# PHARMACOKINETICS – III
# Clinical Pharmacokinetics

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## OUTLINE

A. MAINTENANCE DOSE
B. STEADY STATE CONCENTRATION
C. HALF-LIFE
D. LOADING DOSE
E. DOSING INTERVAL
F. THERAPEUTIC DRUG MONITORING
G. NON-LINEAR PHARMACOKINETICS

## CLINICAL PHARMACOKINETICS

- Clinical pharmacokinetics is built upon the fact that a relationship exists between the pharmacological effects of a drug and an accessible concentration of the drug (e.g. in blood or plasma
- This relationship has been documented for many drugs and is of benefit in the therapeutic management of patients

## CLINICAL PHARMACOKINETICS

- In drug development- to decide on an appropriate dosing regimen for clinical studies of efficacy
- For clinicians-who need to understand how dosage recommendations in the product information provided with licensed drugs have been arrived at if they are to use the drug optimally

## PRESRIBING DIGOXIN....

**THE REGULAR DOSE WILL TAKE A LONG TIME TO ACT, ∴ YOU SHOULD GIVE A LOADING DOSE FOR A QUICK EFFECT....**

## PRESRIBING DIGOXIN....

**THE REGULAR DOSE WILL TAKE A LONG TIME TO ACT, ∴ YOU SHOULD GIVE A LOADING DOSE FOR A QUICK EFFECT....**

Digoxin: British National Formulary

Dose

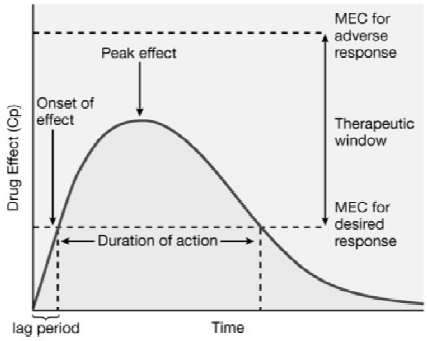
- Rapid digitalisation, by mouth, 1–1.5 mg in divided doses over 24 hours; less urgent digitalisation, 250–500 micrograms daily (higher dose may be divided)
- Maintenance, by mouth, 62.5–500 micrograms daily (higher dose may be divided) according to renal function and, in atrial fibrillation, on heart-rate response; usual range, 125–250 micrograms daily (lower dose may be appropriate in elderly)

**Dose**
**Maintenance, in atrial fibrillation, 125–250 micrograms daily**

## PRESRIBING DIGOXIN....

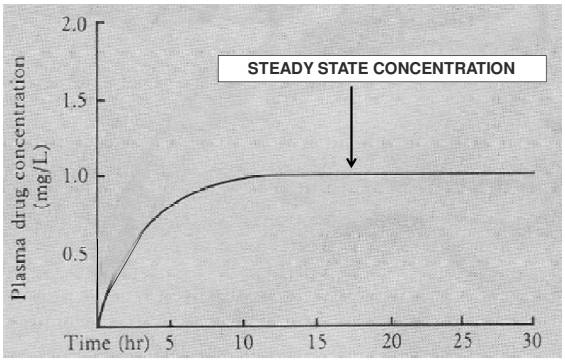
**THE MAINTENANCE DOSE WILL TAKE A LONG TIME TO ACT, ∴ YOU SHOULD GIVE A LOADING DOSE FOR A QUICK EFFECT....**

