Concept of Therapeutic drug monitoring

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Disclosures/Conflict of Interest

No financial, business or personal conflicts of interest to disclose

Outline

Basic Clinical Pharmacokinetics

- Pharmacokinetic parameters relevant for dosage regimen

Concept of Therapeutic drug monitoring

- indications; which drugs; optimal sampling time; what to document

Relationship dose – effect PK - PD

dose → plasma conc. → site of action → effect → clinical outcome

pharmacokinetics (PK)

pharmacodynamics (PD)

What the body does to the drug?

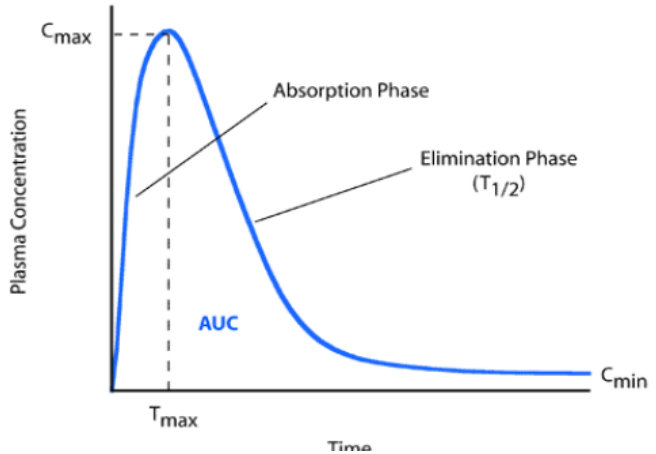
What the drug does to the body?

A – absorption

D – distribution

M – metabolism

E - excretion



Relevance of PK

Answer to questions:

- What dose to give?
- How often to give it ?

- When is steady-state achieved ?

- How to change the dose in certain medical conditions ?
- How some drug-drug interactions occur ?

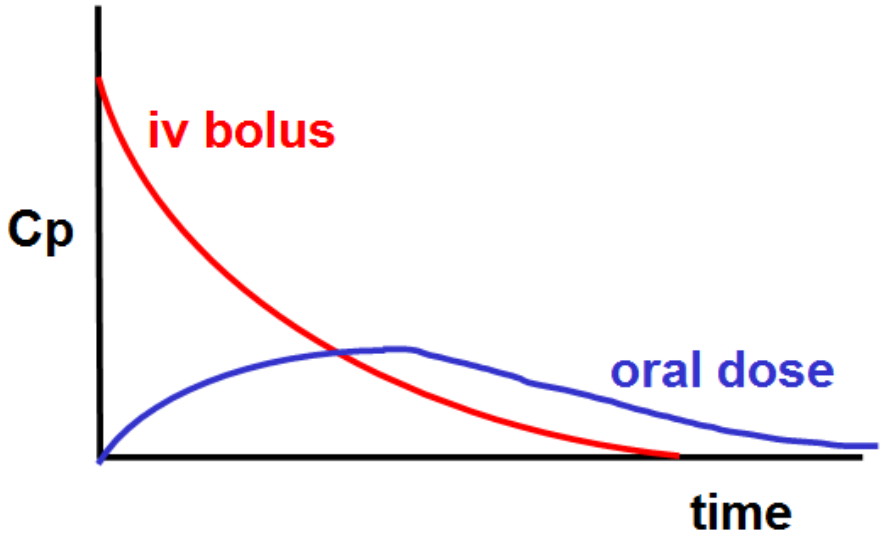
Basic clinical pharmacokinetics Pharmacokinetic parameters

- Bioavailability (F)
- Volume of distribution (Vd)
- Clearance (CL)
- Half-life ($t_{1/2}$)

- Peak conc. ($C_{ss\ max}$)
- Trough conc ($C_{ss\ min}$)
- Area under the curve (AUC)

Bioavailability

The fraction (F) of the administered dose of the drug that reaches the systemic circulation available to have an effect (0-1)



$$F = \frac{AUC_{p.o.}}{AUC_{i.v.}}$$

Bioavailability

Relevance:

If F<1 (100%)

Absorbed dose = administered dose x bioavailability

- Calculation of *p.o*. dose based on F and *i.v.* dose

Question:

If drug Z has 50% bioavailability and standard *i.v.* dose is 100mg, what should oral dose be?

