OPTIMAL USE OF OLD AND NEW AEDS

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Old vs New AEDs

Ideal characteristics for AEDs

| Efficacy | • broad spectrum of indication
|          | • rapid clinical improvement
|          | • sustained efficacy
|          | • lack of paradoxical effect
| Freq, severity |

| Tolerability | • high therapeutic index
|              | • not teratogenic
|              | • few acute SE
|              | • rare idiosyncratic SE
|              | • rare serious or annoying chronic SE
| SE |

| Ease of use | • once/twice daily dosing
|             | • linear pharmacokinetic
|             | • no drug-drug interaction
|             | • no relevant metabolism
|             | • major route of excretion renal
|             | • no titration to lowest effective dose
|             | • no relevant protein binding

Special issue in children

- Absorption: erratic absorption of PHT and PB in neonates
- Distribution: Vd of PB, PHT is larger in neonates than in older infants and children, need larger loading dose but similar loading doses of LZP, DZP
- Elimination: Birth; renal function ~25-30%
  6 mo; renal function ~50-75%
  2-3 yrs; full maturation
Doses of drugs ...excreted predominantly unchanged by kidney...need to be reduced for neonates and infants

Special issue in children

- CYP: Birth; ~50-70% of adult level
  2-3 yrs; exceed than adult level
  puberty; similar to adult level

- CYP3A4: CBZ

- UGT: low level in neonate an reach adult level at age 3-4 years

TABLE 1. Age effects on pharmacokinetic parameters (compared with adult values)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Neonates/Infant</th>
<th>Children</th>
<th>Adults</th>
</tr>
</thead>
<tbody>
<tr>
<td>Renal</td>
<td>↓</td>
<td>≈</td>
<td>≈</td>
</tr>
<tr>
<td>Metabolism</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CYP</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>UGT</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Albumin</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

CYP, cytochrome P450; UGT, uridine diphosphate, glucuronosyl transferase.

Epilepsia 2002;43:53-59
Special issue in children

- Preterm, full-term neonates tend to have 3-9 times longer half-life than adult.
- Difference disappears by 2-6 months.
- Beyond 6 mo, half-life can be shorter than adult in specific drugs and pathway

Case

- Intermittent limbs shaking in the past 2 months
- Often occurs in the morning but also seen at other times
- 13 yrs old girl

Case

- Intermittent limbs shaking in the past 2 months
- Often occurs in the morning but also seen at other times
- Recently, had one episode of GTC
- 13 yrs old girl

![Graphical representation of brain activity]
What would be your AED selection?
A. Depakine
B. Phenytoin
C. Topiramate
D. Lamotrigine
E. Levetiracetam

What is your diagnosis?
A. Non-epileptic seizures
B. Simple partial seizure
C. Juvenile myoclonic epilepsy
D. Partial with secondarily generalized seizure
E. Epilepsy with grand mal seizure upon awakening

Efficacy
- Seizure type and epileptic syndrome

<table>
<thead>
<tr>
<th>Seizure Type</th>
<th>VPA</th>
<th>LTG</th>
<th>TPM</th>
<th>LEV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Myoclonic</td>
<td>✓</td>
<td>?</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>GTC</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Absence</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td></td>
</tr>
</tbody>
</table>

Epileptic disorder 2006: Class IV: CZP, LTG, TPM, VPA, ZNS
ILAE 2013: Level D: TPM, VPA
What's the chance to have good seizure control in this patient?

