CLINICAL PHARMACOLOGY

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Summary

Clinical pharmacology is a broad discipline concerned with describing the interaction between drugs and the body. The disposition of a drug in the body can be described by clinical pharmacokinetic parameters, specifically clearance, volume of distribution and half-life, and by the concepts of absorption, distribution, metabolism and elimination (ADME). The actions of the drug on the body are described by the term pharmacodynamics and are understood in terms of concentration-effect (dose-response) relationships. These pharmacokinetic and pharmacodynamic parameters, and the principles by which they are determined, are generalizable across populations, but between individuals there is substantial variability. This variability may lead to lack of efficacy of a drug in the clinical setting or in excess toxicity. Variability may be due to

factors such as the disposition of the individual, for example, age, weight, or organ dysfunction. Genetics polymorphism within drug metabolizing enzymes or receptor systems is a major contributor to pharmacokinetic and pharmacodynamic variability respectively. In clinical practice, the utility of clinical pharmacology is to explain this variability and allow clinicians to tailor their prescribing to suit the individual patient. As an applied science clinical pharmacology encompasses a broad range of fields, including toxicology, drug development, therapeutics and quality use of medicines, and pharmacoeconomics.

1. Introduction

Clinical pharmacology is the discipline that translates the basic sciences of pharmacology, pharmacokinetics and pharmacodynamics, into clinical practice, or therapeutics. Put in lay terms, clinical pharmacology is the study of how humans (or other animals) interact with drugs. Clinical pharmacokinetics refers to the study of the disposition of drugs entering, within and out of the body, colloquially "what the body does to the drug". Pharmacodynamics refers to the action and effects of the drug on the body. For the purpose of this discussion the term drug is not limited to medicines which are prescribed with therapeutic intent, but also to toxic agents or poisons, as the principles that apply to therapeutic agents are equally applicable to toxicology. Historically, the term drug referred to medicines or pharmaceuticals in which the active ingredient was a small molecule chemical entity. More recently, biopharmaceuticals, biologically derived molecules with relatively large molecular weights, have also been studied in the discipline of clinical pharmacology. The practice of therapeutics allows for anticipation of the behavior of a drug based on probabilistic terms, however it recognizes that individual characteristics of the drug recipient will influence both the disposition and action of the drug in that individual. In its broadest definition, clinical pharmacology also encompasses the science and practice of drug development, toxicology and more clinically oriented fields of applied pharmacology, pharmacovigilance and pharmacoeconomics, as they relate to the rational use of drugs as therapeutic agents within an evidence based framework.

This chapter will consider pharmacokinetics, pharmacodynamics and factors contributing to the variability of these properties, and discuss the relevance of these topics to therapeutics and applied pharmacology. A brief overview of drug development, toxicology, pharmacovigilance, pharmacoeconomics and quality use of medicines within an evidence based framework will be undertaken. An important consideration in the study of clinical pharmacology is to remember that the principles that describe drug behavior when administered to an individual are generalizations, and that in clinical practice, substantial intra- and inter-individual variability has important clinical implications for the drug recipient in terms of the therapeutic objective and the balance between benefit and the risk of toxicity.

2. Clinical Pharmacokinetics

Pharmacokinetics is the study of the disposition of drugs into, within and out of the body. Conceptually, pharmacokinetics may be described as the sum of absorption, distribution, metabolism and excretion of a drug. This categorization is also known as

ADME. Absorption refers to the processes whereby a drug enters the body. Distribution refers to pattern of drug dissemination around the body. Metabolism describes how a drug is altered by the body to produce active and inactive metabolites and excretion describes the elimination of a drug from the body. Each component of ADME can be considered in mechanistic terms and also by the rate and extent or amount to which they occur. It should also be recognized that whilst ADME is discussed and sometimes studied in terms of being distinct partitioned processes, in reality they constitute a dynamic continuum whereby each process is interacting with or influencing the other processes to build the overall pharmacokinetic profile of a drug.

In principle, an understanding of clinical pharmacokinetics allows prediction of the plasma concentration of a drug (C_{p}) over time following administration of a given dose of a drug. These predictions are based on understanding the pharmacokinetic parameters clearance (CL), volume of distribution (V) and the derived parameter half-life ($t_{1/2}$). Likewise, understanding these parameters allows determination of the appropriate dose of a drug. From a clinical perspective being able to make predictions of drug concentration over time should allow better prediction of the effects of a drug on the body over time and so allow safer prescribing. However, in some cases this has proved difficult in the face of the inter-individual variability in response to a given drug concentration, as is discussed later.