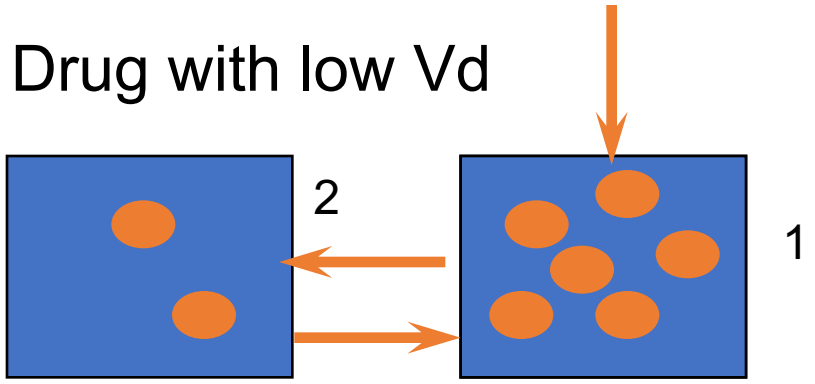
Answer:

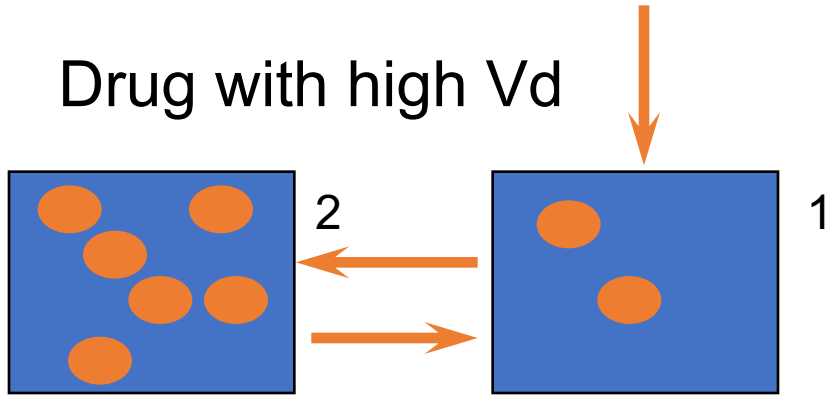
$$D = \frac{100mg}{0.5} = 200mg$$

(apparent) Volume of distribution

- Volume of distribution (Vd) describes the volume into which the drug would have to be distributed in order to obtain the same plasma

$$Vd = \frac{\text{Amount of absorbed drug}}{C}$$





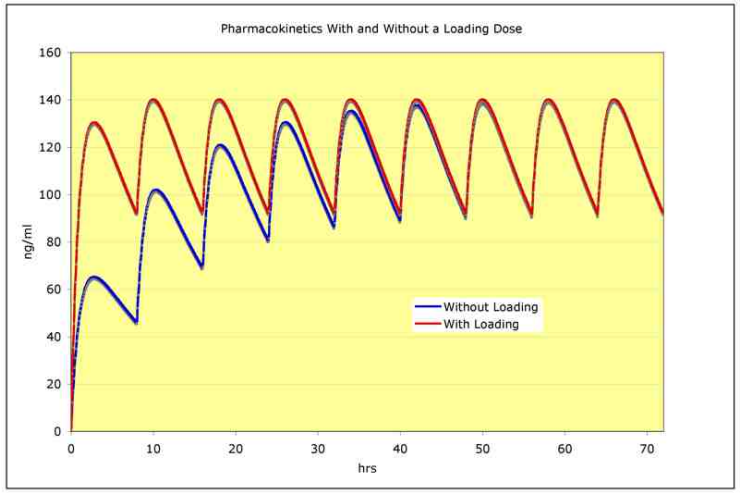
Hihg tissue binding

Volume of distribution

- Relevance:

Loading Dose (LD) = a *dose* of drug sufficient to produce a plasma concentration of drug that would fall within the therapeutic window after only one dose over a very short interval.

$$LD = \frac{C \times Vd}{F}$$



Q: What is a loading dose of Drug Z (Vd is 15L, oral bioavailability 30%, target plasma conc. 5mg/l).

