Mathematical equations which predict the maximum or minimum steady-state plasma concentrations of a drug achieved in the body following repeated administration of equal doses at a fixed interval of time are also available for drugs whose time course in the body is described by the one-compartment open pharmacokinetic model.

Concept of 'loading doses'

The time required for a given drug to reach 95% of the average steady-state plasma concentration is approximately 4.5 biological half-lives. Hence for a drug with a long half-life of 24 hours, it would take more than 4 days for the average drug concentration in the plasma to reach 95% of its steady-state value. For some drugs it is important to achieve plasma levels within the therapeutic range quickly for clinical efficacy, and it would be unacceptable to wait 4 days to achieve therapeutic levels. To reduce the time required for the onset of the full therapeutic effect of a drug, a large single dose of the drug may be administered initially in order to achieve a peak plasma concentration which lies within the therapeutic range of the drug and is approximately equal to the value of C^{ss}_{max} required. This initial dose is known as the *loading dose*. Thereafter, smaller, equal doses are administered at suitable fixed time intervals to maintain the plasma concentrations of drug at the required maximum, minimum and average steady-state levels which provide the patient with the full therapeutic benefit of the drug.

Figure 22.8 shows how rapidly therapeutic steady-state plasma concentrations of drug are achieved when the dosage regimen consists of an initial loading dose followed by maintenance doses compared to a 'simple' multiple dosage regimen of equal sized doses administered at the same dosage intervals.

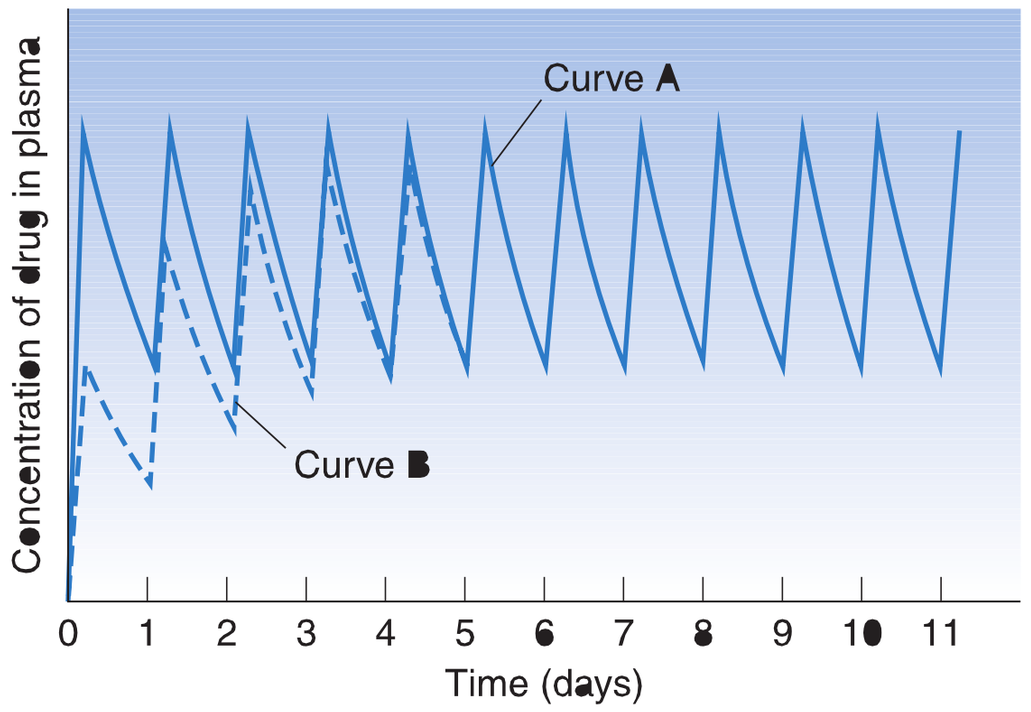

Fig. 22.8 • Diagrammatic representation of how the initial administration of a loading dose followed by equal maintenance doses at fixed time intervals ensures rapid attainment of steady-state plasma levels for a drug having a long biological half-life of 24 hours. Curve A represents the plasma concentration-time curve obtained following oral administration of a loading dose of 500 mg, followed by a maintenance dose of 250 mg every 24 hours. Curve B represents the plasma concentration-time curve obtained following oral administration of a 250 mg dose every 24 hours.

Population data and basic pharmacokinetic parameters

To apply the principles of pharmacokinetics in practice, population data may be employed. Population data are mean pharmacokinetic parameters, such as apparent volume of distribution, which can be used to calculate predicted drug concentrations following a given dosage, or to calculate the dosage regimen, including loading and maintenance doses, required to achieve a particular drug concentration. Population data, i.e. basic pharmacokinetic parameters, can be found in standard reference sources or original pharmacokinetic studies. It is important to identify the correct population data for the type of patient. Interested readers are referred to the texts listed in the Bibliography for further information and examples of the use of such parameters.

Influence of changes in the apparent elimination rate constant of a drug: patients with renal impairment

Whilst the loading dose, maintenance dose and dosage time interval may be varied in order to design a clinically efficacious multiple dosage regimen, one factor cannot normally be adjusted. That factor is the apparent elimination rate constant exhibited by the particular drug being administered. However, the elimination rate constant of a given drug does vary from patient to patient and is influenced by whether the patient has normal or impaired renal function.