Anticonvulsant Poisoning

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Which compound was identified from muscle extracts in 1905?

A. topiramate
B. myostatin
C. phenytoin
D. lamotrigine
E. l-carnitine

What are the manifestations of DRESS Syndrome?

A. coma, hyperammonemia, steatosis

B. fever, eosinophilia, rash

C. psychosis, visual loss, weight gain

D. fatigue, leukopenia, ataxia

E. inappropriate apparel, dementia, diplopia

Phenytoin
Carbamazepine
Phenobarbital
Primidone
Lamotrigine

Presentation Objectives

After studying required readings and lecture notes, students will be able to:

- Describe the pathophysiology and clinical manifestations associated with anticonvulsant poisoning.
- Assess patient risk for anticonvulsant poisoning based on dose, laboratory findings, and patient risk factors.
- Construct a treatment regimen for anticonvulsant poisoning and describe the rationale for each treatment element.

Example Case

A 2 year-old boy ingested seven 50 mg chewable phenytoin tablets within the last 5 minutes. The child is asymptomatic and has no prior medical conditions. He is not taking any medications currently. No treatments have been instituted.

Seizures - Pathophysiology

- Sustained firing of sodium channels
- Excessive Ca conductance
- Increased interaction between glutamate and receptors
- Loss of GABA activity

