INTRODUCTION
Pharmacokinetics explains what happens to a drug in the body, whereas pharmacodynamics describes the actions produced by the drug on the body. Therefore, the effects of a drug result from a combination of its pharmacokinetic and pharmacodynamic characteristics in that individual. Wherever possible, drug administration should be based on a measured patient response, which will incorporate both of these aspects of its pharmacology. However, such an approach may not always be possible. The response may be masked by other factors (e.g. neuromuscular blockers masking signs of anaesthetic depth) or difficult to quantify precisely (e.g. action of antibiotics or anti-emetics). Under these circumstances, previously established pharmacokinetic and pharmacodynamic data are used to guide administration. This article aims to explain and simplify the principles of pharmacokinetics so that their application to clinical practice can be better understood.

GENERAL PRINCIPLES
Membrane transfer
Drugs need to cross cell membranes in order to produce their effects (e.g. gastro-intestinal absorption, reaching intracellular sites of action). Such transfer occurs more readily with a:
- low degree of ionization
- low molecular weight
- high lipid solubility
- high concentration gradient.

The extent of ionization is influenced substantially by environmental pH, an effect that is used to prepare highly ionized, aqueous solutions of acidic drugs such as thiopental (solution pH 10.5) or basic ones such as lidocaine (solution pH 5.2), as shown in Figure 1. In the more neutral pH of the body, much of the drug reverts to the unionized form enabling membrane transfer to reach its site of action. If this change in pH does not occur, the drug cannot become unionized and will be ineffective (e.g. lidocaine in the acidic environment of infected tissue).

Summary
Recommended drug doses are derived from average values in population studies and provide no certainty of response in a specific individual. Elimination half-life at steady state is of limited value in describing the recovery profile of a drug administered for a short period only. Context sensitive half-time provides more useful information under these circumstances. If a drug is given as a constant rate infusion, steady-state concentration will only be achieved after four to five half-lives. Partial pressure largely determines the behaviour of an inhaled drug. For maintenance of anaesthesia, a predictable steady state is easier to achieve with an inhalational agent than an intravenous one.

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There are two ways in which an exponential function can be described (Figure 2). If a specified time period is set, the decline is defined by the fraction by which the concentration has been reduced during this interval. This is the elimination rate constant ($k$), expressed as time$^{-1}$.

Alternatively, a given fractional reduction in concentration is set, and the time taken to achieve this level is found. If a 50% reduction in concentration is used, the time taken is the half-life ($t_{1/2}$); this will be constant whatever starting drug concentration is used. Another time period that can be used to describe the curve is the time constant ($\tau$). This is the point at which the elimination of drug would have been completed if the process had continued at its initial rate; it corresponds with a reduction in concentration to 37% of the original value.

**Pharmacological compartments**

Drugs are not distributed uniformly throughout the body. The speed with which a drug reaches a particular tissue is largely dependent on its local blood flow, and for analytical convenience, similar tissue types are often grouped together into various ‘compartments’ depending on their blood supply.

The capacity of each compartment to act as a reservoir for the drug is determined by a combination of its size and affinity for the drug. It is important to note that pharmacokinetic compartments are mathematical models and do not correspond to actual tissues; they are a concepts enabling the prediction of the pharmacokinetic behaviour of drugs. When performing mathematical modelling, it is likely that a lipid-soluble drug that is widely distributed is likely to have several compartments; a highly ionized drug that remains in the extracellular space is likely to be best described by assuming a one-compartment model. An example of a three-compartment model is shown in Figure 3; these correspond to vessel-rich, intermediate, and vessel-poor tissues, with a central compartment (blood), through which drugs must pass during uptake or elimination.

Because movement between compartments is dependent on the concentration difference between them, the process is exponential and the rate of transfer to the slower tissues decreases as they accumulate more drug.

**Volume of distribution**

When a drug has been fully distributed throughout the body and the system is at equilibrium, the volume within which the drug is contained is called the volume of distribution at steady state (Vd$\_{ss}$). It is a theoretical value expressed as the volume of blood which would be necessary to contain the entire drug present in the body, at the equilibrium concentration (units: l.kg$^{-1}$).

For a lipid-soluble drug (e.g. fentanyl) a litre of fat will hold many times more drug than a litre of blood, and thus its Vd$\_{ss}$ (4l.kg$^{-1}$) will be much greater than the total body volume. In contrast, a highly ionized drug (e.g. glycopyrrolate) that does not readily cross lipid membranes has a Vd$\_{ss}$ of only 0.16l.kg$^{-1}$.

