Therapeutic Drug Monitoring

Therapeutic Drug Monitoring

- **There are inter-individual differences in drug response, and even intra-individual differences at different times or circumstances.**
- **This variability results from two main domains:**

1. Variation in absorption, distribution, metabolism or excretion (pharmacokinetics).

2. Variation at/or beyond tissue receptors or other macromolecular drug targets (pharmacodynamics).

Therapeutic Drug Monitoring

- There must be a continuous variable (biological response) that is readily measured and is closely linked to the desired therapeutic outcome of a drug, as a measure of monitoring.
- 'Surrogate marker' is a measure of effect of a specific treatment that may correlate with a real clinical endpoint.
- In addition, monitoring is needed to reduce the risk of a clinical event (stroke, heart attack, pulmonary embolism, etc.).

Therapeutic Drug Monitoring

- **For example, antihypertensive drugs are monitored by their effect on blood pressure, statins by their effect on serum cholesterol, oral anticoagulants by their effect on the international normalized ratio (INR).**
- **Some times, there is NO good continuous variable to monitor, especially for diseases with an unpredictable or fluctuating course.**

Therapeutic Drug Monitoring

- **Measuring drug concentrations in plasma or serum identifies only pharmacokinetic variability, and may usefully guide dose adjustment. For example in treating an epileptic patient with an anticonvulsant drug.**
- **Measuring drug concentrations for use in this way is often referred to as 'therapeutic drug monitoring'.**

Therapeutic Drug Monitoring

Role of drug monitoring in therapeutics:

- **Measurement of drug concentrations is *sometimes* a useful complement to clinical monitoring to assist in selecting the best drug regimen for an individual patient.**
- **Measurements of drug concentrations in plasma are most useful when:**

Therapeutic Drug Monitoring

1. **There is a direct relationship between plasma concentration and pharmacological or toxic effect, and a therapeutic range has been established.**

- **Drugs that work via active metabolites, and drugs with irreversible actions, are unsuited to this approach.**
- **Tolerance also restricts the usefulness of plasma concentrations measurement.**

2. **Effect can NOT readily be assessed quantitatively by clinical observation.**

Therapeutic Drug Monitoring

3. **Inter-individual variability in plasma drug concentrations from the same dose is large (phenytoin).**
4. **The drug has a low therapeutic index (if the ratio of toxic concentration/effective concentration is < 4).**
5. **Several drugs are being given concurrently and serious interactions are anticipated.**

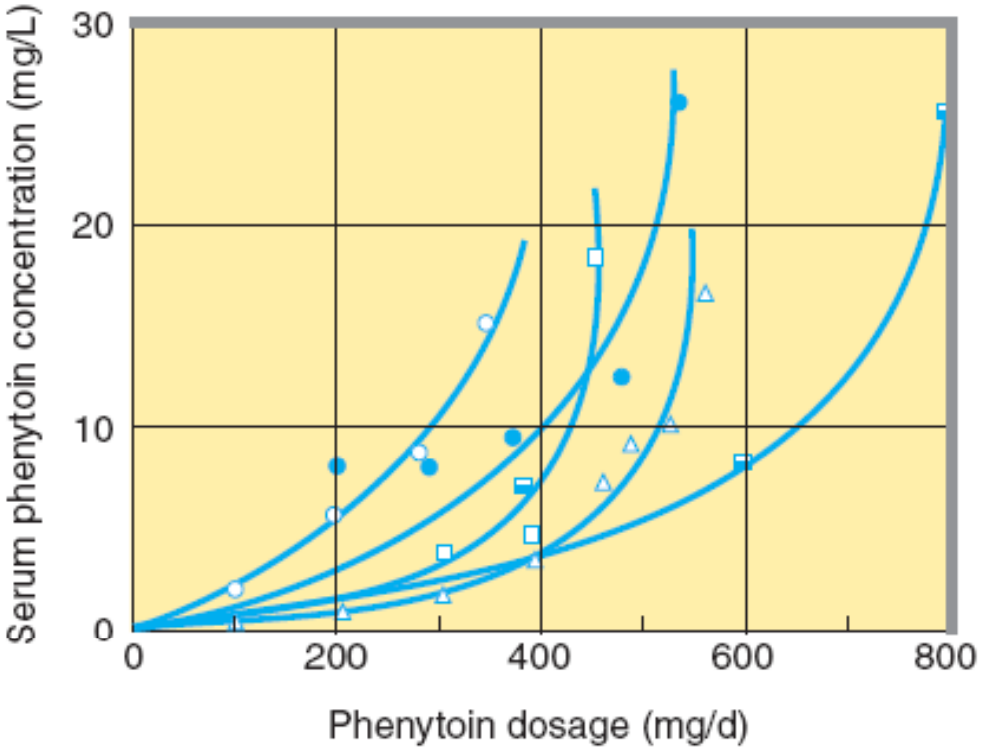


FIGURE 24–5 Nonlinear relationship of phenytoin dosage and plasma concentrations. Five patients (identified by different symbols) received increasing dosages of phenytoin by mouth, and the steady-state serum concentration was measured at each dosage. The curves are not linear, since, as the dosage increases, the metabolism is saturable. Note also the marked variation among patients in the serum levels achieved at any dosage. (Modified, with permission, from Jusko WJ: Bioavailability and disposition kinetics of phenytoin in man. In: Kellaway P, Peterson I [editors]: *Quantitative Analytic Studies in Epilepsy.* Raven Press, 1977.)