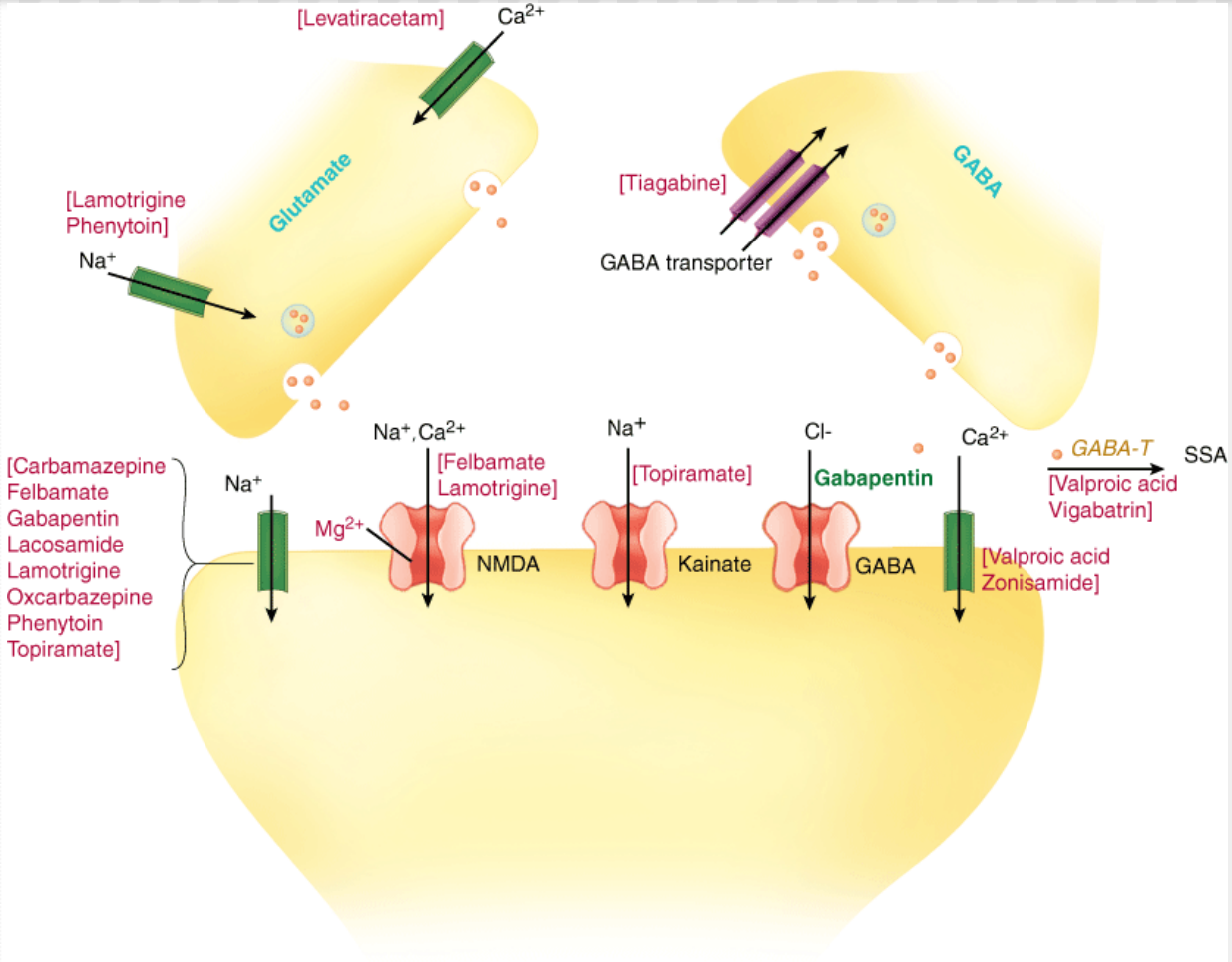
Anticonvulsant MOA

- Inhibition of Na channel function
  - Phenytoin, CBZ, VPA, topiramate, felbamate
  - Lamotrigine, zonisamide, oxcarbazepine
- Increased GABA activity
  - Gabapentin => ⟩ release of GABA from presynaptic vesicles
  - Vigabatrin & VPA => irreversible binding of GABA transaminase => ⟩ GABA
  - Tiagabine => inhibits GABA reuptake

Anticonvulsant MOA

- Inhibition of n-methyl-D-aspartate (NMDA) receptor
  - Felbamate & VPA (glutamate receptor antagonists)
  - Lamotrigine & phenytoin (inhibit glutamate release)
- Modulation of voltage dependent Ca channels
  - Low V:Ethosuximide, VPA, and zonisamide
  - High V: Levetiracetam

Mechanisms of Anticonvulsants



Source: Nelson LS, Lewin NA, Howland MA, Hoffman RS, Goldfrank LR, Flomenbaum NE: *Goldfrank's Toxicologic Emergencies, 9th Edition*: http://www.accessemergencymedicine.com

General Rule of Anticonvulsant Triage

- Patients who achieve a serum concentration within the therapeutic range stay home for observation
- Patient who are above the therapeutic range are referred to ED
- Degree of illness is dependent on serum concentrations established through case reports and case series

Phenytoin (Dilantin)

- Available forms
  - 50 mg, 100 mg, 125 mg/5 mL
- Pharmacokinetics
  - Weak acid with pK of 8.3
  - Vd 0.6 - 0.7, protein binding 90%-95%
  - Metabolized to parahydroxyphenyl derivative; 5% eliminated unchanged
  - Michaelis-Menton kinetics
    - < 10 mg/L => 1st order (t1/2 of 6-24 hours)
    - > 10 mg/L => 0 order (t1/2 of 20-60 hours)
  - Therapeutic levels
    - 10 - 20 mg/L

Fosphenytoin (Cerebyx)

- Available forms
  - Injection 150 mg/2 mL, 750 mg/10 mL
- Pharmacokinetics
  - pH 8-9
  - Converted to phenytoin by circulating phosphates

Phenytoin

- Clinical Manifestations

mg/L	S/sx
15	Nystagmus
30	Ataxia
50	Lethargy, slurred speech, pyramidal and extrapyramidal symptoms

  - Cardiovascular toxicity: usually attributed to IV preparations of phenytoin or large doses of fosphenytoin (5-10 X the therapeutic dose) => bradycardia, hypotension, asystole

Phenytoin

- Adverse Effects
  - gingival hyperplasia (dose-related), facial coarsening, peripheral neuropathy, bone diseases, and vitamin deficiencies
  - Idiosyncratic
    - leukopenia, thrombocytopenia, aplastic anemia

Phenytoin Management

- Supportive Care
  - CPR
- Prevent Absorption
  - AC
- Enhance Elimination
  - MDAC may be helpful
  - Hemodialysis/hemoperfusion are of no benefit

Carbamazepine (Tegretol) Uses

- Structurally related to cyclic antidepressants
- Also used for chronic pain syndromes (trigeminal neuralgias)
- Migraine prophylaxis
- Bipolar affective d/o

Carbamazepine (Tegretol)

- Available Forms
  - Tablets: 100 mg, 200 mg
  - Capsules: 200 mg, 300 mg
  - Liquid: 100/5
- Pharmacokinetics
  - Absorption: Slow, may take up to 24 hour to reach peak
  - Distribution: 0.6 - 2 L/kg; 75%-90% protein bound
  - Metabolism: metabolized through CYP3A4, forms an active metabolite (10,11 epoxide) => carbamazeine diol (inactive); autoinduction occurs during 1st couple of weeks of therapy
  - Therapeutic levels
    - 4 - 12 mg/L

