Therapeutic Drug Monitoring

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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

- **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?**

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, to be used 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.).

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.**

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:

- **Measurement of drug concentration in plasma is 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.**

Therapeutic Drug Monitoring

- **Drug 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).**

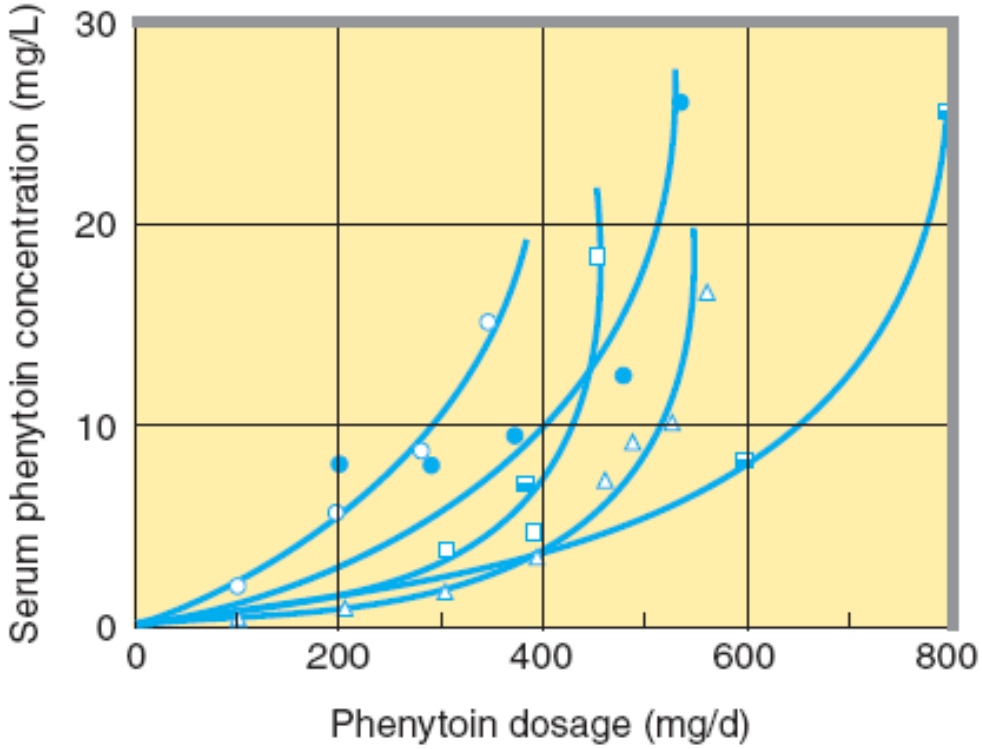


FIGURE 24–5 Nonlinear relationship of phenytoin dosage and plasma concentrations. Five patients (identified by different symbols) received increasing dosages of phenytoin by mouth, and the steady-state serum concentration was measured at each dosage. The curves are not linear, since, as the dosage increases,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

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-adherence to medication is suspected).**