A: LD= 5mg/L x 15L / 0.30 = 250 mg

Clearance

- Clearance (CL) is volume of plasma that is cleared of drug per unit time

- $CL = K_e \times Vd$

- $CL = CL_{renal} + CL_{hepatic} + CL_{lung}$

- Rate of elimination = CL x Concentration

$$CL = \frac{\text{Rate of elimination (mg/h)}}{\text{concentration (mg/L)}} = \frac{\text{volume}}{\text{time}} \qquad CL = \frac{D}{AUC}$$

Clearance

Relevance:

- **Maintenance Dose (MD)** = The dose needed to maintain the concentration within the therapeutic window when given repeatedly at a constant interval
- Dosing rate (mg/h) = D/τ

$$MD = \frac{C \times CL \times \tau}{F}$$

Q: What is MD of CBZ for plasma level of 6mg/L, TID, p.o. CL is 6.5L/h, F is 75%.

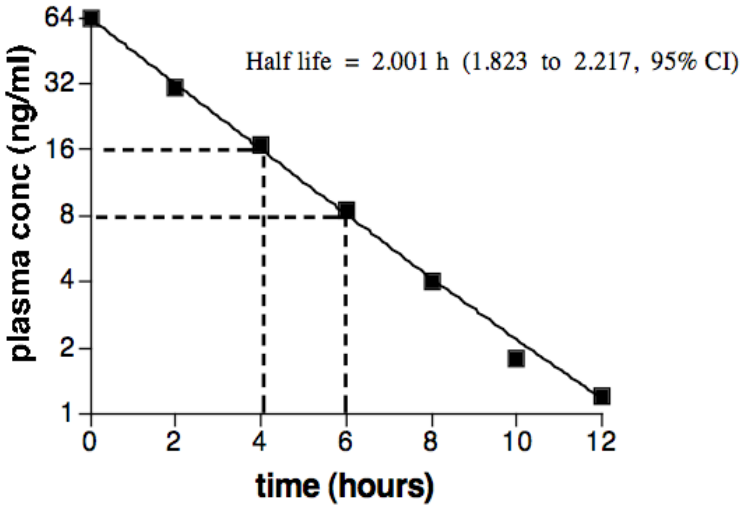
$$A: \ MD = \frac{6mg/L \times 6.5L/h \times 8h}{0.75} = 416mg$$

3 x 400 mg (2x200mg) CBZ

Half-life

- $T_{1/2}$ - time taken for the concentration of drug in blood to fall by a half

$$t_{1/2} = \frac{0.693}{K_e} \qquad t_{1/2} = \frac{0.693 \times Vd}{CL}$$



Half life (linear kinetics) does not depend on:

- dose
- dosage interval

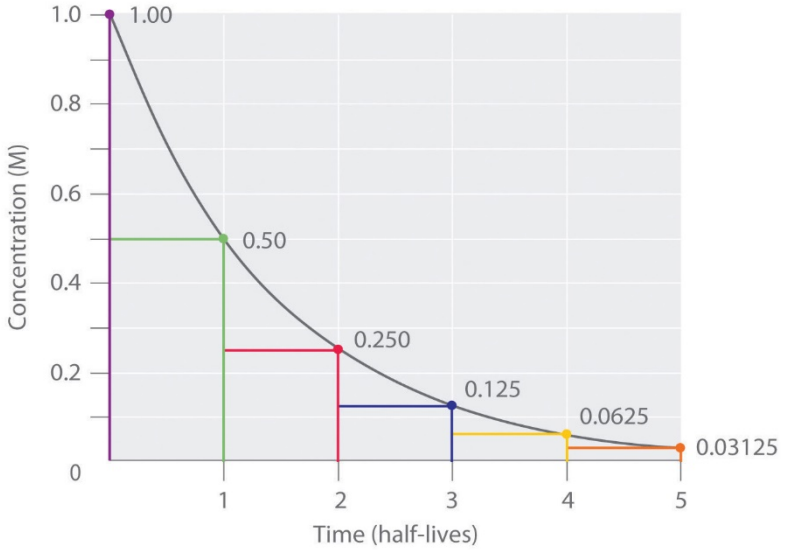
Half - life

- Relevance:

- Dose interval

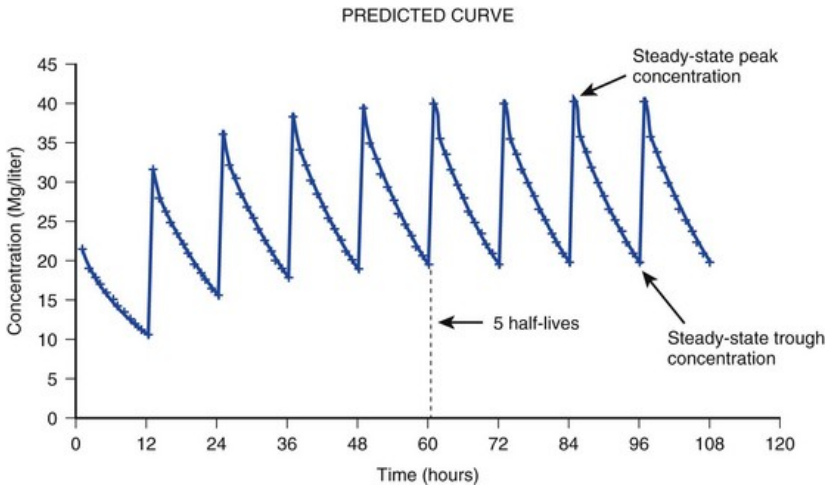
- Time to completely eliminate the drug from the body

$(5 \times t_{1/2})$



- Time to reach steady state (Tss) depends on half life

$Tss = 4 - 5 \times t_{1/2}$



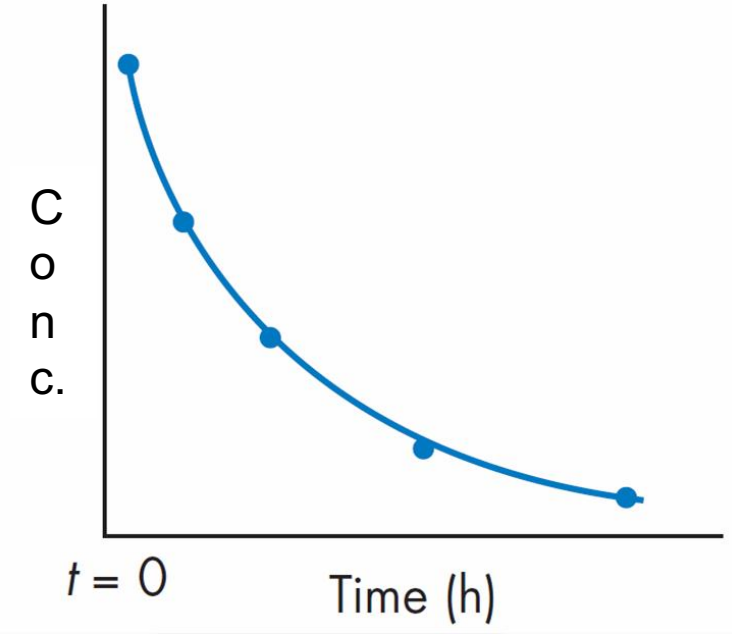
Half–life and elimination rate constant (K)

Relevance:

Time to get to certain concentration (C*):

$$C^* = C_0 \cdot e^{-K \cdot t} \rightarrow e^{-K \cdot t} = \frac{C_0}{C^*} \rightarrow K \cdot t = \ln\left(\frac{C_0}{C^*}\right)$$

$$\rightarrow \quad t = \frac{\ln \frac{C_0}{C^*}}{K}$$



Half–life and elimination rate constant (K)

- Relevance:

- Patient has a potentially toxic digoxin level of 4.4µg/L. Given that the half life of digoxin in this patient is 60h, for how long should digoxin be stopped to allow the level to fall to 1.5 µg/L.

$$K = \frac{0.693}{60\,\mathrm{h}} = 0.01155\ \ 1/\mathrm{h}$$

$$t = \frac{\ln \dfrac{4.4\,\mu\mathrm{g/L}}{1.5\ \mu\mathrm{g/L}}}{0.01155\ \ 1/\mathrm{h}} = 93h$$

Half–life and elimination rate constant (K)