CBZ Poisoning Manifestations

- Neurological
  - Nystagmus, ataxia, dysarthria => lethargy and coma
  - Seizures (55% in patients with levels >40 mg/L)
- Cardiovascular
  - Sinus tachycardia, hypotension, conduction abnormalities (QRS widening; QTc prolongation)
- Chronic
  - Increased vasopressin secretion => hyponatremia (SIADH)
- Correlation to Levels
  - ≥40 mg/L => coma, sz, respiratory depression and cardiotoxicity

CBZ Adverse Effects

- Dose-related
  - irritability, impaired concentration, memory impairment
- Idiosyncratic
  - rash, hepatitis, drug-induced SLE, hemopoetic disorders (leukopenia)

CBZ Management

- Supportive
  - Cardiac arrhythmia: Consider HCO_3
  - Sz: Benzodiazepine
- Enhance Elimination
  - MDAC
  - Possibly hemoperfusion or high efficiency (high flux) hemodialysis

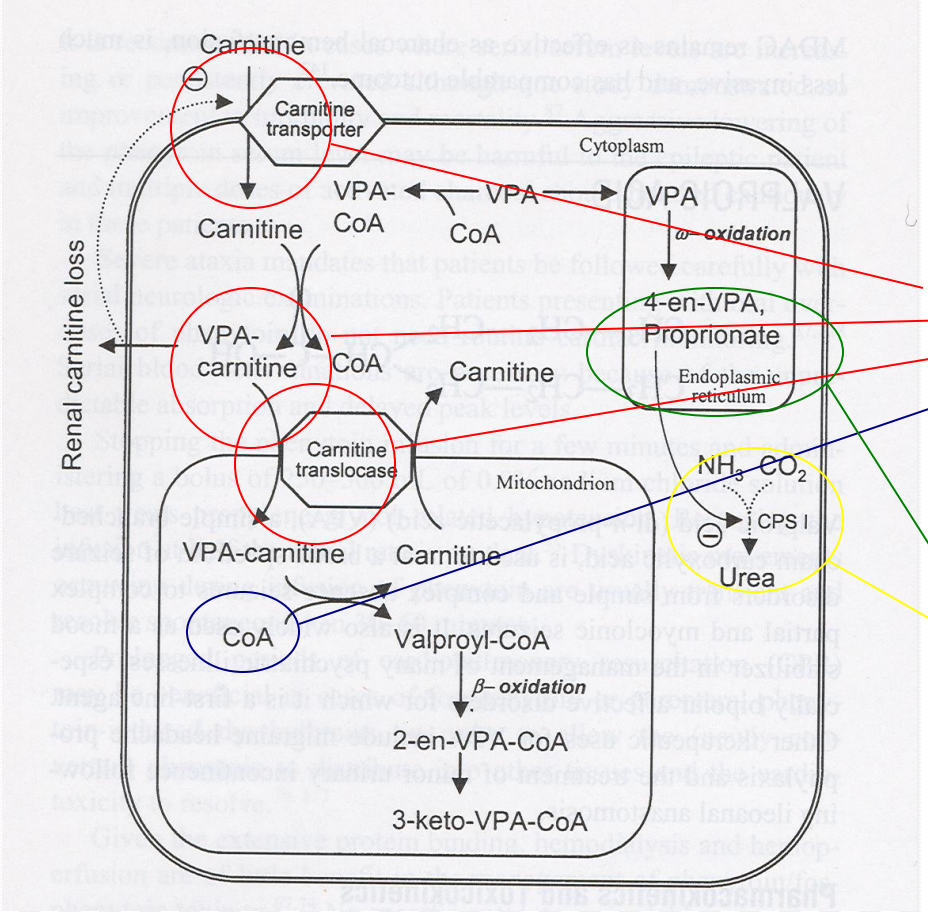
Valproic Acid (Depakene) Uses

- Absence (simple and complex) seizures
- Complex partial seizures
- Myoclonic seizures
- Mood stabilizer
- Migraine headache prophylaxis
- Urinary incontinence

Valproic Acid (Depakene) Divalproex (Depakote)