Therapeutic Drug Monitoring

- **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).**

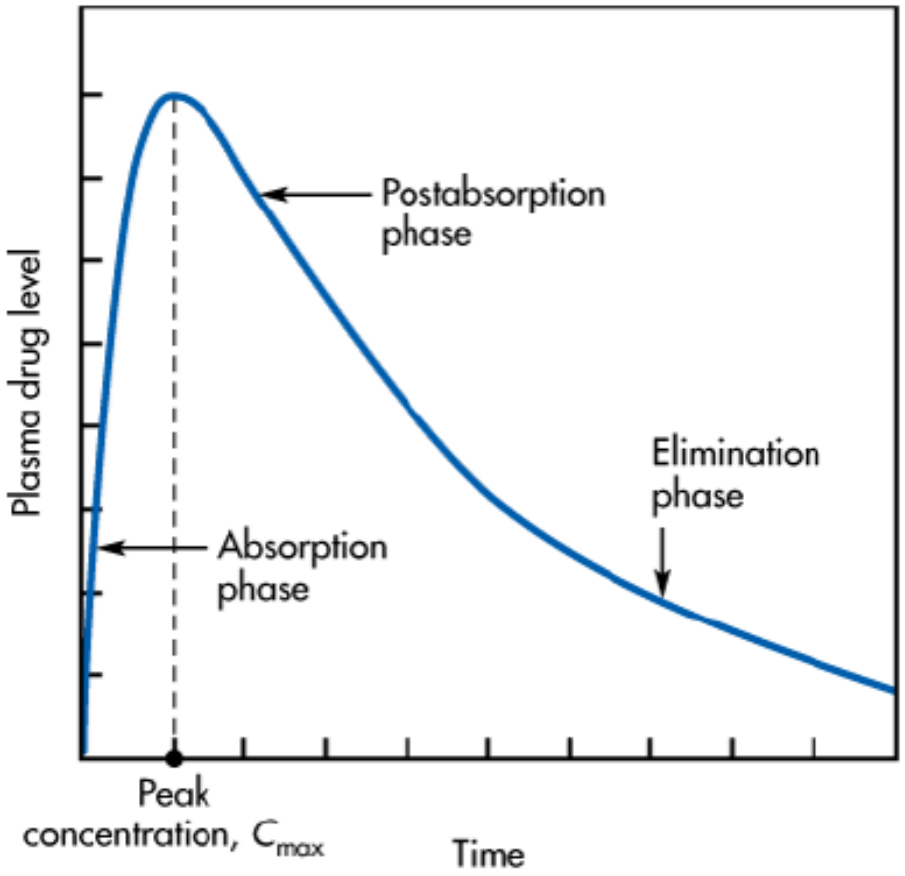
Therapeutic Drug Monitoring

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.**



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

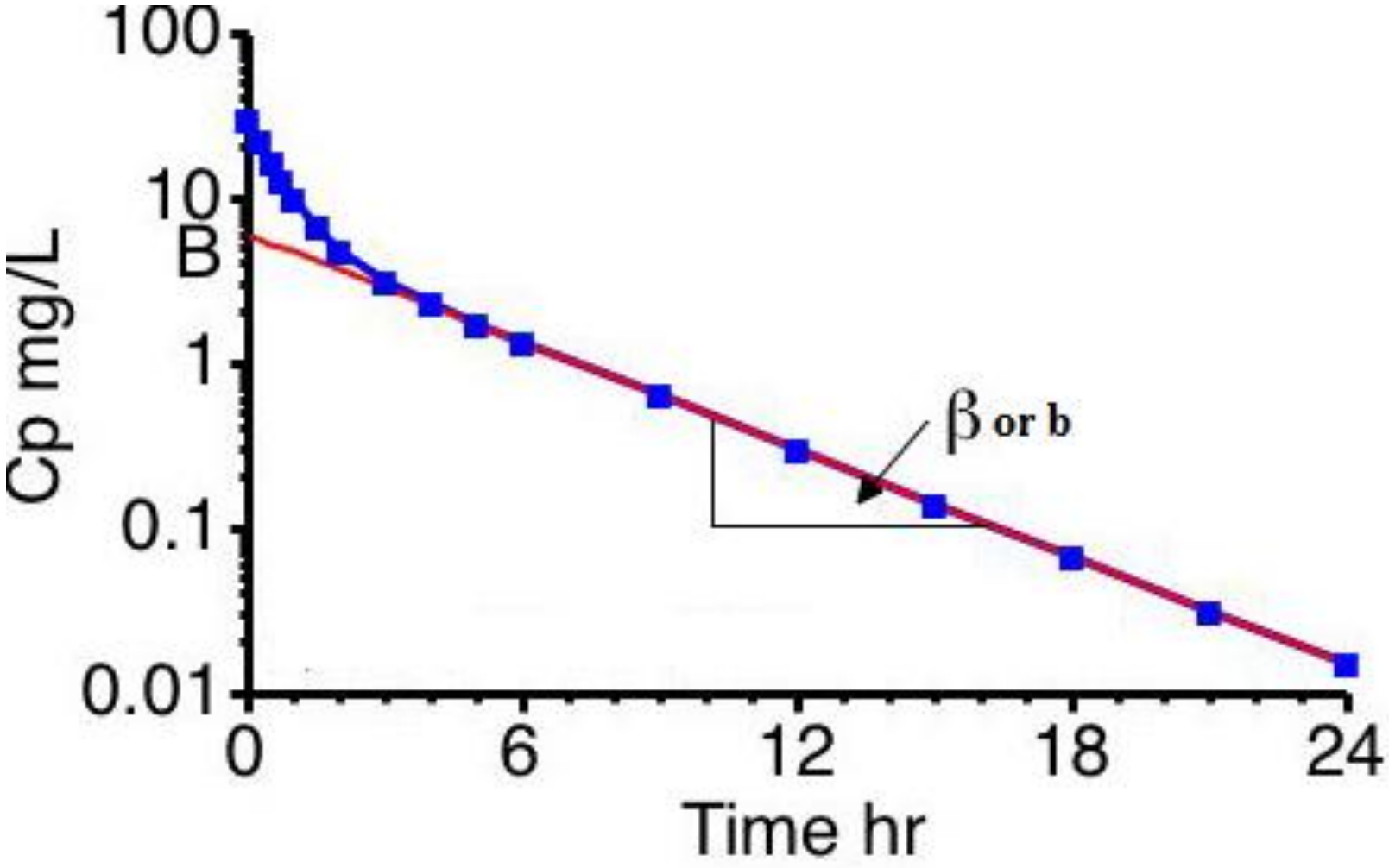
Plasma level–time curve for a drug given in a single oral dose. The drug absorption and elimination phases of the curve are shown.

