Epilepsy Pharmacotherapy: Treatment Considerations with Older AEDs

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Disclosures

- Speaking honoraria:
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AED Options

- Generalized
  - Toxic
  - Toxic-elastic
  - Myoclonic
  - Atonic
  - Infantile Spasms
  - Absence
  - Vigabatrin, ACTH

- Focal
  - Phenytoin, Carbamazepine, eslicarbazepine, Phenobarbital, Gabapentin, Topiramate, Oxcarbazepine, Zonisamide, Lacosamide, Levetiracetam, lamotrigine, pregabalin, rufinamide
Challenges in AED Treatment

- Co-morbidities
- Pharmacokinetic issues
  - Pharmacodynamic issues
  - Noncompliance
- Limited data on efficacy and side effects of AEDs in the elderly

Pharmacokinetic Interactions

- Absorption
  - Adsorption
  - Intestinal Metabolism
  - Transporters
- Distribution
  - Protein Binding
  - Transporters – BBB distribution of drug?
- Elimination
  - Renal Excretion
  - Hepatic Metabolism – polymorphic metabolism?

AEDs & Solubility

- Low Solubility:
  - Phenytoin
  - Carbamazepine
  - Lamotrigine
  - Zonisamide
  - Oxcarbazepine
Hepatic Drug Metabolism

AED effects on Drug Metabolizing Isozymes

Older
- Enzyme inducers (CYP1A2, 2C, 3A, UGT)
  - carbamazepine
  - phenytoin
  - phenobarbital
- Inhibitors
  - VPA (CYP3A4, UGT, EH)

Newer
- No effects on CYP
  - levetiracetam
  - lamotrigine
  - zonisamide
  - vigabatrin
  - Gabapentin/pegabalin
  - Lacosamide
  - rufinamide

Modest inducer
- Oxcarbazepine, Eslicarbazepine, topiramate (CYP3A)

Inhibitors
- Topiramate, oxcarbazepine, Eslicarbazepine (CYP2C19)

Traditional AEDs
- Carbamazepine
- Phenytoin
- Sodium Valproate
- Phenobarbital

Reference: Pharmacokinetics and Drug Interactions
Carbamazepine:
Absorption/Distribution

- Tablet
  - 80% absorbed compared to solution
  - Slow, erratic absorption
  - Peak = 6-12 hours
  - Suspension: more rapidly absorbed
- Sustained/released release tablet & sprinkle
  - Give BID
- IV form finally on the way with cyclodextrin vehicle
- 80-85% protein bound: albumin and alpha 1 acid glycoprotein


Metabolism

- 100% metabolized by the liver
- Carbamazepine epoxide—major metabolite
  - CBZ → CBZepoxide → CBZ dihydrodiol epoxide
  - CYP 3A4 hydrolyase
  - Active metabolite
  - Equal anticonvulsant activity to CBZ
  - May be responsible for many CNS adverse effects
  - Autoinduction of CYP 3A4
    - Adult single dose $t_{1/2} = 33$ hours (18-55 hrs) vs approximately 15 hours in chronic dosing:
      - Takes 4-6 weeks to get maximum auto induction.

Adverse Effects

- CNS side effects common (35-50%), more common during initiation therapy, and may dissipate with chronic therapy
  - Diplopia
  - Ataxia
  - Drowsiness
  - Headache
  - Dizziness
  - Anticholinergic side effects
  - Blurred vision
  - Urinary retention, dry mouth, etc.
  - Paresthesias
  - Hyponatremia
  - Nystagmus
Adverse Effects

- Hematologic
  - Leukopenia
    - Transient leukopenia (2000-4000) and low platelet count
  - Thrombocytopenia
    - 1/50,000 incidence, fatal in 50%. Most patients on other drugs concurrently
  - Aplastic anemia
  - Hepatitis
  - Rash
  - Teratogenicity
  - Osteoporosis