- Available Forms
  - Depakene: 250 mg
  - Depakote: 125 mg, 250 mg, 500 mg
- Pharmacokinetics
  - Absorption: 100% absorbed from GI tract
  - Vd: .14-.23 L/kg; Protein binding: 90% at therapeutic levels, but decreases in overdose
  - Metabolism: Conjugated by glucuronide and then oxidized by either a carnitine-dependent mitrochondrial β- oxidation or by microsomal ω- oxidation (forms a hepatoxic metabolite and causes interruption of urea cycle => ammonia accumulation
  - Therapeutic levels: 50-100 mg/L

Metabolism of VPA



⇩ Carnitine

⇩ CoA

⇧ Hepatoxicity

⇧ ammonia

VPA Toxicity

- Drowsiness=>coma=>cerebral edema
  - >30 mg/kg => coma and respiratory depression
- Metabolic complications
  - Metabolic acidosis with anion gap
  - Hypernatremia
  - Hypocarnitemia
  - Hyperammonemia (>60 umol/L)*

  *seen with chronic or acute on chronic exposures
- Bone marrow suppression
  - 3-5 days after massive overdose
- Rare complications
  - Pancreatitis, hepatic failure, renal failure

VPA Adverse Effects

- Hepatotoxicity (4 types)
  - Transient, reversible elevations of transaminases
  - Reversible hyperammonemia
  - Toxic hepatitis
  - Reye-like syndrome

VPA Laboratory Assessment

- Serial VPA levels
- For ill patients consider:
  - Carnitine levels
    - Carnitine ≤20 uM, or acylcarnitine/free carnitine ratio of ≥0.4 indicative of hypocarnitinemia
  - Urinary 2-enVPA
  - Serum ammonia

VPA Management

- Supportive
  - ABC's
- Prevent Absorption
  - Lavage, AC
- Enhance Elimination
  - MDAC, hemodialysis
- Antidote
  - Naloxone?
  - Carnitine?

Carnitine Therapy

- Indications
  - >400 mg/kg VPA
  - Hyperammonemia or hepatotoxicity
  - Supplement for children <2 and “at risk” for hepatotoxicity
- Dose
  - Loading: 100 mg/kg IV over 30 minutes (max of 6 gm)
  - Maintenance: 15 mg/kg IV over 10-30 minutes every 4 hours
  - Give 3-4 days until clinical improvement

Gabapentin (Neurontin) Uses

- Partial seizures without secondary generalization
- Post traumatic stress disorder
- Behavior/mood disorders
- Bruxism
- Neurologic disturbances

Gabapentin (Neurontin)

- Available forms
  - 100 mg, 300 mg, 400 mg tablets and capsules
- Pharmacokinetics
  - Absorption: 60% bioavailability
  - Distribution: 1-2 L/kg; not protein bound
  - Metabolism: Not metabolized
  - Therapeutic blood level: 2-15 mg/L

Gabapentin OD Manifestations

- Sedation
- Ataxia
- Slurred speech
- Tremulousness*
- Cognitive deficits*
- Withdrawl syndrome

* seen with chronic overdose and in patients with renal failure

Gabapentin Adverse Effects

- Dizziness
- Ataxia
- Fatigue
- Nystagmus
- Headache
- Rhinitis
- Movement disorders

Gabapentin Laboratory Assessment

- Gabapentin blood level (therapeutic is 2-15 ug/mL)

Gabapentin Management

- Supportive Care
  - ABC's
- Prevent Absorption
  - Lavage, AC
- Enhance Elimination
  - No data on value of hemodialysis or hemoperfusion

Felbamate (Felbatrol) Uses

- Structurally related to meprobamate
- Can cause hepatic failure and aplastic anemia so it is a therapy of last resort

Felbamate (Felbatrol)

- Available Forms
  - Tablets: 400 mg, 600 mg
  - Suspension: 600 mg/5 mL
- Pharmacokinetics
  - Absorption: rapid, peak levels in 1-4 hours
  - Distribution: 0.7-1.0 L/kg; 22%-25% protein bound
  - Metabolism: No active metabolites, 90% excreted unchanged
  - Half-life: 13-23 hours
  - Therapeutic blood levels: 18-83 ug/mL

Felbamate OD Manifestations

- Mild lethargy
- Gastrointestinal upset
- Coma
- Respiratory failure
- Crystalluria, hematuria
- Reversible renal failure