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.**

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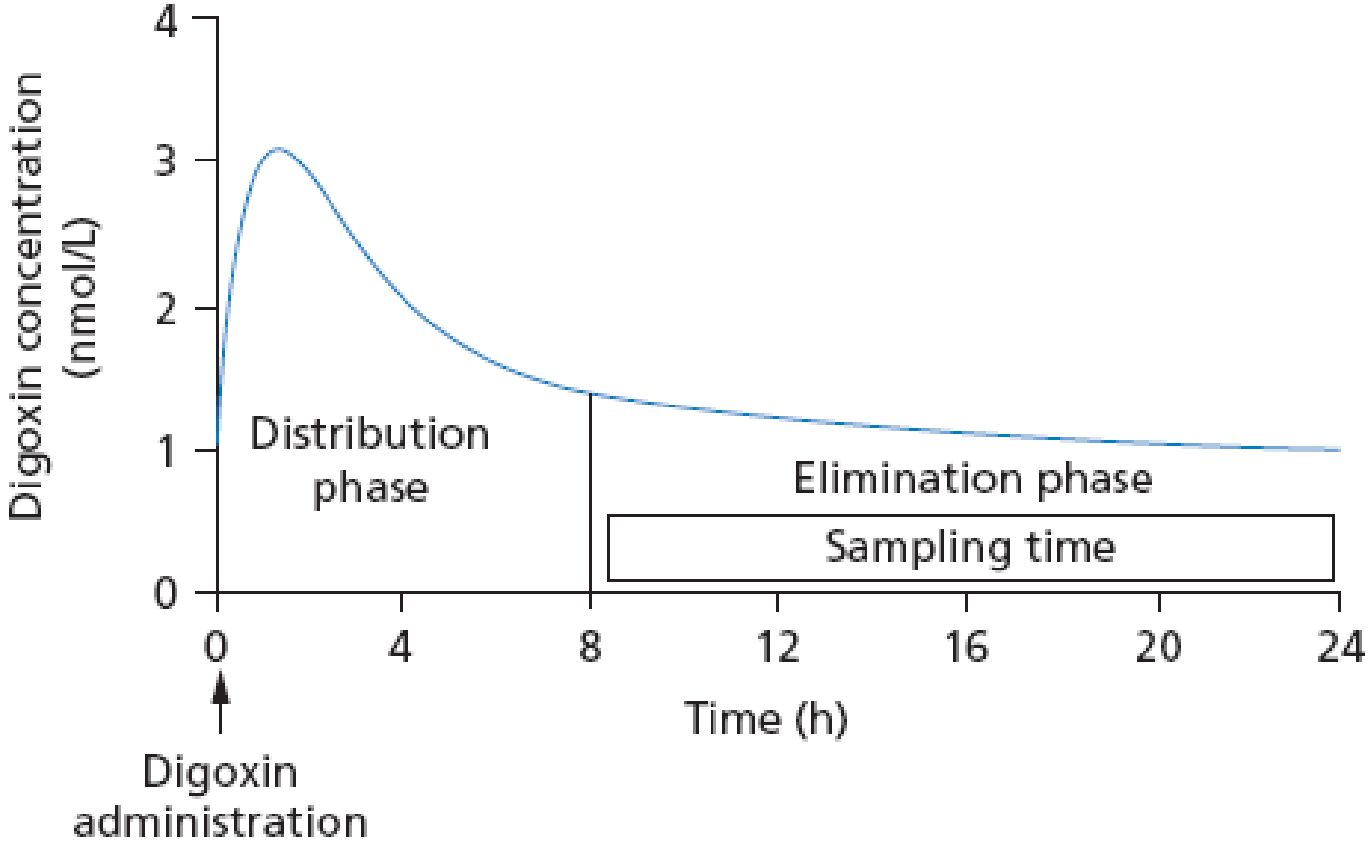
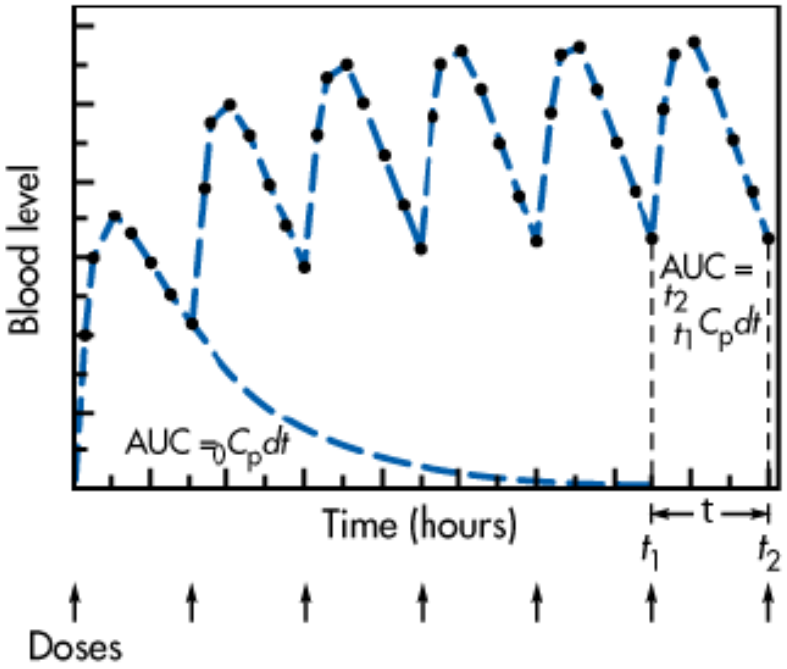
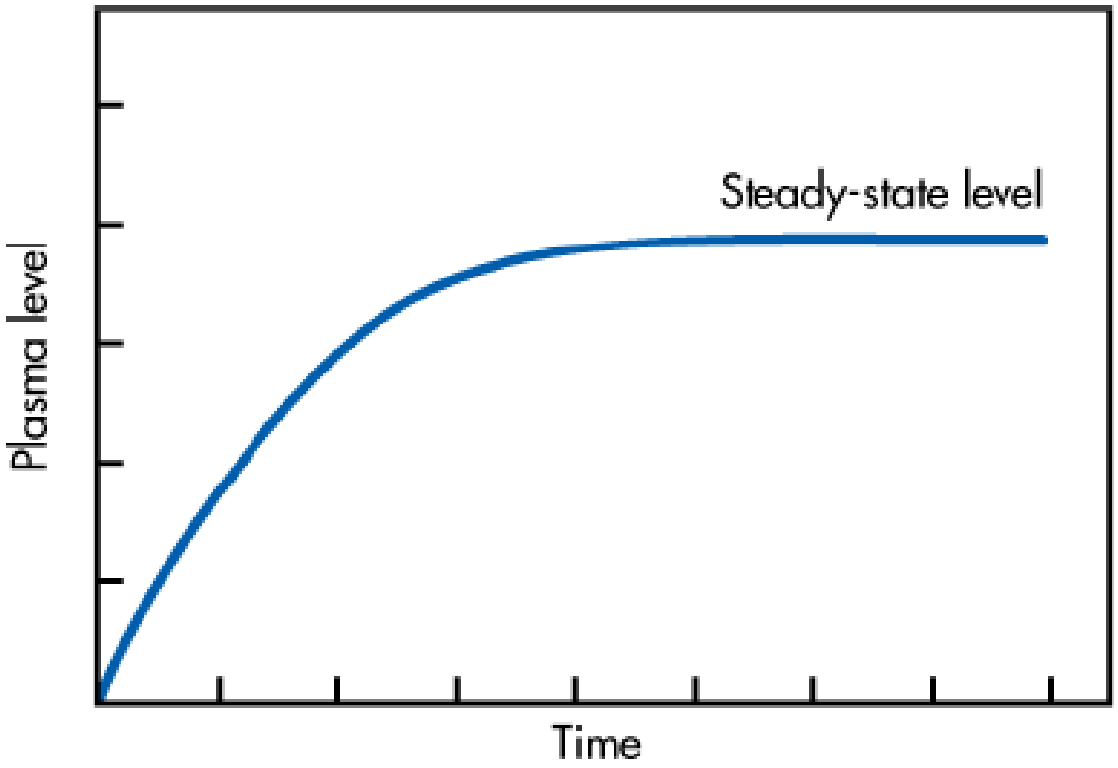


