CH 1.1

GENERAL PHARMACOKINETIC APPLICATIONS

OUTLINE

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SELF-ASSESSMENT PROBLEMS

Half-life

Knowledge of a drug's half-life ($t_{½}$) is useful in pharmacokinetic monitoring of patients because it gives information on (1) how long it would take for a drug to be eliminated from the body (eg, cases of drug overdose) or how long a dose must be held to reach a certain concentration; (2) the length of a dosage interval if a desired therapeutic range is known; and (3) how long a drug must be given before steady state is reached, since approximately five half-lives must elapse before steady state has been achieved.

1. After four half-lives of a drug, how much of a 1,000-mg dose remains in the body (in milligrams)?

Determining the half-life of a drug based on measured concentrations

Assume first-order elimination and one compartment distribution. Also assume that concentrations are in the elimination phase for all of the following problems.

2. The following two concentrations were determined after administration of an IV bolus dose of a drug at time zero. Determine the half-life without using a calculator.

C(mg/L)	10	5
t(hours)	1	6

3. Determine the half-life from this concentration versus time data without using a calculator.

C(mg/L)	16	2
t(hours)	3	12

4. If the lower concentration is not exactly ½, ¼, ⅛, and so on, of the original concentration, the half-life can still be estimated but with slightly reduced accuracy. Estimate the approximate half-life from the following concentration versus time data without using a calculator.

C(mg/L)	9	2
t(hours)	2	12

Determining elimination rate constant (k) and half-life using appropriate equations

5. Determine the elimination rate constant k and then the half-life of the drug based on the following concentration versus time data.*

C(mg/L)	30	8
t(hours)	3	10

6. Determine the elimination rate constant k and then the half-life of the drug based on the following concentration versus time data.

C(mg/L)	7.8	2.5
t	1 p.m.	11 p.m.

7. The following concentrations versus time were obtained after a 500-mg IV bolus dose of amikacin at 8 a.m. What is the half-life of amikacin in the patient?

C(mg/L)	18	3.5
t	10 a.m.	8:45 p.m.

Using half-life (elimination rate constant) to solve for the time that must elapse for one concentration to decrease to a lower concentration

8. A patient received an excessive dose of digoxin, and a digoxin trough concentration was reported as 4.4 mcg/L. The patient's digoxin half-life was estimated to be 2 days. Assume that the measured concentration is postabsorption and postdistribution. How long (in days) would it be estimated to take for the digoxin concentration to decrease to 0.5 mcg/L?

Using half-life (elimination rate constant) to determine a dosage interval

Equation 1 can be used to determine a dosage interval, which is, of course, simply a time change.

9. The therapeutic range for a new drug has been determined to be 6 to 15 mg/L. The average half-life in patients with normal hepatic and renal function is 8.5 hours.
   A. Based on the half-life, what is the maximum dosage interval that might be used?
   B. What is a logical interval that would be used?

Volume of distribution

The apparent volume of distribution is the theoretical volume that would have to be available in which a drug will disperse if the concentration everywhere in the body were the same as that in the plasma or serum. Drug concentration sampling generally occurs in the plasma or serum. **Equation 6** provides three useful values: D (dose), C_{Δ} (the desired concentration change after the dose), and V (the apparent volume of distribution). Each can be solved if the other two are known or can be estimated.

* For numbered equations mentioned in this text, see ***Select Pharmacokinetic Equations,*** Appendix C.

Using volume of distribution to determine a loading dose

10. The estimated volume of distribution of phenytoin in a female patient is 42 L. Estimate a loading dose of IV fosphenytoin sodium (S = 0.92, F = 1) to produce an estimated concentration after the dose (C_0) of 15 mg/L. Although the dose would generally be given over a short period of time, treat as if an IV bolus is given.

11. An 80-kg male patient is to receive an IV bolus dose of a drug (S = 1). The population average weighted volume of distribution is 0.3 L/kg. The desired concentration immediately after the dose is 12 mg/L. Calculate the dose (in milligrams).

Solving for volume of distribution from a concentration determined just after an initial dose

12. The patient in Problem 11 receives the dose you recommend. The actual concentration measured just after the dose is 10.8 mg/L. What is the patient's actual volume of distribution relative to his weight (in L/kg)?

13. Determine the volume of distribution in a patient who has been given a 1,000-mg IV dose of fosphenytoin sodium (S = 0.92) over a few minutes and in whom the concentration of drug measured shortly after the dose is 18 mg/L (assume distribution is complete).

Estimating the concentration after a loading dose

14. A 1.8-kg neonate is given a 25-mg/kg loading dose of phenobarbital sodium (S = 0.9). The estimated volume of distribution of phenobarbital in neonates is 0.96 L/kg. What is the estimated concentration after the loading dose?