## AFTER A SINGLE DOSE....

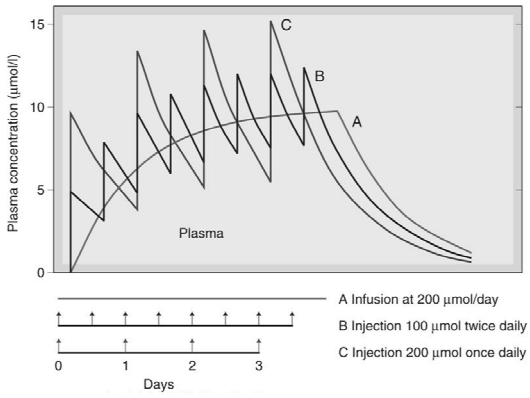



**Cp - plasma drug concentration**
**MEC - minimum effective concentration**

## WITH CONTINUOUS INFUSION....




## WITH REPETITIVE DOSES....




## Intravenous bolus

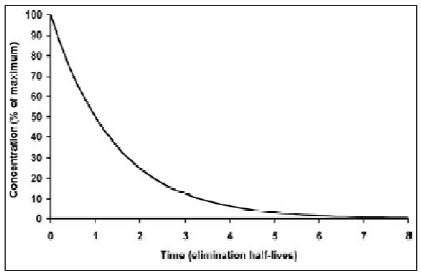



**Figure 3 : Drug concentration vs time after a single intravenous bolus, using a linear concentration scale**

## Intravenous infusion

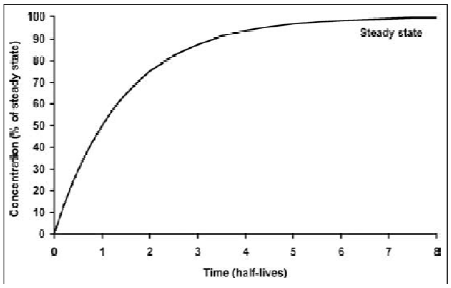
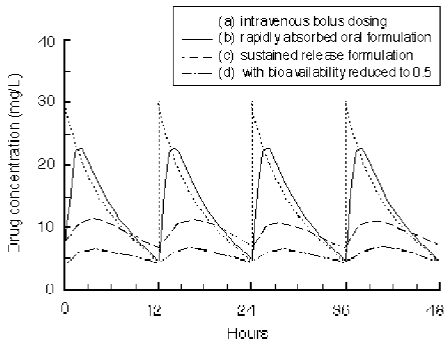
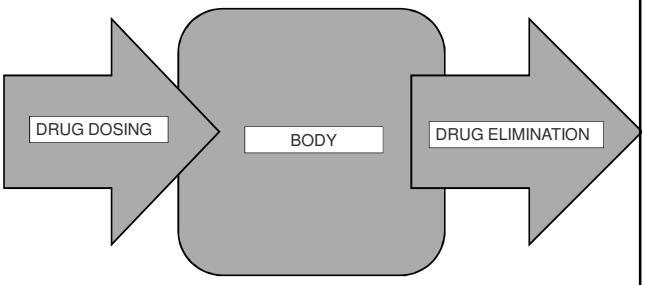



Figure 1: Concentration-time profile for a drug given by a constant rate infusion




## AT STEADY STATE CONCENTRATION...




**DRUG DOSING RATE = DRUG ELIMINATION RATE**

## RENAL CLEARANCE

- Defined as the volume of plasma containing the amount of substance that is removed from the body by the kidneys in unit time

$$CL_r = \frac{C_u \times V_u}{C_p}$$

$C_p$ - plasma concentration
$C_u$ - urinary concentration
$V_u$ - rate of flow of urine

## MAINTENANCE DOSE

$C_u \times V_u$ = Renal elimination

$$CL_r = \frac{\text{Renal elimination}}{C_p}$$

Renal elimination = $CL_r \times C_p$

## MAINTENANCE DOSE

Rate of drug elimination = $CL_{tot} \times C_p$

$Cl_{tot}$ = overall clearance of a drug (the volume of plasma containing the total amount of drug that is removed from the body in unit time by all routes)

## MAINTENANCE DOSE

- Clearance in an individual subject is the same at therapeutic doses

∴ At steady state concentration ( $C_{SS}$ )

**Rate of drug elimination = $CL_{tot} \times C_{SS}$**

## MAINTENANCE DOSE

And, at steady state concentration ( $C_{SS}$ )

**Drug dosing rate ( X) = drug elimination rate**

**$X = CL_{tot} \times C_{SS}$**

**MAINTENANCE DOSE = $CL_{tot} \times C_{SS}$**

## MAINTENANCE DOSE OF DIGOXIN

**MAINTENANCE DOSE = $CL_{tot} \times C_{SS}$**

**$Cl_{tot}$ = 77ml/min**
**$C_{SS}$ = 0.75ng/ml**
**Bioavailability = 70%**

## PRESRIBING DIGOXIN....

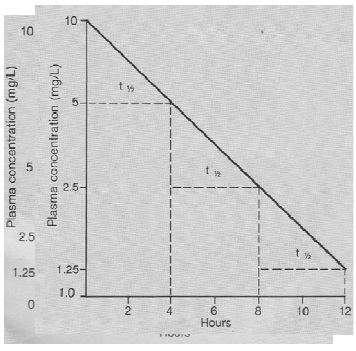
**THE MAINTENANCE DOSE WILL TAKE A LONG TIME TO ACT, ∴ YOU SHOULD GIVE A LOADING DOSE FOR A QUICK EFFECT....**