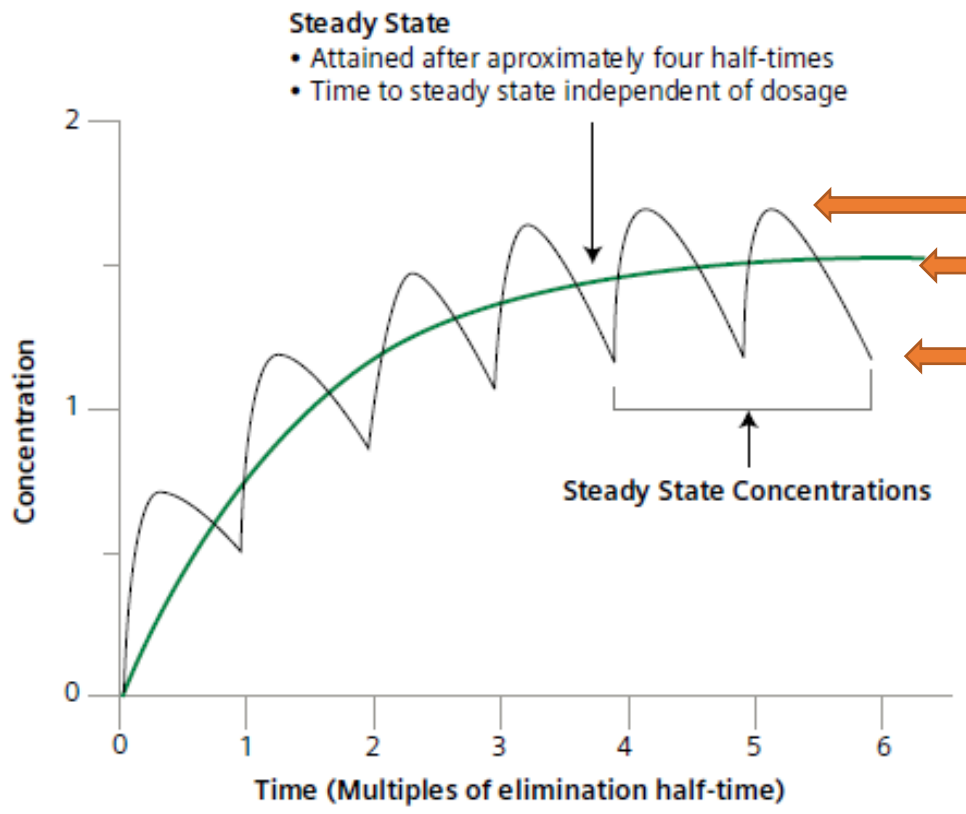
- Relevance:
- Determine a suitable *i.v.* bolus dose for drug A that follows liner, one-compartment pharmacokinetics (half life is 4h, Vd 5L) to maintain plasma conc. above 4mg/L for 12h.

$$C^* = \mathrm{C}_0 \cdot e^{-K \cdot t} \qquad 4mg/L = \mathrm{C}_0 \cdot e^{-0.17x12}$$

$$4mg/L = \mathrm{C}_0 \cdot e^{-2.04} \qquad C_0 = 30.8\ \mathrm{mg/L}$$

$$D = \mathrm{C\ x\ Vd} = 30.8\ \mathrm{mg/L\ x\ 5\ L} = 154\ \mathrm{mg}$$

PK steady state (ss)



Peak conc. ($C_{ss\ max}$)

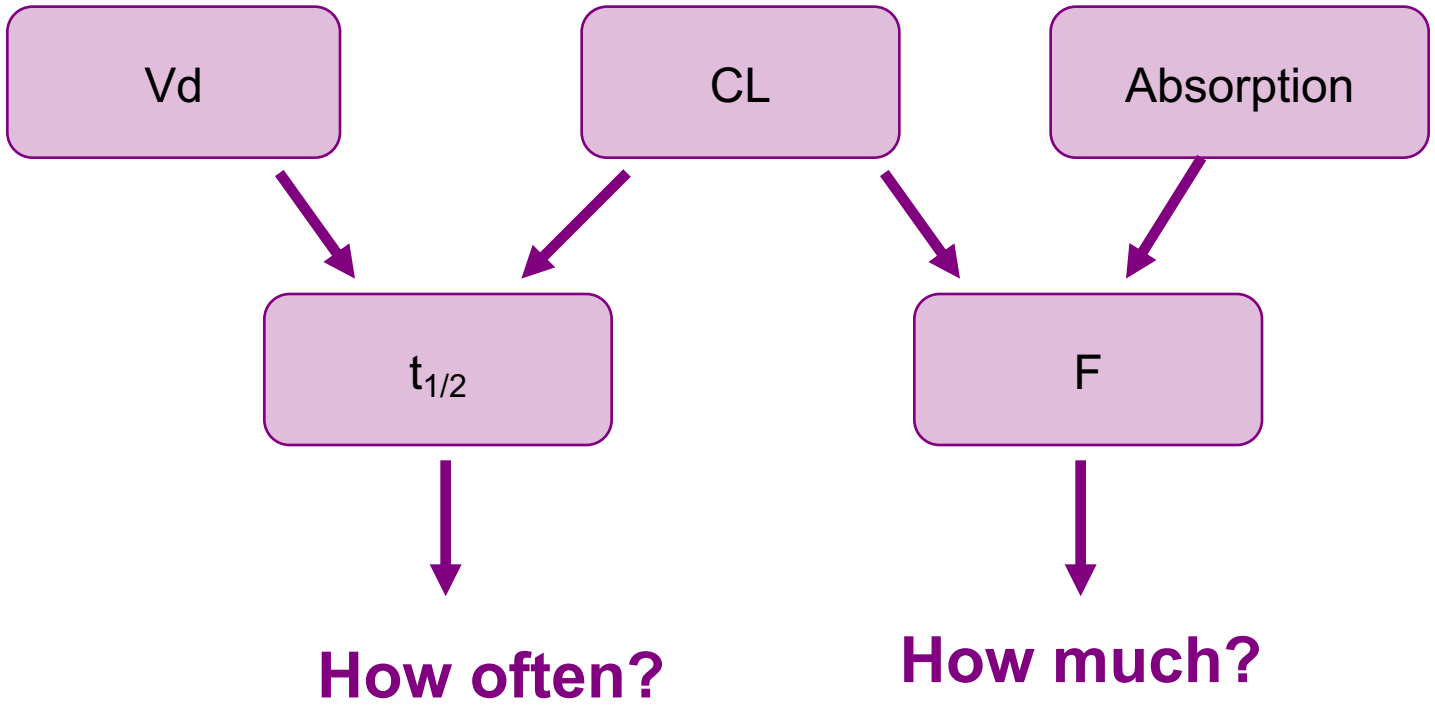
Average conc. ($C_{ss\ avg}$)

