Introduction:

Antiepileptics are used in seizure disorders which has a clearly defined therapeutic range and hence they should be clearly monitored.

Why use TDM for AEDs:

- Optimize the clinical outcome in patients by managing their medication with the assistance of measured drug levels.
- Assure patient's compliance of administration.
- Identify drug-drug interactions
- Establish relationship between dose and blood levels for patient
- Narrow therapeutic range.
- Protein binding can be very important aspect in patient response to medication.
- Different seizure types respond differently

to medication

Drugs:

- Phenytoin
- Carbamazepine
- Valproic acid
- Lamotrigine
- Gabapentin

Phenytoin:

It is used in all types of seizure except absence seizure and seizure caused by theophylline overdose.

- It is also useful for digitalis induced ventricular arrhythmias.

Need for TDM:

Monitoring is imperative as a guide to dosage

adjustment, since phenytoin has a low therapeutic index and exhibits nonlinear kinetics. The relative rate of elimination is slower at higher concentrations than at lower concs of the drug.

Pharmacokinetic Properties:

- Bioavailability: 70-100%

K_a = 50mg/hr saturable kinetics of absorption (0 order)

t_{max} = 3-12 hr (increase with dose)

V_d = 0.6-0.8 l/kg

Albumin bound fraction: 0.9

Biotransformation: 70-90%.

Renal excretion = 1-5%.

Patients	Vmax	Km
Adults	6mg/kg/day	5.7mg/l
6month-6 yrs	12mg/kg/day	4mg/l
7-16 yrs	9mg/kg/day	

THERAPEUTIC RANGE:

Patients	Therapeutic Range
Adult n children	10-20 mg/l
Newborns n children under 3 years	6-14 mg/l
ESRD or hypoalbuminaemia	5-10 mg/l
ESRD with hypoalbuminaemia	3-7 mg/l
Liver disease	7-14 mg/l
Acute hepatitis	8-16 mg/l

ADR:

- They are related to plasma concentrations:

Plasma levels	Symptoms
20-30 mg/l	Nystagmus
30-40 mg/l	Ataxia
>40 mg/l	Mental changes

□ long term effects of phenytoin.

- Gingival hyperplasia
- Acne
- Hirsutism
- Folate n Vit.D deficiency

□ Indications for TDM:

- At the initiation of therapy, in order to achieve a plasma conc. within the therapeutic range.
- When there is intercurrent illness (AIDS, hypoalbuminaemia, renal impairment) or a change in physiological state exists (age, pregnancy).
- When drug toxicity is suspected.
- When the therapy is about to be withdrawn.
- Intervals during the course of therapy.

Sample timing:

- The time required to attain a C_{ss} after initiation of therapy is difficult to predict due to non linear kinetics.
- C_{ss} might not be attained for as long as 3 weeks.
- Thus samples are obtained prior to steady state (after 3-4 days) and at the end of dosage

interval.

- In case of oral phenytoin, the sample can be drawn anytime during the dosage interval as it is slowly absorbed.

Specimens:

- Serum or plasma are generally recommended for total phenytoin measurements.
- Use of anticoagulants are not recommended.
- Saliva is proposed for children.
- Saliva is a useful specimen for monitoring unbound phenytoin conc.

Collection methods and assays:

- Immunoassays are most common methods of measurement.
- Immunoassays that use monoclonal anti-

bodies or HPLC can be used in samples from patients with renal impairment.

DOSAGE RECOMMENDATIONS:

- Phenytoin exhibits nonlinear behavior following therapeutic doses.
- Thus increase in dose rate will produce greater than proportional increase in the average serum conc. during the dosing interval.
- Normograms can b used to estimate individual dosage requirements.

Population	Maintenance dose	Dosage interval
Adults	5-7 mg/kg/day	12 hrs
Children<3months	3-5mg/kg/day	8 hrs
6month-6year	5-15 mg/kg/day	12 hrs
Pregnancy	5-15 mg/kg/day	12 hrs

FACTORS AFFECTING PHENYTOIN PLASMA CONCENTRATION:

- Liver disease
- Hypoalbuminaemia
- Displacement from protein binding
  eg. Aspirin, sodium valproate
- Drug interactions

Inhibition of metabolism	Stimulation of metabolism
✓Amidarone	✓Carbamazepine
✓Allopurinol	✓Chlordiazipoxide
Anti TB drugs	✓Diazepam
✓Cimitidine	Dexamethazone
Chlorpromazine	✓Rifampin
✓Disulfiram	✓Phenobarbitol
H2-antagonists	✓Lamotrigine
✓Sulfonamides	Tiagabine
✓Anticoagulants	Topiramate