Therapeutic Drug Monitoring

6. **"Apparent resistance" to the action of a drug needs an explanation, when non-compliance is suspected.**
7. **Another indication, distinct from therapeutic drug monitoring, for measuring drug concentrations in plasma is in clinical toxicology.**

- **Such measurements can guide management of a poisoned patient (paracetamol or aspirin).**

Therapeutic Drug Monitoring

Practical Aspects:

1. **Drug concentration at the site of action, which is related to drug effect, is proportional to plasma drug concentration.**
2. **A constant tissue to plasma drug concentration ratio only occurs during the terminal β-phase of elimination.**
3. **Earlier in the dose interval, the plasma concentration does not reflect the concentration at the site of action accurately.**

Therapeutic Drug Monitoring

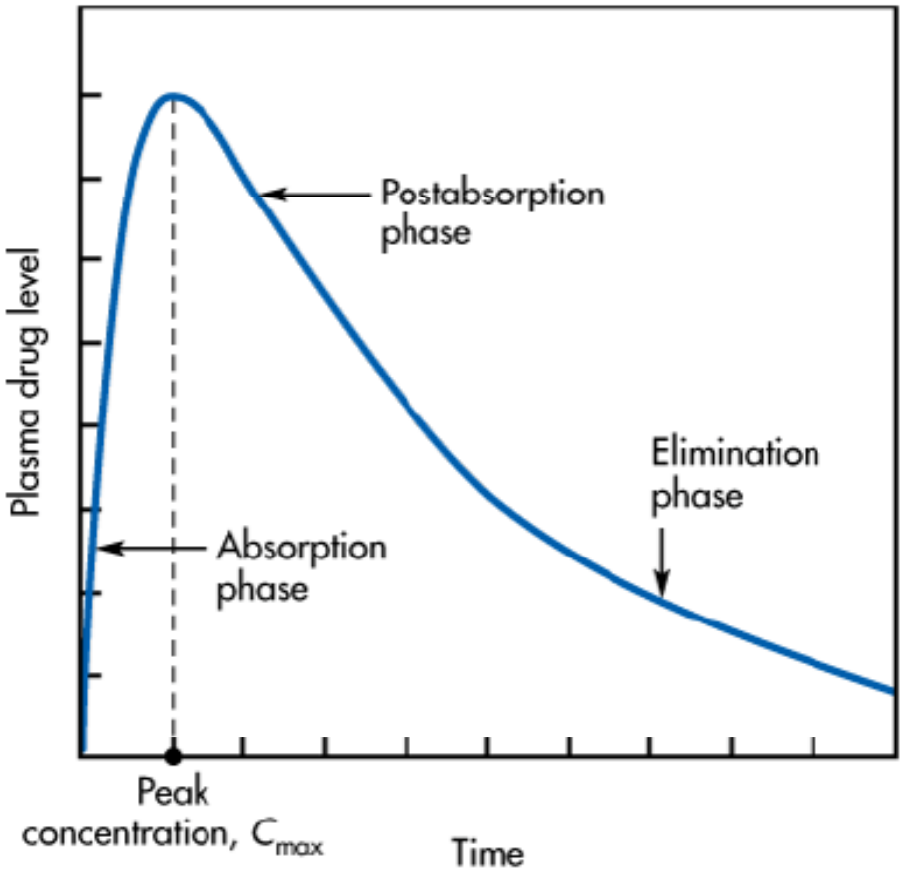
4. **Measurements must be made when distribution of the drug has been completed.**
5. **Timing of blood sampling is, therefore, critical for the measurement to be useful.**

- **There is No place for 'routine' or "random" blood samples for measurement of plasma drug concentration.**

6. **Sampling is only useful if the drug concentration in the body is at a "steady-state".**