## ELIMINATION HALF-LIFE

- Half-life is the time taken for the amount of drug in the body(or the plasma concentration) to fall by half
- The elimination of a drug is usually an exponential (logarithmic) process

A constant proportion of the drug in the body is eliminated per unit time

## ELIMINATION HALF-LIFE



## ELIMINATION HALF-LIFE

- Half-life is determined by both clearance and volume of distribution
- Half-life is increased by an increase in volume of distribution or a decrease in clearance, and vice versa

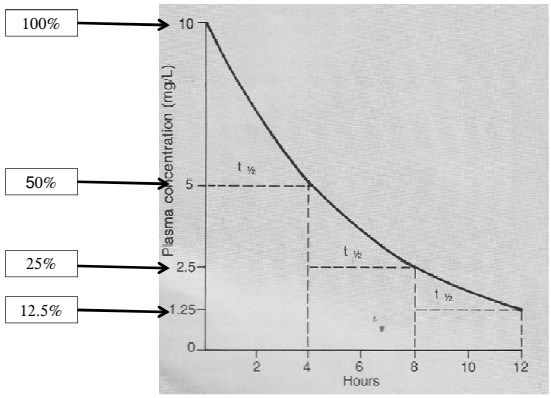
## HALF-LIFE

*Table 1*

**Effects of clearance and volume of distribution in determining half-life**

| *Drug* | *Clearance L/hr* | *Volume of distribution L* | *Half-life hr* |
|---|---|---|---|
| Ethosuximide | 0.7 | 49 | 48.0 |
| Flucytosine | 8.0 | 49 | 4.2 |
| Digoxin | 7.0 | 420 | 40.0 |
| Morphine | 63.0 | 280 | 3.0 |
| Haloperidol | 46.0 | 1 400 | 20.0 |
| Chloroquine | 45.0 | 12 950 | 200.0 |

## HALF-LIFE




## HALF-LIFE

| *Number of half-lives since starting constant rate dosing* | *Mean plasma concentration as a percentage of eventual mean steady state concentration* |
|---|---|
| | % |
| 1 | 50 |
| 2 | 75 |
| 3 | 87.5 |
| 4 | 93.75 |
| 5 | 96.875 |

## HALF-LIFE

- It takes approximately 3-5 half lives to reach the steady state concentration
- ∴ For digoxin it takes ~ $5t_{1/2}$ (40hrs× 5) i.e. about 8 days for therapeutic effect

## PRESRIBING DIGOXIN....

**THE MAINTENANCE DOSE WILL TAKE A LONG TIME TO ACT, ∴ YOU SHOULD GIVE A LOADING DOSE FOR A QUICK EFFECT....**

## LOADING DOSE

- The loading dose is one or a series of doses that may be given at the onset of therapy with the aim of achieving the target concentration rapidly
- A loading dose is used when starting treatment with a drug with a long half-life in the context of the urgency of the clinical situation

  e.g. when treating cardiac dysrhythmias with drugs such as amiodarone or digoxin

## VOLUME OF DISTRIBUTION

**The volume of fluid required to contain the total amount of drug in the body at the same concentration as that present in the plasma**

$$Vd = Q/C$$

Q = amount of drug in body (g)
C = unbound plasma drug concentration (g/liter)

## LOADING DOSE

$$\text{Loading dose} = C \times Vd$$

C = target plasma concentration at steady state

## LOADING DOSE - DIGOXIN

Loading dose = 0.5-2.1 µg/L × 667 L
= 0.3–1.4 mg
As bioavailability is ~70%
= 0.3–1.4 mg × 100/70
Oral Loading dose = 0.4–2.0 mg

## LOADING DOSE - DIGOXIN

Dose

- Rapid digitalisation, by mouth, 1–1.5 mg in divided doses over 24 hours; less urgent digitalisation, 250–500 micrograms daily (higher dose may be divided)
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**Rapid digitalisation, by mouth, 1–1.5 mg in divided doses over 24 hours**

