- the optimal timing to obtain blood samples for therapeutic drug monitoring
- interpreting the likely onset and offset of a potential medicine interaction.

In Table D.9, p. 323, the stated half-life should be considered as a population average. Within the population there may be a twofold to fourfold variation (or more in some cases) in half-life, and in most cases it is not possible to predict what the half-life of a medicine will be in an individual.

Clearance

The clearance (Cl) of a medicine is a measure of how efficiently the body irreversibly eliminates the medicine from the systemic circulation. The higher the clearance the more efficiently the medicine is removed. The term refers to excretion of the unchanged drug from the body via the urine and gastrointestinal contents, expelled in exhaled air and in sweat, and metabolic conversion to a different chemical entity, most usually by the liver. The total body clearance is the sum of the individual organ clearances contributing to the clearance of the drug:

$$\text{Total clearance} = Cl_{(\text{metabolic})} + Cl_{(\text{renal})} + Cl_{(\text{other})}$$

Clearance can be defined as the volume of plasma from which the drug is completely removed per unit of time (e.g. mL per minute, or L per hour).

Clearance may also be normalised for body size; it is then expressed as mL/minute/kg.[2] Table D.9 includes clearance values that have been normalised in this way.

Along with volume of distribution, clearance is an important determinant of a medicine's half-life.

The clinical importance of clearance stems from the pharmacokinetic relationship described by the following equation.

$$\text{plasma concentration} = \frac{\text{rate of drug input into body}}{\text{clearance}}$$

Therefore, for a given dosage rate the plasma concentration of a medicine will double if the clearance of the medicine is halved.

For an individual, the clearance value will be influenced by genetic, physiological and pathological factors. In disease states such as renal or hepatic failure, clearance and volume of distribution can sometimes change in the same direction, exerting opposing effects on half-life (which remains unchanged), while clearance is decreased. Environmental factors (e.g. diet and other medicines) can also alter an individual's clearance value. Indeed, many clinically important interactions occur because one medicine alters the clearance of the other. In summary, clearance is an important parameter in determining the maintenance dose required to achieve a particular target average concentration such that:

$$\text{maintenance dose rate} = C_{ss} \times \frac{CL}{F}$$

where C_{ss} is the average steady state concentration associated with optimal drug effects and F is the bioavailability.

Fraction excreted unchanged

Elimination of unchanged drug via the kidneys is the net result of three processes—glomerular filtration, tubular secretion and tubular reabsorption.

The fraction of a dose excreted unchanged in urine (fe) indicates how a medicine is eliminated from the body. As the relative importance of the kidney as an elimination organ increases the fe value approaches 1, whereas when other (non-renal) mechanisms become dominant fe approaches zero. For a drug that is predominantly metabolised, a low fe value is to be expected. For a drug that is filtered and not resorbed or secreted, renal clearance is determined only by the plasma protein binding (see below) and the glomerular filtration rate.

A drug's fe value indicates whether a reduced dose is likely to be necessary to maintain a safe and effective plasma concentration in renal impairment. Dosage adjustment in patients with impaired renal function is discussed in greater detail in 'Dosing in renal impairment', Section D.

Fraction unbound in plasma

Drugs tend to bind reversibly to plasma proteins such as albumin; the fraction unbound in plasma fu represents the fraction of drug in plasma that exists in the unbound (free) form. Extensively bound medicines include the non-steroidal anti-inflammatory agents, while paracetamol and L-dopa are examples of poorly bound medicines.

For a highly bound drug (fu less than 0.2) the fu value can increase in disease states that are associated with a reduction in plasma proteins (e.g. liver or kidney disease). Similarly, co-administration of two medicines that compete for common plasma-binding sites can also lead to an increase in fu of one or both drugs. As discussed in 'Clinically important drug interactions', Section D, these changes in fu are rarely of clinical importance.