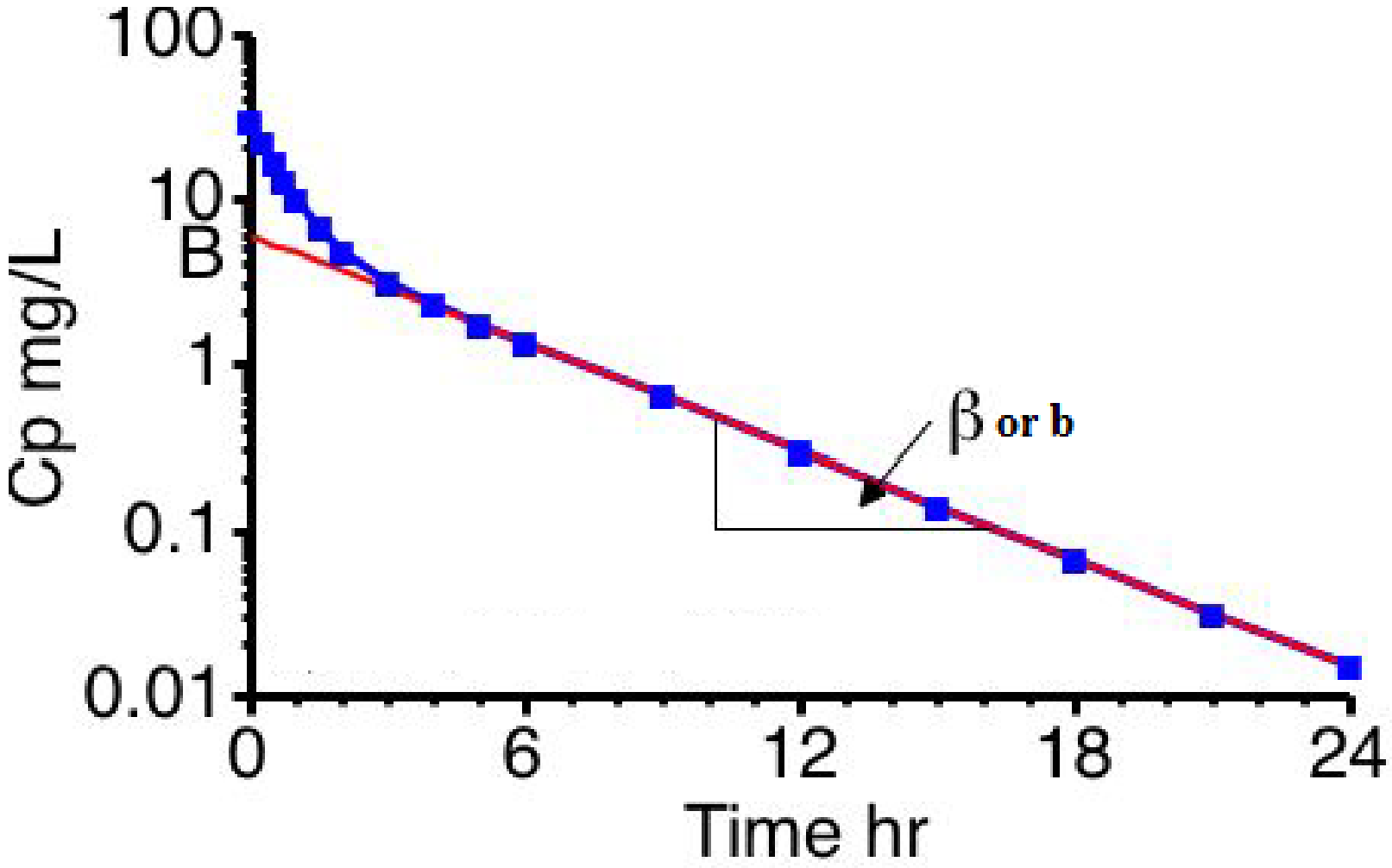
Therapeutic Drug Monitoring

7. **Usually during repeated dosing a sample is taken just before the next dose to assess the 'trough' concentration.**
8. **A sample may also be taken after distribution has been completed to determine the 'peak' concentration.**



Source: Shargel L, Wu-Pong S, Yu ABC: *Applied Biopharmaceutics & Pharmacokinetics, 6th Edition*: www.accesspharmacy.com

Plasma level–time curve for a drug given in a single oral dose. The drug absorption and elimination phases of the curve are shown.


