Appendix B

• Antidotes
• Therapeutics
• Analgesics
• Household Caustics
• Anticonvulsants
• Regulatory/Legal Toxicology

Visit the web-based syllabus for additional material including lecture handouts, additional questions/answers, and other material that may not have been included in the print edition syllabus.
I. Antidotes
  Many types of antidotes. Their purpose is to reduce toxicity by several mechanisms: inhibiting translocation to an effector site, reducing toxin concentration, or reducing toxin action at effector site. Most will be discussed in detail in respective sections.
  General principles:
  • Few antidotes; many, many chemicals.
  • Antidotes, as drugs, may also cause side effects.
  • Need for antidote use must be evaluated before use (risk/benefit)
  • Some antidotes’ therapeutic half lives (naloxone) are shorter than duration of action of drug (heroin).

Here is a list of the different types and/or groupings of various antidotes.

<table>
<thead>
<tr>
<th>Antidote Type</th>
<th>Use</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antivenin</td>
<td>Select spiders, snakes, scorpion, fish</td>
</tr>
<tr>
<td>Atropine</td>
<td>Organophosphates, carbamates, nerve agents</td>
</tr>
<tr>
<td>Calcium gluconate</td>
<td>HF, calcium channel blocker</td>
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<tr>
<td>Chelators</td>
<td>Heavy metals</td>
</tr>
<tr>
<td>Digoxin specific antibodies (Fab)</td>
<td>Digitalis and dig-like substances</td>
</tr>
<tr>
<td>Ethanol</td>
<td>Methanol, ethylene glycol</td>
</tr>
<tr>
<td>Flumazenil</td>
<td>Benzodiazepines</td>
</tr>
<tr>
<td>Fomepizole</td>
<td>Methanol, ethylene glycol</td>
</tr>
<tr>
<td>Glucagon</td>
<td>Beta blockers, calcium channel blockers, hypoglycemia</td>
</tr>
<tr>
<td>Hydroxocobalamin</td>
<td>Cyanide, acetonitrile, propionitrile</td>
</tr>
<tr>
<td>Insulin</td>
<td>Calcium channel blockers</td>
</tr>
<tr>
<td>Iodide</td>
<td>Radioactive iodine</td>
</tr>
<tr>
<td>Leucovorin</td>
<td>Methotrexate; methanol?</td>
</tr>
<tr>
<td>Methylene blue</td>
<td>Methemoglobin producers</td>
</tr>
<tr>
<td>n-Acetylcysteine</td>
<td>Acetaminophen</td>
</tr>
<tr>
<td>Naloxone</td>
<td>Opiates and opioids, clonidine, imidazoline nasal spray?</td>
</tr>
<tr>
<td>Nicotinamide</td>
<td>PNU (Vacor), streptozotocin</td>
</tr>
<tr>
<td>Nitrite</td>
<td>Cyanide</td>
</tr>
<tr>
<td>Octreotide</td>
<td>Sulfonylurea agents</td>
</tr>
<tr>
<td>Phystostigmine</td>
<td>Anticholinergics</td>
</tr>
<tr>
<td>Pralidoxime (2-pam)</td>
<td>Organophosphates, nerve agents</td>
</tr>
<tr>
<td>Protamine</td>
<td>Heparin, dalteparin, enoxaparin</td>
</tr>
<tr>
<td>Prussian blue</td>
<td>Thallium?; radioceus/radiothallium</td>
</tr>
<tr>
<td>Thiosulfate</td>
<td>Cyanide</td>
</tr>
<tr>
<td>Vitamin B6 (pyridoxine)</td>
<td>INH, hydrazines, gyromitra mushroom; ethylene glycol?</td>
</tr>
<tr>
<td>Vitamin K1 (phytonadione)</td>
<td>Coumarin, indandione, long-acting rodenticides (bodifacoum, etc)</td>
</tr>
</tbody>
</table>

Make sure you can match antidote with the substance that it can be used for. Some can be used for more than one thing: ethanol OR fomepizole (for methanol and ethylene glycol).

For each antidote, recognize indications, contraindications, duration of therapy. Chemical structures may be tested. Here are some common ones:

- Atropine
- Fomepizole
- NAC
- Octreotide
- Prussian blue
II. Therapeutics

All the following assume appropriate assessment and management of ABC’s is being done.

A-a gradient = (760-47) x 0.21-(PaCO2/0.8)-PaO2 (assuming sea level and room air).
Normal for adults is 10-15 torr; normal for elderly 30+ torr.

