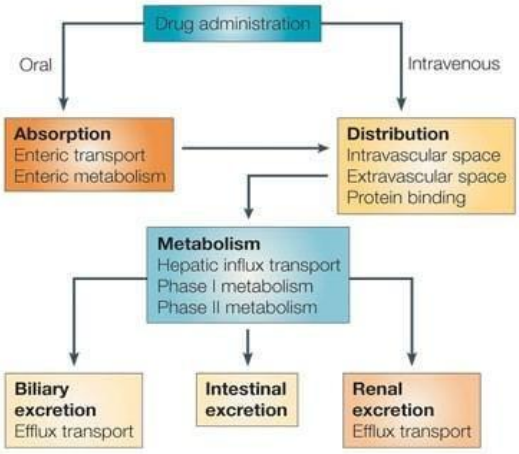
Introduction

The goal of precision medicine is to utilize an individual's genetic, environmental, and lifestyle characteristics to ensure appropriate drug therapy and disease state management. Understanding the factors that contribute to the variability in pharmacokinetics and pharmacodynamics is paramount. For example, progress has been made in determining genetic variability in drug-metabolizing enzymes, drug transporters, and drug target genes, resulting in clinically actionable guidelines for select drugs. The gut microbiome with its trillions of microbial cells including bacteria, viruses, fungi, and archaea has recently emerged as an important contributor to drug action and variability, particularly with orally administered compounds. Genes encoding organisms in the human gut microbiome in recent estimates number at 232 million, far outnumbering human germline genes of ~ 20,00. More than 90% of the gut microbiota are members of two bacterial phyla, Bacteriodetes and Firmicutes. The enormous inter-patient diversity in human gut microbiomes and inter-related factors such as diet, circadian rhythms, and immune function are significant contributors to variability in drug disposition and response(1). Additionally, intra-individual variability across time and influences such as diet are also important considerations when determining relationships between the gut microbiome and drugs. There is a bidirectional nature to the interaction between drugs and the microbiome. Antibiotics, particularly those that impact Gram-positive organisms and anaerobes, can profoundly alter the microbial composition. Some evidence suggests that antibiotic use in infants may change the microbiome ontogeny and lead to long-term adverse immunological, neurological, and metabolic outcomes. In addition, a significant number of non-antibiotic compounds can alter the gut microbiome with up to 240 drugs showing inhibition of at least one bacterial strain in vitro(2).

This may have implications on antibiotic resistance and dysbiosis-induced disease from traditionally Humans and other animals are exposed on a daily basis to many xenobiotics, that is, compounds that are foreign to the

normal energy-yielding metabolism of the body. Exposure to these xenobiotics may occur deliberately, as in the case of drugs and food additives; accidentally, as in the case of food contaminants and pesticides, or coincidentally, as in the case of industrial chemicals and environmental pollutants. In this paper, the terms drug, xenobiotic, and foreign compound will be used interchangeably(4). In the present context, the importance of ADME (absorption, distribution, metabolism, and excretion) principles in drug development will be emphasized, but it should be appreciated that these have comparable applicability in the safety assessment of all types of chemicals to which humans might be exposed. To achieve its effect, whether therapeutic or toxic, a drug and/or its metabolites must be present in appropriate concentrations at its sites of action. The concentration of xenobiotic attained will depend on the dose, formulation, and route of administration, the rate and extent of absorption, its distribution through the body and binding to tissues, biotransformation, and excretion. It is the purpose of this presentation to give an overview of these processes and to comment upon the factors influencing them and their biological significance(3).

Drug administration of oral intravenous:



Absorption

The processes of absorption are those that lead to the entry of a xenobiotic into the systemic circulation of the body. The most important site of absorption is the gastrointestinal tract, although absorption through the skin, the main barrier between the internal milieu and the external environment, and the respiratory tract, which is important for volatile compounds and materials present in aerosols and dust particles, can also occur(6).

