- **Measuring drug concentrations for use in this way is often referred to as 'therapeutic drug monitoring'.**

Therapeutic Drug Monitoring

- especially for those with narrow therapeutic index.
- Individualized dose.

Yacoub Irshaid MD, PhD, ABCP

Department of Pharmacology

sth

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).

interaction with receptors and magnitude of the action

Therapeutic Drug Monitoring

- **Inter-individual and intra-individual differences in drug response necessitate individualization of drug therapy.**
- **That 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?**

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 of the therapeutic effect.
  - E.g: Antihypertensive agent, monitoring measure is BP.
- Monitoring is also needed to reduce the risk of a clinical event (stroke, heart attack, pulmonary embolism, etc.).

Bc some adverse rxns are dose dependant.
E.g; β-blockers → ↓HR but maybe in ↑ dose leads to bradycardia.

Therapeutic Drug Monitoring

- 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.

thus find another way to monitor the drug.

• الفكرة إنه عشان نقيس ليه الدوا بالأنسجة لازم نأخذ biopsy بس هاد الإشي مابزبط
- targeted tissue concentration proportional اللي بكون plasma concentration فبناخذ

Therapeutic Drug Monitoring

- **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'.**

Therapeutic Drug Monitoring

Role of therapeutic drug monitoring:

- **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.** reported

• e.g.: ↑ conc. ↑ action
↓ conc ↓ action

- **Drugs that work via active metabolites, and drugs with irreversible actions, are unsuited to this approach.** * then no meaning for parent drug conc. monitoring.

* unless we monitor the active metabolites conc.

Therapeutic Drug Monitoring

③ ↳ Reduction in the action of the drug with continuous administration of the drug in the same dose

- **Tolerance also restricts the usefulness of plasma concentrations measurement.**

1- ↓ reg. of receptors
2- ↑ in drug metabolism.
3- Depletion of NTs.

2. **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).**

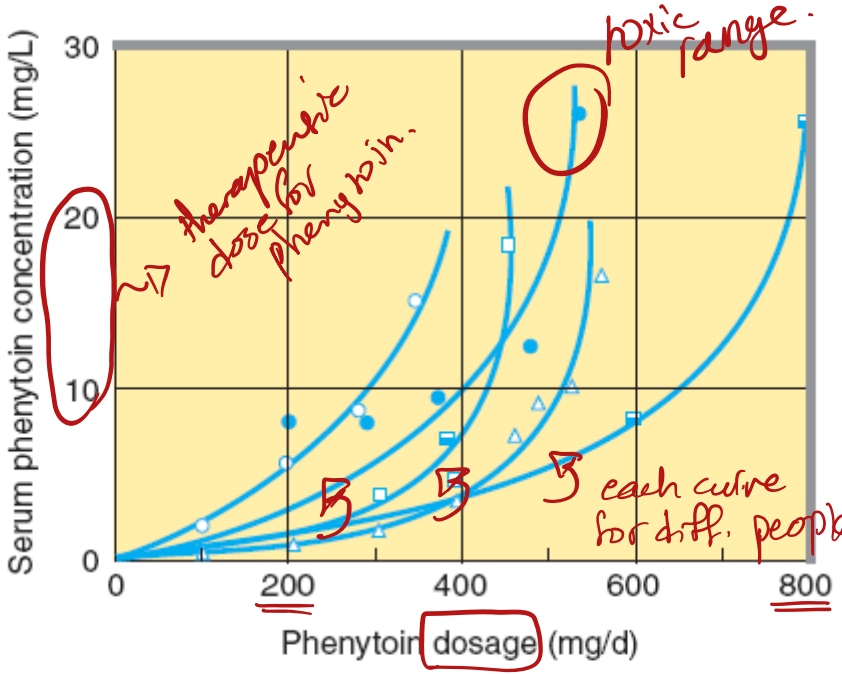


FIGURE 24–5 Nonlinear relationship of phenytoin dosage and plasma concentrations. Five patients (identified by different symbols) received increasing dosages of phenytoin by mouth, and the steady-state serum concentration was measured at each dosage. The curves are not linear, since, as the dosage increases,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

so we need to have therapeutic drug monitoring by measuring the plasma conc of the drug

Therapeutic Drug Monitoring

easily can reach toxicity.

