Pharmacokinetics for the prescriber

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Abstract
Pharmacokinetics is the science that describes (using the ADME approach) the absorption of a drug from its site of administration, its distribution throughout the body, its metabolism or conjugation, and its excretion from the body. Pharmacokinetics can be thought of as what the body does to the drug. This article describes the basic principles and outlines how an understanding of pharmacokinetics can support rational prescribing.

Keywords Drug absorption; drug metabolism; elimination; excretion; half-life; pharmacokinetics

Key points

- Drugs are usually absorbed from the gastrointestinal tract following oral administration, but their bioavailability is reduced compared with intravenous administration because of metabolism in the intestinal wall and first-pass metabolism in the liver
- Drug distribution through the body compartments depends on protein binding and the ability to cross cell membranes
- Volume of distribution (V_d) is a measure of how widely a drug is distributed in body tissues and is derived from the ratio of the total dose administered by bolus injection to the peak plasma concentration (C_{max}) (V_d = Dose/C_{max})
- Drug metabolism occurs mainly in the liver, involving phase I metabolism (oxidation) and phase II metabolism (conjugation), and the efficiency of these processes is influenced by age, environment, genetics and interacting drugs
- Drugs that are water-soluble are excreted mainly by the kidney but also by hepatocytes into the bile, usually in conjugated form
- The combined effects of all these processes produces a concentration–time curve with a rapid increase in concentration after absorption followed by an exponential decline (first-order kinetics)
- The elimination half-life of a drug is the time taken for the circulating concentration of the drug to decrease by 50% and is important because it determines the time taken to achieve 'steady state' with repeated dosing

What is meant by the term 'pharmacokinetics'?

Pharmacokinetics is the study of the processes that control how drug molecules reach their site of action via the plasma (absorption, distribution) and how they are removed from the body (metabolism, excretion). A knowledge of pharmacokinetics is the basis of every licensed drug regimen. A clear understanding of pharmacokinetics enables prescribers to choose doses and dose intervals that make it likely that the target tissues will be exposed to appropriate drug concentrations for a sufficient length of time. This is particularly important when using drugs with a narrow margin between the therapeutic and the toxic concentrations. Differences in pharmacokinetic handling account for most of the inter-individual variation in drug response.

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Drug absorption

Drugs can be absorbed throughout the gastrointestinal tract, but this occurs predominantly in the upper small bowel because of its large surface area. Lipid-soluble drugs are absorbed rapidly by passive diffusion. The absorption of water-soluble drugs is slower and may be incomplete. Most lipid-soluble drugs reach their peak plasma concentrations 30–60 minutes after ingestion, but absorption can be slowed by a heavy meal or by other therapeutic agents that reduce the rate of gastric emptying (e.g. opiates, tricyclic antidepressants, antihistamines, anticholinergics). A reduced absorption rate is important only if the required pharmacological effect depends on attaining a high peak concentration (e.g. antibiotics, analgesics). Hence, patients with severe migraine and gastric stasis may not obtain pain relief from oral aspirin or paracetamol unless gastric emptying is accelerated. At steady state, the extent of absorption of most drugs is more important than the rate of absorption.

Another increasingly recognized factor that influences drug absorption is the P-glycoprotein efflux pump protein, which is located in many tissues, including the duodenum. This pump acts as a barrier to the absorption of many drugs (e.g. ciclosporin) by pumping them out of intestinal enterocytes and back into the bowel lumen.

Effect of food

The absorption of lipid-soluble drugs is generally increased in the presence of food, although the clinical impact is usually small because these drugs are well absorbed.[1] Water-soluble drugs are best taken on an empty stomach, at least 1 hour before a meal, with a full glass of water. If the drug is likely to produce gastrointestinal irritation (e.g. anti-inflammatory agents), it should be taken with food whatever its solubility.

