Clinical Pharmacokinetics

Therapeutic drug monitoring (TDM)

TDM

Is the application of pharmacokinetic principles for the rational design of an individualised dosage regimen

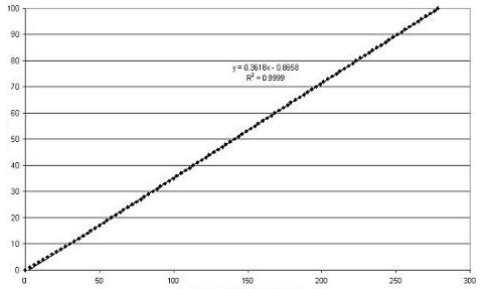
Why?

1. To, maximize therapeutic effectiveness

2. To, minimize toxicity

Until 1960s dosing was empirical

Starting with low dose and then increase the dose gradually until effect is obtained



During the 1970s and early 1980s

Serum drug concentration become better index than dose to guide treatment

Clinical pharmacokinetic hypothesis arose as the relationship between the pharmacological or toxic response to a drug and the accessible concentration of the drug (e.g. concentration of drug in blood)

Clinical pharmacokinetics provide a quantitative relationship between dose and effect

For some drugs, no relation between pharmacological effect and dose.

If cannot evaluate the pharmacological effects of a drug by direct clinical observation → then measurement of drug concentration in blood is performed

Importance of TDM

1. Long-term therapy (e.g. Epilepsy)
2. Acute disorders
3. Drugs which do not follow first order kinetics
4. Multiple drug therapy
5. To, identify:
    a. Non-compliance
    b. Medication errors
    c. Development of tolerance
    d. Toxic reactions
    e. Lack of bioavailability

Drugs for which plasma level measurements may be a useful guide to dosage

1. Antiarrhythmics (digoxin, disopyramide, lignocaine and quinidine)
2. Anticonvulsants (phenytoin, carbamazepine and phenobarbitone)
3. Antibiotics (gentamicin, tobramycin and vancomycin)
4. Miscellaneous (theophylline, methotrexate, TCA and cyclosporin)

Why drug conc(s) in blood following a particular dose may vary widely between patients?

1. Individual variation (absorption, distribution and clearance e.g. 1st pass metabolism
2. Altered pharmacokinetics (hepatic, renal or cardiac disease)
3. Drug interactions
4. Poor compliance

Minimum information should be available for successful interpretation of a conc. measurement

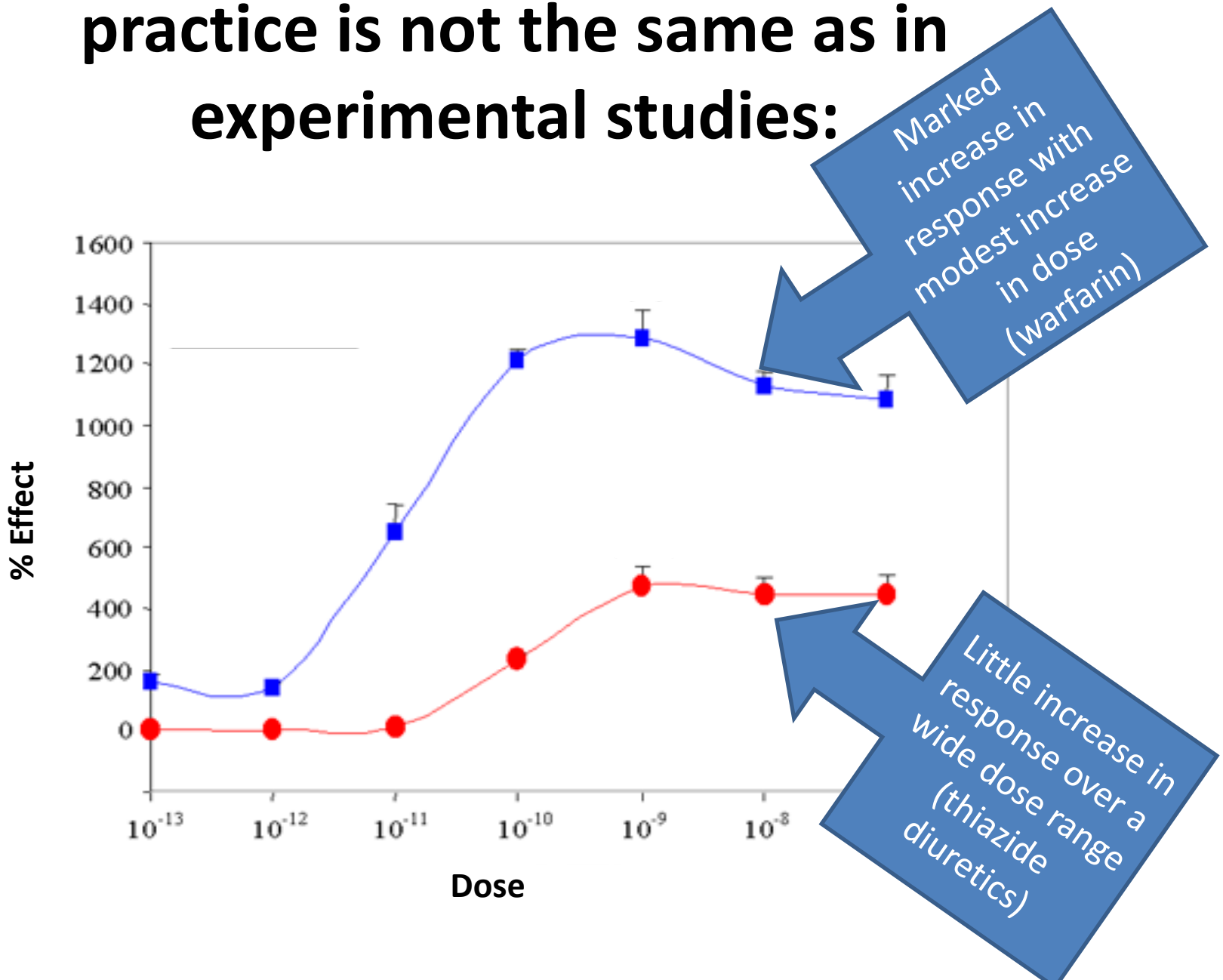
1. Time of sample collection
2. An accurate dosage regimen (drug dose, frequency, route of administration and formulation used)
3. Total duration of therapy (if steady state has been achieved)
4. Patient details (age, sex, weight, creatinine clearance.....

