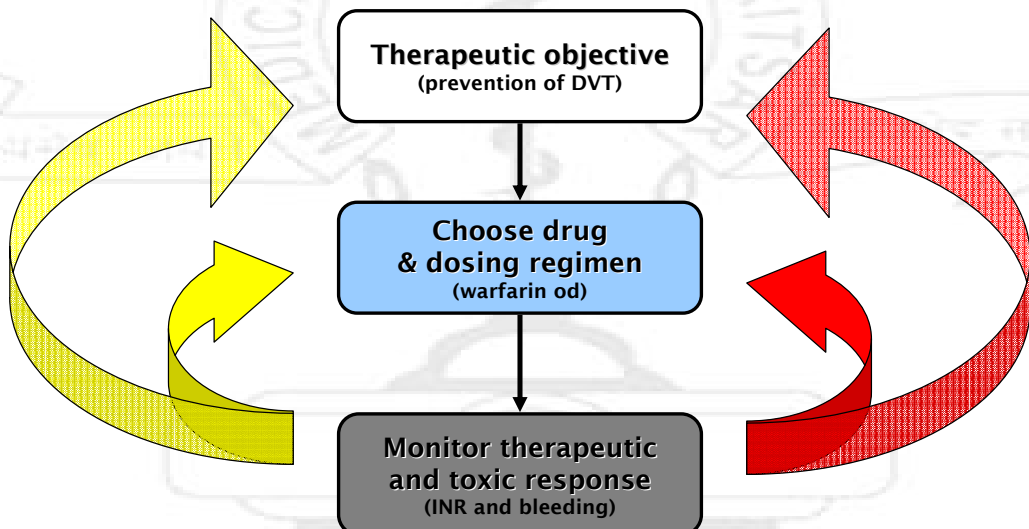


# **THERAPEUTIC DRUG MONITORING**

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## Initiation and management of drug therapy



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# Therapeutic Drug Monitoring (TDM)

- Plasma drug concentration-drug effect.
- Interindividual variation to maintain therapeutic concentration- 5-fold for Warfarin.
- Plasma concentration and clinical effect > dose and effect.
- Plasma drug concentration measurement to individualise and optimise drug therapy.

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## Monitoring drug therapy

### 1. By Clinical Response

	Indication	result to ↓ dose	result to ↑ dose	toxic signs
<b>Frusemide</b>	Heart Failure	↑Urea Dehydration	↑Oedema	Severe hypotension
<b>Carbidopa/DOPA</b>	Parkinson's	Dyskinesias Blepharospasm	Poor Control	Confusion Depression
<b>Thiopentone</b>	Induction	Anaesthesia Too Deep	Insufficient Anaesthesia	Respiratory Failure

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# Monitoring drug therapy

## 2. By an in Vitro Test of Therapeutic Effect

	Indication	result to ↓ dose	result to ↑ dose	toxic signs
<b>Warfarin</b>	TE disease	high INR	low INR	Bleeding
<b>Thyroxine</b>	Hypothyroidism	low TSH	high TSH	Hyperthyroidism
<b>Statin</b>	Raised cholesterol	↑AST/CK	high TC	Myopathy

# Monitoring drug therapy

## 3. By a target concentration strategy provided ...

- Drug level quantitatively correlates with therapeutic & toxic effects.
- High risk of therapeutic failure (lack of response or toxicity)\*

\* **Therapeutic failure** usually arises if the drug has:

- (1) A low therapeutic index
- (2) Highly variable pharmacokinetics due to
  - saturable elimination
  - genetic factors (poor metabolisers)
  - concurrent disease
  - multiple (and interacting) drug therapies

**but remember to confirm compliance in all cases of therapeutic failure**

## ***Plasma Concentration – Not Worth Measuring***

- Dose titration quickly & easily measured effects:
  - Prothrombin time – Oral Anticoagulants.
  - Blood Pressure – Antihypertensives.
  - Body Weight – Diuretics.
  - Blood Sugar – Hypoglycemics.

## ***Plasma Concentration – No relation with Effect***

Drugs that act irreversibly & effects persist long after drug has left plasma.

Such drugs destroy or inactivate enzyme, receptor & restoration occurs only after days or weeks when resynthesis takes place.

- Monoamine Oxidase Inhibitors (MAOIs)
- Cyclo-oxygenase inhibitor on platelets – Aspirin.
- Anticholinesterases.
- Anticancer Drugs.

## **Plasma Concentration–Poor Correlation with Effect**

- Alpha-1 acid glycoproteins levels elevated in inflammatory states.
- Basic drugs; Lidocaine, Disopyramide bind to acute phase proteins.
- Increase in total drug concentration is due to increase in bound (inactive) drug but not free (active) concentration.
- Concentration-effect correlation poor if total drug concentration measured.
- Assay may not measure pharmacologically active metabolites of benzodiazepines.
- Assay may measure pharmacologically active metabolites.

## **Plasma Concentration Measurement**

Dosage may best be monitored according to plasma concentration in relation to defined optimal range.

