

HALF-LIFE

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What is half-life?

Half-life is the time taken for the amount of drug in the body (or the plasma concentration) to fall by half. The elimination of a drug is usually an exponential (logarithmic) process so that a constant proportion of the drug in the body is eliminated per unit time. This is illustrated in Fig. 1 on both linear and semi-logarithmic graphs. When plotted as a logarithm of plasma concentration versus time, a straight line results. This is known as 'first order elimination'.

What determines half-life?

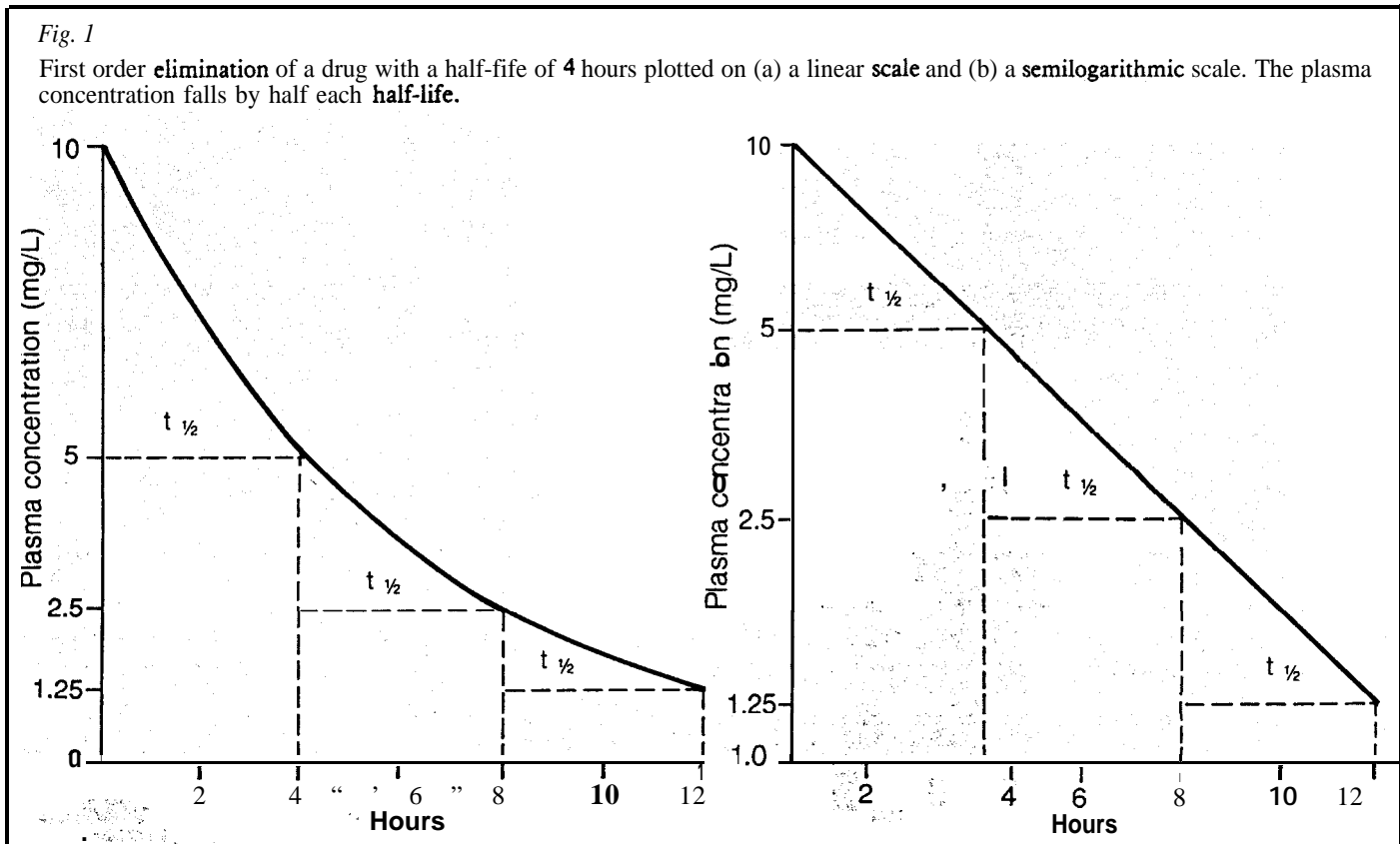
Half-life is a composite pharmacokinetic parameter determined by both clearance (Cl) and volume of distribution (V_D). (The mysterious 0.693 is the natural logarithm of one-half.)