**Clearance**

Although a drug may be widely distributed throughout the body, it is usually removed only from the blood. Clearance (Cl) is a concept used to describe this, and it represents the volume of blood from which the drug is completely eliminated in unit time. For example, if the concentration in blood is reduced by 20% in an hour, the result is equivalent to removing the entire drug from 20% of the blood volume (1000ml), corresponding to a clearance of 1000ml.h$^{-1}$ or 16.7ml.min$^{-1}$; it is stated that clearance is also often adjusted for body weight.

A large elimination rate constant ($k$) produces a short elimination half-life ($t_{1/2}$); this will result from a high (Cl) or a small volume of distribution (Vd$\_{ss}$).

**PHARMACOKINETIC PATHWAY**

In general, the passage of a drug through the body can be separated into three distinct phases: uptake, distribution, and elimination.

**Uptake**

Different routes of administration produce variability in the rate of drug uptake and amount of drug delivered effectively to the body. IV administration of a drug results in the entire dose entering the plasma immediately, although it must pass initially through the pulmonary circulation and some drugs (e.g. fentanyl) have significant take-up by the lungs.

Gastrointestinal (GI) administration requires the drug to cross the intestinal wall. The rate of absorption depends on surface area, pH, and, in some drugs, active systems. In general, unionized drugs (e.g. ethanol) are well absorbed throughout the intestine; absorption of
weak acids (e.g. aspirin) is facilitated by a low pH and weak bases (e.g. morphine) by a high pH. For drugs that remain completely ionized throughout the gut (e.g. glycopyrrolate), passive GI absorption is negligible.

Even after GI absorption, a drug may not reach the systemic circulation. Metabolism can occur in the gut mucosa (e.g. dopamine) or in the liver during its first pass via the portal vein (e.g. propranolol). This problem can be circumvented by administration at a site that avoids the portal circulation such as sublingual or, to some extent, rectal. The degree to which an administered drug reaches the systemic bloodstream is termed its bioavailability (Figure 4).

Uptake after intramuscular or subcutaneous administration is largely dependent on local blood flow rather than ionization or lipid solubility. The transdermal route can be used for highly lipid-soluble drugs (e.g. GTN, fentanyl), where slow absorption eventually produces sustained blood concentrations.

A fundamentally different pattern of uptake is seen for an inhaled drug in that it crosses the alveolar membrane into the blood along its partial pressure gradient. This produces an exponential wash-in, until at equilibrium (i.e. the partial pressure in blood equals that in the inspired and expired gas) no further net uptake occurs.

A clinical effect requires sufficient uptake to exert an adequate partial pressure in the body tissues; it is achieved most rapidly by a:

- high fractional concentration of inhaled drug
- high minute ventilation
- low BGPC.

The faster speed of onset produced by a low BGPC reflects the smaller number of molecules needed in solution to exert a partial pressure. A low cardiac output can also accelerate induction somewhat, with reduced perfusion to areas outside the vessel-rich group resulting in less drug needed to be taken up from the alveoli.

Alveolar partial pressure, measurable from end-tidal exhaled gas, closely reflects that of arterial blood and, in turn, that of the brain, enabling continuous monitoring of an indirect measure of drug delivery to the target site.

**Figure 4. Oral bioavailability. Same dose administered IV and orally on separate occasions. Oral bioavailability = area under curve oral/area under curve IV**

Distribution

After IV administration of a drug, the peak blood concentration is determined by the dose, the rate of administration, and the cardiac output. With a high cardiac output, the effective volume of blood in which the drug is initially diluted is larger, leading to a lower peak concentration. However, the high cardiac output transports the drug quickly to the vessel-rich tissues (including brain), and for highly lipid-soluble drugs, rapid equilibration occurs, leading to a fast onset of action. It is the high blood supply more than the lipid solubility that explains this.

Conversely, a low cardiac output leads to a higher initial peak concentration, because the drug is mixed with a smaller volume of blood during injection, though it will take longer to reach its target site. This explains why a smaller dose of induction agent is required in an elderly or shocked patient but may have a slower onset of action, while a young patient may require a much larger dose, yet will start to feel the effects more quickly.

Other tissues may also have a high affinity for the drug, but can only take up the drug slowly as they receive a lower proportion of the cardiac output. As they do so, however, the blood concentration decreases, soon falling below the brain concentration, whereupon the drug leaves the brain to be redistributed to other tissues. This redistribution is referred to as the a phase and explains the rapid termination of effect of lipid-soluble drugs such as propofol or thiopental following a bolus dose. As the less well-perfused tissues accumulate more drug, the concentration difference between compartments falls and the rate of redistribution slows in a declining exponential fashion. This also acts to slow down the redistribution if further drug is given, and subsequent doses should therefore be amended accordingly.