Clearance, volume of distribution and half-life parameters are the components of a model used to describe how a drug behaves in the body. Prior to considering these parameters individually, the following assumptions concerning the model should be considered. In most scenarios, pharmacokinetics is considered in the context of a one-compartment model. In the one-compartment model the body is considered to be a single vessel or container. When a drug enters this single compartment it is assumed that the distribution of the drug within the container is uniform and effectively instantaneous relative to absorption and elimination. It is also assumed that a steady-state equilibrium can be reached at the point where input into the system (or dosing) is equivalent to the output (or elimination).

Drugs are assumed to follow first-order or exponential elimination. In first-order elimination the rate of decline in plasma concentration varies with the plasma concentration such that the higher the concentration, the greater the rate of elimination. This is described by Eq. (1):

$$C_{\mathrm{p}_t} = C_{\mathrm{p}_0} \exp[-kt] \tag{1}$$

where C_{p_t} is the concentration at time (t), C_{p_0} is the concentration at time zero (0) and k is the elimination rate constant. Typically, this is transformed to a linear equation by taking the natural logarithm of each side of the formula to produce Eq. (2):

$$\ln C_{\mathrm{p}_t} = \ln C_{\mathrm{p}_0} - kt \tag{2}$$

First-order elimination is to be distinguished from zero-order elimination, whereby a

drug is eliminated at a constant rate over time such that the decline in plasma concentration is linear. An example of a drug that follows zero-order elimination is ethanol (alcohol). The zero order kinetics of alcohol has facilitated the ability of forensic toxicology to make predictions about an individual's blood alcohol level after alcohol ingestion.

2.1. Clearance

Clearance is a measure of the rate of elimination of a drug from the body. A drug may be eliminated from the body by virtue of conversion to metabolites (metabolism), usually in the liver, or by excretion as unchanged parent drug into urine, faeces, expired air, or other excreted body fluids such as sweat and saliva.

Clearance is defined as the volume of blood (or plasma when specifically referring to plasma concentration) cleared of drug per unit time. Clearance is expressed in terms of liters per hour (L/h) or comparable notation. By convention, clearance refers to clearance by the whole body, but one may also refer to clearance by individual organs such as liver (hepatic clearance) or kidney (renal clearance).

As previously indicated, the term clearance applies in the setting of first-order elimination. Clearance may be expressed as the constant relating to the rate of elimination to the plasma concentration:

$$\textit{elimination rate}\ (\text{mg/h}) = \textit{clearance}\ (\text{L/h}) \times \textit{plasma drug concentration}\ (\text{mg/L}) \qquad (3)$$

or

$$C(\text{L/h}) = \frac{\textit{elimination rate}\ (\text{mg/h})}{C_{\text{p}}(\text{mg/L})} \qquad (4)$$

To maintain a drug effect, it is assumed for most drugs that a target plasma concentration must be maintained. Clearance is important for determining the dose rate (DR) required to maintain a target plasma concentration for a particular drug. When the rate of drug administration equals the rate of elimination and the plasma concentration remains constant, then steady state has been reached. This may be expressed as:

$$\textit{maintenance dose rate}\ (\text{mg/h}) = \text{C (L/h)} \times \textit{steady state concentration}\ C_{\text{ss}}\ (\text{mg/L}) \qquad (5)$$

or

$$C = \frac{DR}{C_{\text{ss}}} \qquad (6)$$

An alternate perspective on clearance is that it is a determinant of the amount of drug that the body is exposed to following dosing of a drug. The amount of exposure to a drug may be determined by measuring plasma drug concentrations at frequent time intervals after dosing, and plotting those concentrations against time to form a

concentration/time curve. The area under the concentration time curve may be calculated using the trapezoidal rule. The area under the curve, or **AUC**, measures the exposure of the body to a drug over time.
This may be expressed by Eq. (7):

$$C(\text{L/h}) = \frac{dose(\text{mg})}{AUC(\text{mg h/L})} \tag{7}$$

2.2. Volume of Distribution

After clearance, volume of distribution (V) is the second fundamental parameter of drug disposition in the body. The term volume of distribution describes the amount of drug in the body relative to the concentration of drug in the plasma or blood, depending on the volume of plasma or blood. Volume of distribution may be defined as an apparent volume; that is, the volume of distribution is not necessarily a physiological volume or compartment but rather the apparent volume of fluid required to contain the drug at a given concentration. As such, the apparent volume of distribution may be larger than the plasma volume. For example, the average volume of distribution of amiodarone is 66 L/kg; that is, over 4000 L in an average sized individual. Volume of distribution may be calculated as:

$$\frac{Amount\ of\ drug\ in\ the\ body}{V} = C_{\text{p}} \tag{8}$$

Or

$$V = \frac{Amount\ of\ Drug\ in\ the\ Body}{C_{\text{p}}} \tag{9}$$

Volume of distribution is normally expressed in terms of volume (L), but this may be normalized to liters per kilogram (L/kg).