Felbamate Adverse Effects

- Weight gain or weight loss
- Insomnia
- Somulence
- Nausea and vomiting
- Hepatic failure
- Aplastic anemia

Laboratory Assessment

- Felbamate blood concentration
  - Levels > 135 ug/mL are potentially associated with toxicity

Felbamate Poisoning Managment

- Supportive

Lamotrigine (Lamictal) Uses

- Approved as an adjunct medication for treatment of partial seizures or secondary generalized seizures
- Bipolar mood disorders

Lamotrigine (Lamictal)

- Available Forms
  - Tablets: 25 mg, 100 mg, 150 mg, 200 mg
- Pharmacokinetics
  - Absorption: 98% bioavailability
  - Distribution: 1.2-1.5 L/kg; 55%-56% protein bound
  - Metabolism: glucuronidated to inactive metabolite; phenytoin and CBZ induce metabolism lamotrigine ; VPA competes with metabolism of lamotrigine
  - Half-life: 25 hours
  - Therapeutic blood levels: 1-4 mcg/mL

Lamotrigine Overdose Manifestations

- 19 - 64 mg/kg => lethargy, ataxia, nystagmus, slurred speech, seizures, ECG abnormalities
- 19.2 mg/kg => mild lethargy, vertical and horizontal nystagmus, QRS prolongation

Lamotrigine Adverse Effects

- Dizziness
- Headaches
- Diplopia
- Ataxia
- Stevens-Johnson Syndrome

Laboratory Assessment

- >5 mg/L => potentially toxic

Lamotrigine Overdose Management

- Supportive Care
  - EKG monitoring; potentially use HCO_3 for QRS prolongation
- Prevent Absorption
  - Lavage, AC
- Enhancing Elimination
  - No data; Manufacturer states that it is dialyzable

Vigabatrin (Sabril) Uses

- Structurally similar to GABA
- Inhibits GABA-transaminase
- Adjuctive agent for multi-drug refractory complex partial seizures in adults
- Resistant partial seizures and infantile spasms in children and adolescents

Vigabatrin (Sabril)

- Available Forms
  - 500 mg tablet
- Pharmacokinetics
  - Absorption: peak in 0.5-2 hours
  - Distribution: Vd=0.8 L/kg; not protein bound
  - Metabolism: excreted unchanged
  - Half-life: 7 hours
  - Therapeutic blood concentrations: 90-200 nmol/mL

Vigabatrin Overdose Manifestations

- Acute Poisonings
  - 8-10 g => vertigo, tremor, long-term psychosis
  - 30 g + chlorazepate => coma
  - 60 g => severe agitation
- Chronic toxicity => psychosis, vertigo, tremor

Vigabatrin Adverse Effects

- Depression
- Psychosis
- Visual defects
  - Concentric and predominantly nasal field constriction
  - Onset is 1 month to several years
  - Incidence estimated to be 14.5/10,000 patients treated
  - Can be permanent

Laboratory Evaluation

- > 80 mg/L => potentially toxic

Vigabatrin Management

- Supportive

Topiramate (Topamax) Uses

- Adjunctive therapy for patients with partial seizures, generalized tonic-clonic, or Lennox Gastaut syndrome
- Blocks sodium channels, enhances GABA and diminishes action of glutamate
- Advantages of topiramate are long half-life, good tolerability, no hepatoxicity or hematotoxicity.
- A disadvantage is induction of cognitive disturbances (decreased cognition, dulled thinking, blunted mental reactions). Incidence is 30%-40%.

Topiramate (Topamax)

- Available Forms
  - Tablets: 25 mg, 100 mg, 200 mg
  - Capsules: 15 mg, 25 mg, 50 mg
- Pharmacokinetics
  - Absorption: 80% bioavailability; peak levels in 1.5-4 hours
  - Distribution: Vd = 0.6-0.8 L; protein binding 9%-17%
  - Metabolism: limited metabolism (hydroxylation, hydrolysis then conjugation to glucuronides)
  - Half-life: 18-24 hours
  - Therapeutic Blood Levels: Not established

Toprimate Overdose Manifestions

- Lethargy, ataxia, nystagmus, myoclonus, coma, seizures, and status epilepticus
- Non anion gap metabolic acidosis, hyperchloremia
- In the two reported cases patients developed agitation, combativeness, confusion, incoherence, speech impairment, bradykinesia and bradyphasia. Both recovered in 24 hours. Doses were 400-800 mg.