100
10
B
1
0.1
0.01
Cp mg/L
0
6
12
18
24
Time hr
β or b

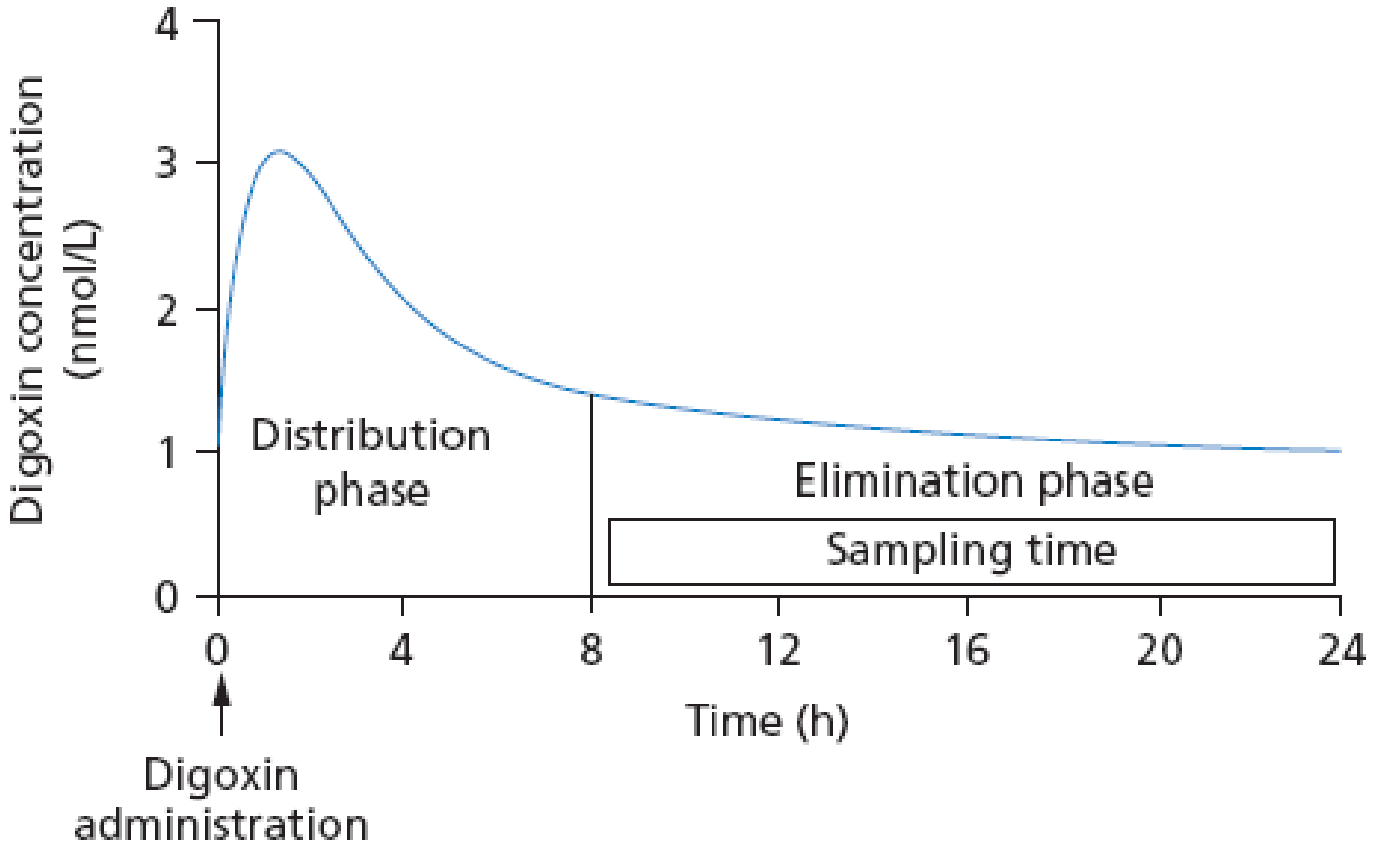
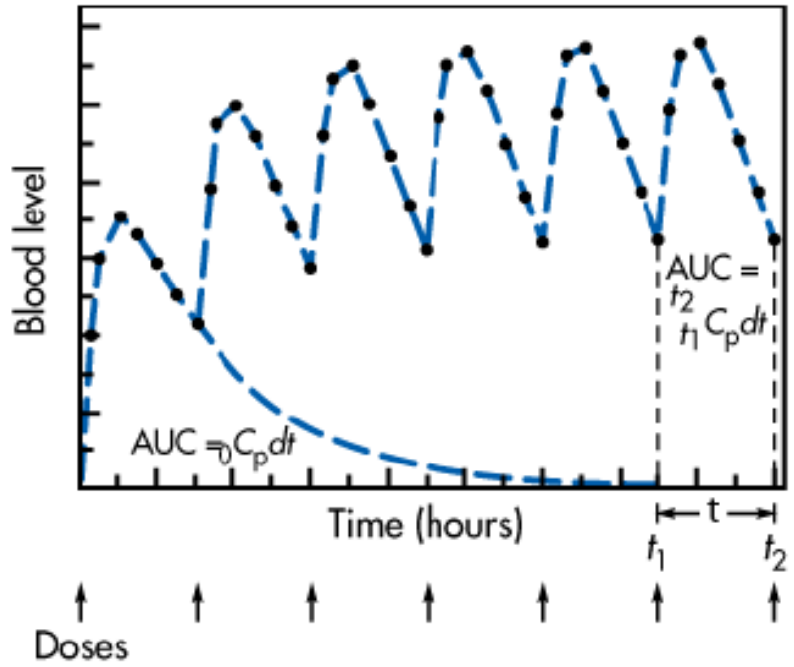
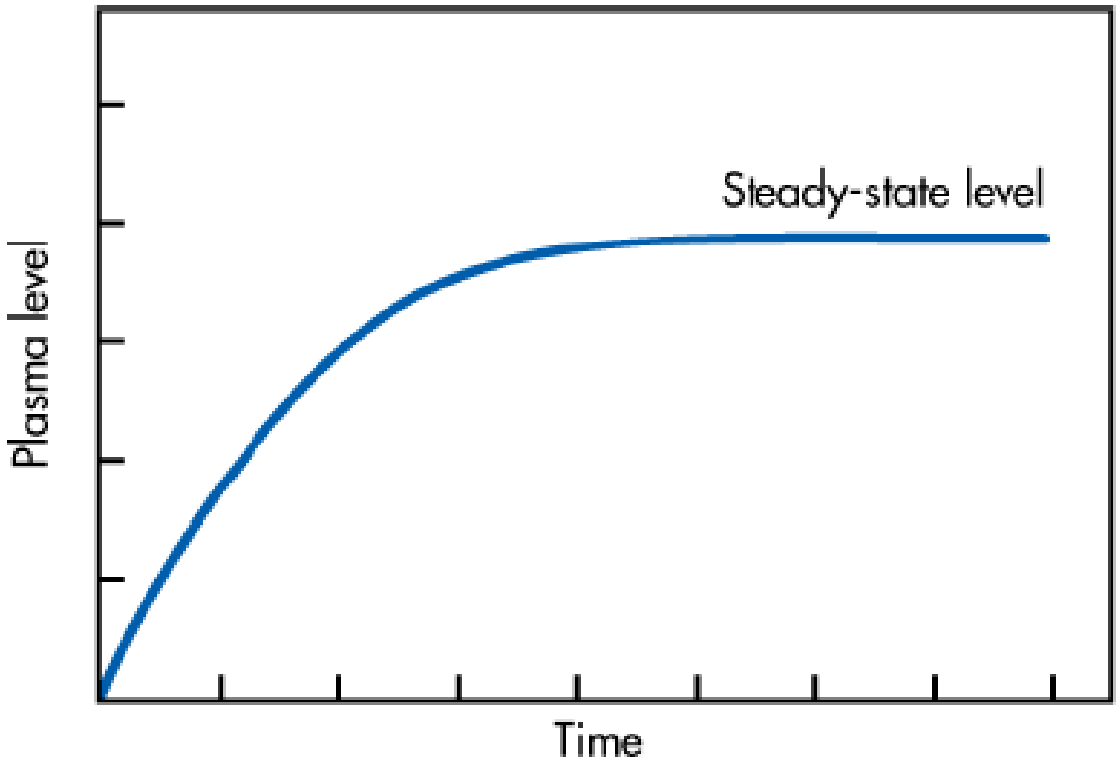


Figure 8.1: Serum concentration–time course following digoxin administration.