$$t_{1/2} = \frac{0.693 \cdot V_D}{Cl}$$

Half-life is increased by an increase in volume of distribution or a decrease in clearance, and vice versa. The opposing

effects of clearance and volume of distribution on half-life are illustrated in Table 1 by reference to several commonly used drugs. For example, **ethosuximide** and **flucytosine** have the same volume of distribution but their half-lives are 10-fold different due to a 10-fold difference in clearance. By contrast, **digoxin** and **flucytosine** have the same clearance but the half-lives are different because of the 10-fold difference in volume of distribution. **Chloroquine** has a high clearance, but a very long half-life because of the very large volume of distribution due to the high lipid volatility of the drug and the resulting extensive distribution into adipose and other tissues.

It is easy enough to understand why a change in clearance would change half-life. A decrease in the activity of the elimination mechanism would be expected to increase the time taken to eliminate the drug. But why should the volume of distribution also determine half-life? The larger the volume of distribution, the more the drug is concentrated in the tissues compared with the blood. It is drug in the blood that is exposed to hepatic or renal clearance, so that when the distribution volume is large these mechanisms have less drug to work on. By contrast, if the volume of distribution is small,



Pharmacokinetics made easy 3

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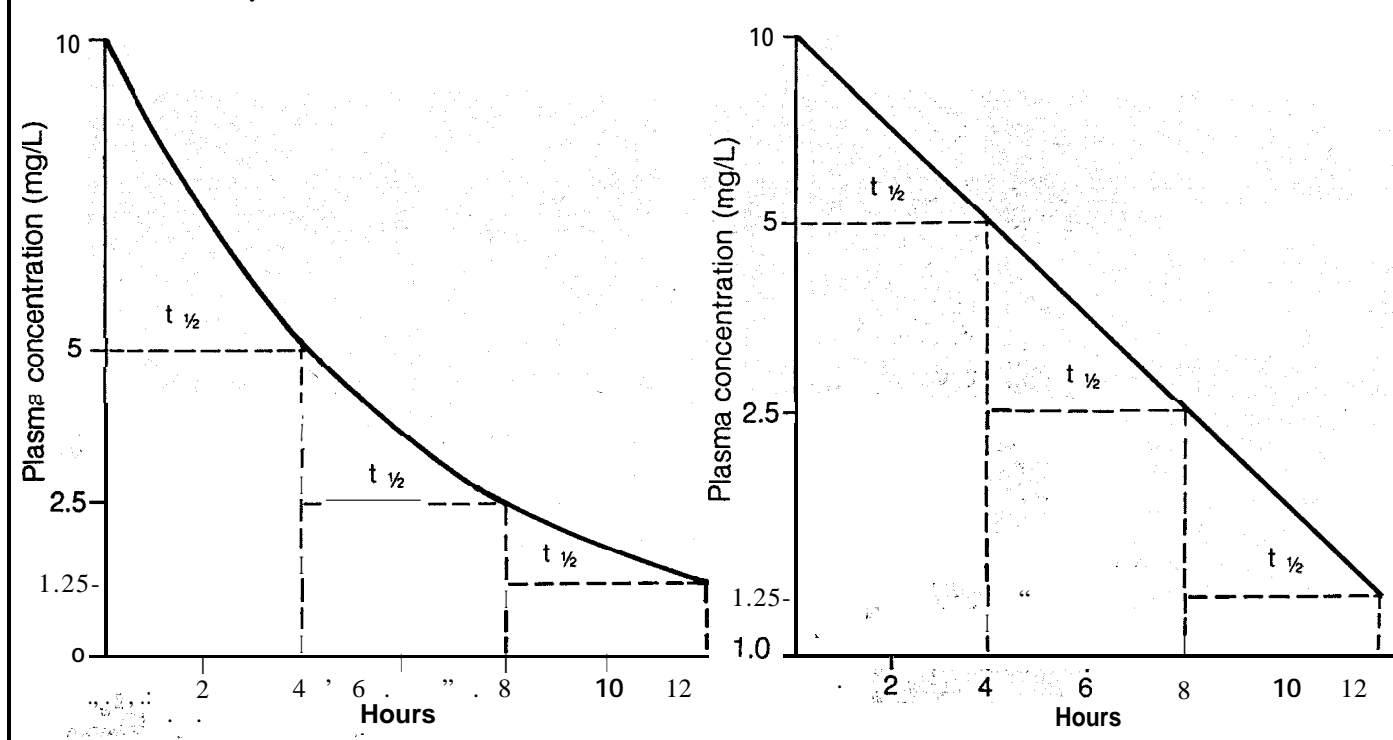
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Fig. 1

First order elimination of a drug with a half-life of 4 hours plotted on (a) a linear scale and (b) a semilogarithmic scale. The plasma concentration falls by half each half-life.



most of the drug in the body is in the blood and is accessible to the elimination processes.