Observation:

- Monitoring of free phenytoin conc. is beneficial in patients with AIDS, hypoalbuminaemia and renal impairment.
- Time to reach C_{ss} increases with dose.
- Time required to achieve 90% of steady state, can be calculated as follows:

$$t_{90\%} = \frac{K_m \cdot V_d}{[V_{max} - (dose/day)]^2} \left[2.3 \times V_{max} - 0.9(dose/day)\right]$$

- Estimation of normalized phenytoin concentration in situation with hypoalbuminaemia can be done using the following equation when unbound concentration is not obtained:

$$[PTH]_{normalized} = \frac{[PTH]_{measured}}{0.25 + [ALB] + 0.1}$$

Valproic Acid:

- Valproic acid is used for the management of absence seizures, partial and generalized tonic-clonic and myoclonic seizures.
- It is also used for bipolar disorders and prophylaxis against migraine headaches.

Indications For TDM:

Valproic acid is highly bound to serum albumin, and at therapeutic plasma concentrations, saturates plasma protein binding sites.

Absorption and Dosage Forms:

F=1.0

Dosage forms: tab, cap, syp, inj, sprinkles

Tmax for syp: 0.5-1.0 hr

cap: 1-2 hr

enteric coated tab: 3-8 hr

sprinkles: 3-8 hr

- Vd = 0.09-0.17 l/kg
- Protein binding = 85-93%
- $T_{1/2}$ = 5-22 hr (adults)
  5-15 hr (children)

THERAPEUTIC RANGE:

- 40-100 mcg/ml

DOSING:

- Loading dose = 15-20 mg/kg
- Maintenance dose = 125-250 mg tid or bid

ADR:

- They are related to the plasma drug concentrations.

Plasma levels	Symptoms
>75 mg/l	Ataxia, sedation, lethargy, fatigue
>100mg/l	Tremor
>175mg/l	Stupor, coma

SAMPLE TIMING:

- 3- 5 days may b required to reach the steady conc.
- The level of VPA varies from interval to interval during the day
- Thus samples r collected prior to the morning dose.

SPECIMENS:

- Serum or heparinized plasma.
- Unbound drug can be estimated from tears.

ASSAYS:

- Immunoassays or HPLC

DOSAGE RECOMMENDATIONS:

- In unbound form it exhibits linear kinetics and thus the level of drug will increase in proportional to dose rate.
- The bound form follows nonlinear kinetics and thus the plasma conc is not proportional to dose rate.

FACTORS AFFECTING PLASMA VPA CONCENTRATION:

- Liver disease
- Nephrotic syndrome
- Cystitic fibrosis
- Burns
- Trauma
- Malnutrition

} hypoalbuminemia

- Age
- Displacement interactions– salicylates, NSAIDS
- Drug interactions : Increases the conc.of lamotrigine lorazepam CBZ

GABAPENTIN INDICATION:

- GPB is used for treating partial seizures with or without secondary generalization in adults. Off-label use in neuropathic pain accounts for the majority of the GBP use.
- Absorption kinetics are dose dependent with decreasing bioavailability with increasing doses, possibly due to a saturable transport system.
- Substantial variation in plasma concentrations at the same daily dose has been found among different patients and the dose dependency of the absorption may also vary substantially between patients. Hence, TDM may be used to clarify whether a poor response to dose increments in the individual case is caused by an impaired absorption.

PHARMACOKINECTIC PARAMETERS

- F = 0.6 at doses< 900mg/day
- 0.27 – 0.47 at doses 1200 – 4800 mg/day
- (saturation of L- amino transporters.)
- Dosage forms – capsules
- T max -- 2 – 3 hrs

- Vd = 0.7- 0.8 l/kg
- T1/2 = 5 - 7 hrs
- Cl/F is proportional to creatinine clearance Cl cr

CLcr (ml/min)	CL/F (ml/min)	T1/2 (hr)
>60	190	6.5
<30	20	52

DOSING

- Loading dose are not needed
- maintenance dosing = initial dose - 300 mg qd
- Titrate to dose of 1200 mg over 1 to 2 days, increase doses until usual maintenance dose of 900 to 3600mg/day TID is reached.
- Decrease GBP doses for CLcr <60ml/min.
- THERAPEUTIC RANGE
- TDM is not clinically used.
- Conc. in clinical trials were 1 - 8 mcg/ml

DRUG INTERACTIONS

No clinical significant drug interactions

SAMPLE TIMING:

- It takes 1 - 2 days to reach steady state. The level of Gabapentin varies from interval to interval during the day
- Thus samples are collected prior to the morning dose.