Figure 8.1: Serum concentration–time course following digoxin administration.



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.

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

- **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.

Lithium:

- **Optimum sampling time:**

  12 h post-dose

Clozapine:

- **Optimum sampling time:**

  trough sample.

Drugs For Which Therapeutic Drug Monitoring Is Used

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.**

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

Teicoplanin:

- **Optimum sampling time:**

  Trough: Immediately before next dose

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:**
  Trough: Immediately before next dose

Carbamazepine:

- **Optimum sampling time:**
  Pre-dose (trough sample)

Ethosuximide:

- **Optimum sampling time:**
  Pre-dose (trough sample)

Drugs For Which Therapeutic Drug Monitoring Is Used

Lamotrigine:

- **Optimum sampling time:**

  Before a dose (trough sample)

Valproate:

- **Optimum sampling time:**

  Before a dose (trough sample)

Drugs For Which Therapeutic Drug Monitoring Is Used

Zonisamide:

- **Optimum sampling time:**

  Trough: Immediately before next dose

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.**
- **Optimum sampling time:**

  As required by protocol, often 24, 48 and (if necessary) 72 h post high-dose therapy.

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.

Sirolimus:

- **Optimum sampling time:**

  Trough (pre-dose) Whole blood sample

Some Drugs for which Therapeutic Drug Monitoring is Used

Tacrolimus:

- **Optimum sampling time:**

  Trough (pre-dose) Whole blood sample

Mycophenolate:

- **Optimum sampling time:**

  Trough (pre-dose) or as needed to determine AUC

Some Drugs for which Therapeutic Drug Monitoring is Used

- **Other drugs such as 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.**

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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.**

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