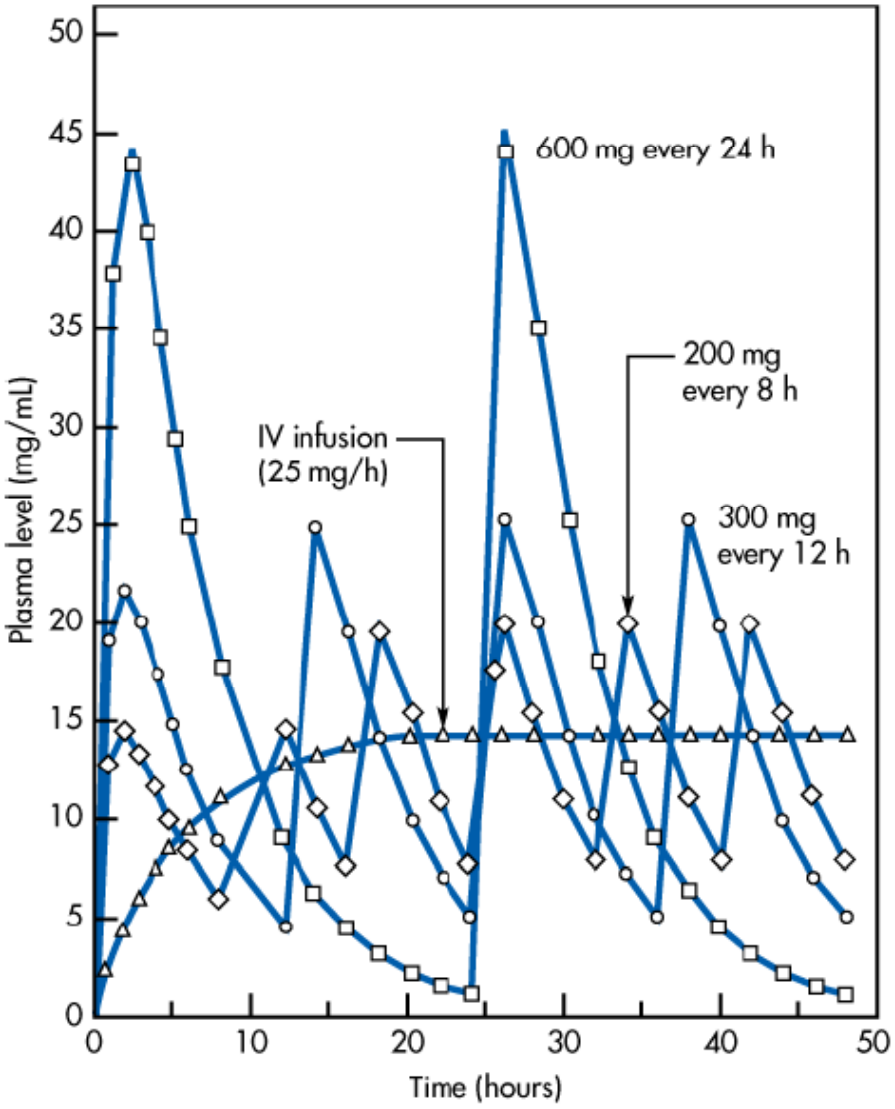
Source: Shargel L, Wu-Pong S, Yu ABC: *Applied Biopharmaceutics & Pharmacokinetics, 6th Edition*: www.accesspharmacy.com

Simulated data showing blood levels after administration of multiple doses and accumulation of blood levels when equal doses are given at equal time intervals.



Source: Shargel L, Wu-Pong S, Yu ABC: *Applied Biopharmaceutics & Pharmacokinetics, 6th Edition*: www.accesspharmacy.com

Plasma level–time curve for constant IV infusion.



Source: Shargel L, Wu-Pong S, Yu ABC: *Applied Biopharmaceutics & Pharmacokinetics, 6th Edition*: www.accesspharmacy.com

Simulated plasma drug concentration–time curves after IV infusion and oral multiple doses for a drug with an elimination half-life of 4 hours and apparent V_D of 10 L. IV infusion given at a rate of 25 mg/hr, oral multiple doses are 200 mg every 8 hours, 300 mg every 12 hours, and 600 mg every 24 hours.

Therapeutic Drug Monitoring

- **Advice on the interpretation of information obtained by measurement of serum drug concentration should be obtained from a local therapeutic drug-monitoring service, provided by clinical pharmacology and/or clinical pharmacy departments.**

Therapeutic Drug Monitoring

- **Plasma drug concentrations must always be interpreted in the context of the patient's clinical state.**
- **Random samples from patients to measure drug concentration are meaningless, misleading, as well as being a waste of time and money.**

Drugs For Which Therapeutic Drug Monitoring Is Used

Digoxin:

- Measuring the plasma concentration can help optimize therapy, especially for patients in sinus rhythm where there is no easy pharmacodynamic surrogate marker of efficacy.
- It is also useful in suspected toxicity or poor compliance.
- Before the use of digoxin monitoring, ~ 14% of all patients receiving digoxin showed evidence of toxicity, and this figure fell to ~ 6% following the introduction of monitoring.

Drugs For Which Therapeutic Drug Monitoring Is Used

- **Optimum sampling time:**
  Trough (pre-dose) or > 8 h post-dose.
- **Time to steady state:**
  7-10 days.
- **Target range:**
  In AF: 0.8-2 µg/L.
  In heart failure: 0.5-1 µg/L.

Drugs For Which Therapeutic Drug Monitoring Is Used

Lithium:

- **Optimum sampling time:** 12 h post-dose
- **Time to steady state:**

  3-7 days of chronic dosing
- **Target range:**

  Usually: 0.4-1 mmol/L.