Importance of the Human ADME Study:

A quantitative description of the ultimate fate of a new molecule in the human body is required for new drug approval .However, of the many clinical pharmacology studies conducted during the development of new medicines, the radiolabelled absorption-distribution-metabolism-excretion (ADME) study offers the richest dataset to understand how the human body handles the drug.1 ADME studies(5) are generally conducted for drugs under development that are organic xenobiotics, whereas for drug candidates that are biological macromolecules containing no xenobiotic elements, radiolabeled ADME studies are often not done.

Many drugs and endogen Volume of Distribution The distribution of a drug within the body is affected by drug properties (e.g., lipophilicity, molecular size) and its interactions with body constituents, including binding to plasma proteins and tissues. The relationship between the apparent volume of distribution, drug binding, and anatomical volumes is given by: where VP is the plasma volume, VT is the tissue volume, and fu and fuT are the unbound fractions of drug in plasma and tissue, respectively. Additionally, although some drugs can passively distribute throughout body compartments, facilitated movement via transporters often governs distribution to and from various tissues(8). Transporters may also form physiological barriers such as the blood–brain barrier (BBB) and placental barrier and limit movement of drugs into tissues. Thus, microbiome effects on transporters, tissue binding, and plasma protein binding may alter the distribution of a drug within the body. These effects may have therapeutic consequences, for example, for a drug that must reach the brain to elicit a pharmacologic response(13).

Distribution:

Following entry of a xenobiotic to the systemic circulation, its distribution into the various tissues of the body will be influenced by tissue hemodynamics, passive diffusion across lipid membranes. the presence of carrier-mediated active transport processes recognizing the xenobiotic. ana protein binding in the blood and tissues. The majority of tissue membranes behave as typical lipid barriers allowing small lipophilic molecules to cross cell membranes. Equilibrium drug concentration ratios are maintained by diffusion of drugs into and out of tissues. Drugs can accumulate in tissues at a higher concentration than predicted by simple diffusion under the influence of pH gradients, binding to intracellular constituents, or partitioning into

lipid depots. Larger or more polar substances do not cross lipid membranes by passive diffusion and require specific transporters to enter the tissues. If a drug does enter a tissue by an active transport mechanism, its concentration in the tissue may be many times greater than its plasma concentration. Active uptake processes tend to show stereoselectivity and can be particularly important for xenobiotics that may be analogy of nutrients(15). The operation of specific uptake mechanisms for xenobiotics may play an important role in the toxicity of some compounds. For example, amantadine and phalloidin are toxic cyclopeptides of the fungus Amanita phalloides. The toxins enter the liver via an active transport system involved in the transport of bile acids.

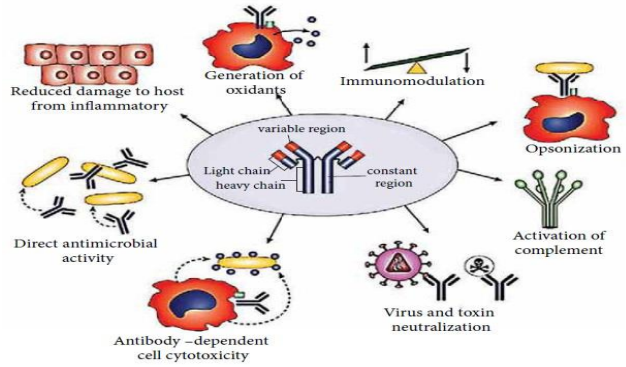


Figure:2 Metabolism of all Parts

Metabolism:

Drugs and other xenobiotics that gain access to the body may undergo 1 or more of 4 distinct fates, as follows: 1. Elimination unchanged 2. Retention unchanged 3. Spontaneous chemical transformation 4. Enzymic metabolism Each of these fates are of importance but, in quantitative terms it is enzymic metabolism, often also referred to as biotransformation, that predominates. The main site of metabolism of foreign compounds is the liver, although extrahepatic tissues, frequently the site of entry to or excretion from the body (e.g., lungs, kidneys, gastrointestinal mucosa), also play a role in the metabolism of xenobiotics (24 and references therein).(13) Compounds eliminated unchanged are generally either (a) highly polar such as strong carboxylic or sulfonic acids (e.g., sodium cromoglycate) or quaternary amines (e.g., pancuronium), which if absorbed are rapidly cleared into the urine or bile, or (b) volatile and hence readily lost via the lungs. In contrast, nonpolar, highly lipophilic compounds may be retained for long periods in tissue lipids, as occurs with chlorophenothane and many polyhalogenated aromatics(18).