Decontamination principles

Ocular: irrigate with plain water or saline. Check pH, and continue irrigating till corrected.
Skin: skin absorption depends on lipid solubility, skin condition, location, caustic effect, physical conditions, and solvent effects. Remove clothing, copious irrigation, and utilization of appropriate PPE according to risk. Examples of substances that are absorbed easily: organophosphates, organic metal compounds, aniline, phenol, hydrogen cyanide, ethylene bromide.

Gastrointestinal

Emesis: limited use. Consider if no contraindication (compromised airway, coma, seizure, impaired gag reflex, aspiration potential from toxin), and ingestion time less than 60 minutes. Complications: diarrhea, lethargy, drowsiness, Mallory-Weiss tears, pneumomediastinum, aspiration pneumonia, intracranial bleed, and prolonged vomiting

Lavage: limited use. Consider if no contraindication (corrosives, sharp objects ingested, unprotected airway, risk of bleeding from varices), and ingestion time less than 60 minutes. Complications: aspiration, esophageal perforation, tension pneumothorax, empyema, epistaxis (from nasal tubes), and electrolyte imbalance if solutions other than saline used.

Activated charcoal: may have more effect than emesis or lavage if given within 60 minutes of ingestion. Traps toxins in the range of 100–1000 Daltons. Does not bind well to elemental metals, cyanide, ethanol, petroleum distillates, malathion. Multiple dose activated charcoal may be of benefit in interrupting enterohepatic circulation or producing a reverse dialysis for some products. May be of value for theophylline, phenobarbital, carbamazepine, quinine, and aspirin.

Cathartics: No definite indications! Generally not used now.

Whole bowel irrigation: isotonic solutions used (polyethylene glycol). No established indications! May help with massive amounts of highly toxic drugs, iron tablets, cocaine packets, sustained release preparations, etc. Little evidence that it actually lessens morbidity/mortality.

Enhancing Elimination

Urinary pH alteration

Urinary acidification: not used!

Urinary alkalization: enhances salicylate excretion for mild/moderate cases; also helps with Phenobarbital excretion. Complications: cerebral and pulmonary edema, hypomagnesemia, hyperkalemia, hypernatremia, alkalemia, hypocalcemia. 1-2 mEq/kg sodium bicarbonate 1 D5W or D1/2NS and run over 3-4 hours. Urine pH should be periodically checked and should be 7.5-8 after one hour, and additional doses/infusion of bicarbonate may be needed.

Diuresis: not used. Appropriate urinary flow rates should be maintained.

Hemodialysis: toxin needs to be able to pass dialysis membrane. Properties that enhance this include low molecular weight (< 500 Daltons), high water solubility, and low protein binding. Indication typically includes an assessment of clinical condition AS WELL AS serum levels: salicylates, phenobarbital, isopropanol (typically not used for this), lithium, and theophylline. For methanol and ethylene glycol the indication may be history of ingeston/suspicion of ingestion and clinical condition (acidosis).

Hemoperfusion: high molecular weight, protein binding and poor water solubility NOT limiting! Charcoal cartridge removes polar and non-polar drugs and metabolites. Resin cartridge (Amberlite XAD-4) effective for non-polar lipid soluble drugs (ethchlorvynol); better than charcoal cartridge. Availability is a problem, and hemodialysis can usually be initiated much quicker than hemoperfusion.

Peritoneal dialysis: not used.

Antidotal Therapy

Some toxins have antidotes available (see antidote handout)

Two antidotes given universally in patients having CNS depression: oxygen, glucose (or at least a quick bedside test), and naloxone.

Supportive Care Measures

Always assess and maintain appropriate status of ventilation, oxygenation, perfusion, temperature, and seizure control.

Handouts: Antidotes; Therapeutics; Analgesics; Poison Center Management; Household Caustics. JG Benitez, MD, MPH
III. Analgesics

**Salicylates**: many products contain salicylates. “Children’s” tabs contain 80 mg, adult ASA contain 325 or 500 mg. Some are enteric coated so may delay peak concentrations. Bismuth subsalicylate contains equivalent of 8.77 mg/ml of salicylic acid. Methylsalicylate (oil of Wintergreen) 1 tsp = 7000 mg ASA. A 1 oz tube of topical liniment (20% methyl salicylate) contains about the equivalent of 4 ml of oil of Wintergreen which has been fatal in children.