ASSAY: Gabapentin can be determined in plasma by means of high-performance liquid chromatography (HPLC).

SPECIAL POPULATIONS:

- children - no pharmacokinetic data are available
- elderly patient - GBP dose need to be decreased proportional to Cl cr
- Renal disorder- same

- pregnancy – no data are available
- Lactation- no data available.

CARBAMAZEPINE

- Carbamazepine is used to prevent partial seizures and generalized tonic-clonic seizures as well as bipolar disorder and trigeminal neuralgia.
- Carbamazepine has been experimentally used for relief of pain or control of seizures associated with multiple sclerosis, acute idiopathic polyneuritis, peripheral diabetic neuropathy, post-traumatic paresthesias, "lightning" pains of tabes dorsalis, alcohol withdrawal, and restless leg syndrome. It has also been used for its ant diuretic effects to treat diabetes insipidus and in the treatment of bipolar mood disorder.

NEED FOR TDM

- CBZ is subjected to undergo auto induction i.e., the drug induces its own metabolism by CYP 3 A4 inducers and decreases its plasma concentration. This increases the concentration of metabolite (10, 11- epoxide) which has little anticonvulsant action and precipitates some serious ADRs.
- CBZ shows Time-dependent kinetics. The clearance is high at multiple doses than following a single dose.

Pharmacokinetics of Carbamazepine

- **Dose: Adults: Oral: 0.8-1.2 g/day maintenance** for seizure control for anxiety 0.2-1.2 g/day for neuralgia
- **Half-life: Initially ~ 35 hrs; ~ 8-20 hrs** after 3-4 weeks of administration
- **Transport: ~ 60-70% plasma protein bound**
- **Metabolism: Hepatic: Carbamazepine** -10, 11-epoxide; Carbamazepine 10, 11-transdihydrodiol(inactive)
- **Elimination: ~ 1-2% unchanged in the urine**
- F= 0.75 to 0.85.
- Time to peak: 4 to 8 h (tab, CR), 1 to 2h (suspension)
- No significant effect on food on absorption.
- Humidity can reduce CBZ bioavailability by 50%; CBZ needs to be stored in a dry place.

- Vd = 0.8 to 2.0 l/kg
- Protein binding: 75% is bound to albumin and α1 – acid glycoprotein.

Therapeutic and Toxic Levels

- The monitoring of Carbamazepine levels in the blood is critical.
- Common toxic reaction seen with this drug includes drowsiness, dizziness, nausea with vomiting, light headedness, skin rash, ataxia (uncoordinated muscle movement in the absence of other symptoms and spasticity) alopecia, and photosensitivity.
- Extreme toxicity can cause hepatitis, rare hematologic reactions, aplastic anemia,thrombocytopenia, and agranulocytosis and death due to cardiorespiratory arrest.

Therapeutic range	:	**4-12 µg/mL** 17-51 µmol/L
Possible toxic levels	:	**>15 µg/mL** 63 µmol/L
Critical levels	:	**>20 µg/mL** >85 µmol/L

FORMULATIONS

- CBZ is available as a 200 mg- intermediate-release tablet, 100 mg chewable tablet and a suspension.
- For patients switched from a brand name to a generic product or from generic to generic, the plasma concentrations should be monitored weekly for 2 weeks to determine the effect, if any, of the substitution.

Sample timing

- Because CBZ induces its own metabolism, it is recommended that initial dose rates of CBZ be relatively low and gradually increased over time.
- For maximal induction or deinduction to occur, 2-3 weeks may be required after the maximum dose rate has been attained.
- Thus, a total of 6-7 weeks may be required for a true steady state to be reached after initiation of therapy.
- After any dose rate changes or addition/discontinuation of enzyme-inducing drugs, 2-3 weeks will be required to reach a new steady state.
- The absorption of immediate-release CBZ tablets from the GIT is relatively slow and erratic reaching a peak between 3 and 8 hrs after a dose.

- If CBZ is administered every 6 or 8 hrs, serum levels during the dosing interval will remain fairly flat and all levels will be fairly representative of a trough concentration.

Specimens, collection methods and assays:

- Either serum or plasma collected in EDTA-treated tubes are acceptable for total CBZ measurements.
- Saliva has been proposed as a convenient noninvasive alternate, especially for children and for home monitoring.
- immunoassays

REFERENCES:

- Pharmacokinetics in Drug Discovery and Drug development - Ronald D. Schoenwald.
- Basic Clinical Pharmacokinetics, 4th edition
  - Michael E. Winter.
- Biopharmaceutics and Clinical Pharmacokinetics – Milo Gibaldi