  Elderly: 0.4-0.8 mmol/L.

  Acute bipolar disorder: up to 1.2 mmol/L.

Drugs For Which Therapeutic Drug Monitoring Is Used

Clozapine:

- **Optimum sampling time:**

  trough sample.

- **Time to steady state:**

  5-7 days of chronic dosing.

- **Target range:**

  ~ 350 µg/L, and clozapine/norclozapine ratio ~ 1.3

Drugs For Which Therapeutic Drug Monitoring Is Used

Aminoglycoside antibiotics:

- **Peak concentrations measured 30 minutes after dosing and trough levels, measured immediately before a dose.**
- **With extended interval aminoglycoside single daily dosing, a single drug concentration determined at a specified time after the completion of the distribution phase.**

Drugs For Which Therapeutic Drug Monitoring Is Used

Amikacin:

- **Optimum sampling time**:
  Peak (only used on divided-dose regimes):
  1 h post-dose (30-60 min after infusion complete)
  Trough: Immediately before next dose
  Time to peak 1 h
- **Time to steady state:** 10-15 h with normal renal function
- **Target range:**
  Trough: < 10 mg/L
  Peak: 20-30 mg/L.
  On once-daily dosing, target is a trough concentration of < 5 mg/L

Drugs For Which Therapeutic Drug Monitoring Is Used

Gentamicin, Tobramycin:

- **Optimum sampling time:**

  Peak: 1 h post-dose (30-60 min after infusion complete)

  Time to peak 1 h
- **Time to steady state:**

  10-15 h with normal renal function
- **Target range:**

  Multiple dose regimes:

  Trough: < 2 mg/L

  Peak: 5-10 mg/L

Drugs For Which Therapeutic Drug Monitoring Is Used

Vancomycin:

- **Optimum sampling time:**
  Peak: 1 h post-dose (30-60 min after infusion complete)
  Trough: Immediately before next dose
  Time to peak 1 h
- **Time to steady state:**
  20-35 h with normal renal function
- **Target range:**
  Trough: 5-15 mg/L
  Peak: 20-40 mg/L

Drugs For Which Therapeutic Drug Monitoring Is Used

Teicoplanin:

- **Optimum sampling time:**

  Trough: Immediately before next dose

- **Time to steady state:**

  14 days or more

- **Target range:**

  Trough: 10-60 mg/L (15-60 mg/L in endocarditis, 20-60 mg/L for *Staphylococcus aureus)*

Drugs For Which Therapeutic Drug Monitoring Is Used

Phenytoin:

- It is important to be aware of:

1) its non-linear pharmacokinetics
2) the possible effects of concurrent renal or hepatic disease on its pharmacokinetics
3) the possible effects of pregnancy on its distribution.

- Serum albumin concentration is necessary for appropriate interpretation of concentration.

Drugs For Which Therapeutic Drug Monitoring Is Used

Phenytoin/Fosphenytoin

- **Optimum sampling time:**

1) In steady-state this is not too important because of long half-life of elimination.
2) A trough sample if on short-term fosphenytoin.

- **Time to steady state:**

  2-6 days of chronic dosing

- **Target range:**

  Total phenytoin: 5-20 mg/L

  Free phenytoin: 0.5-2 mg/L

Drugs For Which Therapeutic Drug Monitoring Is Used

Carbamazepine:

- **Optimum sampling time:**

  Pre-dose (trough sample)
- **Time to steady state:**

  2-6 days of chronic dosing
- **Target range:**

  4-12 mg/L

Drugs For Which Therapeutic Drug Monitoring Is Used

Ethosuximide:

- **Optimum sampling time:**

  Pre-dose (trough sample)

- **Time to steady state:**

  5-15 days of chronic dosing

- **Target range:**

  40-100 µg/L

Drugs For Which Therapeutic Drug Monitoring Is Used

Lamotrigine:

- **Optimum sampling time:**

  Before a dose (trough sample)
- Elimination half-life:

  20-35 h (shorter in children). ~ 15 h when given with enzyme inducers. ~ 60 h when given with valproate
- **Time to steady state:**

  5-7 days of chronic dosing
- **Target range:**

  < 24 mg/L

Drugs For Which Therapeutic Drug Monitoring Is Used

Valproate:

- **Optimum sampling time:**

  Before a dose (trough sample)
- **Time to steady state:**

  3-7 days of chronic dosing

  Protein binding ~95% (concentration dependent, decreasing binding above ~ 80 mg/L; also affected by endogenous metabolites)
- **Target range:**

  There is little evidence for the 50-100 mg/L range often cited, or the range of 50-125 mg/L cited for bipolar disorder monitoring.

  Plasma concentrations show poor correlation with effect.

Drugs For Which Therapeutic Drug Monitoring Is Used

Zonisamide:

- **Optimum sampling time:**

  Long half-life makes sampling time less critical in steady-state (however, sampling at trough is advised)

- **Time to steady state:**

  ~ 2 weeks of chronic dosing

- **Target range:**

  10-20 mg/L

Drugs For Which Therapeutic Drug Monitoring Is Used

Methotrexate:

- **Plasma concentration is an important predictor of toxicity.**
- **Concentrations of 5 µmol/L 24 hours after a dose, or 100 nmol/L 48 hours after dosing, usually require folinic acid administration to prevent severe toxicity.**

Drugs For Which Therapeutic Drug Monitoring Is Used

- **Optimum sampling time:**

  As required by protocol, often 24, 48 and (if necessary) 72 h post high-dose therapy.
- **Time to steady state:**

  1-2 days of chronic low dosing
- **Target range:**

  < 1 µmol/L 48 h post high-dose therapy or according to protocol.