Using e^{-kt}

Estimating a concentration some time after a known concentration

15. A patient has a gentamicin concentration measured at 1 p.m. that is reported to be 7.6 mg/L. You would like to estimate the concentration at 8 p.m. just before the next dose is given. You estimate the patient's half-life to be 3.3 hours. What is the estimated trough concentration at 8 p.m.?

Estimating an earlier concentration

16. A vancomycin concentration is drawn at 7:30 p.m. just before an 8 p.m. dose on a patient receiving IV vancomycin every 12 hours at 8 a.m. and 8 p.m. The measured concentration is reported as 14 mg/L. You estimate the patient's vancomycin half-life to be 9 hours. What would you estimate the vancomycin concentration to have been at 10 a.m., 1 hour after a 1-hour dose infusion? Assume distribution of the dose is complete.

Solving for k and V from two concentrations after a single IV bolus dose

17. A patient is given a single IV bolus dose of 500 mg of amikacin (S = 1). The following concentration-time data were determined after the dose:

$C(mg/L)$	17	3.8
$t(hours)$	1	12

A. Determine k and $t_{½}$.

B. Determine volume of distribution.

Using clearance

Solving for maintenance infusion rate (R_0)

18. An 80-kg nonsmoking male is to be started on theophylline therapy for chronic obstructive pulmonary disease.

A. What infusion rate of aminophylline (S = 0.8) should be used to produce an estimated theophylline concentration of 12 mg/L if the estimated theophylline clearance is 2.4 L/hr?

Solving for clearance

B. Assume the patient is started on a 36 mg/hr infusion of aminophylline. After an appropriate amount of time has elapsed (ie, it is estimated that steady state has been achieved), a concentration is drawn and reported as 10 mg/L. What is the patient's actual clearance (in L/hr)?

Solving for estimated steady state concentration

C. The patient has his infusion rate increased to 50 mg/hr. What is the patient's estimated steady state concentration on this new infusion rate?

Using equation 5 manipulated to solve for dose

D. The patient is to go home on oral theophylline (S = 1). The available tablet strengths are 100 mg, 200 mg, and 300 mg. The tablets are known to be 90% bioavailable (F = 0.9). What dose should he receive to produce approximately the same average steady state concentration determined in part C if theophylline must be given on an every 8-hour interval due to short half-life?

Solving for estimated steady state concentration from a concentration measured prior to steady state

E. A patient is started on an infusion of a drug at a rate of 100 mg/hr. The therapeutic range of

the drug is considered to be 20 to 40 mg/L. The estimated half-life of the drug in the patient is 15 hr. A concentration measured 24 hr after the start of the infusion is reported as 32 mg/L. What is the estimated steady state concentration of the drug in this patient?

ADDITIONAL PROBLEMS

Solving for a concentration after IV bolus dosing at steady state

19. A 60-kg, 35-year-old female is to be given tobramycin 120 mg (S = 1) every 12 hours by IV bolus (not the usual method, but we will use this for the example; it is usually given as short infusion). Her estimated volume of distribution is 0.3 L/kg, and her estimated half-life is 4 hours.
    A. What would the estimated tobramycin concentration be at 1 hour after a dose at steady state?
    B. What concentration would be predicted at the time the true trough occurs (ie, at 12 hours after a dose)?

Solving for k (and half-life) and volume from two concentrations measured after an IV bolus dose given every τ hours at steady state

20. A patient is given 500 mg of amikacin (S = 1) IV bolus every 12 hours. The following concentration-time data were determined after a dose at steady state:

C(mg/L)	17	3.8
t(hours)	1	12

    A. Determine k and $t_{½}$.
    B. Determine volume of distribution.

Solving for k (and half-life) and volume from two concentrations measured after a short IV infusion dose given over t′ time every τ hours at steady state

21. A patient is given 500 mg of amikacin IV (S = 1) as a 0.5-hour infusion every 12 hours (at 12 noon and 12 midnight). The following concentration-time data were determined after the start of a dose infusion at steady state:

C(mg/L)	17	3.8
t(hours)	1	12

    A. Determine k and $t_{½}$.
    B. Determine volume of distribution.

Predicting concentrations after short infusion dosing to steady state

22. A female patient is to receive gentamicin (S = 1) at a dose of 360 mg every 24 hours. Doses are given as 30-minute infusions. The patient's half-life is estimated to be 6.2 hours and her volume of distribution to be 24 L.
    A. Predict her steady state peak concentration (in mg/L) that is to be drawn 30 minutes after the end of the dosing infusion.
    B. Predict the steady state trough concentration; the measurement will occur 0.5 hours before the next dose.

Determining loading and maintenance dose infusions for a drug given as short infusions every τ hours at steady state

23. Vancomycin (S = 1) is to be given every 12 hours to a patient as 1-hour infusions. The predicted half-life of the drug in the patient is 11 hours, and the volume of distribution is 55 L. The desired steady state trough concentration, measured 30 minutes before a dose, is 15 mg/L.
    A. Determine a loading dose to produce the trough of 15 mg/L before the first maintenance dose.
    B. Determine a maintenance dose to produce a steady state trough of 15 mg/L.