CBZ RASH - Genetics

- Increased risk of serious rash (toxic epidermal necrolysis, Stevens-Johnson syndrome) in patients with HLA-B*1502 & HLA-A*3101
- Found almost exclusively in patients with Asian ancestry -10-15% of patients from China, Thailand, Philippines, Malaysia, and Indonesia may test positive. Far less common (1%) in patients from Japan or Korea
- HLA-A*3101 - 2.5% prevalence in N. European

Phenytoin Absorption/Distribution

- Good overall bioavailability, but may display marked day-to-day variability in absorption. Decreased & delayed absorption with larger doses (>400 mg)
- Extensively protein bound -90% to serum albumin
- Renal failure, hypobuminemia, pregnancy, liver disease - alter protein binding


Individual Total Phenytoin Serum Concentrations in Elderly Nursing Home Residents

PHENYTOIN: Metabolism

- Pharmacokinetics
  - Long $t_1/2$: mean = 18.5-24 hrs; range = 7-42 hrs
  - Michaelis-Menten metabolism, 90-95% liver metabolized by saturable kinetics
  - CYP 2C9 & 2C19 isozymes involved
  - Genetic slow and fast metabolizers
  - Liver disease - decreased metabolism

Phenytoin-Simulated Dosing Requirements in Elderly vs Younger Adults

Phenytoin: Adverse Effects

- Concentration related
  - Nystagmus (> 20 ug/ml)
  - Ataxia (> 30 ug/ml)
  - Confusion (> 40 ug/ml)
  - Encephalopathy

Phenytoin: Adverse effects

- Rash – 5-10% (no genetic link confirmed yet)
- Gingival hyperplasia (30%-50%)
- Hirsutism and coarse facial features
- Osteopenia/osteoporosis possibly related to increased 1,25D metabolism

Vitamin D Metabolism

- 7-DehydroCholesterol
- Vitamin D3
- 25-HydroxyVitamin D3
- 1,25-HydroxyVitamin D3
- Skin, UVB
- Liver 25-Hydroxylase (CYP27B1)
- Kidney 1a-hydroxylase (CYP24A1)
- Degradation P450C24
**Sodium Valproate (VPA): Absorption**
- 90-100% absorption for syrup and capsules
- Time to peak:
  - 0.5-1.0 hr syrup
  - 1.0-2.0 hr regular capsules
  - 3.0-8.0 hr enteric coated tablets

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**VPA: Distribution**
- Saturable protein binding within therapeutic range
  - [VPA] < 50 ug/ml  FF = 7-11%
  - [VPA] 50-100 ug/ml  FF = 11-15%
  - [VPA] 100-150 ug/ml  FF = 15-25%
  - [VPA] 150-200 ug/ml  FF = 25-30%

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**VPA Metabolism**
- 97% metabolized by the liver
- Glucuronidation, beta-oxidation - major routes
- CYP mediated oxidation - minor
- T1/2 = 14 hrs (5-22 hr) adults
  - 11 hrs (5-15 hr) children
- Polytherapy with inducers can double clearance
VPA: Adverse Effects

- Drowsiness
- Tremor
- Confusion - encephalopathy
- Hyperammonemia
- Inhibition of platelet aggregation, lowering of platelet count
- Drug induced Parkinsonism

- Alopecia
- Weight gain

- Hepatotoxicity
  - Transient elevations of serum hepatic enzymes common (15-30%)
  - Fulminant hepatic failure, highest incidence age 0-2 years only
  - Usually slowly evolving, mental state normal until last few days
  - Usually responds to increasing aminotransferase
  - Incidence increases with polytherapy with inducers
  - Usually occur 0-3 months (mean 60 days)

- Pancreatitis - rare, primarily seen in children
- Teratogenicity
- Menstrual cycle abnormalities

PCO & VPA Treatment Unifying Hypothesis

- Valproate related weight gain
  - Obesity
  - Insulin resistance
  - Increased insulin secretion
  - SHBG
  - Hyperinsulinemia
  - IGFBP-1
  - Bioactive androgens
  - Ovarian androgen synthesis
  - Structural changes in the ovaries