PRINCIPLES OF PAEDIATRIC PHARMACOLOGY

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For my daughters Ailsa, Rowena and Moira

PREFACE

Pharmacology is fundamental for therapeutics. This is well recognised in the field of internal medicine, for which pharmacological textbooks abound. Paediatric pharmacology however, has largely been viewed as a subsection of general medicine. This is incorrect: it should be seen as a separate and important entity.

This book is written from the viewpoint of a paediatrician, but it is addressed to all who have responsibility for the care of children, particularly physicians and pharmacists. As the latter may lack familiarity with certain diseases of children, I have added a clinical appendix in certain pertinent areas. My approach in each chapter has been to show the interdependence of physiology and pharmacology. Thus I make no apology for providing a physiological review for most topics. Each chapter is reasonably self-contained. I have presumed that a majority of readers will most often go directly to that section relevant to their immediate requirements, and therefore I have sometimes had to restate important points in more than one place. Nevertheless, for the cover-to-cover reader, there will not be an excess of repetition. Since this is not a textbook of adult therapeutics, there will be no discussion of such things as coronary vasodilators. Likewise, the obstetric pharmacology of parturition has been omitted, although I have thoroughly covered the pharmacological problems of the fetus and the infant.

I am greatly obliged to generations of my students, both undergraduate and postgraduate. Teaching them about children stimulated me to write this book. The task was enormously eased by the help and encouragement of my wife, Mary. My secretary of many years, Mrs Gloria Turnbull, skilfully organised the manuscript through several drafts; she has my deep gratitude. I am greatly obliged to Mrs Colleen Lloyd who did the art work; and I thank Professor Felix Bochner who reviewed some of the manuscript, and Professors G.S. Dawes and James Tanner who allowed me to reproduce material for Figures 3.2 and 5.2.

CONTENTS

1 PRINCIPLES OF DRUG ACTION AND DISPOSITION

Chemical Identity of Drugs

A majority of drugs are chemicals with a variety of functional groupings such as acids, alcohols, amides, bases, esters, imides, inorganic salts, ketones, sulphones and neutral small molecules. Many active drugs are weak acids or bases, and therefore in solution can exist in the ionised or non-ionised form.

They may have their therapeutic effect on subcellular structures, cells proper, or tissue systems. In each, the fundamental phenomenon is the interaction between the drug molecules and the molecules of the biological entity: thus chemical bonding is an attribute of all pharmacological reactions.

Bonding Mechanisms

These are constantly occurring physicochemical interactions, often between small drug molecules and biological macromolecules such as exist on the outer cell-membrane.

The common types of bonding are co-valent and electrostatic. The former is irreversible, and occurs as part of a degradation or detoxification process, or between strongly alkylating agents and the cell to be affected. Electrostatic bonds are relatively weak, reversible, and commonplace in the processes of absorption, transfer and metabolism. Common forms of electrostatic bonds are ionic, dipole-dipole, hydrogen and induced dipole bonds, either single or of the Van der Waals type. Hydrophobic bonding may occur when water layers surrounding the hydrophobic groups of two separate molecules coalesce to surround the same groups. Bonding and bond-dissolution are the basis of most of the chemical reactions involved in the absorption and biotransformation of drugs.

In general the kinetics of these reactions are based upon the law of mass action. This states that the rate at which a chemical reaction proceeds is proportional to the active masses (or molar concentrations) of the reactants. The law may be further illustrated by assuming that

the reaction occurs because of collision between the interacting molecules. Thus the *rate* of reaction will be proportional to the number of collisions, and the number of collisions in turn is proportional to the molar concentrations of the reacting molecules.

Reaction Kinetics

Consider the model in which a substance is diffusing across a membrane from compartment A to compartment B. Let the concentration of the substance in compartment A equal A, then the concentration in compartment B is B. If the direction of transfer is