Drugs For Which Therapeutic Drug Monitoring Is Used

Theophylline:

- It has a narrow therapeutic index, and many factors influence its clearance.
- Measurement of plasma theophylline concentration can help to minimize toxicity (cardiac dysrhythmias or seizures).
- A therapeutic range of 5–20mg/L is quoted.
- (Plasma concentrations 15mg/L are, however, associated with severe toxicity in neonates due to decreased protein binding and accumulation of caffeine, to which theophylline is methylated in neonates, but not in older children).

Drugs For Which Therapeutic Drug Monitoring Is Used

- **Optimum sampling time:**

  Trough: immediately before next dose

  Peak: 4-8 h post-dose (modified release preparations); 2 h post-dose (rapid-release)

  Time to peak 1-2 h post-dose (rapid-release) 4-8 h post-dose (modified release)
- **Time to steady state:**

  2-3 days (oral dosing, adults)
- **Target range:**

  10-20 mg/L

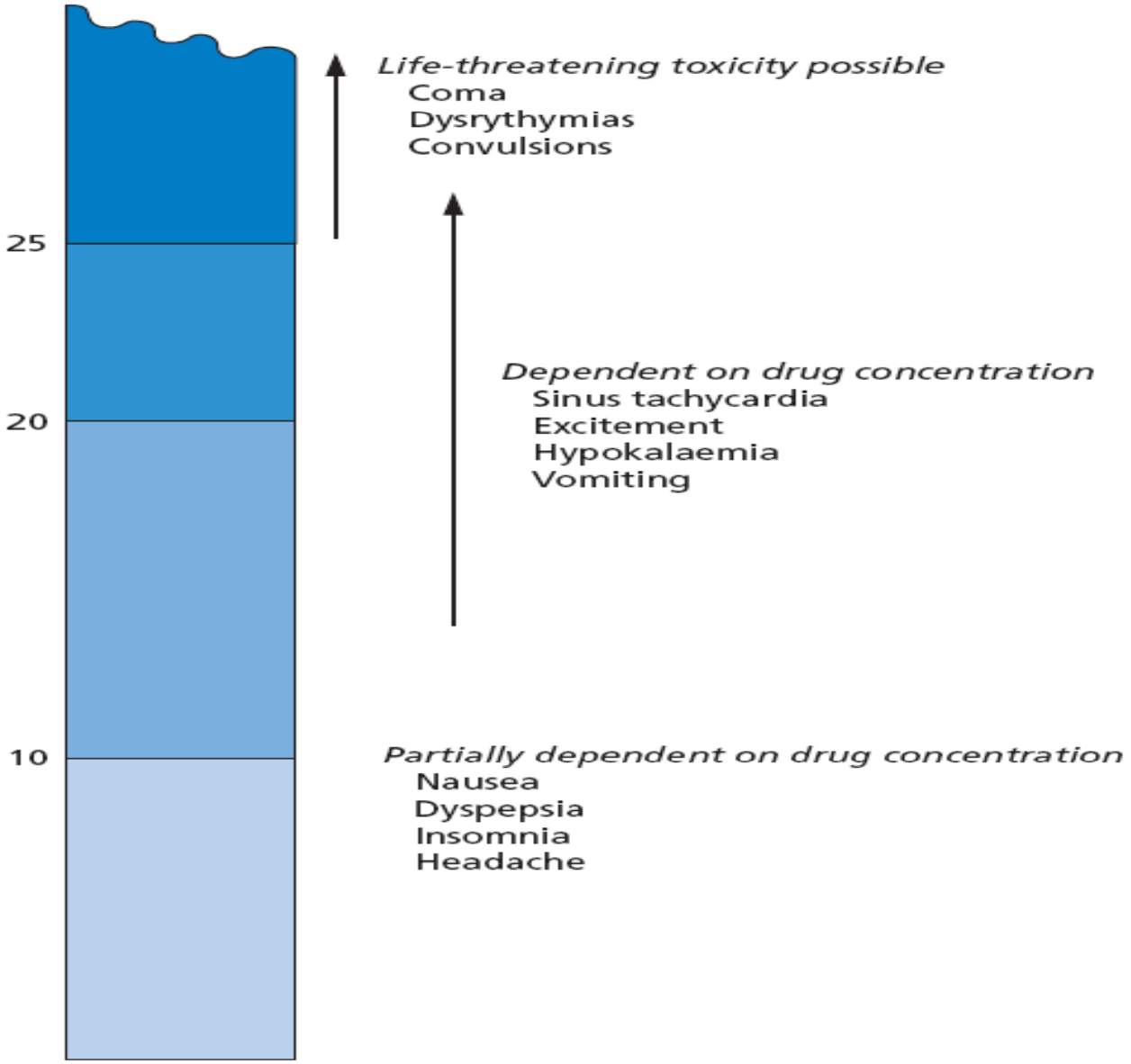


Figure 8.2: Theophylline plasma concentrations (mg/L). Note that there is a wide variation in the incidence and severity of adverse effects. (Adapted from Mant T, Henry J, Cochrane G. In: Henry J, Volans G (eds). *ABC of poisoning. Part 1: Drugs*. London: British Medical Journal.)