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 may, therefore, not change although clearance is decreased. As clearance determines steady state plasma concentrations, half-life is not a good measure of such effects.

Why is half-life important?

Half-life is a major determinant of:

- (i) *The duration of action after a single dose.* After a single dose, the longer the half-life the longer the plasma concentration will stay in the effective range. However, the duration of action is a logarithmic, not linear function of the dose. Thus a 10-fold increase in dose is required to produce a 2-fold increase in duration of action.
- (ii) *The time required to reach steady state with chronic dosing.* With a constant rate infusion, the accumulation of drug to steady state is a mirror image of the elimination when dosing is stopped. This was illustrated in the article on volume of distribution (Aust Prescr 1988; 11 :36-7) in relation to the use of a loading dose. The approach to steady state in terms of half-lives is shown in the box. It can be seen that it takes 3-5 half lives to reach the desired plasma concentration (approximate steady state). From Table 1 it can be seen that it will take about 16 hours to reach steady state with flucytosine, 12 hours with morphine, 160 hours (7 days) with digoxin, and about 5 weeks with chloroquine. This is why chloroquine prophylaxis must be started some weeks before the patient goes to a malarious area.

Number of half-lives since starting constant rate dosing	Mean plasma concentration as a percentage of eventual mean steady state concentration
	%
1	50
2	75
3	87.5
4	93.75
5	96.875

The importance of these considerations can also be seen in relation to monitoring theophylline plasma concentrations during an aminophylline infusion. The theophylline half-life may be as long as 20 hours in patients with severe cardiac failure and/or liver disease. A plasma concentration measured 20 hours after starting an infusion will only be 50% of the concentration that will eventually be reached if the infusion is continued at the same rate, and this must be taken into account when considering adjustments to the infusion rate. Even when a loading dose is given before the infusion, it still takes the same time to reach steady state although the starting concentration is, of course, closer to the eventual steady state concentration.

- (iii) *The dosing frequency required to avoid too large fluctuations in plasma concentration during the dosing interval.* With steady state dosing, the extent to which the plasma concentration fluctuates over the dosage interval is determined by the half-life and the time between doses. If

Fig. 2

Effect of half-life and frequency of dosing on the fluctuation in plasma concentration over the dosing interval. The example shown is for theophylline treatment of a 20 kg child, who has a theophylline half-life of 4 hours, at a total daily dose of 600 mg. The therapeutic 'window' for theophylline is 10 to 20 mg/L. To stay in this range with an immediate release preparation, 100 mg doses must be given every 4 hours day and night (A). This is because the plasma theophylline concentration falls by half (from 20 mg/L to 10 mg/L) over the 4 hour half-life. If the same preparation is given 12 hourly at the same dose rate (300 mg every 12 hours), concentrations fluctuate between 35 mg/L (toxic) and 4.5 mg/L (ineffective) (B, blue). Effective 12 hourly dosing can be achieved by the use of a slow release formulation (B, red), because the fluctuation over the dosing interval is then determined by the absorption rate rather than the elimination rate. Note that in each case the AVERAGE concentration over the dosing interval is the same (15 mg/L) as this is determined only by the clearance which is 0.17 L/hr in this child (see Article 1).