**Pathophys**: inhibit prostaglandin synthesis, prevent thromboxane production, and inhibit some clotting factors. Salicylates inhibit oxidative phosphorylation leading to increased metabolic rate, increased oxygen consumption, increased ventilation (hyperventilation), elevated temperature, and increased glucose utilization. Salicylates interfere with Krebs cycle and blocks both lipid and carbohydrate metabolism resulting in metabolic acidosis (organic acids accumulation).

**Levels**: acute salicylate poisoning occurs as levels approach 100 mg/dl, but is variable. Chronic poisoning occurs at much lower levels (60 mg/dl).

**Treatment**: Supportive (ABC’s, fluid resuscitation, cooling, PEEP, intubation-with caution to not inhibit compensatory hyperventilation), urinary alkalization, metabolic support, seizure treatment (benzo’s), dialysis. Typical indications for hemodialysis include cardiac or renal failure, intractable acidosis, severe, fluid imbalance, salicylate serum concentrations near 100 mg/dl (acute OD) or 60 mg/dl (chronic OD).

**Acetaminophen**: The most common analgesic reported to poison centers. Many products contain APAP. Has analgesic and antipyretic properties by inhibiting prostaglandin synthesis. Rapidly absorbed with peak therapeutic concentrations in 1 hour. Eliminated (90%) by liver by conversion to sulfate or glucoronide. Sulfate pathway predominates in children till about age 8-10. Small proportion is metabolized through P450 system (CYP2E1, CYP1A2) to produce NAPQI (n-acetyl-p-benzoquinoneimine). Other elimination is through urine unchanged.

**Pathophys**: nausea/vomiting may develop with hours, but liver function test normal within the first 24 hours following acute ingestion. Abdominal pain, progressing to RUQ pain may start as early as 18 hours and develop over the next 2-3 days. If hepatic failure does not develop resolution typically occurs after the 3rd day. Hepatotoxicity from toxic intermediary (NAPQI) covalently binding to proteins and other cellular enzymes within hepatocytes leading to a centrilobular necrosis. This is normally prevented by detoxification of NAPQI. However, when glutathione levels drop below ~30%, then tissue necrosis occurs. Fulminant hepatic failure may develop from 3-6 days following overdose. Jaundice, encephalopathy, raised intracranial pressure, DIC, hemorrhage, acidosis, hypoglycemia and renal failure are also noted. The same metabolic pathway exists in the kidney and renal toxicity may also occur. Oliguric renal failure may be noted 24-48 hours after overdose.

**Levels**: immunoassay is utilized and therapeutic levels range from 5-20 mcg/ml.

**Treatment**: for acute overdose, the Rumack nomogram is used to plot level vs time from ingestion. If above the probable or high risk line treatment with NAC is initiated. Chronic is treated based on clinical history, detectable levels of APAP, and status of liver function tests. IV NAC: 150 mg/kg over 1 hour, followed by 50 mg/kg over 4 hours, followed by 100 mg/kg over 16 hours. Many continue treatment if liver function tests are still abnormal after 21 hours of standard treatment.

**NSAID’s**: rapidly expanding class. MOST cases are benign. Some have been withdrawn due to cardiotoxicity.

**Pathophys**: inhibit prostaglandin synthesis. Inhibit protective gastric prostaglandins, which are gastric mucosal protectant prostaglandins. COX-2 selective NSAIDs have less likelihood of gastric GI irritation, but are pro-thrombotic. Rofecoxib withdrawn from US market, and other COX2 NSAIDs with warning for cardiovascular risk. Generally minimal to no toxicity with acute overdose. Symptoms, if present are due to mild GI (abdominal pain, N/V) or neurological (lethargy, headache, confusion) in nature. Duration of effects is short. Severe problems include metabolic acidosis, GI bleeding, dizziness, seizures, coma, hepatic and renal injury. Chronic NSAID use, and being elderly increases risk of renal, hepatic or cardiovascular adverse events.

**Levels**: not predictive or useful in managing overdose, if available.

**Treatment**: Supportive. Dialysis not helpful.

**Special mention**: seizures(mefenamate), aplastic anemia, agranulocytosis (ibuprofen, piroxicam, naproxen and etodolac)
**IV. Poison Center Management/Functions**

Several positions or functions need to be provided by each certified poison center. A poison center usually elects to be a "certified" poison center by applying to the American Association of Poison Centers and demonstrating that they meet certain criteria. A brief outline of criteria follows:

I. Determination of Region
   Geographic Characteristics/State Designation (must have a designation from the appropriate state responsible department)