For inhalational agents, the pharmacokinetic model for distribution is similar; however, because the rate of administration is slower, the various compartments fill simultaneously, although at different rates depending on their blood supplies. Because there is never a rapid loading dose to any one compartment, redistribution between compartments is minimal. As administration continues, the vessel-poor and intermediate compartments become progressively saturated, delaying subsequent recovery, particularly for agents with a high lipid solubility.1 Regardless of the period of administration, however, the partial pressure in any tissue will never exceed that administered.

Elimination

Although the initial effects of a drug may wear off because of redistribution, full recovery depends upon the removal of the drug from the body. Such elimination may result from excretion, metabolism, or a combination of both. Large molecular weight drugs are often excreted in the bile, but most drugs are renally excreted. In order for the kidneys to handle lipid-soluble drugs, they need to be metabolized into a polar, water-soluble form. Most of this metabolism occurs in the liver and can be divided into Phase 1 and Phase 2 reactions. Phase 1 reactions include oxidation, reduction, and hydrolysis; in Phase 2 reactions, the resulting metabolites are conjugated with sulphate, glucuronide, or other groups.

For most drugs, elimination occurs in an exponentially declining manner, the rate of elimination being proportional to the plasma
concentration, as the downstream end of the gradient remains at zero. This system (i.e. the amount of drug being removed is a constant fraction in unit time rather than a constant amount) is known as first-order kinetics.

For some drugs, elimination may depend on the action of an enzyme or transporters which can become saturated. Once the relevant blood concentration is reached, elimination becomes constant, limited to a maximum amount in unit time. This is referred to as zero-order kinetics and can result in dangerously high concentrations with continued, unmonitored drug administration. It may be encountered at high concentrations with aspirin, ethanol, phenytoin, or thiopental.

With inhalational agents (halothane excepted), minimal metabolism occurs and elimination is via the reverse process to uptake. Recovery is reliant on adequate ventilation, but its duration is usually more dependent on the extent of tissue saturation.

PRACTICAL APPLICATIONS

Establishing steady state

If a drug is given as a constant infusion, it will eventually reach a steady state (i.e. with the whole Vdss containing the drug at a stable concentration, and elimination occurring at the same rate as administration). It takes four to five elimination half-lives to achieve this.

The target concentration can be attained far more rapidly using an initial loading dose followed by further additional drug in a declining exponential fashion as redistribution to other tissues occurs. Computer-driven target-controlled infusion (TCI) systems deliver this pattern automatically, adjusted for patient age, weight, and target concentration. Alternatively, this can be approximated closely using a stepped manual infusion scheme.

Context-sensitive half-time

Elimination half-life relates to the decline in plasma drug concentration from steady state following distribution throughout the whole Vdss. It provides a useful guide to dosage intervals for longterm drug maintenance. However, in anaesthetic practice, few drugs are administered long enough to reach the steady state. The context-sensitive half-time (CST) then becomes a more useful descriptor, detailing the plasma half-life after an infusion of a specified duration (Figure 5).

For drugs such as fentanyl, in which redistribution is the main mechanism responsible for the decline in plasma concentration after a brief infusion or bolus, the CST will initially be short. As the duration of infusion continues, redistribution becomes progressively less important and the CST increases, until ultimately it equals the elimination half-life. For a drug with a small volume of distribution, such as remifentanil, redistribution is very limited and the CST changes little even with prolonged infusion.

Predictability

Established pharmacokinetic and pharmacodynamic data are derived from averaged population studies. When based on these, even the most sophisticated dosage schemes for IV drugs will produce substantial variation in response between individuals, in both the blood/brain concentration (pharmacokinetics) and the subsequent effects (pharmacodynamics).

In contrast, for inhalational anaesthetic agents, although pharmacodynamic variability will still occur, pharmacokinetic behaviour will be far more predictable, because of the physics of gas/vapour solution in a liquid. Indeed, at equilibrium the partial pressure of an inhalational agent in blood (and other tissues) will precisely equal that in the inhaled gas mixture. Furthermore, the end-tidal partial pressure of an inhalational agent can be measured in real-time, providing a value very close to that in arterial blood.

REFERENCES

1. Eger E. II, Saidman LJ. Illustrations of inhaled anesthetic uptake, including intertissue diffusion to and from fat. Anesth Analg 2005; 100: 1020–33

Figure 5. Context-sensitive half-times of fentanyl, alfentanil, and remifentanil