Trough conc.($C_{ss\ min}$)

Dosing interval (τ)

Rate in =Rate out

Contributing factors to dosing



+ age, gender, liver and kidney function, weight, other concurrent diseses, the other medicines…

Altering dose regimen

- We can not control: CL, Vd, F

  Change in F will alter Css avg (not Peak:Trough)

  Change in Vd will alter Peak:Trough (not Cssavg)

  Change in CL will alter both Peak:Trough and Cssavg

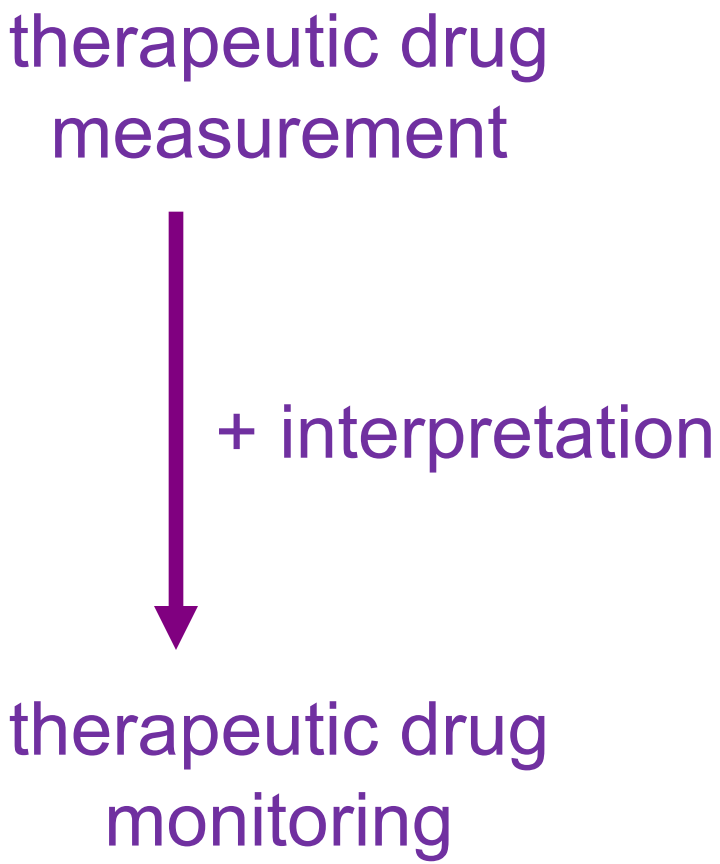
  If disease, age, renal/hepatic function, the other drugs.. change CL, F, V

- We can control Dose rate (D/τ)

Therapeutic drug monitoring (TDM)

Therapeutic drug monitoring (TDM)

- TDM involves the measurement of drug concentrations in biological fluid and the interpretation of those concentrations.
- TDM is the clinical assessment of a drug's pharmacokinetic properties.
- **Interpretation** requires knowledge of the pharmacokinetics, sampling time, drug history and the patient's clinical condition.