::: As a guide to effectiveness of therapy ,e.g.

- Plasma Gentamicin against sensitive bacteria.
- Plasma Theophylline for Asthma.
- Blood Cyclosporin to avoid transplant rejection.

## TDM: Aminoglycosides

**Monitoring is mandatory in ALL patients**

AG accumulate in the renal cortex to levels 100-fold > plasma

>95% of AG are cleared by glomerular filtration

• **Toxicity manifests as:**

• **NEPHROTOXICITY** (Proximal tubule)

• **OTOTOXICITY** (Hair cells)

cochlear (hearing deficits)  
- neomycin/amikacin

vestibular (disturbed balance)  
- streptomycin/gentamicin

**Targets for IV GENTAMICIN**

peak 30-60 min post-dose = 5-10 mg/L ) BUT toxicity can emerge below these levels

Trough before next dose < 2 mg/L ) if loop diuretics co-administered

**If impaired renal function** either REDUCE DOSE or INCREASE DOSE INTERVAL

(in anephric patients creatinine clearance = 0 : adjustment,  $knr/kr = 1/20$  so ...

dose reduced to 0.25mg/kg/d or interval increased to 160h)

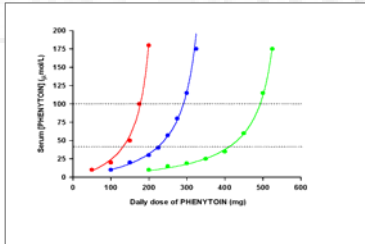
## **TDM (Antiepileptics)**

When desired effect is suppression of infrequent sporadic events such as epileptic seizures

- Phenytoin 10 microgram/ml controls seizures.
- Phenytoin 20 microgram/ml- Toxic( Nystagmus)
- Phenobarbitone 10 micrograms/ml/daily dose of 1 mg/kg in adults.
- Phenobarbitone 5-7 micrograms/ml/1 mg/kg in children.
- 10-35 microgram/ml for seizure control.
- 15 microgram/ml for control of febrile convulsions.

## TDM: Anticonvulsants (PHENYTOIN)

- **Therapeutic range** - 40-80 $\mu$ mol/L (NB total drug)  
Hypoalbuminaemia and urea both  $\uparrow$  the free fraction
- **Toxicity** - manifests as nystagmus, ataxia and confusion  
(dose-dependent in that order)



Extensive but **saturable hydroxylation** in the liver i.e. switches from zero to 1<sup>st</sup> order elimination within the TR - 'apparent'  $t_{1/2}$  may rise from 10-15h to >150h \*

\* **dose increments within the TR should be no more than 25-50mg**

Mild P450 inducer and will increase clearance of:  
warfarin, OCP, dexamethasone, cyA and pethidine.

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## **TDM (Antiepileptics)**

- Primidone 1 mg/kg per daily dose shows primidone and phenobarbital 1microgram/ml and 2microgram/ml.
- Primidone > 10 microgram/ml- Toxicity.
- Carbamazepine < 6-12 microgram/ml – therapeutic concentration.
- Carbamazepine >9 microgram/ml – CNS Toxicity.
- Valproic acid 30-100 microgram/ml.

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# TDM (Antiarrhythmics)

- Dysopyramide 2-5 mg/L
- Lignocaine 1.5-6 mg/L
- Mexeletine 0.5-2 mg/L
- Flecainide 0.2 mg/L
- Esmolol 0.15-2 mg/L
- Digoxin 1-2 microgram/L

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## TDM: Digoxin

**Therapeutic range** 1-2ng/L (taken >6h post-dosing; 1 ng/L=1.3nmol/L) for inotropic effect not AF.

• **Toxicity** - may be nonspecific eg nausea, vomiting, abdo pain & confusion **but remember** bradycardia with increasing of heart block especially with AV junctional escape rhythms and visual disturbance (xanthochromia).

• **PK problems** - 10% population have enteric bacterium (*E. lentum*) that can metabolize digoxin. Large volume of distribution ( $\approx 5L/kg$  lean BW) and predominately excreted unchanged in the urine with  $CL \propto GFR$ .

• Large of number of interactions -

	Mechanism	Condition/Drug(s)
<b>PK</b>	$\uparrow V_d$ and $CL$	Thyrotoxicosis/T4
	$\downarrow V_d$ and/or $CL$	Verapamil, amiodarone, propafenone
	$\uparrow$ absorption	Erythromycin, omeprazole
	$\downarrow$ absorption	Exchange resins, kaolin
	$\downarrow GFR$	Any cause of renal impairment/Cyclosporine
<b>PD</b>	increase block of the Na pump	Hypokalaemia/Kaluretic diuretics

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## TDM

To reduce the risk of adverse drug effects:

- ❖ Otic damage with aminoglycoside antibiotics.
- ❖ Adverse effects of Lithium, Digoxin
- ❖ Drugs with low therapeutic index.