How to determine a dosage regimen?

From published recommended dosages:

- Pharmacopoeia
- National formulary
- Physician's desk reference
- Manufacturer's data sheets

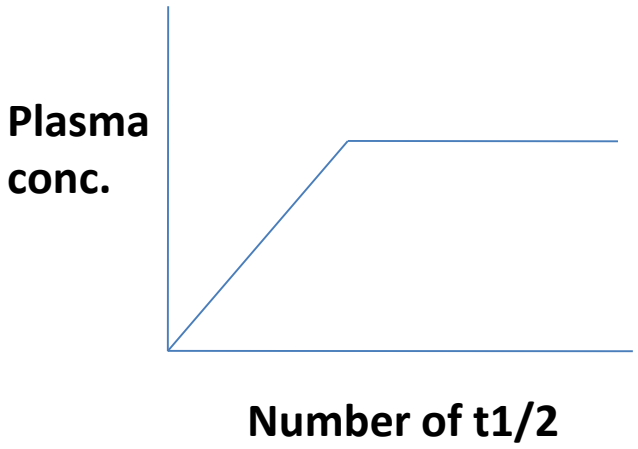
Dose-response relationship in clinical practice is not the same as in experimental studies:



A drug could be given as

Continuous I.V. infusion

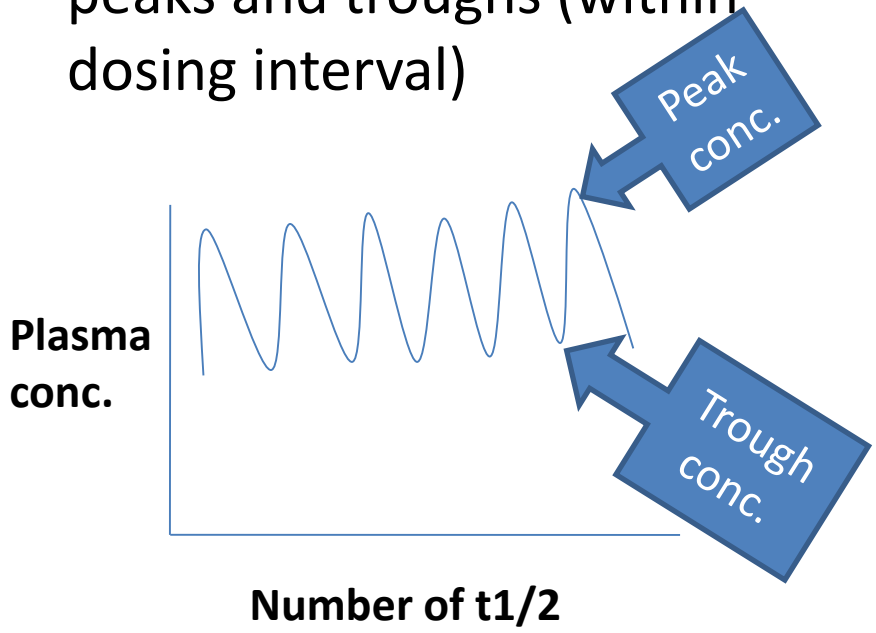
- Steady state conc. Of drug in plasma (Cpss) is reached and stay constant



•Sampling → once reach steady state

Repetitively (by mouth)

- Cpss will fluctuate between peaks and troughs (within dosing interval)



•Sampling for drugs with short t1/2 → Immediately before next dose (trough conc)

Is the amount of time between consecutive doses of a regularly administered drug

DOSING INTERVAL

•Sampling for drugs with short t1/2 → Immediately before next dose (trough conc)

•Sampling for drugs with long t1/2 → samples collected at any point in the dosage interval is satisfactory

The drug conc. At which body is in equilibrium (i,e. Rate of drug absorption = drug elimination

STEADY STATE CONC.

Time required for the drug conc. in plasma to be reduced by 50%

HALF-LIFE (T1/2)

Volume of blood (plasma) that can be completely cleared of a drug per unit time

CLEARANCE

Proportion of drug which reach systemic circulation

BIOAVAILABILITY

Is the amount of drug administered to maintain a steady state concentration

MAINTENANCE DOSE

Is the amount of drug administered to bring the drug concentration in blood to therapeutic range rapidly

LOADING DOSE

Loading dose = V X desired concentration

- Sampling ⟶ within few minutes after loading dose to ensure that conc. Is within therapeutic range

Apparent volume of distribution (V):

Is the Volume of fluid into which a drug apparently distributes

Factors affecting (V):

1. Pka of drug
2. Partition coefficient of drug in fatty tissue
3. Regional blood flow

Why TDM is not widely used?

- For some drugs other parameters are available
- It is very costly