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

[Diagram showing mechanisms of action of different anticonvulsant drugs, including Glutamate, GABA, and various ions and molecules involved in their interactions.]


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General Rule of Anticonvulsant Triage

- Patients who achieve a serum concentration within the therapeutic range stay home for observation
- Patients 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
    - $< 10 \text{ mg/L} \Rightarrow$ 1st order (t1/2 of 6-24 hours)
    - $> 10 \text{ mg/L} \Rightarrow$ 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

<table>
<thead>
<tr>
<th>mg/L</th>
<th>S/sx</th>
</tr>
</thead>
<tbody>
<tr>
<td>15</td>
<td>Nystagmus</td>
</tr>
<tr>
<td>30</td>
<td>Ataxia</td>
</tr>
<tr>
<td>50</td>
<td>Lethargy, slurred speech, pyramidal and extrapyramidal symptoms</td>
</tr>
</tbody>
</table>

- 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, hemopoietic disorders (leukopenia)
• Supportive
  - Cardiac arrhythmia: Consider HCO$_3$$_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)  
Divalproe (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 mitochondrial β-oxidation or by microsomal ω-oxidation (forms a hepatotoxic metabolite and causes interruption of urea cycle => ammonia accumulation)
  ▪ Therapeutic levels: 50-100 mg/L
Metabolism of VPA

- Carnitine
- CoA
- Hepatotoxicity
- Ammonia
VPA Toxicity

- Drowsiness => coma => cerebral edema
  - >30 mg/kg => coma and respiratory depression
- Metabolic complications
  - Metabolic acidosis with anion gap
  - Hypernatremia
  - Hypocarnitremia
  - 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 \( \leq 20 \text{ uM} \), or acylcarnitine/free carnitine ratio of \( \geq 0.4 \) 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*
- Withdrawal 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 Management

• 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

- $>5 \text{ mg/L} \Rightarrow$ 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 hepatotoxicity 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: $V_d = 0.6-0.8$ 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 Manifestations

- 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)

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 adjunctive 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**
  - $V_d=0.7$ L/kg
  - Protein bind 40%-60%
  - Half-life 1-2.5 hours

- **MHD (10-hydroxycarbazepine)**
  - $V_d=0.7$ 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)

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

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
<table>
<thead>
<tr>
<th>Author</th>
<th>Conc (mg/L)</th>
<th>Clinical Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Naito (1988)</td>
<td>143 (est T0)</td>
<td>Coma, bradycardia, hypotension, dec respiration</td>
</tr>
<tr>
<td>Sztajnkrycer (2003)</td>
<td>44 @ ???</td>
<td>Death</td>
</tr>
<tr>
<td>Hofer (2011)</td>
<td>182 @ 8 hrs</td>
<td>QRS widening, QTc prolongation, mild acidosis, coma</td>
</tr>
<tr>
<td>Wightman (2011)</td>
<td>110 @ 5.5 hrs</td>
<td>CNS depression, sz-like activity</td>
</tr>
<tr>
<td>Agent</td>
<td>Distinguishing Clinical Effects*</td>
<td>Toxic Threshold</td>
</tr>
<tr>
<td>----------------</td>
<td>---------------------------------</td>
<td>------------------------------------------</td>
</tr>
<tr>
<td>Phenytoin</td>
<td>Nystagmus, ataxia, lethary</td>
<td>15 mg/L, 30 mg/L, 50 mg/L, 80 mg/L</td>
</tr>
<tr>
<td>Carbamazepine</td>
<td>Seizures and arrhythmias</td>
<td>40-80 mg/L (24 mg/kg)</td>
</tr>
<tr>
<td>Valproic acid</td>
<td>CNS depression and hyperammonemia</td>
<td>&gt; 30 mg/L</td>
</tr>
<tr>
<td>Gabapentin</td>
<td>None</td>
<td>Unknown; Therapeutic 2-15 ug/mL</td>
</tr>
<tr>
<td>Felbamate</td>
<td>Chronic: aplastic anemia and hepatic failure</td>
<td>&gt; 135 ug/mL</td>
</tr>
<tr>
<td>Lamotrigine</td>
<td>Same as phenytoin + QRS prolongation</td>
<td>≥ 19 mg/kg</td>
</tr>
<tr>
<td>Vigabatrin</td>
<td>Psychosis</td>
<td>&gt; 80 mg/L</td>
</tr>
<tr>
<td>Topiramate</td>
<td>Agitation, bradykinesia, bradyphasia, nonion gap acidosis</td>
<td>450 mg</td>
</tr>
<tr>
<td>Ethosuximide</td>
<td>None</td>
<td>Unknown</td>
</tr>
<tr>
<td>Tiagabine</td>
<td>Myoclonus, rigidity, agitation, status epilepticus*</td>
<td>420 ng/mL* *seizures seen at therapeutic doses</td>
</tr>
<tr>
<td>Oxcarbazepine</td>
<td>Same as carbamazepine</td>
<td>Unknown</td>
</tr>
<tr>
<td>Levetiracetam</td>
<td>CNS + respiratory depression</td>
<td>30 gms</td>
</tr>
</tbody>
</table>
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:

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

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.