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).

- Inter-individual and intra-individual differences in drug response necessitate individualization of drug therapy.
- This means giving the right dose for the individual, in contrast to the population dose.
- Therefore, monitoring of drug therapy (for therapeutic and adverse effects) becomes essential.
- How?
- 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 of the therapeutic effect.
- Monitoring is also needed to reduce the risk of a clinical event (stroke, heart attack, pulmonary embolism, etc.).
- For example, antihypertensive drugs are monitored by their effect on blood pressure, statins by their effect on serum cholesterol, warfarin by its 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.
- Measuring drug concentrations in plasma or serum identifies only pharmacokinetic variability, and may usefully guide dose adjustment. (e.g: anticonvulsants).
- Measuring drug concentrations for use in this way is often referred to as 'therapeutic drug monitoring'.

Role of therapeutic drug monitoring:

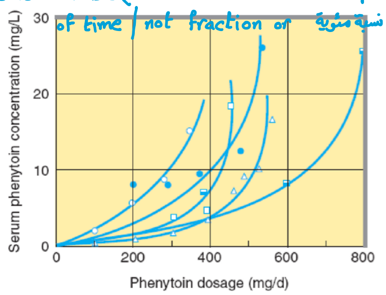


FIGURE 24–5 Nonlinear relationship of phenytoin dosage and plasma concentrations. Five patients (identified by different symbols) received increasing dosages of phenytoin by mouth, and the steady-state serum concentration was measured at each dosage. The curves are not linear, since, as the dosage increases, 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.)

- Measurements of drug concentrations in plasma are most useful when:

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. Drug effect can NOT readily be assessed quantitatively by clinical observation.
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.
6. "Apparent resistance" to the action of a drug needs an explanation. (when non-compliance is suspected).

- Another indication, distinct from therapeutic drug monitoring, for measuring drug concentrations in plasma is for clinical toxicology purposes.
- Such measurements can guide management of a poisoned patient (paracetamol or aspirin).

Practical Aspects:

1. Drug concentration at the site of action, which is related to drug effect, should be proportional to plasma drug concentration.

• A constant tissue to plasma drug concentration ratio only occurs during the terminal β-phase of elimination.

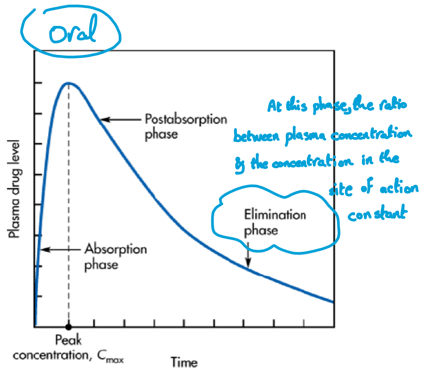
2. Earlier in the dose interval, the plasma concentration does NOT reflect the concentration at the site of action accurately.

3. Measurements must be made when distribution of the drug has been completed.

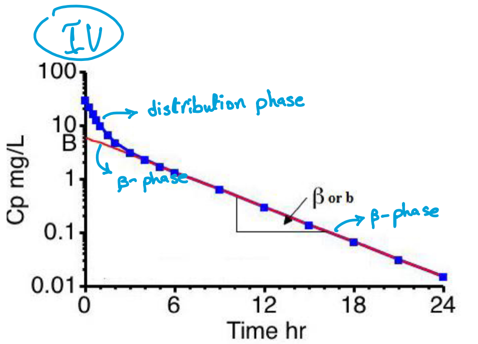
4. Timing of blood sampling is, therefore, critical for the measurement to be useful.

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

5. Sampling is only useful if the drug concentration in the body is at a "steady-state". → administration rate is equal to elimination rate



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



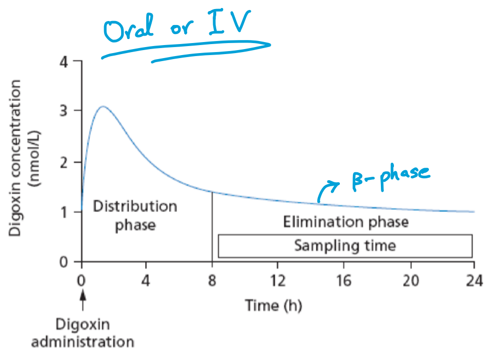
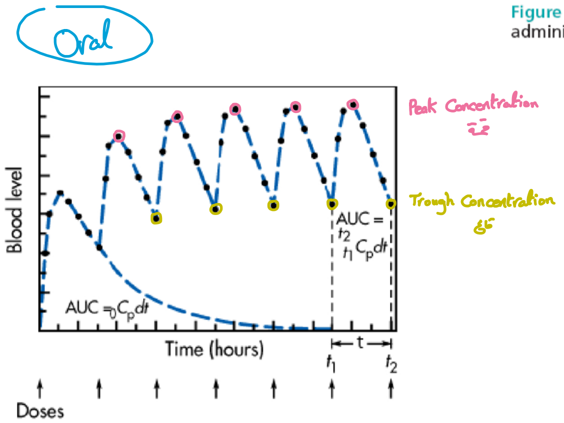