Not only may the volume of distribution of a drug exceed the plasma volume, but it may also exceed the volume of the drug recipient, as in the example of amiodarone listed above. The reason for the large volume of distributions is that many drugs may display preferential affinity for other compartments, including fat, muscle, particular receptors and plasma proteins. In addition, as the size of these compartments varies, the volume of distribution may vary between individuals of differing weight, age, gender and overall body composition.

2.3. Half-life

The final core parameter of pharmacokinetics is half-life ($t_{1/2}$). Half-life is the time for plasma concentration to fall by 50 percent and is generally assumed to be a fixed interval in the one-compartment model. Half-life is dependent on clearance and volume of distribution and may be defined by the formula:

$$t_{1/2} \cong 0.693 \times \frac{V_{ss}}{CL} \quad (10)$$

Generally, as clearance decreases, half-life increases, assuming a constant volume of distribution. Similarly, the larger the volume of distribution, the longer the predicted half-life.

Half-life is generally a good indicator of the time to achieve steady state with repeated dosing; that is, when a drug is dosed at intervals similar to the half-life of the drug, then steady state is generally reached in four to five half-lives. Likewise, a drug is generally considered to be eliminated from the body after four to five half-lives. From a clinical perspective this generalization holds true, however, as analytical techniques have improved in sensitivity, it has been demonstrated that for some drugs the elimination half-life is greater than previously identified. Furthermore, in practice, many drugs have a multi-exponential decrease in plasma concentration, with different elimination half-life values being calculated for different phases of elimination.

2.4. Dose Determination

Knowledge of clearance, volume of distribution and half-life facilitate the determination of an appropriate dose regimen for a drug. By regimen, we refer to both the amount of drug administered (the dose) and the frequency it should be administered if the aim is to achieve steady state.

A drug may be administered continuously, for example by intravenous infusion, or intermittently, for example by intermittent intravenous boluses or oral dosing. For an intravenous infusion, the concentration at steady state (C_{SS}) is dependent on the clearance of the drug and the rate at which the drug is dosed.

$$C_{SS} = \frac{Maintenance\ dose\ rate}{clearance} \quad (11)$$

In the setting of an intravenous infusion, C_{SS} is generally constant. In some situations this is desirable, whereas in other situations it is acceptable to intermittently dose an intravenous drug. In this situation, if the drug is given at the same overall dose rate at intervals which are the same as the half-life of the drug, the same average C_{SS} will be achieved, but the peaks and troughs around the dosing time point will vary by two-fold in terms of concentration.

In some clinical situations, it is not appropriate to wait four to five half-lives for an intravenous infusion to reach steady state. In this situation, a loading dose may be given to rapidly achieve the target concentration of drug. The magnitude of the loading dose is determined by the formula:

$$Loading\ Dose = Target\ Concentration \times Volume\ of\ Distribution \quad (12)$$

It is assumed that for intravenous infusions, 100% of the drug reaches the systemic

circulation. For oral dosing this is not the case, and generally only a fraction of the dose is available to the systemic circulation. This fraction is described by the term bioavailability. Bioavailability is described in greater detail in the section titled *ADME: Drug Absorption and Bioavailability*. In the case of oral dosing, maintenance dose rate is still determined by clearance and target concentration, but it is also dependant on the bioavailability of the drug. As such:

$$Maintenance\ dose\ rate\ (oral) = (Clearance \times C_{SS})/F \quad (13)$$

where F is the term that describes the bioavailability of the orally administered drug.