II. Regional Poison Information Service
   A. Operations (must operate 24/7)
   B. Accessibility – participation in national 1-800-222-1222 phone system.
   C. Information Resources
   D. Guidelines
   E. Staff Requirements and Qualifications
      1. Toxicological Supervision
         Medical Direction and Medical Back-up: must have medical director(s) who are Board certified in Medical Toxicology, or at least Board Prepared, must have clinical privileges at facility, must show evidence of seeing tox patients (in person, or via phone), regularly consult with SPIs, and must devote enough time in a poison center.
         Managing Direction needs to be full time, and if they are part of clinical supervision, they must be ABAT boarded (if non-physician) or Medical Toxicology Boards (if physician).
      2. Specialists in Poison Information (training overseen by medical director(s)).
      3. Other Poison Information Providers (training overseen by medical director(s)).
      4. Poison Center Specialty Consultants
      5. Administrative Staff
      6. Education Staff
   F. Quality Improvement Program

III. Regional Treatment Capabilities
   Treatment Centers
   Working Relationship with All Treatment Facilities
   Analytical Toxicology Services – survey of lab capabilities in region
   Patient Transportation System – protocol for working with EMS
   Antidote Availability – survey of antidote stocks in region.

IV. Data Collection System
   Medical Records
   Participation in the Toxic Exposure Surveillance System/National Poison Data System
   Annual Report
   Monitoring of Poison Hazards

V. Professional and Public Education Programs
   Professional Education - Programs throughout designated region (not just in same city as poison center), and supervised by medical director.
   Public Education throughout designated region, and supervised by medical director and/or managing director.

VI. Association Membership
   Current Membership
   Current Account
   Annual Membership Application
   TESS/NPDS Data Submissions
V. Household Caustics
- Caustic = corrosive
- WIDELY AVAILABLE
- Cause tissue injury on contact
- Acids and Bases
  - Most household products have less than 10% concentration or 2% by weight
- Alkali
  - Liquid drain cleaner – 30% KOH
  - Crystal lye – prolonged burn due to prolonged contact
  - Granular automatic dishwashing detergents
  - Crystal drain cleaners – as much as 75% NaOH
  - Household bleach – usually 5.25% NaOCl (sodium hypochlorite)
  - Hair perm relaxers – sodium hydroxide
  - Cement – topical burns
- Alkali pathophysiology
  - Saponification of fatty acids
  - Liquefaction necrosis
    - Both processes allow continuing penetrance into tissue
    - 22-30% NaOH for 1-10 seconds results in FULL thickness burn
- Acids
  - Liquid drain cleaners – 93% H2SO4
  - Toilet bowl cleaner – 26 % HCl
  - Anticorrosive cleaner – 31% muriatic acid (HCl)
- Caustic diagnosis
  - Asymptomatic: observe, endoscope?, return if symptoms develop
  - Symptomatic: vomiting, dysphagia, odynophagia, drooling, stridor, dyspnea
    - Endoscopy at 12-24 hours
    - Chest x-ray, abdominal flat plate
- Caustic treatment
  - Supportive
  - Irrigate
  - Corticosteroids: perhaps second degree?
  - Antibiotics: no, unless clinical or endoscopic clues to perforation or infection
ANTICONVULSANTS

G. Patrick Daubert, MD; Michelle Burns-Ewald, MD

CORE CONTENT

2.1.11.2 Anticonvulsants

ANTICONVULSANTS

- Traditional Anticonvulsants
  - Phenobarbital (Luminol)
  - Phenytoin (Dilantin)
  - Carbamazepine (Tegretol)
  - Valproic acid (Depakote, Depakene)
  - Clonazepam (Klonopin)
  - Ethosuximide (Zarontin)
  - Primidone (Mysoline)
  - Trimethadione (Tridione)

- Mechanisms of Action
  - Sodium channel inhibition
    - Inhibit Na\(^+\) influx \(\rightarrow\) ↓ rate of firing
    - PHT, CBZ, OxCBZ, VPA, lamotrigine, felbamate
  - GABA-A receptor augmentation
    - Increase inhibition \(\rightarrow\) ↓ neuronal activity
    - PHB, benzos, VPA, gapapentin, vigabatrin
  - Calcium channel (T-type) inhibition
    - Inhibit Ca\(^{2+}\) mediated NT release
    - Ethosuximide, VPA, trimethadione

- Phenytoin (PHT)
  - Na\(^+\) channel blocker (Class IB)
  - Delayed absorption, highly protein bound
  - Therapeutic level 10-20 mg/L
  - Propylene glycol diluent in IV forms
  - P450 inducer/inhibitor
  - Saturation kinetics (Michaelis-Menton)

