Pharmacokinetic variation

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Abstract

Pharmacokinetics is the study of how the body handles an administered drug, including absorption, distribution, metabolism and excretion. Pharmacokinetic variation is when there is variability in the drug concentration at the effector site after administration of a standard dose. This can result in one dose of a drug being ineffective in one patient, but potentially toxic with unwanted side effects in another. There are four factors which are responsible for pharmacokinetic variation: absorption, distribution, metabolism and excretion. This article will review how physiological, pathological and pharmacological processes can influence all of these factors.

Keywords Absorption; distribution; excretion; metabolism; pathological; pharmacodynamics; pharmacokinetics; physiological

Royal College of Anaesthetists CPD Matrix: 1A01; 1A02

Learning objectives

After reading this article, you should be able to describe:

- how normal physiological processes can lead to altered drug levels at the target site
- how pharmacokinetic processes can be affected in disease states
- how pharmacological processes can affect pharmacokinetic variation
- the importance of cytochrome P450 in pharmacokinetic variation

Introduction

Pharmacokinetics is the study of how the body handles an administered drug, including absorption, distribution, metabolism and excretion. Absorption is both drug and route specific (e.g. oral, intravenous, inhalational, dermal, rectal, etc.). Distribution of a drug depends on factors that influence the passage of drugs across the cell membrane, such as molecular size, lipid solubility, degree of ionization and protein binding. Metabolism usually reduces the activity of a drug, but it can increase it, such as with a prodrug. Metabolism generally produces a more polar (water soluble) molecule that can be excreted in bile or urine. Excretion refers to the processes of removal of the drug from the body.

Pharmacokinetic variation is when there is variability in the drug concentration at the effector site after administration of a standard dose. This can result in one dose of a drug being ineffective in one patient, but potentially toxic with unwanted side effects in another. Therefore it is very important to understand what factors influence pharmacokinetic variation, to aid our decisions regarding effective yet safe drug doses for our patients.

Bioavailability of a drug is defined as the fraction of a drug dose reaching the systemic circulation compared to the same dose given intravenously. Factors influencing bioavailability include route of administration, patient factors, pharmaceutical preparation, physiochemical interactions, pharmacokinetic interactions and first-pass metabolism.

In contrast, pharmacodynamics, is what effect the drug has on the body. There is an association between the plasma concentration of a drug and its pharmacodynamics effect, therefore factors affecting the pharmacokinetics of a drug, can indirectly affect the pharmacodynamics.

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Sources of pharmacokinetic variation

There are four factors which are responsible for pharmacokinetic variation; absorption, distribution, metabolism and excretion. Physiological, pathological and pharmacological processes can influence all of these factors.

Physiological

Age

Absorption: Neonates have prolonged gastric emptying and intestinal transit times which results in delayed absorption of oral drugs. Although some basic drugs (e.g. penicillins) have increased absorption due to elevated gastric pH. With increasing age, studies have shown that there is actually no change in absorption of drugs unless a pathological process is present.

Distribution: Adults have lower total body water (TBW) per kilogram than neonates and infants. This can result in differing plasma concentrations dependent on the degree of lipid or water solubility of a drug. Polar drugs that are predominantly water-soluble tend to have smaller volumes of distribution (VD) resulting in higher serum levels in older people, including gentamicin and digoxin.

In contrast, body fat increases with age, which results in increasing VD of lipid soluble drugs, such as thiopentone and propofol. Blood brain barrier permeability also increases with age, therefore a greater central nervous system (CNS) drug concentration of lipid soluble drugs will be seen in the elderly.

Metabolism: Neonates have an immature hepatic microsomal enzymes system, therefore reduced drug metabolism, however this reaches full maturity by 6 months of age. First-pass metabolism is reduced with increasing age, due to reduction in hepatic blood flow, mass and reduced hepatic microsomal

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enzymes. As a result, the bioavailability of drugs undergoing extensive first-pass metabolism such as propranolol can be significantly increased. However, prodrugs such as enalapril need to be activated in the liver, therefore, their first-pass activation might be slowed or reduced with advancing age.

Excretion: Renal excretion is reduced in both neonates and the elderly due to reduced glomerular filtration rate. The clinical importance this is dependent on the likely toxicity of the drug. Drugs with a narrow therapeutic index such as digoxin and lithium are likely to have serious adverse effects if they accumulate only marginally more than intended.

Sex

Absorption: Males produce more acidic gastric secretions, which can alter the absorption of acid/bases depending on specific drug ionization.