## TDM

- Lack of therapeutic effect and toxicity may be difficult to distinguish:
  - ✓ Digoxin is both treatment and cause of cardiac supraventricular tachycardia.
  - ✓ Drug plasma measurement will decide whether arrhythmia is due to too little or too much of digoxin.

## **TDM**

- When no quick and reliable assessment of effect, e.g. Lithium for MDP.
- To diagnose and treat overdose:
  - ..Lithium therapeutic conc 0.4-1mmol/L, blood sample taken prior to morning dose as close as possible to 12 hr after evening dose. Check plasma conc every 3 months after steady state.
- ✓ Lithium intoxication at plasma conc >1.5mmol/L.
- ✓ To check patient compliance when therapeutic failure with antiepileptics expected to be beneficial.

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## **TDM**

- Moderate overdose of salicylates (500-750 mg/L)
- Large overdose, plasma salicylate >750 mg/L
- Plasma paracetamol conc. 1.32 mmol/L at 4 hr and 0.33 mmol/L at 12 hr- serious hepatic damage.

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# TDM-Interpretation

- Target therapeutic conc.-guide to optimise dosing, evaluate other clinical indicators.
- 5 t<sub>1/2</sub> must elapse since commencement of dosing or since last dose change.
- Allow 2-4 weeks to elapse between dose change and plasma conc. measurement for inducing drugs e.g Carbamazepine, Phenytoin
- Monitor peak (15min after i.v. dose) and trough (just before next dose) Conc. Of Gentamicin – Short t<sub>1/2</sub>.
- Long t<sub>1/2</sub> – sample just before due dose, CYCLOSPORIN t<sub>1/2</sub> – 27 hr.

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# TDM-Peak Concentrations

- Acetaminophen/Paracetamol 20µg/ml
- Acetylsalicylic Acid 24 ± 4µg/ml
- Amlodipine 18.1 ± 7.1ng/ml
- Chloroquine I/V : 837 ± 248 ng/ml  
I/M : 57 ± 480 ng/ml  
Oral : 76 ng/ml
- ✓ Cyclophosphamide 121 ± 21 µM  
600 mg/m<sup>2</sup> IV bolus.

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# TDM-Peak Concentrations

## Contd....

➤ Digoxin	NT :	1.4 ± 0.7 ng/ml
	T :	3.7 ± 1.0 ng/ml
➤ Gentamicin	IV :	4.9 ± 0.5 µg/ml
	IM :	5.0 ± 0.4 µg/ml
➤ Isoniazid	RA :	5.4 ± 2.0 µg/ml
	SA :	7.1 ± 1.9 µg/ml
➤ Lithium Carbonate	IR :	1-2 mM
	SR :	0.7 – 1.2 mM
➤ Oxytocin		8.0 pg/ml
➤ Sildenafil		212 ± 59 ng/ml

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## TDM: Theophylline

**Therapeutic range** - 5-20µg/ml (28-110µmol/L)

- **Toxicity** - manifest as tachyarrhythmias, vomiting & convulsions.
- **PK problems** - Bioavailability varies widely between preparations and lower in MR formulations given PM vs. AM. Non-linear CL: 90% eliminated by the liver & 10% unchanged in the urine (reversed ratio in neonates) i.e. No adjustment for renal failure required but ↓ dose in presence of impaired hepatocellular function.

Whenever possible establish drug level before administering IV and if in doubt do not give bolus loading dose.

Alteration in Clearance	increased	decreased
	rifampicin	erythromycin
	anticonvulsants	ciprofloxacin
	smoking (>10cigs/d)	verapamil
		propranolol

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## TDM: Lithium

**Therapeutic range** 0.6-1.2 mmol/L NB at plateau (pre-dose) & avoid Li-heparin tubes!

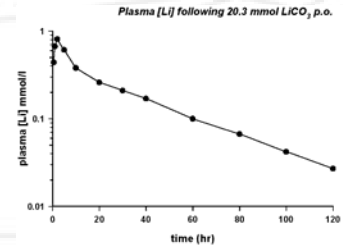
**Toxicity** - signs as a guide - TR: **fine** tremor especially at dosing peak  
 - moderate intox (1.5-3): **coarse** tremor, ataxia & diarrhoea  
 - severe intoxication (>3): confusion & fits

**PK problems** **Complete absorption** - SR formulations to reduce peak levels.  
 >95% excreted by the kidney - initial  $t_{1/2}$  12h  
 but terminal  $t_{1/2}$  much longer  $\Rightarrow$

70-80% reabsorbed in PCT with no distal reabsorption (unlike Na) .:

**PCT retention (hence toxicity risk) is  $\uparrow$  by:**

- reduced exchangeable Na from any cause
- loop or thiazide diuretics
- NSAIDs or ACEIs.



### **Special problems**

**Pregnancy** - Dose requirements increase due to  $\uparrow$  renal clearance. Li is also teratogenic and excreted in breast milk

**Severe intoxication** - usually requires dialysis but because of slow clearance from some compartments rebound rises in Li levels may necessitate HD.

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