Toprimate Adverse Effects

- Lethargy
- Confusion
- Somulence
- Ataxia
- Diplopia,
- Paresthesias
- Nephrolithiasis

Topiramate OD Management

- Supportive Care
  - Monitor ECG for QRS prolongation
- Prevent Absorption
  - Lavage, AC
- Enhancing Elimination
  - Should be dialyzable; clearance across dialysis membrane is 120 mL/minute

Ethosuximide (Zarontin)

- Used in treatment of absence (petit mal) seizures

Ethosuximide (Zarontin)

- Available Forms
  - Capsules: 250 mg
  - Syrup: 250 mg/5 mL
- Pharmacokinetics
  - Absorption: peak levels in 2-4 hours
  - Distribution: Vd = 0.6-0.7 L/kg
  - Metabolism: 80% metabolized in liver to 3 inactive metabolites
  - Half-life: 30 hours
  - Therapeutic Blood Level: 40-100 ug/mL

Ethosuximide OD Manifestations

- Confusion
- Sleepiness
- Unsteadiness
- Flaccid muscles
- Coma
- Slow, shallow respirations
- Hypotension
- Cyanosis
- Hypo or hyperthermia
- Absent reflexes
- Nausea
- Vomiting

Ethosuximide Adverse Effects

- Behavioral disturbances
  - Confusion, instability, mental slowness, depression, hypochondriacal behavior, night terrors, aggressiveness, inability to concentrate
- Stevens-Johnson syndrome
- Aplastic anemia
- Drug induced SLE
- Renal damage

Tiagabine (Gabitiril)

- GABA uptake inhibitor
- Adjunctive therapy for partial seizures

Tiagabine (Gabitiril)

- Available Forms
  - Tablets: 4 mg, 12 mg, 16 mg, 20 mg
- Pharmacokinetics
  - Absorption: peak levels in 45 minutes with single therapeutic doses
  - Distribution: 96% protein bound
  - Metabolism: CYP3A4, one inactive metabolite
  - Half-life: 7-9 hours

Tiagabine OD

- Usual dose: 4 - 32 mg/day
- Usual blood levels: 1-234 ng/mL
- There have been several overdoses reported. The clinical features observed include myoclonus, rigidity, agitation, and status epilepticus.
- Symptoms seen at 2X top end of therapeutic blood conc (420 ng/mL)

Forbes RA, Kalra H, Hackett LP, Daly FF. Deliberate self-poisoning withtiagabine: an unusual toxidrome. Emerg Med Australas. 2007 Dec;19(6):556-8.
Wiśniewski M, Sein Anand J, Chodorowski Z, Kosińska-Tomczyk H. [Tiagabineoverdose--report of two cases]. Przegl Lek. 2007;64(4-5):308-9.
Fulton JA, Hoffman RS, Nelson LS. Tiagabine overdose: a case of statusepilepticus in a non-epileptic patient. Clin Toxicol (Phila). 2005;43(7):869-71.
Cantrell FL, Ritter M, Himes E. Intentional overdose with tiagabine: anunusual clinical presentation. J Emerg Med. 2004 Oct;27(3):271-2.

Tiagabine Adverse Effects

- Sedation
- Chest pain, tachycardia, hypertension
- Muscle weakness

Tiagabine OD Management

- Supportive
  - ABC's
- Preventing Absorption
  - Lavage, AC
- Enhancing Elimination
  - Dialysis and hemoperfusion are likely not helpful since the drug is highly protein bound

Oxcarbazepine (Trileptal)

- Antiepileptic derived from carbamazepine
- Used in monotherapy or adjuctive therapy in treatment of partial seizures in adults and children.
- Effective in treating trigeminal neuralgia.
- Potential alternative to CBZ in intolerant patients

Oxcarbazepine & MHD Pharmacokinetics

- Oxcarbazepine
  - Vd=0.7 L/kg
  - Protein bind 40%-60%
  - Half-life 1-2.5 hours
- MHD (10-hydroxycarbazepine)
  - Vd=0.7 L/kg
  - Protein binding 40%
  - Half-life 10 hours

Oxcarbazepine (Trileptal)

- Induces CYP2C19 and CYP3A4/5
- Lower incidence of skin rashes than CBZ
- Somulence, tinnitus, bradycardia and hypotension
- Will likely produce QRS prolongation
- Produces SIADH

Oxcarbazepine OD Treatment

- Supportive care
  - ABC's
- Preventing Absorption
  - Lavage, AC
- Enhancing elimination
  - Not useful (based on single case report)

Furlanut M, Franceschi L, Poz D, Silvestri L, Pecorari M. Acute oxcarbazepine, benazepril, and hydrochlorothiazide overdose with alcohol. Ther Drug Monit. 2006;28(2):267-8.