2.5. ADME: Drug Absorption and Bioavailability

Bioavailability, also known as oral availability, is a term that describes the amount of drug that reaches the systemic circulation. By this, it is meant that for any orally dosed drug, a certain amount of the original dose is lost through incomplete absorption and hepatic first-pass metabolism. Absorption refers broadly to the movement of a drug from the site of dosing or administration to the central compartment. Most of the discussion below relates to oral administration of drugs, as this is the most common route of administration in clinical practice, however drugs may be administered parenterally through intravenous, subcutaneous and intramuscular injections. Drugs may also be administered across mucosa through sublingual, rectal and pulmonary routes, and through transdermal administration. Peritoneal delivery and also topical application to mucosa is also used in situations where systemic absorption should be minimal, as it is either unnecessary or undesirable. In the case of oral administration, absorption means passage from the gut lumen, through the gut wall, into the portal circulation. Absorption occurs through both passive diffusion and active transport. Nonionized and lipophilic drugs are best suited to passive diffusion when in the gut lumen. Numerous other factors may alter oral absorption, including gastric emptying rate and intestinal motility, the dissolution characteristics of the dosage form, binding interactions with other drugs and/or food, local chemical or bacterial degradation and metabolism in the bowel wall. The amount absorbed is referred to as the fraction absorbed (f_g).

Once an orally dosed drug has entered the portal circulation it must pass through the liver into the systemic circulation. Some of the drug may be metabolized or extracted, hence the term first-pass clearance or first-pass metabolism. The fraction avoiding first-pass clearance is termed f_H. Hepatic extraction ratio (E_H) refers to the amount of drug removed by one pass of blood through the liver and may range from 0 to 1.0.

$$F_H = 1 - E_H \quad (14)$$

By definition, for drugs with a low f_H, hepatic extraction ratio approaches 1.0. Hepatic clearance is dependant on both hepatic extraction ratio and hepatic blood. If the hepatic extraction ratio approaches 1, then the hepatic clearance will be dependent on hepatic blood flow. Conversely, if the hepatic extraction ratio is low, then increasing blood flow will have little impact on hepatic clearance. Taken together then, bioavailability is the fraction of intact drug reaching the systemic circulation, described by the term F. Bioavailability depends on the fraction absorbed and in turn the amount avoiding first

pass metabolism, or:

$$F = f_g \times f_H \tag{15}$$

In practice, the absolute oral bioavailability is determined by administering a drug intravenously and orally on separate occasions to determine the drug AUC through pharmacokinetic measurements. The ratio of AUC_{oral} to $AUC_{intravenous}$ (AUC_{iv}) defines the bioavailability of the drug by the oral route with the assumption that the availability of drug administered intravenously to the systemic circulation is 100%.

$$F = \frac{AUC_{oral}}{AUC_{iv}} \tag{16}$$

It is often important to know whether or not two formulations of a medication provide similar exposure of the drug to the systemic circulation. It is assumed that if two different formulations provide similar exposure to a drug, then the physical effects of administering the different formulations will also be similar. This scenario usually arises when a drug company develops a generic formulation of an existing medication, a so-called generic drug. The aim is to determine the relative bioavailability of the new formulation compared to the original formulation by determining the ratio of their oral AUC.

$$F = \frac{AUC_{formulation2}}{AUC_{formulation1}} \tag{17}$$

Although there are some variations between pharmaceutical regulatory jurisdictions, it is generally accepted that two different formulations of a drug are bioequivalent if they are pharmaceutically equivalent; that is, they contain the same dose of 'active' drug in the same dosage form for the same dosage route and they have similar bioavailability. Similar (or the same) bioavailability is commonly defined as the 90% confidence intervals of the AUC of the different formulations lying between 0.8 and 1.25. It is common practice to also compare the C_{max} (peak or maximal concentration) and the t_{max} (time to maximal concentration) of the two formulations. Drugs with a narrow therapeutic index may need to meet tighter definitions of bioequivalence, as small changes in exposure may result in substantial changes to the chances of efficacy or toxicity with the drug.

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Biographical Sketch

Dr Winston Liauw, MBBS MMedSci FRACP has trained as a medical oncologist and clinical pharmacologist and completed a MMedSci in Pharmaceutical Development (University of NSW). His clinical practice is based around gastrointestinal cancer with a specialty in regional and intraperitoneal chemotherapy. His research interests are based around pharmaceutical development and he is currently a principal or co-investigator on numerous industry and investigator initiated clinical trials, including phase 1 research and consults for the biotechnology industry and contract research organizations. He has been heavily involved in research ethics and regulation and is Deputy Chair of the Shared Scientific Assessment Scheme Core Committee and the Cancer Institute NSW Human Research Ethics Committee (Clinical Trials). He has recently been appointed Chair of the St George Hospital Human Research Ethics Committee. He has published the results of clinical trials, cancer outcomes research, on adverse event reporting in clinical trials and the review of clinical trial protocols. Dr Liauw's other interests include medical education and health informatics.