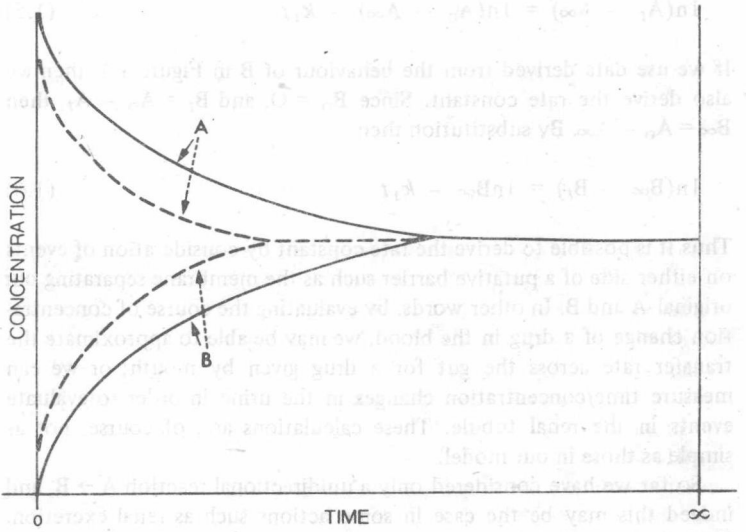
$$A \rightarrow B \tag{1.1}$$

and is one-way, then the rate of transfer follows from the way in which A decreases, and B increases with time. This may be further expressed as $-dA/dt$ or $+dB/dt$ and is illustrated in Figure 1.1 which shows two rates of transfer. One (——) is slower than the other (– – –). It is also clear that the rate-process value such as $-dA/dt$ is not constant, but continuously diminishing. It is indeed only capable of definition at any specific time t. This makes it numerically difficult to compare the two processes which are visually quite distinct in Figure 1.1. However, experiment will show that the processes shown in Figure 1.1 approximate in behaviour to the general expression

$$\frac{dx}{dt} = -kX^n \tag{1.2}$$

In this X is defined as the *transferable concentration* and the constant k is the proportionality constant of the reaction $A \rightarrow B$ (equation 1.1). Now, equation 1.2, $dX/dt = -kX^n$ states that the concentration of transferable material (X) at time t is the product of a proportionality constant k multiplied by the transferable concentration raised to the power n. If we again consider Figure 1.1 we can further examine the concept of X as the transferable concentration remaining at any time. At equilibrium or infinity – time$_\infty$, X will always be zero. From Figure 1.1, if the final concentration of A at infinity is A_∞ then the concentration to be transferred, X, at any time t, is the difference between the concentration at that time and the concentration at infinity, or $X = A_t - A_\infty$. Review of Figure 1.1 also shows that $A_0 - A_\infty = B_\infty$, and that the concentration of A + B at any time is the same as A at time zero; or $A_t + B_t = A_0$. This expression can be used to calculate the value of X

Figure 1.1: Concentration Time Course of Substances A and B in Two Compartments. The direction of diffusion is from A to B. In —— the rate-process is slower than in – – –. This would represent theoretically a difference in membrane characteristics



(the transferable concentration) from the findings in compartment B. Thus

$$X = (A_t - A_\infty) \text{ and also } = (B_\infty - B_t) \qquad (1.3)$$

Now from equation (1.2) i.e. $dX/dt = -kX^n$, we can calculate the rate constant k; this is a numerical constant which is not time dependent. It will also be different for each of the processes illustrated in Figure 1.1. The differences between the values of k can then be used to compare each of these rate phenomena.

First Order Processes

In general this implies that a reaction A → B is determined by one of the reactions, or in terms of equation (1.2), n = 1, so that $dX/dt = k \cdot X$ where k is the first-order rate constant. By separating the variables and integrating, the general working equation (1.4) is derived.

$$\ln X_t = \ln X_o - k_1 t \qquad (1.4)$$

Into such an equation can be introduced measured data, say in terms of Figure 1.1. Since we know how to derive X from equation (1.3), we can substitute in equation (1.4) to yield

$$\ln(A_t - A_\infty) = \ln(A_0 - A_\infty) - k_1 t \tag{1.5}$$

If we use data derived from the behaviour of B in Figure 1.1, then we also derive the rate constant. Since $B_0 = 0$, and $B_t = A_0 - A_t$, then $B_\infty = A_0 - A_\infty$. By substitution then

$$\ln(B_\infty - B_t) = \ln B_\infty - k_1 t \tag{1.6}$$

Thus it is possible to derive the rate constant by consideration of events on either side of a putative barrier such as the membrane separating our original A and B. In other words, by evaluating the course of concentration change of a drug in the blood, we may be able to approximate the transfer rate across the gut for a drug given by mouth; or we can measure time/concentration changes in the urine in order to evaluate events in the renal tubule. These calculations are, of course, not as simple as those in our model.

