Antiepileptic Drug levels: use & abuse

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Advice on AED levels…

• Confused
• Oversimplified
• Overly negative

• AED levels can be useful
• BUT…
• Use with care
AED levels

• Basic principals of clinical pharmacology
• Historical perspective
• Clinical value of AED levels
• Indications for AED levels
• Misunderstandings about AED levels
Clinical Pharmacology

• Dose response curve
• Transient nature of drug-receptor interactions
• Pharmacodynamics
• Pharmacokinetics
• Individual biological variation
Dose Response Curve

- Pick a response or effect to measure
- Pick doses from a range
  - Sub-therapeutic to Supra-maximal
- In an individual
  - Patch of cell membrane
  - Cell
  - Tissue sample
  - Organism / person
  - Sample of population
Dose Response Curve

• The desired effect(s)
• The unwanted effect(s)

• The dose
  – Administered
  – Circulating
  – At the receptor
Drug – Receptor interactions
Midazolam

- Anaesthetic
- Antiepileptic
- Hypnotic
- Anxiolytic
- Sedative

- Toxic “poisonous”
- Ineffective “weak”
- Efficacious “powerful”
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a) Dose response curve

max
y
50%
sub
1 2 x 3
b) Log dose response curve

- max
- 50%
- sub

\[ y \]

\[ \log x \]

1 2 3
But what about time?
c) Time concentration graph

- \( iv \) max
- \( iv \) 50%

- \( oral \) max
- \( oral \) 50%

- Time of 1 \( iv \) max
  - 2 \( iv \) 50% max
  - 3 oral max
  - 4 oral 50% max
What is pharmacokinetics?
What is pharmacokinetics?

- Route of administration
- Absorption
- Bioavailability
- Distribution
- Metabolism
- Excretion
- Elimination
Dose intervals

• PK properties
• T1/2 linear or 1st order kinetics
• mg/hr zero order kinetics
• Intermediate Michaelis-Menten kinetics
• Individual biological variation
• Disease states
• Drug interactions
d) Time concentration graph

- steady state
- 1st oral max
- 1st oral 50%

1 2 3 4
Puffer fish
May-July 1968:
51 patients on phenytoin presented with 2-4 weeks:
Ataxia, diplopia, vomiting:
The phenytoin story


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Had high serum levels (87% were above 10-20 mg/L).
All on 100 mg capsules from same manufacturer.
All capsules contained 100 mg +/- 2 mg.
Old capsules likewise....

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November 1967 change in excipient:
increased bioavailability
Blood phenytoin concentrations in a patient taking phenytoin (400 mg./day), with excipients respectively as shown (lactose, calcium sulphate, lactose). Vertical columns represent daily faecal excretion of phenytoin when measured.
The phenytoin story

- Bioavailability
- Anticipating toxicity & dose adjustment
- Target Range vs Therapeutic Range
- Width of Therapeutic Index
Drug manufacturing

Regulations are tight:

• Amount must be consistent mg/tablet

• Bioavailability must be consistent:
  – Between batches
  – Between manufacturers

  1. AUC
  2. $C_{\text{max}}$
  3. $T_{\text{max}}$

Single or multidose studies in 12 or more healthy adult volunteers: 90%CI: 80-125%
c) Time concentration graph

- $iv$ max
- $iv$ 50%
- Oral max
- Oral 50%
- AUC
- $C_{\text{max}}$
- Time of $iv$ max
  - 2 $iv$ 50% max
  - 3 oral max
  - 4 oral 50% max
tetrodotoxin
AED dose adjustment

• Treatment goal

• Risks of toxicity

• Seizure frequency

• Constructing a narrative
When to measure AEDs
<table>
<thead>
<tr>
<th>Drug</th>
<th>mg/l</th>
<th>µmol/l</th>
</tr>
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<tbody>
<tr>
<td>Carbamazepine</td>
<td>4-12</td>
<td>16-50</td>
</tr>
<tr>
<td>Ethosuximide</td>
<td>40-100</td>
<td>300-750</td>
</tr>
<tr>
<td>Lacosamide</td>
<td>10-20</td>
<td></td>
</tr>
<tr>
<td>Lamotrigine</td>
<td>1.5-20*</td>
<td></td>
</tr>
<tr>
<td>Levetiracetam</td>
<td>6-40</td>
<td></td>
</tr>
<tr>
<td>Phebobarbitone</td>
<td>10-50</td>
<td>45-225</td>
</tr>
<tr>
<td>Phenytoin</td>
<td>10-25</td>
<td>40-100</td>
</tr>
<tr>
<td>Topiramate</td>
<td>5-20</td>
<td></td>
</tr>
<tr>
<td>Valproate</td>
<td>40-100</td>
<td>270-700</td>
</tr>
</tbody>
</table>
When to measure AEDs

- ICU; PICU; NICU
- ED
- OPD
Sodium channel $\alpha$ sub-unit
Conclusions

• AED levels can be very useful
• But not often needed as a routine (PHT)
• Not often needed at steady state *per se*
• Not often needed strictly timed

• Compliance / Adherence / Concordance /
• Communication / Partnership