Determining a trough concentration for a new antirejection agent

24. A new antirejection agent for the treatment of patients with kidney transplants has been shown to be therapeutically effective, with avoidance of renal toxicity at trough concentrations of 200 to 400 mcg/L. The population volume of distribution is 1.7 ± 0.4 L/kg, and clearance is 0.11 ± 0.05 L/hr/kg. Actual body weight is used for dosing unless patients weigh more than 150 kg. Bioavailability of the suspension dosage form is 0.5 ± 0.1 (or 50% ± 10%) and S = 1.
    A. Determine a dose (in milligrams) of oral suspension to be given every 12 hours to a 90-kg male to produce a predicted steady state trough concentration of 300 mcg/L just before the next dose. **Equation 8** for IV bolus dosing may be used in the calculations because absorption is rapid relative to elimination. Bioavailability must be considered in the equation (ie, add it to the equation).
    B. A decision is made to reduce the number of times doses are given each day by changing to an every-24-hour schedule. Determine the dose (in milligrams) of oral suspension to be given every 24 hours to produce a steady state trough concentration of 300 mcg/L just before the next dose. As before, use the equation for IV bolus dosing with addition of bioavailability fraction.

Estimating half-life and elimination rate constant from population clearance estimates

25. A method for estimating vancomycin clearance and volume of distribution in adults is as follows:

    CL_{vanc} = 0.689 × CrCl + 3.66 (where CL_{vanc} and creatinine clearance [CrCl] are in mL/min)

    Population volume of distribution for adults with CrCl > 60 mL/min is estimated to be 0.72 L/kg of actual body weight.

    Estimate the vancomycin volume of distribution (in liters), k (in hr^{-1}), and $t_{½}$ (in hours) for a 34-year-old male who weighs 90 kg (ideal body weight 70 kg) and has an estimated CrCl of 97 mL/min.

Considering need for dosage adjustment

26. An adult patient weighing 65 kg is receiving a drug with a therapeutic range of 1 to 2 mg/L. The population average clearance for adult patients is 0.004 L/hr/kg, and volume of distribution is 0.1 L/kg. The current dose is 3 mg every 12 hours. F = 0.9 and S = 1. A concentration measured approximately 6 hours after a dose at steady state (assume = Css_{avg}) is reported as 0.2 mg/L.
    A. Estimate the measured concentration based on the population values and the patient's weight.
    B. What dose would be predicted to be necessary to increase Css_{avg} from 0.2 mg/L to 1.2 mg/L?
    C. What approaches should be taken to determine the need for dose adjustment? List all that might apply.
        1. Increase the dose enough to get the steady state concentration into the therapeutic range and then monitor outcomes at the next scheduled clinic visit.
        2. Increase the dose modestly (eg, 2-fold) to get closer to the therapeutic range.
        3. Determine adherence by speaking with the patient and/or checking refill history.
        4. Ensure that the concentration was drawn from the patient and not someone else.
        5. Verify that the laboratory report is correct.
        6. Evaluate the patient's response to therapy in terms of efficacy and toxicity.
        7. Examine the medical record for possible drug-drug interactions that might increase clearance of the object drug.

ANSWERS

1. 62.5 mg
2. 5 hours
3. 3 hours
4. ~4.5 hours
5. 3.7 hours
6. 6.1 hours
7. 4.6 hours
8. 6.3 days
9. A. 11.2 hours
   B. 12 hours
10. 685 mg
11. 288 mg
12. 0.33 L/kg
13. 51.1 L
14. 23.4 mg/L
15. 1.75 mg/L
16. 29.2 mg/L
17. A. k = 0.136 hr^{-1} $t_{½}$ = 5.1 hours
    B. 25.7 L
18. A. 36 mg/hr
    B. 2.88 L/hr
    C. 13.9 mg/L
    D. Exact = 356 mg
    Dose used would be 400 mg
    E. 47.8 mg/L
19. A. 6.4 mg/L
    B. 1 mg/L
20. A. k = 0.136 hr^{-1} $t_{½}$ = 5.1 hours
    B. 31.9 L
21. A. k = 0.136 hr^{-1} $t_{½}$ = 5.1 hours
    B. 33 L
22. A. C = 14.8 mg/L
    B. C = 1.2 mg/L
23. A. Dose = 1,649 mg
    B. Dose = 875 mg
24. A. Dose = 109 mg
    B. Dose = 345 mg
25. V = 64.8 L
    k = 0.065 hr^{-1}
    $t_{½}$ = 10.7 hours
26. A. Css_{avg} = 0.87 mg/L
    B. Dose = 18 mg every 12 hours
    C. 2, 3, 4, 5, 6, 7