So far we have considered only a unidirectional reaction $A \rightarrow B$, and indeed this may be the case in some actions such as renal excretion. However, many reactions are reversible, such as the drug to receptor reaction, or the adsorption of drugs onto plasma proteins. Thus our example is really

$$A \rightleftharpoons B \tag{1.7}$$

which is a reversible reaction. The forward reaction $A \rightarrow B$ will have a first-order rate constant k_f and the reverse reaction $B \rightarrow A$, a rate constant k_r; or

$$A \underset{k_r}{\overset{k_f}{\rightleftharpoons}} B \tag{1.8}$$

The expression for rate becomes

$$\frac{-dA}{dt} = k_f A - k_r B \tag{1.9}$$

Now any single rate constant for the system is k_1 and this must be a

combination of the constants k_f and k_r. This can be developed as follows: if the system is at equilibrium the concentrations in each compartment are equal, i.e.

$$\frac{-dA}{d_t} = 0 = k_f A - k_f B \tag{1.10}$$

or

$$k_f A_\infty = k_f B_\infty \tag{1.11}$$

Now by Figure 1.1 $A_\infty = B_\infty$, so by rearrangement,

$$\frac{k_f}{k_r} = \frac{B_\infty}{A_\infty} = K \tag{1.12}$$

This constant K is the apparent equilibrium constant. As suggested by Figure 1.1 we can calculate the *rate* constant k_1: now $k_1 = k_f + k_r$ and both k_1 and K the equilibrium constant are measurable by experiment. Thus we can calculate the forward rate constant

$$k_f = \frac{k_1 K}{K} \tag{1.13}$$

and the reverse constant

$$k_r = \frac{k_1}{K + 1} \tag{1.14}$$

An apparently more complex form of the reversible reaction is that represented as

$$A + B \rightleftharpoons C + D \tag{1.15}$$

By the law of mass action, as A + B decreases, the rate of forward reaction also decreases. Simultaneously C + D are increasing, and the rate of reverse reaction to A + B also increases until equilibrium is reached. This is not really very different from equation (1.7) which was $A \rightleftharpoons B$, at least in terms of the kinetics. Thus from equation (1.15) if Co is the concentration of any component then the forward reaction rate varies with $[Co_A]$ $[Co_B]$ or, the forward rate = $k_{A+B}[Co_A][Co_B]$;

the reverse rate will be $k_{C+D}[Co_C][Co_D]$. At equilibrium these ratios are identical so that

$$k_{A+B}[Co_A][Co_B] = k_{C+D}[Co_C][Co_D]$$

and

$$\frac{k_{A+B}}{k_{C+D}} = \frac{[Co_C][Co_D]}{[Co_A][Co_B]} = (K_{eq})_{A+B}$$

where $(K_{eq})_{A+B}$ is the equilibrium constant. Some of these values can be measured and thus used. Conventionally the concentrations of starting reagents (A + B) are used as the denominator in determining the equilibrium constants.

Zero-Order Reactions

These are also of the form A → B, with the reaction proceeding at a constant rate, and independent of the concentration of A. If plotted on linear graph paper, a straight line results. This type of reaction is not common in pharmacology but results, for example, in an enzymatic reaction where the substrate is in excess. The decay of blood alcohol levels is an example. This will be linear because the reaction is limited by the absolute amount of dehydrogenase present although the reaction is proceeding at its maximal rate.

The general equation for the rate process is $dX/dt = kX^n$ (equation 1.2), where n is the order of the rate process. If n = 0, then $dX/dt = -k_o$ where k_o is the zero-order constant. If the variables are separated and integrated between the limits of $t = 0$ and t and X_o and X_t then