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.

we give the drug but no therapeutic effect

6. "Apparent resistance" to the action of a drug needs an explanation. (when non-compliance is suspected).

Therapeutic Drug Monitoring

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

• check conc.
if reached low levels; means it exerted its effect well
and you cannot reverse the process then.

Recorded

Therapeutic Drug Monitoring

should be there

Practical Aspects:

هو ال بهمنا طب لسلك بنجسو بدل plasma

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

not equal

for example 2-4 mg/L in plasma gives a conc. at site of action which is effective.

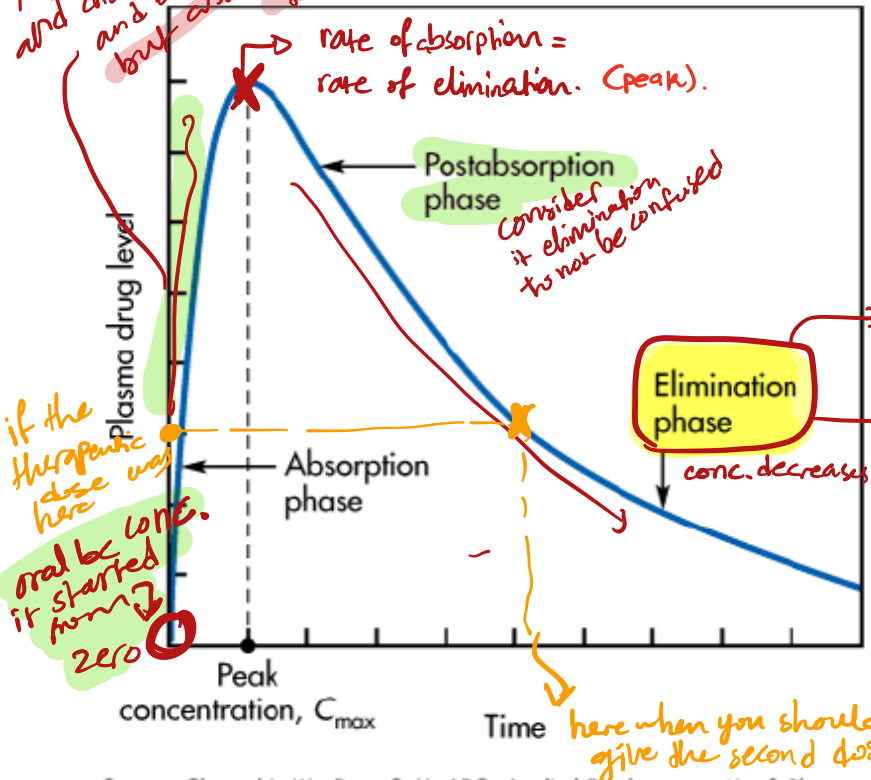
- *A constant tissue to plasma drug concentration ratio only occurs during the terminal β-phase of elimination.

Absorbtion + Distribution.

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

Absorption and distribution and even elimination but absorption is the fastest.

oral administration.



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.

Therapeutic Drug Monitoring

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.