Distribution: Men generally have larger body weights with greater TBW; however, women have a higher fat percentage. This results in a higher VD of fat-soluble drugs in women, and higher VD of polar drugs in men.

Metabolism: Generally the differences in metabolism between the sexes are eliminated when height and weight are taken into account despite the fact that men do have an increased basal metabolic rate. There is some evidence that males demonstrate a higher activity of the isoenzyme CYP1A2, which is involved in the metabolism of clozapine. CYP3A4 enzyme activity is increased in females, which has been shown to be involved in the metabolism alfentanil and clarithromycin. However, even if there are true sex differences in drug pharmacokinetics, only few drugs exhibit significantly different plasma concentrations in women.

Excretion: Renal clearance is reduced by 10% in females; this is due to reduction in GFR, tubular secretion and tubular reabsorption.

Pregnancy

Absorption: Nausea and vomiting in early pregnancy may decrease the amount of drug available for absorption following oral administration. Gastric acid production is also decreased during pregnancy, leading to an increase in gastric pH, which can increase ionization of weak acids (e.g. aspirin) and reduce their absorption. In contrast to previous reports, evidence now shows that gastric emptying is not reduced in normal pregnancy. However due to peripheral vasodilation resulting in increased tissue perfusion, intramuscular drug delivery is enhanced.

Distribution: Increased TBW will increase VD for hydrophilic drugs, leading to lower plasma concentrations. In addition, maternal body fat increases which results in increasing the VD for lipophilic drugs. Albumin and α-1-acid glycoprotein levels fall and placental hormones may displace drugs from protein binding sites, increasing the levels of free drug.

Metabolism: Due to elevated oestrogen and progesterone levels, the activities of CYP3A4, CYP2A6, CYP2D6, and CYP2C9 are all increased during pregnancy resulting in increased metabolism of drugs such as nifedipine and phenytoin. By contrast, CYP1A2 and CYP2C19 demonstrate decreased activity. Other extrahepatic enzymes, such as plasma cholinesterase, have reduced activity during pregnancy.

Excretion: GFR is 50% higher by the first trimester and continues to increase until the last week of pregnancy leading to the increased elimination of renally excreted drugs. In contrast, the clearance of drugs that are excreted by the biliary system may be attenuated owing to the cholestatic properties of oestrogen.

Pathological

Obesity

Absorption: Gastrointestinal absorption is unaffected by obesity. Epidural and intrathecal drug doses need to be reduced by 20–25% due to the engorgement of epidural veins and the increased epidural fat causing a reduction in the volume of the epidural and intrathecal spaces. Intramuscular injections may end up being subcutaneous in obese individuals.

Distribution: Obese individuals have larger lean body masses and higher total body fat mass, with a reduced TBW fraction and increased blood volume. This has been shown to have a variable effect upon drug distribution. Lipid soluble drugs such as thiopentone have an increased VD, therefore lower plasma concentrations, but longer offset time due to re-distribution. Some volatile drugs such as desflurane have some beneficial properties when used to anaesthetize obese patients, due to the low oil:gas partition coefficient leading to a rapid onset of action, minimal distribution into fat stores, and hence rapid wake up.

Metabolism: Drug metabolism by the liver is only really affected in obese patients if there is significant fat infiltration into the liver. Hepatic blood flow increases a moderate amount but hepatic enzyme activity appears to be unaffected.

Excretion: Renal blood flow, GFR and tubular secretion are all increased in obese individuals and the clearance of drugs that are renally excreted is enhanced.

Hepatic disease

Absorption: Many drugs undergo significant first-pass metabolism, which reduces their systemic bioavailability. Hepatic dysfunction can result in reduced hepatic blood flow and the development of portosystemic shunts results in oral drugs avoiding first-pass metabolism, with increased systemic availability. Failure of first-pass metabolism will result in greater bioavailability of active drugs.

Distribution: The synthesis of plasma proteins such as albumin and α-1-acid glycoprotein can be decreased in hepatic disease, reducing drug binding and increasing the amount of free drug. The significance of this is dependent upon the degree to which the drug concerned is normally protein bound. The greater the degree of protein binding, the greater the potential for an alteration in drug concentration. Drugs that are very highly protein bound such as warfarin (>99% protein binding) must therefore be closely monitored and doses reduced.

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Oedema and ascites result in increased TBW and consequently lead to a larger VD for polar drugs, therefore lower plasma concentrations, with patients often requiring a larger initial loading dose.

Metabolism: The capacity of the liver to metabolize drugs is dependent upon liver enzyme activity and hepatic blood flow. The CYP-mediated oxidative reactions are most sensitive to reductions in hepatocellular perfusion.

