Antiepileptic Drugs: Basic Pharmacology for Daily Practices

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Frequent Mistakes in Management of Epilepsy

- Wrong diagnosis:
  - Seizure VS Pseudoseizure
  - Type of seizure
- Wrong selection of AED
- Premature change of AED
- Inappropriate method of AED administration
- Drug interaction
- Delayed referral for further investigation & management

Principles in Therapy of Epilepsy

- Goal of AED treatment in epilepsy is to abolish seizure completely with minimal of drug-related adverse reaction
- Freedom of seizures should not pursued at any cost and risk of drug-induced adverse reactions
- Increased numbers & dosage may jeopardize social and mental well-being of patients

Panayiotopoulos CP: The Epilepsies 2005

Principles in Pharmacologic Therapy in Epilepsy

- Pharmacokinetics
  - Study of the time course of a drug and its metabolite in humans
  - Quantitative description of what happens to the drug in human body
- Pharmacodynamics

Principles in Pharmacologic Therapy in Epilepsy

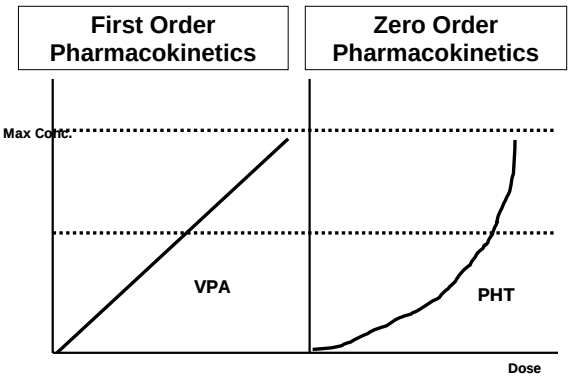
- Pharmacokinetics
- Pharmacodynamics
  - Biochemical and physiological effects of drugs and their metabolisms of action
  - Study of the effect of a drug on humans

Pharmacokinetics

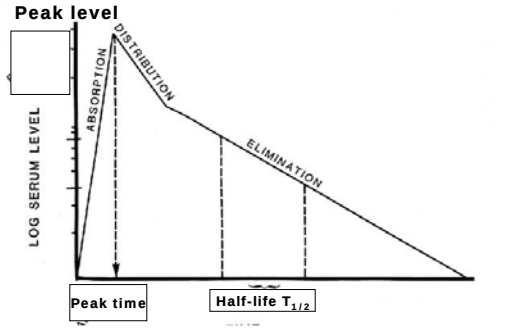
- Oral bioavailability-absorption
- Distribution
- Elimination Half-life ($T_{1/2}$)
- Steady state
- Protein binding

Oral bioavailability

- Proportion of a drug taken orally that reaches the systemic circulation
- Most AEDs have nearly total bioavailability (80% - 90%)
- Saturation fashion of absorption: GBP
- Different formulations, different bioavailability ie.
  extended release VS conventional



Pharmacokinetics of AED

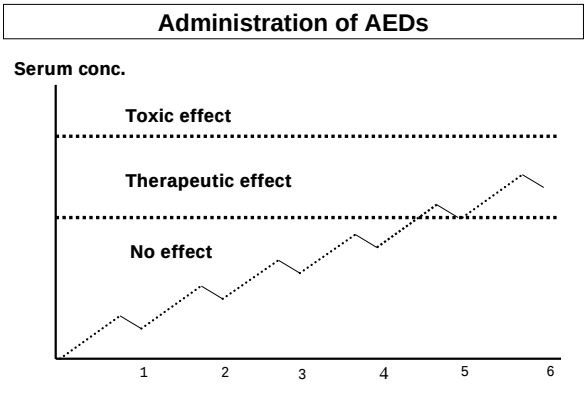


Distribution

- Absorption→ drug will be distributed within blood components & body tissues
- Rate & extent of penetration vary from one to the others
  - Chemical properties
  - Degree of drug binding to plasma & tissue
  - Blood flow
  - Biologic barrier: BBB lipophilic > hydrophilic
  - Volume of distribution

Elimination Half-life

- The length of time for drug's plasma concentration to decline by half
- Useful for determination of time to steady state
- Apply for dosing interval



Loading Dose

- Concentration of drugs = $\frac{\text{amount of drug}}{\text{volume of distribution of that drug}}$
- $C = \frac{D}{V}$

V= BW X volume of distribution(Vd)
Vd varies from one drug to the other

Steady State

- Equilibrium after initiation of continuous AED treatment
- State that ingested amount of drug equals eliminated amount of that drug (rate of input = rate of output)

Major Metabolism & Elimination Hepatic Pathway

- Carbamazepine
- Clobazam
- Clonazepam
- Pheytoin
- Phenobarbital
- Valproate
- Lamotrigine
- Topiramate
- Oxcarbazepine
- Tiagabine
- Zonisamide
- Ethosuximide

Major Metabolism & Elimination Renal Pathway

- Gabapentin
- Levetiracetam
- Pregabalin
- Vigabatrin

AED & Hepatic Metabolism

AEDs	Enzyme Induced	Enzyme Inhibited
PB	CYP2C, CYP3A,	None
	Microsomal epoxide hydrolases	
	UGTs	
DPH	CYP2C, CYP3A,	None
	Microsomal epoxide hydrolases	
	UGTs	
CBZ	CYP2C, CYP3A, CYP1A2	None
	Microsomal epoxide hydrolases	
	UGTs	

AED & Hepatic Metabolism

AEDs	Enzyme Induced	Enzyme Inhibited
LTG	UGTs	None
OXC	CYP3A4, UGTs	CYP2C19
TPM	Dose-dependent enzyme inducer CYP3A	CYP2C19
	β-oxidation	

AED & Hepatic Metabolism

AED	Enzyme Induced	Enzyme Inhibited
VPA	None	CYP2C9
		Microsomal epoxide hydrolases
		UGTs

AEDs Interactions

- Drugs that induce metabolism of other drugs: carbamazepine, phenytoin, phenobarbital
- Drugs that inhibit metabolism of other drugs: valproate, felbamate
- Drugs that are highly protein bound: valproate, phenytoin
- Other drugs may alter metabolism or protein binding of antiepileptic drugs

Protein Binding

- Drugs: unbound (free) or bound
- Active AEDs are mostly free (unbound)
- Change in bound fraction, alteration of active fraction
  - Physiologic (pregnancy)
  - Pathologic (renal diseases, hepatic diseases)
  - Concomitant administration

Pharmacokinetics of Traditional AEDs

AED	Absorption	Binding	Elimination	Half life (hrs.)
CBZ	80%	75-85%	100% (hepatic)	8-28
PB	100%	50%	75% (hepatic)	37-73
PHT	95%	90%	100% (hepatic)	5-14
VPA	100%	80-95%	100% (hepatic)	8-15

Traditional AEDs & Their Likelihood of Pharmacokinetics

Issues	PHT	CBZ	PB	VPA
Metabolism is inducible	+	+	+	+
Metabolism is inhitbitable	+	+	+	
Hepatic enzyme inducer	+++	+++	+++	
Hepatic enzyme inhibitor				+++

+ = Modest pharmacokinetic variance through this mechanism

Inappropriate AED Administration

- Unpractical dosage
- Preparation of AED
  - Liquid
  - Capsule
  - Sugar-coated tablet
  - Enteric-coated tablet
  - Prompt release/ slow release / long acting
- Route and method of administration
- Generic VS original drug