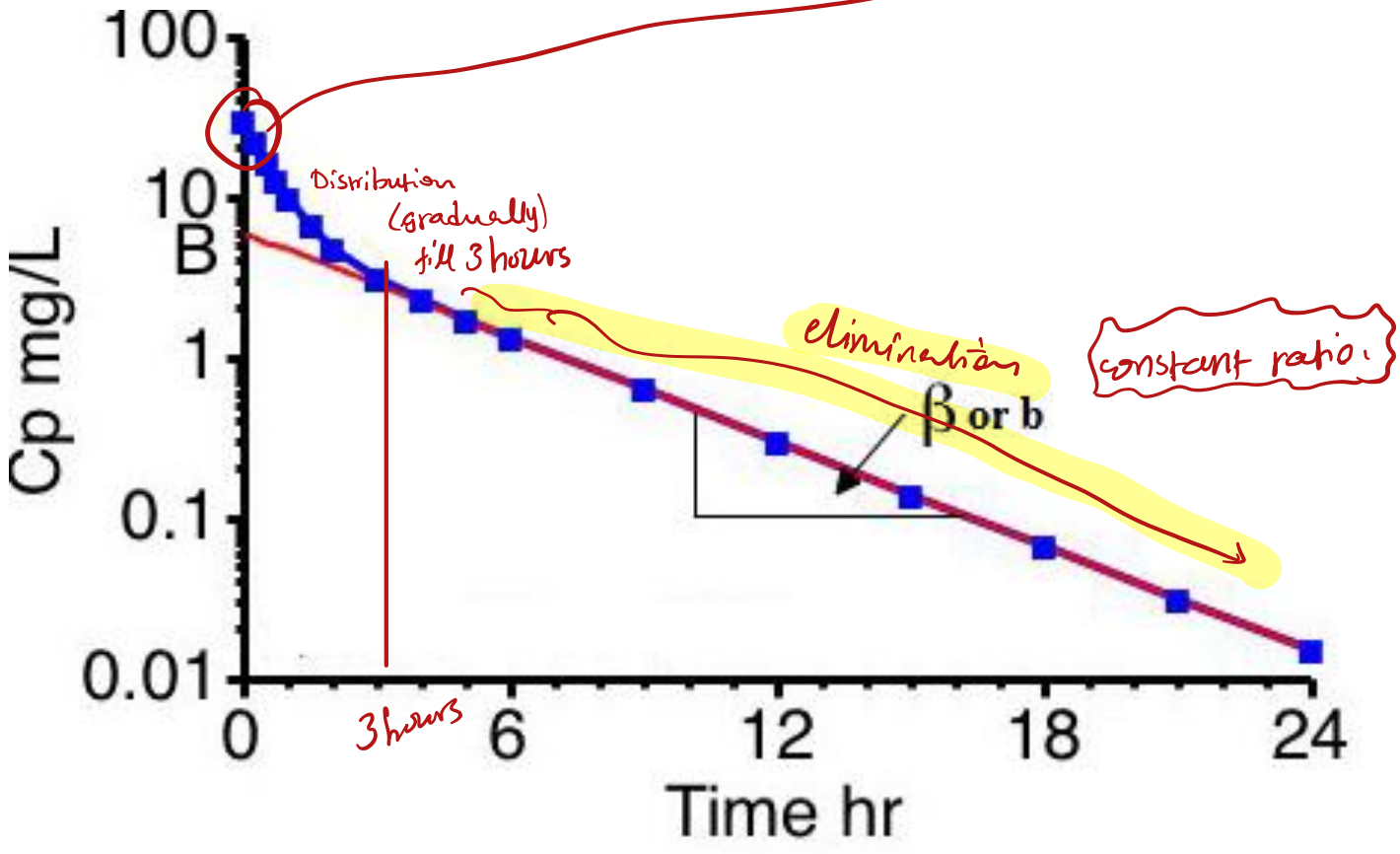
- There is No place for 'routine' or "random" blood samples for measurement of plasma drug concentration for TDM.

متى آخذ العينة المناسبة للوقت
اللي أعطيني فيه الدواء.