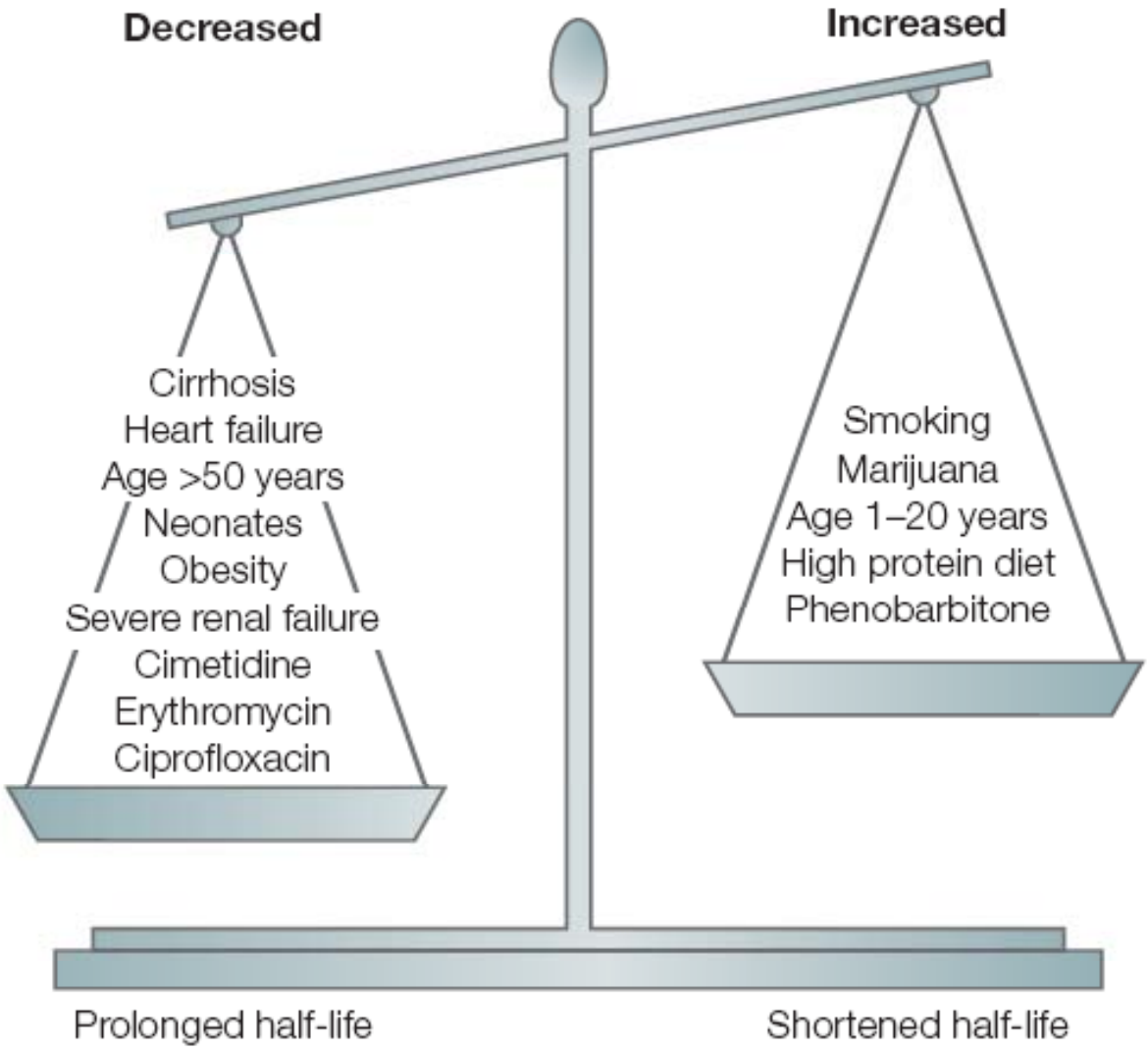


Figure 8.3: Theophylline clearance. (Adapted from Mant T, Henry J, Cochrane G. In: Henry J, Volans G (eds). *ABC of poisoning. Part 1: Drugs*. London: British Medical Journal.)

Some Drugs for which Therapeutic Drug Monitoring is Used

Immunosuppressants:

- **Cyclosporine compliance is a particular problem in children, and deterioration in renal function can reflect either graft rejection due to inadequate cyclosporine concentration or toxicity from excessive concentrations.**
- **Sirolimus use should be monitored, especially when used with cyclosporine or when there is hepatic impairment or during or after treatment with inducers or inhibitors of drug metabolism.**

Some Drugs for which Therapeutic Drug Monitoring is Used

Cyclosporine:

- **Optimum sampling time:**

  Trough (C_0) or 2 h post dose (C_2) whole blood sample.

- **Time to steady state:**

  2-6 days

- **Target range:**

  Varies widely with sample time transplant type and time after transplantation

Some Drugs for which Therapeutic Drug Monitoring is Used

Sirolimus:

- **Optimum sampling time:**
  Trough (pre-dose) Whole blood sample
- **Time to steady state:**
  5-7 days
- **Target range:**
  With cyclosporine: 4-12 µg/L
  Off cyclosporine: 12-20 µg/L

Some Drugs for which Therapeutic Drug Monitoring is Used

Tacrolimus:

- **Optimum sampling time:**
  Trough (pre-dose) Whole blood sample
- **Time to steady state:**
  2-5 days
- **Target range:**
  Varies with sample time transplant type and time after transplantation. Typically 15 µg/L following kidney transplantation, reducing to 5-10 µg/L

Some Drugs for which Therapeutic Drug Monitoring is Used

Mycophenolate:

- **Optimum sampling time:**
  Trough (pre-dose) or as needed to determine AUC
- **Time to steady state:**
  N/A
- **Target range:**
  Varies with transplant type, time of sample, method used and other medication

Some Drugs for which Therapeutic Drug Monitoring is Used

Antiarrhythmic drugs also require TDM