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

Pharmacokinetics

- Oral bioavailability-absorption
- Distribution
- Elimination Half-life (T1/2)
- Steady state
- Protein binding

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
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 i.e., extended release VS conventional

First Order Pharmacokinetics

<table>
<thead>
<tr>
<th>First Order Pharmacokinetics</th>
<th>Zero Order Pharmacokinetics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Max Conc.</td>
<td>VPA</td>
</tr>
<tr>
<td></td>
<td>PHT</td>
</tr>
</tbody>
</table>

Pharmacokinetics of AED

- 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

Distribution

Administration of AEDs
**Loading Dose**

- Concentration of drugs = \( \frac{\text{amount of drug}}{\text{volume of distribution of that drug}} \)

\[
C = \frac{D}{V}
\]

\( V = \text{BW} \times \text{volume of distribution (Vd)} \)

\( \text{Vd} \) 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
- Clofazamide
- Clonazepam
- Phenytoin
- Phenobarbital
- Valproate

**Renal Pathway**

- Gabapentin
- Levetiracetam
- Pregabalin
- Vigabatrin

**AED & Hepatic Metabolism**

<table>
<thead>
<tr>
<th>AEDs</th>
<th>Enzyme Induced</th>
<th>Enzyme Inhibited</th>
</tr>
</thead>
<tbody>
<tr>
<td>PB</td>
<td>CYP2C, CYP3A</td>
<td>None</td>
</tr>
<tr>
<td></td>
<td>Microsomal epoxide hydrolases</td>
<td></td>
</tr>
<tr>
<td>DPH</td>
<td>CYP2C, CYP3A</td>
<td>None</td>
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<tr>
<td></td>
<td>Microsomal epoxide hydrolases</td>
<td></td>
</tr>
<tr>
<td>CBZ</td>
<td>CYP2C, CYP3A, CYP1A2</td>
<td>None</td>
</tr>
<tr>
<td></td>
<td>Microsomal epoxide hydrolases</td>
<td></td>
</tr>
<tr>
<td></td>
<td>UGTs</td>
<td></td>
</tr>
</tbody>
</table>

**AED & Hepatic Metabolism**

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<tr>
<th>AEDs</th>
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<th>Enzyme Inhibited</th>
</tr>
</thead>
<tbody>
<tr>
<td>LTG</td>
<td>UGTs</td>
<td>None</td>
</tr>
<tr>
<td>OXC</td>
<td>CYP3A4, UGTs</td>
<td>CYP2C19</td>
</tr>
<tr>
<td>TPM</td>
<td>Dose-dependent enzyme inducer CYP3A</td>
<td>CYP2C19</td>
</tr>
<tr>
<td></td>
<td>( \beta )-oxidation</td>
<td></td>
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</table>
AED & Hepatic Metabolism

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<tr>
<th>AED</th>
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</tr>
</thead>
<tbody>
<tr>
<td>VPA</td>
<td>None</td>
<td>CYP2C9</td>
</tr>
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<td></td>
<td>Microsomal epoxide hydrolases</td>
<td>UGTs</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>AED</th>
<th>Absorption (%)</th>
<th>Binding (%)</th>
<th>Elimination (%)</th>
<th>Half life (hrs.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CBZ</td>
<td>80%</td>
<td>75-85%</td>
<td>100% (hepatic)</td>
<td>8-28</td>
</tr>
<tr>
<td>PB</td>
<td>100%</td>
<td>50%</td>
<td>75% (hepatic)</td>
<td>37-73</td>
</tr>
<tr>
<td>PHT</td>
<td>95%</td>
<td>90%</td>
<td>100% (hepatic)</td>
<td>5-14</td>
</tr>
<tr>
<td>VPA</td>
<td>100%</td>
<td>80-99%</td>
<td>100% (hepatic)</td>
<td>8-15</td>
</tr>
</tbody>
</table>

Traditional AEDs & Their Likelihood of Pharmacokinetics

<table>
<thead>
<tr>
<th>Issues</th>
<th>PHT</th>
<th>CBZ</th>
<th>PB</th>
<th>VPA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metabolism is inducible</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Metabolism is inhibitable</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Hepatic enzyme inducer</td>
<td>+++</td>
<td>+++</td>
<td>+++</td>
<td>+++</td>
</tr>
<tr>
<td>Hepatic enzyme inhibitor</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>--</td>
</tr>
</tbody>
</table>

* ++ = 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