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

(after 4t1/2) bc = the therapeutic range

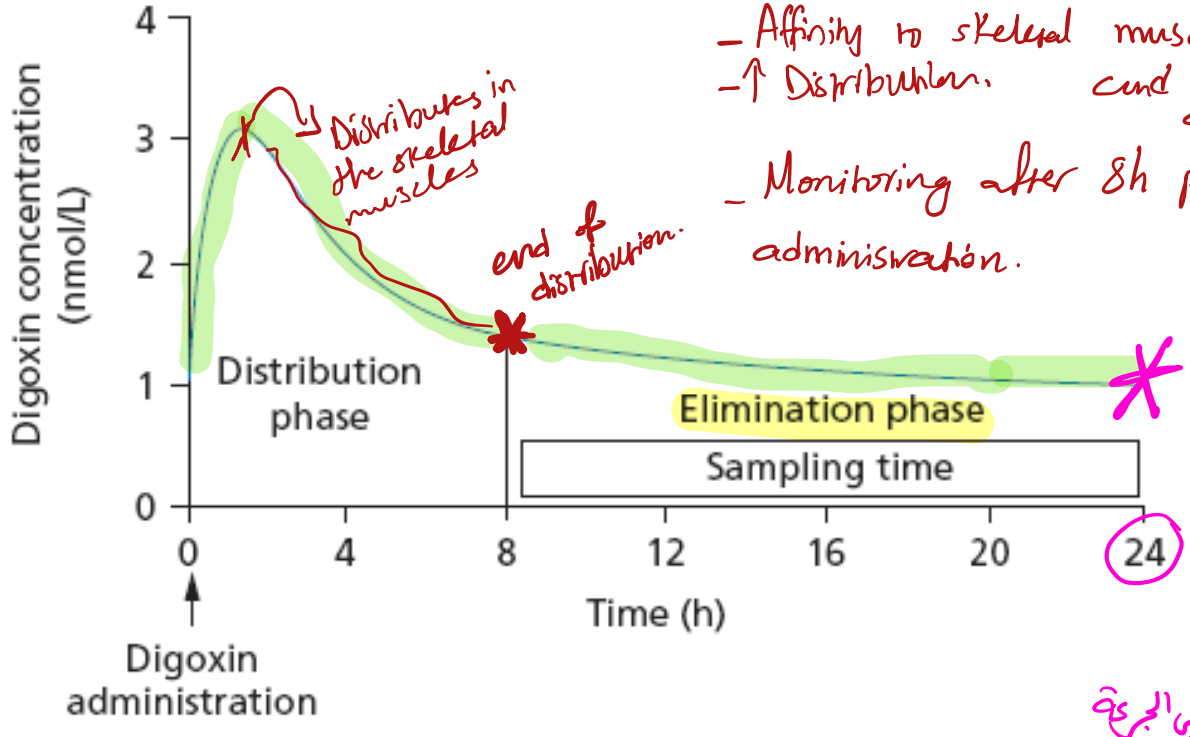
• IV not oral administration



* This is an exception, bc the drug goes to site other than the target site (heart).

- Oral digoxin administration for HF

- Affinity to skeletal muscle cells and cardiac cells.
- ↑ Distribution.
- Monitoring after 8h post administration.



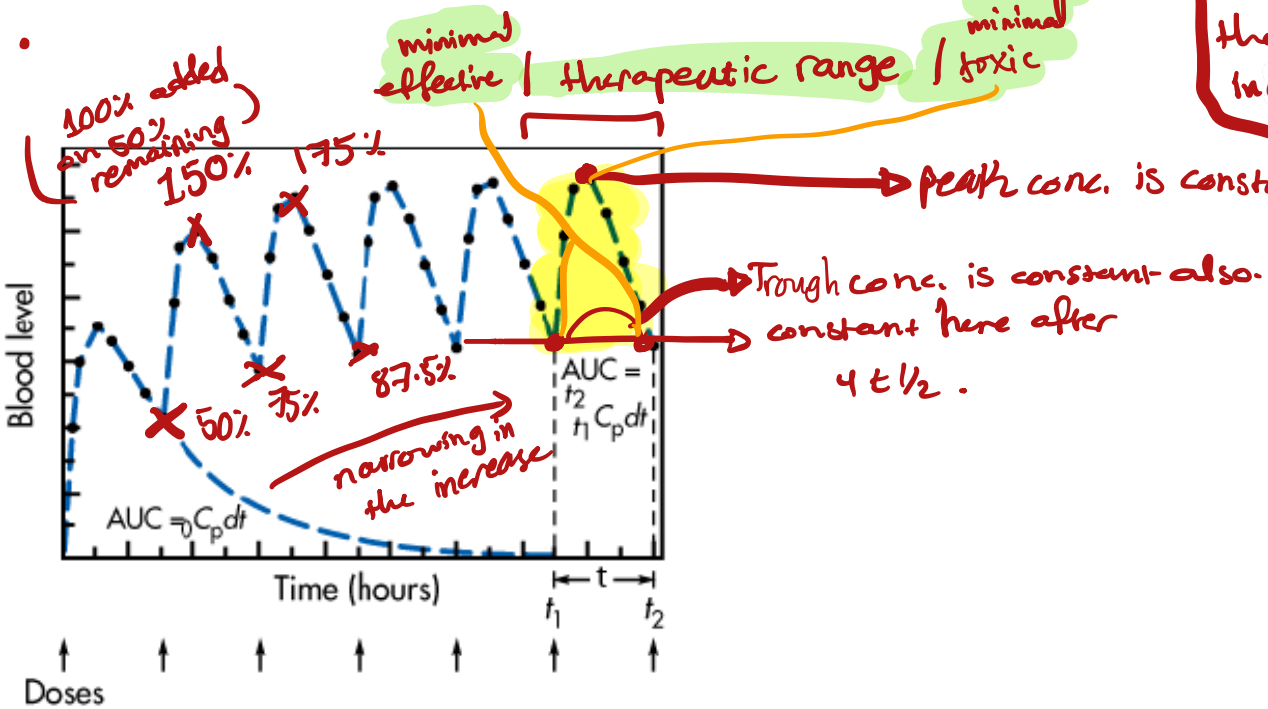
* trough conc. just before the next dose.