Compounds that bind to glutathione-S-transferases include bilirubin, estradiol, cortisol, testosterone, tetracycline, penicillin, and indocyanine green. A number of catechol, phenol, and alcohol compounds are excreted as sulphate conjugates. This reaction between substrate and sulphate donor, 3′-phosphoadenosine-5′-phosphosulfate, is catalysed by a family of sulfotransferase enzymes. The sulfotransferases have a cytosolic location and are found in many tissues including the liver, adrenals, lung, brain, jejunum, and blood platelets(19).

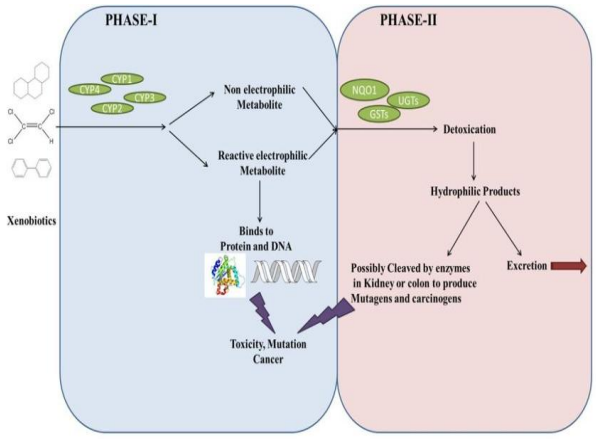


Figure:3 Metabolism Phase-1 and Pase-2

Drug Disposition: Metabolism and Excretion:

Determining the differential contributions of the intestine and liver to drug metabolism and excretion can be challenging and the contribution of the microbiome to these routes is emerging. It is increasingly evident that there is significant cross-talk between the intestine and liver and that bile acids, produced in the liver and modified by bacteria in the gut, are important signalling molecules that regulate host metabolism(13). Bile acids achieve their signalling properties by binding to G-protein-coupled receptors such as the foresaid X receptor and TGR5; and binding of bile acids to the foresaid X receptor modulates CYP3A and transporter activity. Other microbial products such as the secondary bile acid lithocholic acid (LCA), lipopolysaccharides produced from Gram-negative bacteria, and indole-3-propionic acid have also been shown to activate the nuclear receptor, PXR, another nuclear receptor involved in regulating drug metabolism and transport(16). Animal data support the role of the gut microbiome in modifying host drug metabolism and transport. The protein expression of several CYPs and transporters such as Oatp and Bcrp1 were altered in germ-free and antibiotic-treated mice; and ciprofloxacin-treated mice had significantly reduced LCA-producing

bacteria in their faeces. In germ-free mice given LCA, CYP3A expression was significantly elevated suggesting that LCA activated farnesoid X receptor and PXR. Hepatic CYP3A and the activity of the CYP3A substrate midazolam were significantly lower in germ-free mice compared with conventional mice, suggesting that gut microbes may alter the metabolic activity of CYP3A. One example of gut microbes altering host liver metabolism is with the analgesic acetaminophen. Acetaminophen undergoes glucuronidation and bacterial glucuronidases can deconjugate the glucuronide metabolite allowing for reabsorption of the parent acetaminophen or further metabolism to sulphate and/or glucuronide conjugates(20). With antibiotic treatment, there is a decrease in the sulphate conjugate of acetaminophen. In addition, gut bacteria produce a metabolite of aromatic amino acid metabolism, p-cresol, that competes with acetaminophen for binding to the enzyme sulfotransferase 1A1. Individuals who produce high levels of p-cresol were shown to have a low capacity for sulfonate acetaminophen. Therefore, antibiotic therapy and/or high levels of the bacterially derived metabolite p-cresol could predispose individuals to the hepatotoxic effects of acetaminophen. Drugs Affected by Microbiome Alterations with Clinical Significance Digoxin is a cardiac glycoside for the treatment of atrial fibrillation and congestive heart failure. Digoxin is a positive inotropic drug that inhibits the Na+/K+-ATPase pump, resulting in increased intracellular calcium in cardiac myocytes. The narrow therapeutic window (target concentration range 0.5–2 mcg/L) of digoxin requires therapeutic drug monitoring. Digoxin relative F is influenced by the form