$$X_t = X_o - k_o t \tag{1.16}$$

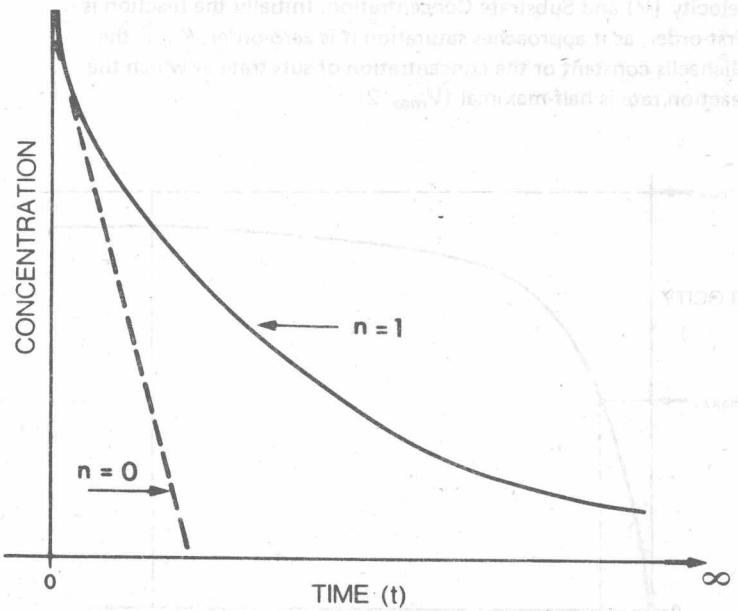
X is, as already defined, the transferable concentration. Concentration changes in a compartment which occur by zero and first order kinetics are illustrated in Figure 1.2.

Michaelis–Menten Kinetics

This is the approach to enzyme-catalysed reactions which may be capacity limited as in the metabolism of some drugs. The general conditions are:

$$\text{enzyme} + \text{substrate} \rightleftharpoons \text{complex} \rightarrow \text{products} + \text{enzyme} \tag{1.17}$$

Figure 1.2: Zero-order and First-order Kinetics



The plot is linear: the curve n = 1 is a first-order process, and the line n = 0 is a zero-order process

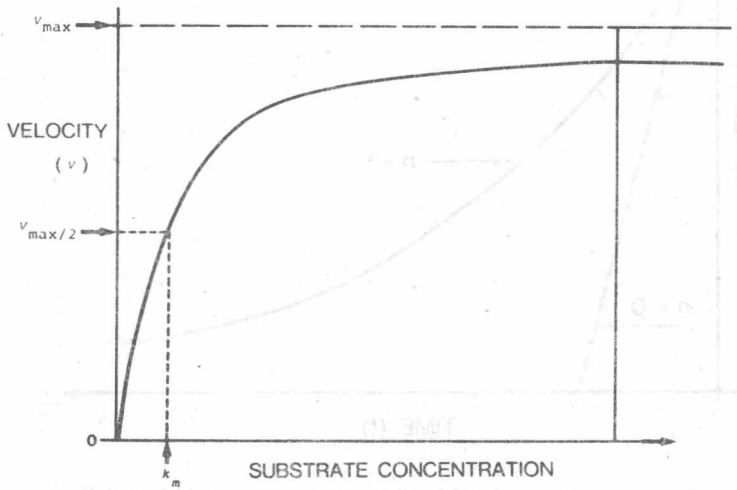
As the new complex forms, the concentration of the enzyme decreases, and is not restored until the complex disintegrates into products + enzyme. In other words, the initial rate of reaction is first-order i.e. substrate and enzyme are plentiful, and fruitful reactions readily occur. As the enzyme becomes saturated, the process occurs at a constant rate, or as a zero-order process. This is illustrated in Figure 1.3.

Processes which behave in accordance with Michaelis-Menten kinetics have a velocity (V) described in equation (1.18) i.e.

$$V = \frac{V_{max}(X)}{K_m + (X)} \qquad (1.18)$$

where V_{max} is the maximum reaction rate, X is the drug concentration which may change, and the Michaelis constant is K_m = the value of X at which $V = V_{max}/2$ (see Figure 1.3). If X is $< K_m$ the denominator

Figure 1.3: Michaelis–Menten Kinetics – the Relationship of Reaction-velocity (V) and Substrate Concentration. Initially the reaction is first-order, as it approaches saturation it is zero-order. K_m is the Michaelis constant or the concentration of substrate at which the reaction rate is half-maximal ($V_{max}/2$).



approaches K_m so that equation (1.18) becomes

$$V = \left(\frac{V_{max}}{K_m}\right) X \qquad (1.19)$$

and since V_{max}/K_m is constant this represents a first-order reaction similar to $-dX/dt = K(X)$, provided $X < 0.1K_m$. However, if $X \gg K_m$ then $V = V_{max}$, which is constant if $X > 10K_m$ i.e. the kinetics are zero-order.

Between values $X < 0.1K_m$ and $X > 10K_m$, the kinetics are intermediate.

In general, first-order kinetics apply in the reactions accompanying drug absorption from the gut, and figure largely in the kinetics of drug biotransformation and drug excretion. Only a few reactions are of the