قبل ما تعطي الجرعة خذ عينة دم.

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

- 1 $t_{1/2}$ = 50% of drug eliminated.
-

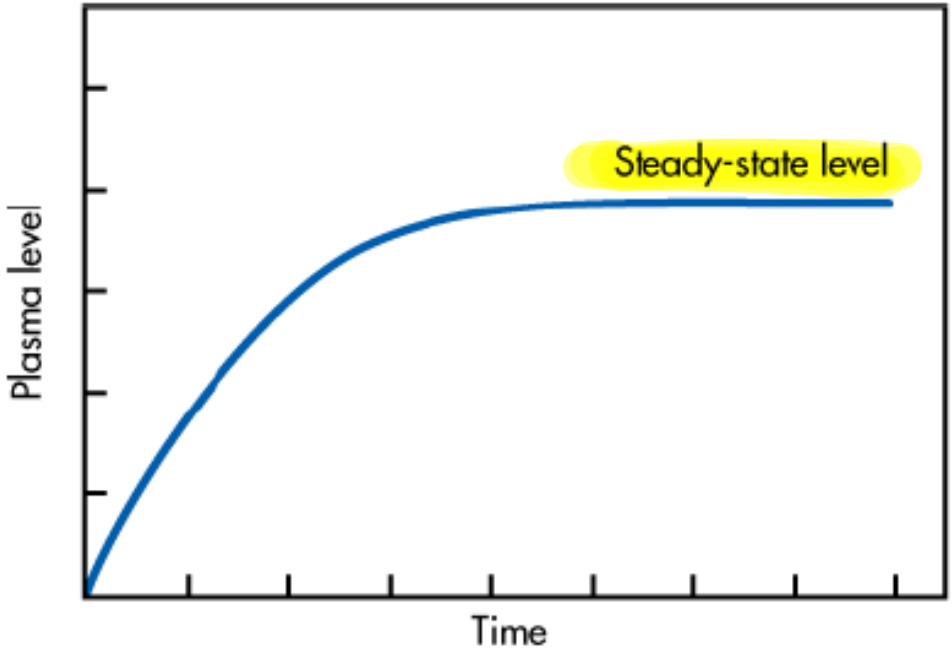
Fluctuation in the concentration in oral administration



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.

IV infusion

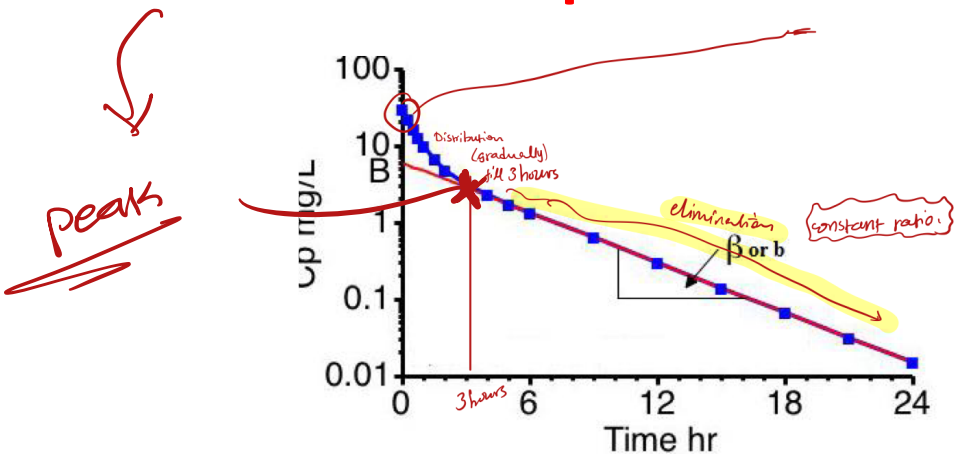


Source: Shargel L, Wu-Pong S, Yu ABC: *Applied Biopharmaceutics & Pharmacokinetics, 6th Edition*: www.accesspharmacy.com

Plasma level–time curve for constant IV infusion.