- Oral Phenytoin Overdose
  - Toxic effects common at levels > 30 mg/L
  - Nystagmus, ataxia, slurred speech, confusion
  - Oral PHT does not cause cardiac toxicity
  - Supportive care in most cases
  - Multidose AC may help eliminate PHT faster but outcome data is lacking
  - Paradoxical seizures and death are rare

- Fetal hydantoin syndrome
  - Microcephaly, developmental delay, telecanthus, short nose and flat nasal bridge, antverted nares, long shallow filtrum, thin upper lip, hypoplastic nails
• **Carbamazepine (CBZ)**
  - Structurally similar to imipramine
  - Only given orally
  - Erratic absorption common
  - Therapeutic level 8-12 mcg/ml
  - Estimated toxic dose 5-10 mg/kg
  - Active metabolite – 10,11 epoxide
    - Less anticonvulsant activity but equally as toxic
  - CBZ Receptor Promiscuity
    - Type 1A antidysrhythmic
      - Prolonged QRS → seizures, VT/Vfib
    - Cardiac K⁺ channel blocker
      - Prolonged QT → TdP
    - Antimuscarinic
      - Classic toxidrome with ↑HR and AMS
    - Adenosine type 1 blockade
      - Seizures
  - CBZ Treatment
    - Cardiac monitor
    - NaHCO₃ for wide QRS and > 3mm terminal R wave in aVR
    - Lidocaine for VT/Vfib
    - Magnesium for wide QTc and TdP
    - BZD for seizures
    - Multidose AC – be aware of gut motility
    - Hemodialysis/Hemoperfusion may be effective

• **Valproic Acid**
  - Branched chain fatty acid
  - It is available as Depakene (sodium VPA) or an enteric coated form of two molecules of VPA linked (divalproex or Depakote)
  - Therapeutic level 50 – 100 mg/L
  - Highly protein bound
  - Onset and peak levels often delayed in overdose
  - Saturation kinetics above 90 mg/L
  - Metabolism
    - Many of the VPA metabolites (hydroxyvalproate, 2-propylgluturate, 2-propylpent-4-enoate, 5-hydroxyvalproate, and 4-hydroxyvalproate) contribute to toxicity without having any therapeutic benefit. Most of the toxicity can be linked to carnitine depletion and increase ω-oxidation.
    - Carnitine is necessary for transport of fatty acids into the mitochondria and to maintain the ratio of acyl CoA to CoA across the mitochondria. Without this balance, toxic acyl groups accumulate in the cell and destabilize the membrane, which can impair several enzymatic processes. Hepatotoxicity and hyperammonemia also occur due to carnitine depletion and increase ω-oxidation. ω-oxidation increases levels of 4-en-VPA which inhibits carbamyl phosphate synthetase (CPS1) and enzyme necessary in converting ammonia to urea. As the metabolism shifts from β to ω-oxidation, there is a decrease in acetyl-CoA and ATP. Acetyl-
CoA is needed to synthesize N-acetyl glutamic acid (NAGA). NAGA activates CPS1, which again is an enzyme necessary in converting ammonia to urea.

- **Clinical Presentation**
  - CNS depression/coma
    - Common with ingestions > 30 mg/kg
    - Ataxia, nystagmus, slurred speech generally *do not* occur
  - Other less common findings
    - Hypernatremia, hypoglycemia, hypoglycemia, QT prolongation
    - Pancreatitis
    - Bone marrow suppression days 3-5 after ingestion

- **VPA Hepatitis**
  - Transient elevation of enzymes
  - Reversible elevation of ammonia
  - Frank hepatitis
  - Reye-like steatosis

- **Treatment**
  - Supportive care for CNS depression
  - Multi-dose charcoal
  - Hemodialysis for levels 800-1000 mg/L
  - L-carnitine
  - Probably not beneficial in CNS depression alone
  - Children < 2, multiple anticonvulsants, ketogenic diet, malnourished
  - Elevated ammonia, CNS depression, hepatitis deserve consideration

- **Anticonvulsant Hypersensitivity Syndrome**
  - Insufficient detoxification of epoxide hydrolase
  - Aromatic structures
    - Carbamazepine (HLA link?)
    - Phenytoin
    - Phenobarbital/Primidone
  - Onset 4 weeks to 3 months
  - Clinical picture
    - Mucocutaneous eruptions (may progress to TEN)
    - Fever
    - Hepatitis (ominous finding)
    - BM suppression
    - Pneumonitis
  - Diagnosis: lymphocyte killing assay with mouse microsomes