Levetiracetam (Keppra)

- Mechanism is unknown
- Pharmacokinetics
  - Not metabolized by CYP 450
  - Vd=0.7L/kg; No protein binding
  - Half-life: 6-8 hrs
- SE's: somulence, asthenia, psychiatric symptoms; polycythemia and leukocytosis

Levetiracetam OD

- 30 gram OD in a 38 yo produced respiratory depression requiring intubation. (Barrueto F Jr. Williams K. Howland MA. Hoffman RS. Nelson LS. A case of levetiracetam (Keppra) poisoning with clinical and toxicokinetic data. [Case Reports. Journal Article] Journal of Toxicology - Clinical Toxicology. 40(7):881-4, 2002.)

Levetiracetam Treatment

- Supportive care
  - ABC's
- Preventing Absorption
  - Lavage, AC
- Enhancing elimination
  - No reported experience

Zonisamide (Zonegran)

- Mechanism is unclear. Probably blocks sodium and T-type calcium channels.
- Pharmacokinetics
  - Peak in 2-5 hours; F=100%
  - Vd = 0.8-1.6 L; PB 40%-50%
  - 50% metabolized by CYP3A4; 20% acetylated; 10% unchanged
  - Therapeutic range: 20 – 30 mg/L
- SE's: Somulence, anorexia, dizziness, headache, nausea, agitation/irritability

Zonisamide OD

Author	Conc (mg/L)	Clinical Effects
Naito (1988)	143 (est T0)	Coma, bradycardia, hypotension, dec respiration
Sztajnkrycer (2003)	44 @ ???	Death
Hofer (2011)	182 @ 8 hrs	QRS widening, QTc prolongation, mild acidosis, coma
Wightman (2011)	110 @ 5.5 hrs	CNS depression, sz-like activitiy

Summary Table

Agent	Distinguishing Clinical Effects*	Toxic Threshold	Potential Methods To Enhance Elimination
Phenytoin	Nystagmus, ataxia, lethary	15 mg/L, 30 mg/L, 50 mg/L	MDAC?
Carbamazepine	Seizures and arrhythmias	40-80 mg/L (24 mg/kg)	MDAC, HP, HD
Valproic acid	CNS depression and hyperammonemia	> 30 mg/L	MDAC, HD
Gabapentin	None	Unknown; Therapeutic 2-15 ug/mL	
Felbamate	Chronic: aplastic anemia and hepatic failure	> 135 ug/mL	
Lamotrigine	Same as phenytoin + QRS prolongation	≥ 19 mg/kg	HD
Vigabatrin	Psychosis	> 80 mg/L	
Topiramate	Agitation, bradykinesia, bradyphasia, nonion gap acidosis	450 mg	HD
Ethosuximide	None	Unknown	
Tiagabine	Myoclonus, rigidity, agitation, status epilepticus*	420 ng/mL* *seizures seen at therapeutic doses	
Oxcarbazepine	Same as carbamazepine	Unknown	
Levetiracetam	CNS + respiratory depression	30 gms	

Case Write-Up

S: A 2 year-old boy ingested seven 50 mg chewable dilantin tablets within the last 5 minutes. The child is asymptomatic and has no prior medical conditions. He is not taking any medications currently. No treatments have been instituted.

O: Not available

A: This patient's estimated blood concentration is:

$$Conc = \frac{Amount}{Volume} = \frac{50mg \times 7tablets}{0.6L/kg \times 10kg} = \frac{350mg}{6L} = 58.3mg/L$$

This blood concentration is consistent with significant lethargy (seen at concentrations of 50 ug/mL). The patient will need to be treated in a healthcare facility.

Management Plan

1. Supportive care

   Intubation and mechanical ventilation if the patient loses respiratory drive (unlikely)

2. Prevent further absorption

   Administer activated charcoal.

3. Provide antidote

   Not applicable

4. Enhance elimination

   Consider multiple dose activated charcoal if patient becomes severely intoxicated.