Figure 8.1: Serum concentration–time course following digoxin administration

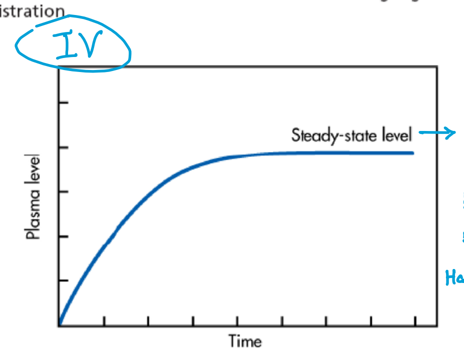
• After single dose the peak is when the absorption rate = elimination rate

• But, steady-state is when: administration rate = elimination rate which is the dosing rate

لما تعطي ال dose الثانية، بتعطيها on the top / not on zero of the remaining dose



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



Plasma level-time curve for constant IV infusion.

ما بجيب أبداً monitoring قبل ما أوصلها ← for most drugs after 5 half-lifes of administration

Half-life	→ steady-state
2h	8h
8h	32h
2d	8d
50d	200d

مثل ← 50d: Amiodarone

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

• 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.

• 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:

- 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.

You keep monitoring at the same time

Lithium:

- Optimum sampling time:
12 h post-dose
- Time to steady state: 3-7 days of regular 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.

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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

Aminoglycoside antibiotics:

- Peak concentrations measured 30-60 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.

Amikacin, Gentamicin, Tobramycin:

- 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	Amikacin	Gentamicin, Tobramycin
Trough	< 10 mg/L	< 2 mg/L
Peak	20-30 mg/L	5-10 mg/L

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

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)

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.

Carbamazepine:

- Optimum sampling time:
Pre-dose (trough sample)
- Time to steady state: 2-6 days of chronic dosing
- Target range:
4-12 mg/L

Ethosuximide:

- Optimum sampling time:
Pre-dose (trough sample)
- Time to steady state: 5-15 days of chronic dosing
- Target range:
40-100 µg/L

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

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

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.

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

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.

- 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.

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.

Cyclosporine:

- Optimum sampling time:
Trough (C0) or 2 h post dose (C2) whole blood sample. *Not plasma or serum*
- Time to steady state: 2–6 days
- Target range:
Varies widely with sample time, transplant type and time after transplantation

→ في ناس بحكوا ما بكفي بدنا Area under the curve ⇝ so we need also concentration in between to calculate it.

so, Cyclosporine might have:
1- Trough
2- Peak 2 h post the dose
3- One concentration in between
} to calculate Area under the curve

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

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

Mycophenolate:

→ Also this drug needs: Area under the curve (3 concentrations) or Trough

- 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

Theophylline and Antiarrhythmic drugs also require TDM

→ The main use → premature apnea in newborn → improves central breathing activity & contraction of the diaphragm

Clinical Consequences of Not performing Therapeutic Drug Monitoring - Cases

1. A patient with diabetes was admitted to hospital to undergo aggressive therapy for osteomyelitis of the foot as a result of a foot injury. The patient was discharged on gentamicin therapy and followed by community nurses. Five weeks later, the patient was diagnosed with ototoxicity and vestibular dysfunction associated with gentamicin toxicity. Expert review of case was not supportive, noting that there was no indication for using gentamicin for such a prolonged period based on culture results taken while in hospital. The case was considered indefensible from a quality of care and causation perspective. https://www.hiroc.com/resources/risk-reference-sheets/failureperformcommunicate-therapeutic-drug-

2. A patient with diagnoses of kidney disease, COPD, asthma, and type 2 diabetes, under the care of multiple physician-specialists, was prescribed a course of Methotrexate (MTX). The patient continued to receive MXT for approximately one month. Within 2 weeks following the suspension of MTX, the patient attended at the Emergency Department for internal bleeding. The patient's condition deteriorated and passed away: the autopsy revealed patient expired secondary to methotrexate toxicity. Expert review of the care and decisions was not supportive. Experts noted that the treatment was initiated despite concerns raised by the care team, as well as, a verbal order to hold treatment by the primary care physician, both of which failed to be documented in the medical chart. During this period, symptoms consistent with MXT toxicity were observed, including skin ulcers, generalized erythema, facial edema, and gait issues. However, these symptoms were not communicated to the treating physician directly, despite requests to do so by multiple family members. Patient complexity, competing physician orders, poor charting practices, and lack of patient and family-centered care contributed to a delay in acting on patient symptoms. https://www.hiroc.com/resources/risk-reference-sheets/failure-performcommunicatetherapeutic-drug-monitoring-0

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