Therapeutic Drug Monitoring

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.**



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

• epileptic patients — phenytoin 10-20 dose. it's highly protein bounded thus the patient might have liver disease thus proteins are low thus ↑ free fraction

- **Plasma drug concentrations must always be interpreted in the context of the patient's clinical state.**

Shift between equilibrium (measure the total not free

- **Random samples from patients to measure drug concentration are meaningless, misleading, as well as being a waste of time and money.**

so if the patient was taking low dose but responding don't increase the dose then!

Drugs For Which Therapeutic Drug Monitoring Is Used

- **Digoxin:**
- **Optimum sampling time:**

  Trough (pre-dose) or > 8 h post-dose.

  first 8 hours distribution ends then elimination starts

- **Time to steady state:**

  7-10 days.

  t 1/2 = 36
  steady state = 6 days

- **Target range:**

  In AF: 0.8-2 µg/L.

  In heart failure: 0.5-1 µg/L.

* don't monitor digoxin until 1 days of administration

or any drug not before the steady state.

Drugs For Which Therapeutic Drug Monitoring Is Used

Lithium:

- **Optimum sampling time:**

  12 h post-dose not trough nor peak

- **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.

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

IV

Aminoglycoside antibiotics:

- **Peak concentrations measured 30-60 minutes after dosing and trough levels, measured immediately before a dose.** + 3doses /day. each 8hours
- **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, Gentamicin, Tobramycin :

- **Optimum sampling time:**

  not in a single dose.

  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

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

Immunosuppressant.

Teicoplanin:

- **Optimum sampling time:**

  Trough: Immediately before next dose

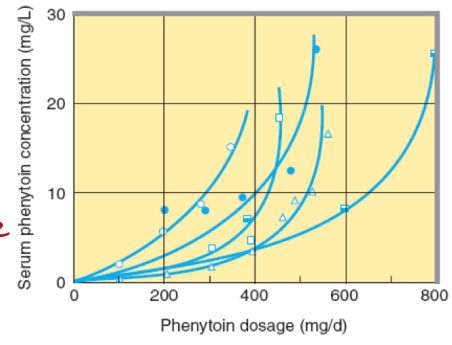
- **Time to steady state:**

  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:

its increase in conc is out of proportion in the ↑ in dose

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

protein binding.

3) the possible effects of pregnancy on its distribution.

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

↳ ∴ if low albumin, low doses could be effective and no need to increase serum albumin.

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.** but still it's better to take
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: Anti folate drug

not therapeutic conc.

- **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.**

to normal cells.

- folinic acid rescue, to protect normal cells.

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

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.**

to know the exact cause we need bx.

- **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:**

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

  whole blood sample not plasma or serum be most of cyclosporine is attached to RBCs.

- **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 Area under the curve. → 3 concentrations at different times (3 samples) are required to determine AUC.

- **Time to steady state:**

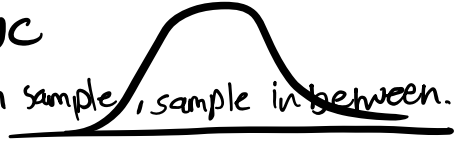
  N/A

- **Target range:**

  Varies with transplant type, time of sample, method used and other medication

Cyclosporine AUC

2h post dose, trough sample, sample in between.



Some Drugs for which Therapeutic Drug Monitoring is Used

used to treat neonatal apnea in NNICU, bc

now substituted by amiodarone (broad spectrum).

Theophylline and Antiarrhythmic drugs also require TDM

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.**

Aminoglycoside

neglect!

renal (shouldn't be used > 5 days)

https://www.hiroc.com/resources/risk-reference-sheets/failure-performcommunicate-therapeutic-drug-monitoring-0

Clinical Consequences of Not performing Therapeutic Drug Monitoring - Cases

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-performcommunicate-therapeutic-drug-monitoring-0