

Table 22.3 Relationship between dose, half-life and the amount of drug present in the body at steady state

Dose (mg)	Amount in the body (mg)	Amount eliminated (mg)	Number of half-lives
100	100	50	1
100	150	75	2
100	175	87.5	3
100	187.5	93.75	4
100	197.5	98.75	5
100	198.75	99.37	6
100	199.37*	99.68	7

*To continue at this rate of dosage the amount of drug in the body will remain effectively constant.

first-order kinetics, the oral administration of equal doses at fixed intervals of time may not result in the attainment of steady-state plasma levels of the drug. With repeated dosing, the average concentration of drug in the body and plasma tends to continue to accumulate, rather than reaching a plateau.

Important factors influencing steady-state plasma concentrations of a drug

Dose size and frequency of administration

The regimen must consider the plasma concentration profile at steady state and in particular the fluctuations in the C_{\max}^{ss} and C_{\min}^{ss} . A word here about symbols used for drug concentrations. In the case of drug levels measured at steady state, the superscript ss is often added to the C (i.e. C^{ss}). In the specific case of concentrations of drug in blood plasma, an additional subscript p may be included in the symbol (e.g. C_{pt} , C_{pmax} , C_{pmin} , etc).

Only two factors can be adjusted for a given drug, namely the size of the dose and the dosage interval. These are discussed below:

Size of dose

Figure 22.6 shows the effects of changing dose size on the concentration of drug in the plasma following

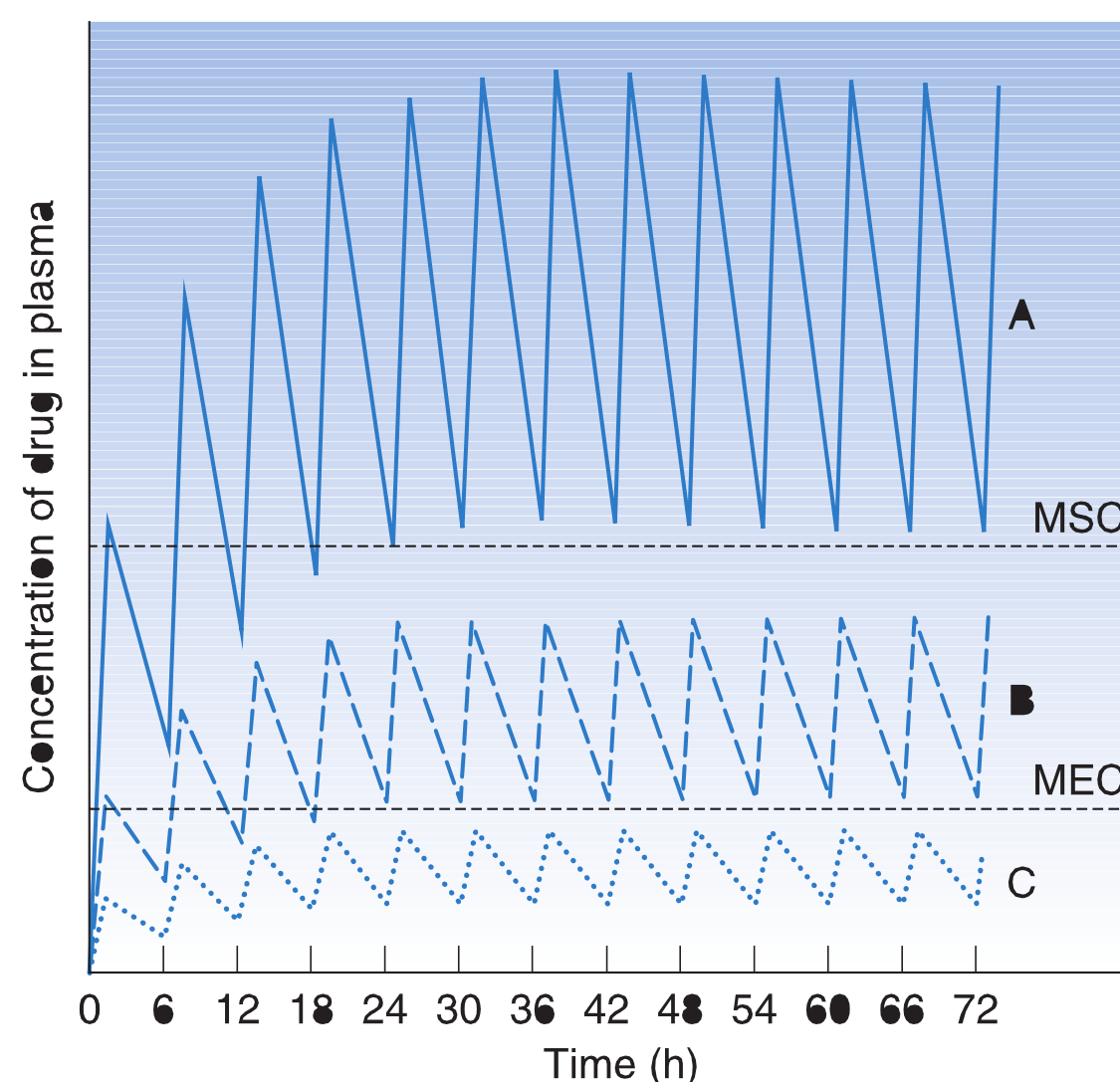


Fig. 22.6 • The effect of dose size on the plasma concentration-time curve obtained following oral administration of equal doses of a given drug at fixed intervals of time equal to the biological half-life of the drug. Curve A: each dose = 250 mg. Curve B: each dose = 100 mg. Curve C: each dose = 40 mg.

repetitive administration of oral doses at equal time intervals. As the size of the administered dose is increased, the higher are the corresponding maximum, minimum and average plasma drug levels, C_{\max}^{ss} , C_{\min}^{ss} and C_{average}^{ss} respectively, achieved at steady state. An important factor to consider is the impact of the dose on the fluctuations in the plasma levels, i.e. they should be within the therapeutic range. The larger the size of dose administered, the larger the fluctuation between C_{\max}^{ss} and C_{\min}^{ss} during each dosing time interval. Large fluctuations between C_{\max}^{ss} and C_{\min}^{ss} may lead to toxicity if the maximum safe concentration is exceeded, or therapeutic failure if the minimum effective concentration is not achieved. This will impact clinically for drugs such as digoxin which have a narrow therapeutic range. Figure 22.6 also illustrates that the time required to attain steady-state plasma concentrations of a drug is independent of the size of the administered dose.

Time interval between successive equal doses

Figure 22.7 illustrates the effects of a constant dose administered at various dosing intervals. It is important to consider the relationship between the dosage