- **New Anticonvulsants**
  - Felbamate (Felbatol)
  - Oxcarbazepine (Trileptal)
  - Fosphenytoin (Cerebyx)
  - Tiagabine (Gabitril)
  - Gabapentin (Neurontin)
  - Topiramate (Topamax)
  - Lamotrigine (Lamictal)
  - Vigabatrin (Sabril)
  - Levetiracetam (Keppra)
  - Zonisamide (Zonegran)
• **New Anticonvulsant Pearls**
  o Felbamate (Felbatol)
    ▪ Mild CNS depression
    ▪ Aplastic anemia
  o Gabapentin (Neurontin)
    ▪ Decreased bioavailability in OD
    ▪ Not metabolized - no interactions
  o Lamotrigine (Lamictal)
    ▪ Coma, seizures, QRS prolongation
    ▪ Hypersensitivity Syndrome
  o Oxcarbazepine (Trileptal)
    ▪ Inhibits CYP2C19
    ▪ Hyponatremia (SIADH), seizures
  o Tiagabine (Gabitril)
    ▪ Coma, seizures
  o Topiramate (Topamax)
    ▪ Removed by hemodialysis
    ▪ Renal nephrolithiasis - calcium phosphate
    ▪ Acute angle closure glaucoma
    ▪ Hyperammonemia - carbonic anhydrase inhibition slows ammonia urinary excretion
  o Vigabatrin (Sabril)
    ▪ Agitation and psychosis
  o Zonisamide (Zonegran)
    ▪ Carbonic anhydrase Inhibitor
    ▪ Nephrolithiasis

**QUESTIONS**

1. A 37-year-old male is transported to the emergency department via ambulance because of decreased mentation. His vital signs are normal and his physical exam is unremarkable except for a decreased level of consciousness and asterixis. His ammonia level is 145 ug/dL (normal < 20 ug/dL). His friend tells you that he is on a medication for seizures. Which anticonvulsant is he most likely taking?
   A. Carbamazepine (Tegretol)
   B. Lamotrigine (Lamictal)
   D. Phenytoin (Dilantin)
   C. Phenobarbital (Luminal)
   E. Valproic acid (Depakote)

The patient’s presentation is consistent with valproic acid toxicity. The most distinctive feature is the elevated ammonia level. None of the other medications would produce this in acute toxicity.

2. What is the diluent found in intravenous phenytoin that is responsible for cardiotoxicity with rapid infusions and production of lactic acid with prolonged infusions?
A. Ethylene glycol
B. Propylene glycol
C. Polyethylene glycol
D. Diethylene glycol
E. Ethylene glycol monobutyl ether

The diluent in intravenous phenytoin is propylene glycol. Ethylene glycol would not be used as a pharmaceutical diluent. Diethylene glycol has been used as a diluent with disastrous results. Diethylene glycol poisoning causes severe renal failure and acidosis following exposure.

3. Which of the following anticonvulsant drugs is most likely to require cardiac monitoring in acute oral overdose?
   A. Carbamazepine
   B. Gabapentin
   C. Levetiracetam
   D. Phenytoin
   E. Valproic acid

Carbamazepine is the most cardiac active of the medications listed with its cyclic antidepressant structure. Valproic acid can cause prolonged QT intervals but is not expected to be as problematic as carbamazepine. Gabapentin and levetiracetam are not known to cause cardiac toxicity. Oral exposures to phenytoin do not result in cardiac toxicity as opposed to rapid intravenous administration of phenytoin (due to propylene glycol).

4. A patient presents to you from an outside clinic where she was receiving follow-up for post-traumatic seizures. She was taking phenytoin (Dilantin) 300 mg TID but developed break-through seizures prompting the family physician to increase her dose to 400 mg TID. She is now ataxic, with slurred speech, notable incoordination, and horizontal nystagmus. Her phenytoin level is 48 mg/L. What is the likely cause of this patient’s phenytoin toxicity?
   A. Auto-inhibition of phenytoin on P450 due to the increase in dose resulting in elevated levels
   B. Her symptoms are likely due to the diluent propylene glycol
   C. Poor outpatient compliance with her medication
   D. She has been consuming alcohol with her medication
   E. She is demonstrating Michaelis-Menten kinetics with the increase dose of phenytoin

Phenytoin demonstrates Michaelis-Menten kinetics at serum levels greater that approximately 20 mg/L. Serum levels will decrease at a much slower rate than levels in the therapeutic range.