Bioavailability

It is only after intravenous administration that prescribers can be certain that all of the administered dose is available for distribution in the body. There is inevitably a loss of some of the dose at several points when it is absorbed by any other route. The proportion of the dose that reaches the circulation intact is usually referred to as 'bioavailability' or bioavailability fraction, F, which can range between 0 (none of the dose reaches the circulation) and 1 (the entire dose reaches the circulation). The F value of carbamazepine is 0.78 regardless of sex and racial differences,[2] which means that 78% of the dose of carbamazepine administered orally reaches the circulation as intact drug. Because only the absorbed dose has an effect on the body, the effective dose of a medication can be defined as follows:

$$\text{Effective dose} = F \times \text{dose administered}$$

First-pass metabolism

An important factor that reduces oral bioavailability is drug inactivation in the gastrointestinal tract or metabolism in the gut wall or liver before it enters the systemic circulation (Figure 1). This effect is called the 'first-pass' metabolism or the 'first-pass' effect, and usually results from metabolism in the liver. Propranolol is metabolized to an inactive compound, which explains the 20-fold difference between the effective intravenous and oral doses. Grapefruit juice can inhibit metabolizing enzymes in the duodenum, leading to an increased bioavailability of drugs such as felodipine, terfenadine and ciclosporin; in several cases, this interaction has been fatal. It is sometimes possible to bypass the liver using routes of administration other than oral; for example, glyceryl trinitrate can be given sublingually, buccally or transdermally, and other drugs (e.g. morphine) can be given rectally.

Drug distribution

Once a drug reaches the systemic circulation, it may be bound to circulating proteins, usually albumin (although basic drugs such as propranolol and disopyramide bind largely to globulins and acute-phase reactants such as α_1-acid glycoprotein). Most drugs must be unbound (free) to have a pharmacological effect. Protein binding is rarely of clinical importance unless a drug is highly protein-bound (>90%) with minimal distribution into the tissues (e.g. phenytoin, warfarin). For other drugs, any change in protein binding has little impact on the amount of unbound drug available at the site of action.

For drugs that are highly protein-bound, the equilibrium between the bound and free drug can be affected if the capacity for protein binding is altered. Factors that alter protein binding include hypoalbuminaemia (albumin <25 g/litre), the third trimester of pregnancy (partly as a result of hypoalbuminaemia), renal failure (in which the affinity of proteins for drugs appears to be altered) and displacement by other drugs. The change in protein binding is likely to be sudden only when displacement by other drugs has occurred. In the other cases, the changes are gradual and do not alter the effects of the drugs because the compensatory increase in the rate of clearance from the body prevents the build-up of a high concentration of bound drug in the plasma. However, these effects alter the relationship between the total plasma concentration of a drug and its unbound concentration.

Volume of distribution

The volume of distribution (V_d) is a measure of how widely a drug is distributed in the body tissues. It is commonly expressed as the ratio of the total dose administered by bolus injection to the peak plasma concentration (C_{max}) (V_d = Dose/C_{max}); for example, if a dose of gentamicin is 100 mg and the peak concentration is 5 mg/litre, V_d is 20 litres.

The concept of V_d is notional; it does not relate to any particular compartment of the body. However, it is useful in determining how extensively a drug is distributed. An average V_d for ciclosporin, for example, is 100 litres. This value is literally larger than the patient, but indicates that the drug is widely distributed to most body tissues. A knowledge of V_d is also relevant to dosing regimens — when V_d changes, the loading dose must be changed.

Drug metabolism

Most drugs are lipid-soluble and must be biotransformed to more water-soluble products before they can be excreted in bile and/or urine. Inactivation of a drug is the most common effect of metabolism. The principal site of drug metabolism is the liver, although other organs (e.g. gut, lung, kidney) can to some extent metabolize drugs. The metabolism of many substances occurs in two phases — oxidation (I) and conjugation (II) (Figure 2).

A few pro-drugs (e.g. ciclosporin, enalapril, levodopa, cyclophosphamide, sulindac, codeine, tamoxifen) have little or no biological activity and require metabolic activation. Many pro-drugs have some level of activity (e.g. oxycodone), although variation in metabolism can be an explanation for the range of clinical responses seen at a given dosage.

Oxidation (phase I) reactions

The enzymes responsible for oxidation and similar phase I reactions (mono-oxygenases, mixed function oxidases) are located in the hepatic endoplasmic reticulum and are collectively termed 'cytochrome P450'.[3] Phase I reactions can produce inert compounds, but many oxidated metabolites have biological activity, and occasionally a toxic moiety (e.g. from paracetamol overdose) or a carcinogenic moiety (e.g. from cigarette smoke) is formed. Products of phase I reactions can be excreted directly or further