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# Contents

# 2

# Pharmacokinetics

## CHAPTER SUMMARY



The therapeutic effects seen when a drug is taken by a patient, for example lowering of blood pressure, are determined by the pharmacological properties of the compound. These effects are usually produced by an interaction of the drug with a specific macromolecule, such as a receptor or enzyme (Chapter 1). This aspect is termed the *pharmacodynamics* of the drug and is the subject of subsequent chapters. In contrast, the time to onset of action and the duration and intensity of effect are usually determined by the rate at which the drug is transferred from the site of administration to the site of action and the rate at which it is eliminated from the body by metabolism or excretion. These aspects are called the *pharmacokinetics* of the drug which, as the name implies, is concerned with all processes involved in the movements of the drug within the body.

Pharmacokinetics may be divided into three basic processes:

(1) *Absorption* — The transfer of the drug from the site of administration to the general circulation.
(2) *Distribution* — the transfer of the drug from the general circulation into the different organs of the body.
(3) *Elimination* — the removal of the drug from the body which may involve either *excretion* or *metabolism*.

Each of these processes will be described in terms of their chemical, biochemical and physiological basis and in mathematical terms. For many students the mathematics remain abstract concepts that seem to relate poorly to the more readily understood biology of the processes. To help to relate the biology to the mathematics, those clinical variables which can affect drug handling, such as drug interactions, age and disease, are discussed at the end of the chapter in both biological and mathematical terms.

## THE BIOLOGICAL BASIS OF PHARMACOKINETICS

It will be readily apparent to the student familiar with the intermediary metabolism of carbohydrates, fats, proteins, etc. that most of the drug structures given in this book bear little resemblance to such endogenous molecules. Although drugs may bind to particular macromolecular sites, such as the receptor for a specific neurotransmitter, they are only rarely substrates for the carrier processes or metabolizing enzymes which handle the natural ligand. Thus the movement of drugs around the body is usually by simple passive diffusion, whilst metabolism is usually by "drug metabolizing enzymes" of low substrate specificity. However, students should be aware that there are exceptions to each of the generalizations in this chapter but that these generalizations provide an essential framework.

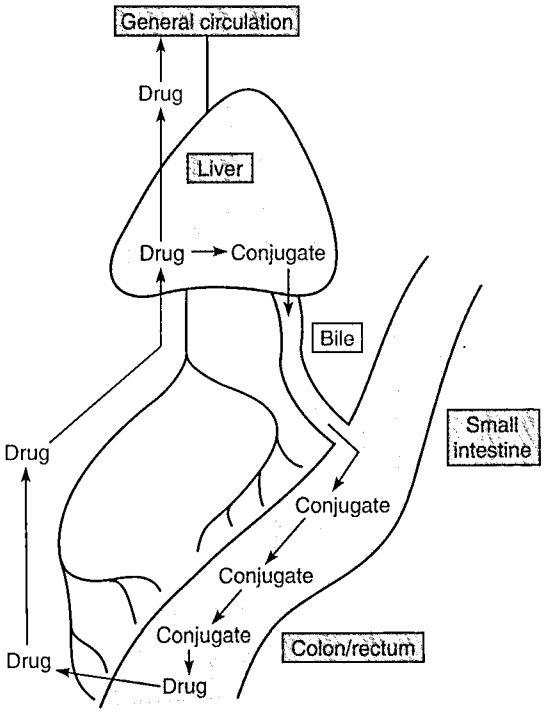


**Figure 2.10** The enterohepatic circulation of drugs.

the lower intestine may hydrolyse the conjugate back to the original substrate and glucuronic acid. The original substrate will have a greater lipid solubility and therefore be absorbed from the gut lumen and enter the hepatic portal vein (see Fig. 2.10).

## THE MATHEMATICAL BASIS OF PHARMACOKINETICS

The use of mathematics to describe the fate of a drug in the body can be complex and rather daunting for undergraduates. Nevertheless, a basic understanding is invaluable for an appreciation of many aspects of drug handling and for the rational prescribing of drugs. The following account describes the fate of a single dose of a drug and the mathematics of absorption, distribution and elimination, before brief considerations of chronic administration and factors which can affect pharmacokinetic processes.

## GENERAL CONSIDERATIONS

Two different but complimentary approaches are used:

(1) *Compartmental analysis* — in which the plasma concentration–time curve is described by an equation containing one or more exponential functions. This approach gives a precise description of concentration–time relationships and allows the prediction of the concentration of the drug in plasma at any time after dosing. This approach requires an appropriate model to be defined and fitted to the data. However, it provides little information on the physiological disposition of the compound.

(2) *Model independent analysis* — may be related more closely to the physiological processes governing the disposition of the chemical and therefore is more useful in predicting and assessing the influence of variables such as disease, age and the administration of other compounds. However, this approach cannot be used to predict the concentration at any time after dosing (unless the compound fits the simplest model possible).

The model independent methods are of greater potential value to medical undergraduates and are the basis of the following account.

Each of the three basic processes of absorption, distribution and elimination will be described in terms of *rate*, that is the speed at which a process occurs, and *extent*, that is the proportion of the dose which is handled by the process.

Before each process is considered in detail it is necessary to define the different types or orders of reaction which commonly occur. If we consider a simple decrease in concentration (e.g. during drug elimination) there are two important types of reaction possible:

(a) *Zero order reactions* — in which the change in concentration $\frac{dC}{dt}$ occurs at a fixed amount per time, that is:

$$\frac{dC}{dt} = -k$$

The units of $k$ (the reaction rate constant) will be an amount per unit time (e.g. $\mu g\ ml^{-1}\ min^{-1}$ or $\mu g\ min^{-1}$). A graph of concentration against time will produce a straight line with a slope of $-k$ (Fig. 2.11); examples are ethanol (see Chapter 58) and phenytoin (see Chapter 24).

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