Drugs with large hepatic extraction ratios such as propofol have high clearance rates, which are reduced when hepatic blood flow is reduced, resulting in prolonged clinical effect. Conversely, metabolism of drugs with a low extraction ratio such as phenytoin is limited by hepatic enzyme function or protein binding, and affected very little by alteration in hepatic blood flow. Severe liver disease may also result in a reduction in the production of extrahepatic enzymes, such as plasma cholinesterase, impairing the metabolism of drugs such as suxamethonium. Prodrugs such as angiotensin converting enzyme inhibitors require hepatic conversion to the active form, and this is decreased in individuals with cirrhosis.

Excretion: Obstructive cholestasis will impair clearance of drugs removed via the biliary system, such as the aminosteroid muscle relaxants. There is also often co-existent renal pathology, which can affect drug clearance as described below.

Renal disease

Absorption: Uraemia can result in an increase in gastric pH. If renal failure is associated with a metabolic acidosis, this will also affect active transport processes. Delayed gastric emptying is often present as a feature of co-existing disease.

Distribution: Uraemia can also reduce the binding of many acidic drugs to albumin. In contrast, the binding of basic drugs to α-1-acid glycoprotein is largely unchanged. The VD of some drugs, such as digoxin, is decreased in renal failure owing to a reduction in tissue binding, but it may be increased in others, such as phenytoin, because of a reduction in plasma protein binding. VD is increased for polar drugs due to increased TBW.

Metabolism: Chronic renal failure can significantly reduce non-renal clearance of drugs by affecting hepatic metabolism. Work carried out in animals with advanced renal impairment has shown a major down regulation of some of the isoenzymes in the cytochrome P450 system. Some phase II reactions, such as glucuronidation, have a variable response to renal failure, with some enzyme systems showing inhibition and others induction. As a result, hepatic drug metabolism can be increased, decreased or remain unchanged in patients with renal failure.

Excretion: The kidneys are responsible for excretion of most drugs and metabolites. Those significant to the practice of anaesthesia include the active metabolites of morphine and pethidine (morphine-6-glucuronide and norpethidine respectively), which may accumulate with clinically significant side effects, in the presence of renal dysfunction.

Drugs which alter metabolism through inhibition or induction of the cytochrome P450 system

Inhibitors	Inducers
• Sodium Valproate	• Sulphonylureas
• Isoniazid	• Carbamazepine
• Cimetidine	• Rifampicin
• Ketoconazole	• Phenytoin
• Fluconazole	• Phenobarbital
• Acute alcohol use	• Chronic alcohol use
• Chloramphenicol	• Griseofulvin
• Erythromycin	
• Sulfonamides	
• Ciprofloxacin	
• Omeprazole	
• Metronidazole	

Table 1

Pharmacological

Drug interaction

Drugs can affect the metabolism of other drugs largely through the induction or inhibition of the cytochrome P450 enzyme system (Table 1). Cytochrome P450 enzymes are essential for the metabolism of many medications. While this class has more than 50 enzymes, 6 of them metabolize 90% of drugs, with the two most significant enzymes being CYP3A4 and CYP2D6. Cytochrome P450 enzymes can be inhibited or induced by drugs, resulting in clinically significant drug–drug interactions that can cause unanticipated adverse reactions or therapeutic failures.

Genetic variation

Genetic variability (polymorphism) in P450 enzymes may influence a patient's response to commonly prescribed drug classes. For example, CYP2D6 is responsible for the metabolism of codeine, of which 10–15% is metabolized to morphine. Between 6% and 15% of Caucasian people have reduced CYP2D6 activity owing to the presence of two null alleles, resulting in a reduction in the analgesic effect.

Some patients with a genetic predisposition will demonstrate idiosyncratic reactions to certain drugs. These are type B adverse reactions, which are novel responses that are not expected from the known pharmacological actions of the drug. Malignant hyperpyrexia triggered by suxamethonium or volatile anaesthetics and suxamethonium apnoea are but a few examples of this.

Conclusion

Pharmacokinetic variation is a broad subject affected by patient, physiological and pathological factors leading to changes in absorption, distribution, metabolism and excretion. This produces variability in the drug concentration at the effector site after administration of a standard dose, which can result in one dose of a drug being ineffective in one patient, but potentially toxic with unwanted side effects in another. Therefore it is very important to understand the numerous factors that influence

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pharmacokinetic variation, in order to aid our clinical decisions regarding effective yet safe drug doses for our patients. ◆

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