Indications for TDM ('why do it')

- Individualizing therapy (assesment of MD, τ ; adjustment of D)

- Toxicity
  – diagnosing toxicity when the manifestation of toxicity and disease state are similar (theophylline)
  – avoiding toxicity (aminoglycosides)
- Assessing compliance

- Diagnosing failed therapy (TDM can help distinguish between ineffective drug treatment and non-compliance)

- Change in patient's clinical state

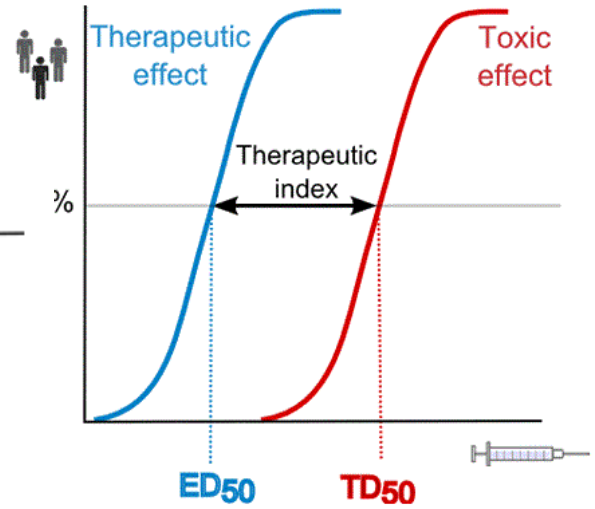
- Monitoring and detecting drug interactions

- Guiding withdrawal of therapy

Which drugs?

- narrow therapeutic index (NTI) drugs

$$\text{Therapeutic index} = \frac{TD_{50}}{ED_{50}}$$



- significant pharmacokinetic variability
- a reasonable relationship between plasma conc. and clinical effects
- established target concentration range
- availability of cost-effective drug assay.

Timing of the plasma sample('when to do it')

In most cases when SS is reached

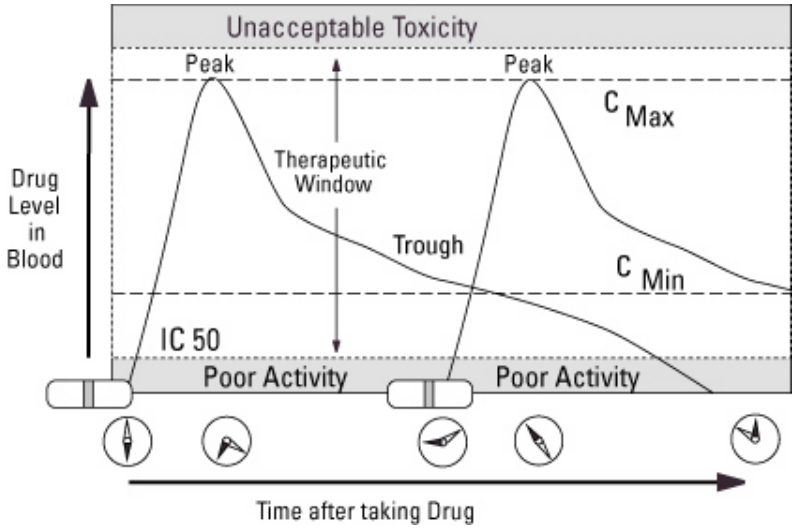
- earlier if toxicity is suspected.

At the appropriate time in relation to the last dose

- generally measured in the elimination phase (correlates with C_{trough});
  gives a more reliable guide to drug dosing;

- C_{peak} some antibiotics (aminoglycosides)

- not during the distribution phase
  (not equilibrium between
  plasma and tissue conc.)



Therapeutic drug monitoring request ('what to document')

Details to include on the request form

- Time sample collected
- Time dose given
- Dosage regimen (dose, duration, dosage form)
- Patient demographics (age/gender)
- Comedications
- Relevant co-morbidities (e.g. renal/liver disease)
- Indications for testing (e.g. toxicity, non-compliance)

REQUEST FORM OF TDM

Patient Name.....Date.....Age.....Gender.....

Wt.....Ht.....Ward.....Ordered by.....Phone No.....

DRUG LEVEL REQUESTED.....

REASON FOR REQUEST :

( ) Suspected toxicity ( ) Compliance ( ) ( ) Absence of therapeutic response

Please indicate when level is needed :( )within 24 h ( )within 1-2 h ( )others....

