Pharmacokinetic variation

Iain Glen

The consequence of pharmacokinetic variation is that the administration of a given dose of a drug results in a range of different drug concentrations in a population of patients. If the concentration is low, lack of efficacy may result and if the concentration is high, side-effects may be increased. An understanding of possible sources of variation in the pharmacokinetic behaviour of a drug can help to ensure that in an individual patient the most appropriate dose to achieve a desired clinical end-point is selected. Variation in the response to a given concentration of drug at the effector site is also important in predicting the overall response to the administration of a particular dose.

Measuring pharmacokinetic variability

Information on pharmacokinetic variability is usually obtained after administration of a drug by serial measurement of its concentrations in blood. In this way, the mean time–concentration profiles, and inter-individual variability at particular time points, can be examined. More sophisticated studies may use the principles of population pharmacokinetic analysis whereby a small number of blood samples are collected from a large and diverse population of patients. Analysis of the data obtained quantifies inter- and intra-patient variability and attempts to link variation to patient characteristics, organ function or co-administered drugs.

Predictions of the likely effect of pathophysiological changes on pharmacokinetic variability may also be obtained from studies in experimental animals, where the contribution of individual organs to total body clearance can be investigated by looking at arteriovenous concentration differences across a particular organ such as the liver or kidney. *In vitro* systems, incorporating recombinant human drug-metabolizing enzymes have been used to investigate drug metabolism and to predict the likelihood of possible pharmacokinetic interactions with other drugs.

Physiological models

Physiological models have been used to predict how blood and tissue concentrations of a drug change with time. These models require detailed information on the mass of different tissues, their blood flow as a proportion of cardiac output and partition coefficients. Once established, they can be used to predict the influence

---

Iain Glen *qualified in veterinary medicine at Glasgow University and became a lecturer in veterinary anaesthesia. Until recently he was a clinical specialist in anaesthesia at AstraZeneca and was closely involved in the development of Diprivan and the Diprifusor target-controlled infusion system.*

of changes in physiological parameters and have particular benefits when modelling drugs the pharmacological effects of which include changes, for example in cardiac output, which could influence their own disposition. One of the earliest models was developed by Price and his colleagues in 1960 and used to demonstrate the importance of redistribution to the termination of the effect of a bolus dose of thiopental. This model also explained the reduced dose requirements of patients in haemorrhagic shock because the fraction of the dose received by the brain was then high and its rate of removal slow, owing to the decreased blood flow to other tissues. Recently, another model for thiopental disposition in man has predicted greater peak arterial concentrations in patients with low versus high cardiac output and in those who are lean versus the obese. Changes with gender and age were relatively minor. This model indicates that differences in basal cardiac output may explain much of the variability between patients in early thiopental disposition. As increasingly sophisticated models are developed they may be incorporated in desktop computer simulation programs or in whole-body anaesthesia simulators for teaching and training.

Sources of pharmacokinetic variability

The four main processes that determine the pharmacokinetic behaviour of a drug are absorption from the site of administration, distribution within the body, metabolism and excretion. In many patients, age, weight, physiological changes caused by pregnancy or disease processes, drug interactions, and the effects of anaesthesia and surgery may also affect pharmacokinetics. Assay sensitivity or the duration of sampling may also account for variable results.

Absorption

Gastrointestinal absorption may be slowed by atropine or opioids, which inhibit gastrointestinal motility, or accelerated by metoclopramide, which hastens gastric emptying. Peak blood concentrations of some orally administered drugs are normally limited by first-pass metabolism in the liver. In elderly patients, a reduction in hepatic blood flow may reduce this first-pass effect leading, for example, to increased blood concentrations of propranolol. First-pass metabolism of drugs metabolized by cytochrome P450 (e.g. midazolam, diazepam) may be reduced by inhibitors of this enzyme (e.g. itraconazole, grapefruit juice) leading to increased bioavailability of the hypnotic agents. The addition of a vasoconstrictor to local anaesthetic drugs injected into tissues or the epidural space reduces their systemic uptake, leading to prolongation of the local block and a reduction in the peak concentrations obtained in blood. Central neuraxial blockade produces circulatory changes (vasodilatation in regions denervated by the block and compensatory vasoconstriction in other areas) such that differences may occur in venous drug concentrations depending on the sampling site, with values closer to arterial concentrations in vasodilated regions.

Distribution

The initial volume of distribution (V_1) is not simply the circulating blood volume but includes tissues that equilibrate rapidly with the blood concentration. The peak concentration reached after a bolus or short infusion of thiopental or propofol, is influenced by body weight, changes in blood volume and the mass of rapidly equilibrating tissues, and cardiac output. The greater the cardiac output, the greater the dilution of blood entering the pulmonary artery during the administration of a bolus or short infusion. Thus, peak blood concentrations in the systemic situation may be decreased, and dose requirements increased, when cardiac output is increased, for example with anxiety or hyperthyroidism, in young children compared with adults, and in the later stages of pregnancy. Conversely, a decrease in cardiac output leads to less initial dilution, higher peak concentrations and slower redistribution to peripheral tissues.

The overall volume of distribution at steady state (V_{ss}) depends on the mass of tissue available, the physicochemical nature of the drug (lipid-soluble drugs have a greater V_{ss} than water-soluble agents) and protein binding. Only unbound drug can diffuse across cell membranes, but the total amount of drug in some tissues may be greater than in others because of binding to tissue components. A reduction in plasma albumin is commonly associated with hepatic or renal failure. This leads to decreased plasma binding, an increased free drug concentration and more rapid distribution of drug from plasma, thus increasing V_{ss}.

Muscle mass is greater and adipose tissue mass smaller in men compared with women. Thus, when compared on a ml/kg basis, water-soluble drugs have larger distribution volumes in men and highly lipid-soluble drugs (e.g. diazepam, propranolol) have larger distribution volumes in women. A decline in lean tissue mass with age occurs in men and women.

Metabolism

Drug metabolism occurs primarily in the liver. Drugs such as propranolol or propofol that show total body clearance values close to hepatic blood flow (i.e. about 1.5 litre/min) are known as high-extraction drugs (Figure 1). For these drugs, clearance depends on liver blood flow and is minimally affected by changes in plasma protein binding because virtually all drug passing through the liver is extracted, whether bound or not. With low-extraction drugs (e.g. phenytoin, warfarin) hepatic clearance is limited by drug-metabolizing enzyme activity and the extent of protein bind-

Factors influencing hepatic clearance

Highly extracted drugs

Clearance = Hepatic blood flow (e.g. propranolol)

- Clearance affected by changes in hepatic blood flow
- Enzyme induction/inhibition or changes in protein binding have minimal effect

Poorly extracted drugs

Clearance < < Hepatic blood flow (e.g. warfarin)

- Clearance affected by changes in hepatic metabolic activity, enzyme induction or inhibition
- Changes in protein binding may affect clearance

1