5. Which of the following anticonvulsants is most likely to cause hyperammonemia following acute or chronic toxicity?
   A. Oxcarbazepine (Trileptal)
B. Tiagabine (Gabitril)
C. Topiramate (Topamax)
D. Vigabatrin (Sabril)
E. Zonisamide (Zonegran)

Topiramate (Topamax) may cause carbonic anhydrase inhibition slowing ammonia urinary excretion. Oxcarbazepine (Trileptal) is most notable for hyponatremia (SIADH) and seizures. Tiagabine (Gabitril) most commonly results in CNS depression and possibly seizures. Vigabatrin (Sabril) is reported in several cases to cause agitation and psychosis. Zonisamide (Zonegran) is a carbonic anhydrase inhibitor and may cause metabolic acidosis. It is also associated with nephrolithiasis.

1E 2B 3A 4E 5C
Regulatory/Legal Toxicology

- Environmental Protection Agency (EPA)
- Resource Conservation & Recovery Act (RCRA)
- Comprehensive Environmental Response, Compensation, & Liability Act (CERCLA)
- Superfund Amendments & Reauthorization Act (SARA)
Environmental Protection Agency

- Nixon, December 2, 1970
- Led by "Administrator" (appointed by Pres.)
  - Not a Cabinet agency
  - Administrator given cabinet rank

- The SEALs of all agencies
  - Charge: protect the nation's land, air, and water

Environmental Protection Agency

- Prior to EPA, federal govt not structured to comprehensively regulate pollutants which harm human health & degrade the environ

- Assigned the task of repairing the damage already done to the natural environ. & to establish new criteria to guide in making a cleaner, safer America
Environmental Protection Agency

- What it does
  - Conducts environmental assessment, research, and education
  - Setting and enforcing national standards
    - Environmental laws (preserve public health and environment)
    - Consultation with state/local government
    - Delegates monitoring and enforcements to states
    - Fines & sanctions
    - Voluntary pollution prevention programs and energy conservation efforts

RCRA

Resource Conservation & Recovery Act (RCRA)

- Regulation from EPA; 1976
- Gave EPA authority to control hazardous waste from “cradle to grave”
- Grew out of amendments to the Solid Waste Act, 1965
- Haz. Waste = may cause or contribute to an increase in M&M or pose a present or potential hazard to human or environ health
Resource Conservation & Recovery Act (RCRA)

- **Cradle to the Grave**
  - Includes: generation, transportation, treatment, storage, and disposal of haz waste
- Focus = *active and future facilities*
- Also a framework for mgt of nonhaz waste

Comprehensive Environmental Response, Compensation, & Liability Act (CERCLA)

- Regulation from EPA; 1980
- **The Superfund**
  - Est prohibitions & requirements concerning closed & abandoned haz waste sites
  - Provided for liability of persons responsible for release of haz waste at these sites
  - Est a trust fund to provide for cleanup & remediation when no responsible party could be identified
Comprehensive Environmental Response, Compensation, & Liability Act (CERCLA)

- Generators of hazardous waste are taxed
  - Chemical & petroleum industries
  - Proceeds go to superfund
- $1.6 million financed over 5 years by fees levied on petroleum (87.5%) with remainder from taxes
- Release
  - Does not = occ exposures, exhaust emissions, radioactive material, normal appl of pesticides
- Govt response = limited to 6 mo or $1 million
- Mandatory reporting of haz release (fines!)

Superfund Amendments & Reauthorization Act (SARA)

- Regulation from EPA; 1986
- Reflected EPA's experience with Superfund
- Amended & Reauthorized CERCLA
  - 1) Stressed importance of permanent remedies & innovative technology in cleanup
  - 2) Expand and consider requirements from other states
  - 3) New enforcement authorities & settlement tools
Superfund Amendments & Reauthorization Act (SARA)

- 4) Increased state involvement in every phase of Superfund
- 5) Increased focus on human health problems posed by haz waste sites
- 6) Encouraged greater citizen participation in making decisions on how sites should be cleaned

- 7) Increased size of trust fund to $8.5 million
- 8) Required EPA to beef up Hazard Ranking System to accurately assess degree of risks
- 9) Community “right to know” (i.e. ?amnt is released/yr)

Regulatory/Legal Toxicology

- Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA)
- Clean Air Act
- Clean H2O Act
- Toxic Substances Control Act (TSCA)
Regulatory/Legal Toxicology

- Center for Disease Control (CDC)
- Agency for Toxic Substances & Disease Registry (ATSDR)
- World Health Organization (WHO)