WHEN THE THERAPY STARTED….. TIME AND DATE OF LAST DOSE:….. Route : IV, IM, SC, PO, others....

Dosage form.....

Time..... Dose..... Freq.....

THIS DRUG LEVEL IS FOR :

SAMPLING TIME : ( ) Trough or predose level Date.....Time.....

( ) Peak level Date..... Time.....

DOES THE PATIENT HAVE ORGAN-SYSTEM DAMAGE ?

( ) Renal ( ) Hepatic ( ) Cardiac ( ) GI ( ) Endocrine ( ) Others.....

OTHER DRUG(S) PATIENT IS TAKING:.....

DRUG LEVEL & USUAL THERAPEUTIC RANGE.....

Technologist/Chemist.....

INTERPRETATION.....

.....

Pharmacists/Pharmacokinetics/Pharmacologist

Date..... Time.....

Interpretation
Potential for error

- Assuming patient is at steady-state
- Assuming patient is adherent to the therapy

- Not knowing the sampling time in relation to dose administration
- Not considering decreased renal/hepatic function
- Not considering drug interactions
- Using reference range as absolute values

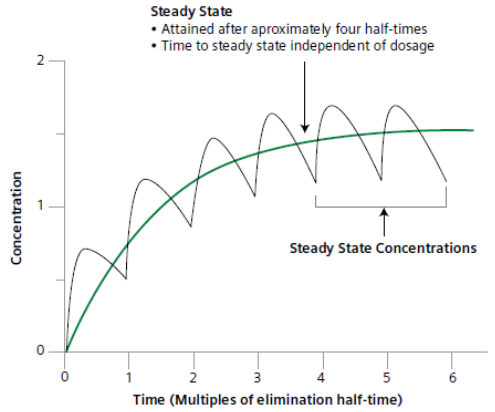
Interpretation sample concentration

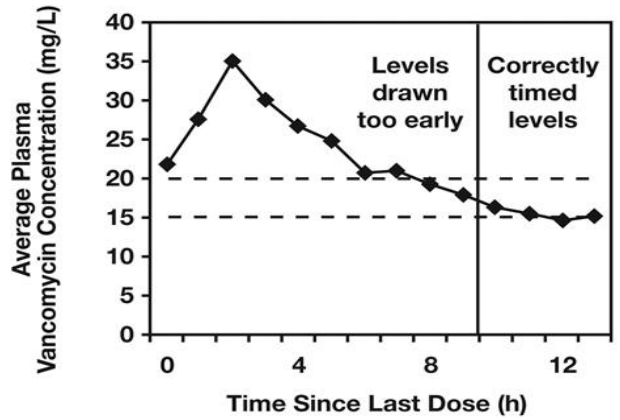
Lower than anticipated

- Patient noncompliance
- Error in dosage regimen
- Rapid elimination
- Poor bioavailability
- Drug-drug interaction (ind.)
- not achieved SS

Higher than anticipated

- Patient noncompliance
- Error in dosage regimen
- Slow elimination
- Decreased renal/hepatic function
- Drug–drug interaction (inh.)
- Time sampling





Interpretation

- Before making dose adjustments, consider:

- if the sample was taken at the correct time with respect to the last dose,
- if a steady state has been reached
- If the patient is adhered to the treatment
- If there is a drug-drug interaction
- If there is a liver/kidney dysfunction

+ the individual patient without rigid adherence to a target range.

Methods available to individualize drug therapy

- Clinical pharmacokinetic principles using simple mathematical relationships that hold for all drugs that obey linear pharmacokinetics

$$D^* = \frac{\mathrm{Css}^*}{\mathrm{Css}} x\, \mathrm{D} \qquad t = \frac{\mathrm{lnCss} - \mathrm{lnCss}^*}{\mathrm{K}}$$

- Bayesian calculations represent the gold standard TDM approach

- (complex) computer programs that could cover more drugs.

Conclusion

Knowledge and understanding of basic principles of Clinical pharmacokinetics are necessary for interpretation of measured concentration and individualization of drug dose.

Measurement of serum drug conc. without appropriate interpretation is useless (or even misleading).

TDM is complementary to and not a substitute for clinical judgement so it is important to treat the individual patient and not the laboratory value.

Successful TDM service requires a coordinated effort among physicians, clinical pharmacists, and laboratory personnel.

THANK YOU

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