ADME study is that it enables the addition of a second period wherein the same subjects are administered an intravenous microdose of carbon-14 labelled material. With intravenous administration, the fundamental and important pharmacokinetic parameters clearance and volume of distribution can be calculated. Combining these data with the data from period 1 permits estimation of fraction of dose absorbed.

Excretion:

There are 2 main elimination routes from the body for xenobiotics and their metabolites. In both the kidneys and the liver, polar compounds are excreted more efficiently than lipophilic compounds. Thus, lipid-soluble compounds are not readily excreted from the body unless they are first metabolized to more polar, more water-soluble compounds. Renal Excretion the mechanisms involved in renal excretion are filtration, secretion, and reabsorption. Substances that are polar or charged and have little binding to plasma proteins are eliminated primarily by glomerular filtration(16). Examples include the aminoglycoside antibiotics and vancomycin. In contrast, compounds extensively bound to plasma proteins tend to remain in the blood and do not undergo extensive filtration (e.g., indocyanine green, bilirubin. Secretion. Some drugs are removed from plasma and secreted into the proximal tubules by the cells of the tubular wall. Secretion occurs via active transport mechanisms that can differentiate among compounds on the basis of charge. The first system transports weak acids, including numerous drug conjugates produced in the liver, penicillin, and a number of thiazide diuretics. The second system transports basic substrates including cimetidine, histamine, and choline. The carrier systems are relatively nonselective, and xenobiotics of similar charge compete for transport Reabsorption.

Results and Discussion:

Two hundred and forty-nine drugs were identified from published reviews3,7,9 as of potential interest during pregnancy, covering a wide range of therapeutic areas. Existing pregnancy PBPK models were found in the literature for 74. The majority of those models (n = 54) have been published in the last 3 years. There is an evident increase in the number of publications reporting the use of PBPK in pregnancy in the recent past. Table 1 focuses on recent advancements and enlists the compounds for which a model has been reported in the literature from 2020 onwards(9). The major clearance pathway was reported for each drug. Renally excreted drugs constituted 14 of them. For compounds not primarily eliminated unchanged in urine, main hepatic enzymes were presented. Nearly half (45%) of the drugs were metabolised by CYP3A4 either as the sole major hepatic enzyme involved (21%) or with noteworthy

Challenges can arise due to gaps in the information (e.g. lack of quantitative proteomics data about the expression of specific metabolic enzymes or transporters during pregnancy) and incorporation of this information into existing system models(20). While certain software platforms offer libraries of drug models validated for predicting PK in healthy or disease populations, they require specific validation to predict PK for special populations, for example, pregnancy or paediatrics.

Conclusion

The way that the gut microbiota functions and how it affects pharmacokinetics and pharmacodynamics in the clinic is currently being studied. Although there are instances of the direct metabolism of drugs by gut microbes influencing drug pharmacokinetics, there are still unanswered questions regarding the particular species and strains involved, the diversity and redundancy of the microbial community to metabolize these drugs, and other factors like immunity, diet, other medications, and circadian rhythms that may impact these activities. There is proof that the gut microbiome indirectly affects how drugs are metabolized through the interaction of gut microbial metabolites like bile acids with the machinery of the host. It is crucial to conduct more animal and/or in silico research to look into the processes underlying these effects, as well as human studies to ascertain the clinical importance of these interactions. We have looked at a number of examples of pharmaceuticals where changes in the taxonomy of gut microbes can significantly affect the pharmacokinetics and/or pharmacodynamics.

Author contributions

All authors are contributed equally.

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Declaration of Competing Interest

The authors have no conflicts of interest to declare.

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