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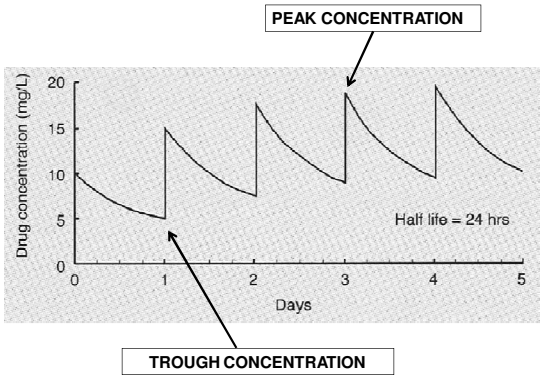
## PRESRIBING DIGOXIN....

125 MICROGRAMS DAILY

THE MAINTENANCE DOSE WILL TAKE A LONG TIME TO ACT, ∴ YOU SHOULD GIVE A LOADING DOSE FOR A QUICK EFFECT....

## DOSING INTERVAL




## DOSING INTERVAL

- If dosing interval is too far apart,
  - Peak concentration can reach toxic levels
  - Trough concentration can go down to sub-therapeutic levels
- If the dosing interval chosen to be equal to the $t_{1/2}$, then the total fluctuation would be 2-fold
- A two-fold variation is often a tolerable

## DOSING INTERVAL

- A dosing interval of about a half life is appropriate for drugs with half-lives of approximately 8-24 hours allowing dosing once, twice or three times daily
- If such a drug has a large therapeutic index, so that a large degree of fluctuation does not result in toxicity, it can be given at intervals longer than the half-life

## THERAPEUTIC DRUG MONITORING

- Therapeutic drug monitoring refers to the individualization of dosage by maintaining plasma or blood drug concentrations within a therapeutic range
- Also used in the assessment of drug toxicity

## THERAPEUTIC DRUG MONITORING

- This is helpful when,
  - Marked pharmacokinetic variability
  - Concentration related therapeutic and adverse effects
  - Narrow therapeutic index
  - Defined therapeutic concentration range
  - Desired therapeutic effect difficult to monitor

## THERAPEUTIC DRUG MONITORING

| Category | Example(s) |
|---|---|
| Immunosuppressants | Ciclosporine, tacrolimus |
| Cardiovascular | Digoxin |
| Respiratory | Theophylline |
| CNS | Lithium, several antiepileptic drugs |
| Antibacterials | Aminoglycosides |
| Antineoplastics | Methotrexate |

## THERAPEUTIC DRUG MONITORING

- Samples should be collected pre-dose as this is the least variable point in the dosing interval
- Generally samples should be collected after reaching the steady state

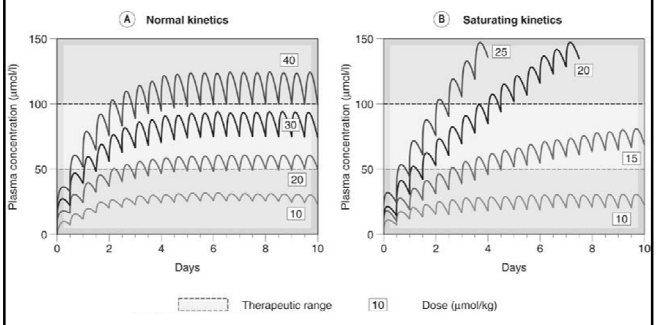
## THERAPEUTIC DRUG MONITORING

- The ratio between the measured and desired concentrations can be used to adjust the dose appropriately
- $\text{Dose (New)} = \frac{C_{ss}\text{ (Predicted)}}{C_{ss}\text{ (Measured)}} \times \text{Dose (Previous)}$

## NON-LINEAR PHARMACOKINETICS

- When the dose of a drug is increased, we expect that the concentration at steady state will increase proportionately i.e. first-order kinetics
- In non-linear pharmacokinetics /zero-order kinetics the plasma drug concentration changes result in steady-state plasma concentrations steep and unpredictable

## NON-LINEAR PHARMACOKINETICS




## NON-LINEAR PHARMACOKINETICS

- Usually is due to saturation of either protein binding, hepatic metabolism, or active renal transport of the drug
- Drug is removed at a constant rate that is independent of plasma concentration
  e.g. **ethanol**, **phenytoin** and **salicylate**