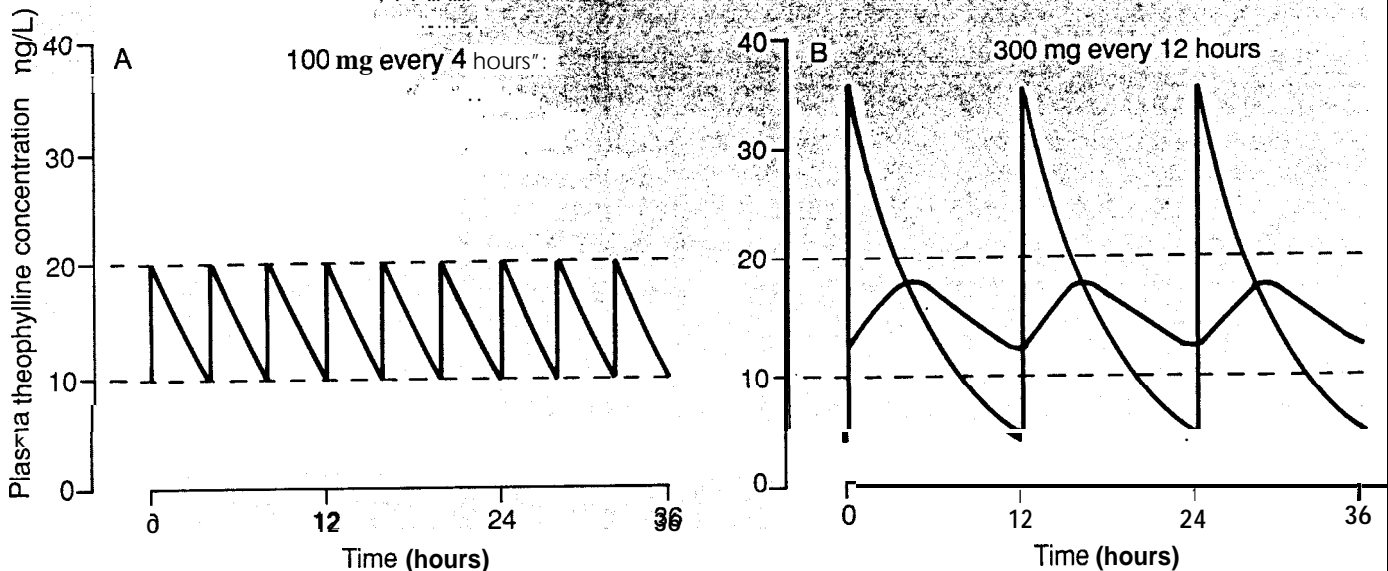


Table 1
Effects of clearance and volume of distribution in determining half-life

Drug	Clearance L/hr	volume of distribution L	Half-life hr
Ethosuximide	0.7	49	48.0
Flucytosine	8.0	49	4.2
Digoxin	7.0	420	40.0
Morphine	63.0	2 8 0	3.0
Haloperidol	46.0	1 400	20.0
Chloroquine	45.0	12950	200.0

a drug is given every half-life and is rapidly absorbed to reach a maximum (peak) concentration, then over one half-life the concentration will fall to half the peak concentration. That is, the peak concentrations will be double the trough (predose) concentrations and the fluctuation in plasma concentration over the dosage interval will be 100%. If a drug is given more frequently than every half-life, the fluctuations will be small. If the

half-life is short and the drug shows dose related toxicity, it is often difficult to dose frequently enough to avoid toxicity at the peaks, and lack of effect as the plasma concentration falls to low levels before the next dose. An example is theophylline therapy in children, who have theophylline half-lives as short as 2-5 hours. The therapeutic plasma concentration range for theophylline concentration is 10-20 mg/L, so a rapidly absorbed preparation would have to be given every 4 hours to stay within this range (Fig. 2). As this is clearly impracticable, sustained release formulations are used which ideally mimic a constant rate infusion. The fluctuation in plasma concentration is then determined by the slow absorption rate rather than the rapid elimination rate, and they can be given every 12 hours which is a much more feasible proposition.

Summary

Half-life is a parameter determined by both clearance and volume of distribution. It determines the duration of action after a single dose of a drug, the time taken to reach steady state with constant dosing and the frequency with which doses can be given.

New drugs (from page 54)

NEW FORMULATIONS

Carboplatin

Carboplatin Injection (David Bull)
10 mg/10 mL solution

Erythromycin

Erythromycin (Abbott)
250 mg enteric-coated tablets

Ketoprofen

Orudis SR (May & Baker)
100 mg sustained-release capsules

Neutral insulin injection 30%

Isophane insulin injection 70% (mixed)

Human insulin (e.m.p.)

Actraphane HM Penfill (CSL-Novo)
Injection — 100 U/mL

Isophane insulin injection

Human insulin (e.m.p.)

Protaphane HM Penfill (CSL-Novo)
Injection — 100 U/mL

Vancomycin hydrochloride

Vancocin Pulvules (Lilly)
125 mg and 250 mg capsules

NEW STRENGTH

Nifedipine

Adalat (Bayer)
5 mg capsules

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