A. 60%
B. 70%
C. 80%
D. 90%
E. 100%

The main reason for Rx JME with other AEDs than VPA

- The occurrence of side effects
  - Tremor
  - Weight gain
  - Loss of hair
- Pregnancy

Continued Case

- Patient was given with VPA
- Titrate to 1,000 mg/day
- Good seizure control
- One year later...the patient is pregnant

Intrauterine exposure to AED increases risk of congenital malformations

- MCMs = structural abnormalities with surgical, medical or cosmetic importance.
- Minor malformation, facial dysmorphism, were not considered in statistic analysis

Intrauterine exposure to AED increases risk of major congenital malformations

- VPA > 1,000 mg/day (some > 1,500)
- PB > 200 mg/day
- CBZ + VPA
- CBZ + VPA + PB+- PHT
- PB+ PHT + primidone
- Benzodiazepines + other AEDs
- Caffeine + PB+- other AEDs

The prevalence of MCM is

- 2.2% in all pregnancy
- 3.7% pregnancy c monoRx AED
- 6% pregnancy c polyRx AED

AED regimens with relatively high teratogenicity

- Samra et al, Battino et al, Lindou et al, Dansky
- Greater malformation in VPA > 1,500 mg/day
- No association between epilepsy type or GTC in the 1st trimester and a greater risk of major congenital malformation
- LTG > 200 mg/day in UK study but not others

**Neural tube defects: risk factors**

<table>
<thead>
<tr>
<th>Medical</th>
<th>Non medical</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prior NTD</td>
<td>Chemicals and pesticides</td>
</tr>
<tr>
<td>Partner with NTD</td>
<td>Cleansing solvents and disinfectants</td>
</tr>
<tr>
<td>Close relative with NTD</td>
<td>Radiation</td>
</tr>
<tr>
<td>DM type 1</td>
<td>Anesthetic agents</td>
</tr>
<tr>
<td>AED: VPA, CBZ</td>
<td>Hot tubs, Saunas, Fever</td>
</tr>
<tr>
<td>Pre-pregnancy obesity &gt; 110 kg</td>
<td>Lead</td>
</tr>
<tr>
<td></td>
<td>Tobacco smoke</td>
</tr>
</tbody>
</table>

**Intrauterine exposure to AED reduces cognitive outcome**

Recommendation to reduce risk of poor cognitive outcomes

- Cognitive risk related to AED exposure may be present throughout pregnancy
- Level B: MonoRx should be considered in place of polyRx
- Level B: Avoiding VPA should be considered
- Level C: Avoiding PHT, PB may be considered

**Case 1:** 11 yrs old boy

- F/U epilepsy case in OPD
- Underlying PDD, VSD
- Good seizure control in the past 6 months
- The mother asks about gum hypertrophy

**Case 2:** 11 yrs old

- Underlying PDD, hyperactive child, VSD
- Epilepsy starts at age 5 years old
- Sz: body stiffening and left sided jerking, often seen in sleep, 2-4 times/day
- EEG: Rt T sharp/slow wave : B-TP/CP spike/slow wave
- 1st MRI : negative
Which AEDs would be your choice?
A. Phenytoin
B. Carbamazepine
C. Depakine
D. Topiramate
E. Levetiracetam

Which AEDs would be your 1st AED?
A. Phenytoin
B. Carbamazepine
C. Depakine
D. Topiramate
E. Levetiracetam

After commenced on 1st AED
• No seizure improvement
• What should we do next?
A. Switch to 2nd monotherapy
B. Add on 2nd AED

Add on 2nd AED
A. Phenytoin
B. Carbamazepine
C. Depakine
D. Phenobarbital
E. Levetiracetam

Add on 2nd AED
A. Phenytoin
B. Carbamazepine
C. Depakine
D. Phenobarbital
E. Levetiracetam
Gum hypertrophy, Gingival enlargement/overgrowth

Drug induced enlargement
- AEDs: PHT, PB, LTG, VPA, VGB, ETX, TPX, primidone: 50%
- Cyclosporin: 30%
- Ca channel blockers: amlodipine, nifedipine, verapamil: 10-20%

Inflammatory enlargement

Enlargement associated with systemic factors/condition (pregnancy, Vit C def, leukemia, neoplasm)

Take home message: AED selection

1. Seizure type
   - Clinical history, EEG, VEM
   - +/- imaging
2. Efficacy & Tolerability
   - Mechanism
   - Indication/side effect
3. Mono or polyRx
   - Indication
   - Basic science
4. Drug interaction
   - With AEDs
   - With other medications