Federal Insecticide, Fungicide, and Rodenticide Act

**FIFRA**

Federal Insecticide, Fungicide, and Rodenticide Act

- 1947: Regulated production, use, and distribution of all pesticides in U.S.
- **EPA** given authority to administer and enforce FIFRA regulations since 1970
Federal Insecticide, Fungicide, and Rodenticide Act

- ALL pesticides MUST be registered with the EPA & are classified for either general use or restricted use by licensed/certified applicators
- Pesticide manufacturer must be reg with EPA
- EPA & FDA est tolerance levels for agric/foods
- 1978 Amendment = States enforce… EPA #1

Federal Insecticide, Fungicide, and Rodenticide Act

- FIFRA protection of population’s health
- If Health Hazard
  - Permissible workplace exp limits issued
  - Products may be removed from sale
  - Registration may be canceled
  - Restrictions on use/application ordered
  - Tolerance levels may be set (residue= food, H2O)

Federal Insecticide, Fungicide, and Rodenticide Act

EPA Toxicity Classification (Rodenticides)

<table>
<thead>
<tr>
<th>Category/Signal Word</th>
<th>Oral LD50 (mg/kg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>I        DANGER (Highly Toxic, Thallium, As, Strych, Ba…)</td>
<td>0 - 50</td>
</tr>
<tr>
<td>II WARNING (Mod Toxic, ANTU, Cholecalciferol)</td>
<td>50 - 500</td>
</tr>
<tr>
<td>III CAUTION (Low Tox, Bromethalin, Warfarins…)</td>
<td>500 - 5000</td>
</tr>
<tr>
<td>IV NONE</td>
<td>&gt; 5000</td>
</tr>
</tbody>
</table>
Clean Air Act


Clean Air Act Amendments of 1990 proposed emission trading, added provisions for antimining and tailoring, increased regulation and fines for offenders, and established a national permits program. The amendments once again established new standards for preventing hazardous emissions, set forth Emission Standards (PDES) standards for control of evaporative emissions from gasoline and mandated that the new gasoline formulations be sold from May-September in many states.

- EPA is charged with regulation of air pollutants from stationary & mobile surfaces

- Regulated air emissions by setting maximum pollutant standards

Clean Air Act

- National Ambient Air Quality Standards for Criteria Pollutants
  - 6 “Big Hitter” Pollutants
  - 1) CO
  - 2) NOx
  - 3) Lead
  - 4) SO2
  - 5) O3 (VOCs & NOx)
  - 6) Particulates (PM10 = diam of <10 μm)
Clean H2O Act

- 1972
- Began as the Fed H2O pollution act (1948)
- Amendments (1977 & 1978)

- Purposes
  - Provide fed assistance for construction of publicly owned sewage treatment plants
  - Regulate the discharge of pollutants from pnt sources
  - Regulate spills of hazardous waste & oil
  - Make waters fishable & swimmable
Clean H2O Act

- Requires the EPA to set standards for
  - Direct discharge of toxic pollutants into waterway
  - Pretreatment of waste that is discharged by a private company into publically owned waste treatment facilities
  - Regulation of thermal pollution (i.e. power plants)

- Federal Permit System
  - Enforces H2O quality standards & effluent standards
  - Sanctions applied if no permit

TOXIC SUBSTANCES CONTROL ACT

Toxic Substances Control Act

- 1976
- Goal
  - Regulates hazardous chemicals currently in existence and prevents chemicals from entering the market that may have an unreasonable risk to health or the environment
Toxic Substances Control Act

- Mandates the EPA to track, maintain, and publish an inventory of industrial chemicals (< 75,000) manufactured or processed in U.S.

- Manufacturers
  - Required to report to EPA data concerning uses, amounts produced, by-products, # exposed workers, & adverse effects of chemical (health & environ)
  - Required to give EPA a 90 day notice prior to manufacturing or use (public aware with risks posed)

Toxic Substances Control Act

- EPA
  - Can require testing of chemicals
  - Authority to prohibit use, production, processing, distribution, or disposal of chemical
  - Labeling and proper recordkeeping are required

CAUTION
HIGHLY TOXIC CHEMICAL

CDC
**Center for Disease Control**

- Agency of the US Dept of Health & Hum Serv
- Based in GA, adjacent to Emory university
- **To protect public health and safety**
  - By providing info to enhance health decisions
  - Partnerships with state health depts & other orgs
  - Developing and applying Dz prev & control (ID)
  - Environmental Health
  - Occ safety and health
  - Health promotion
  - Prevention and education activities
  - All to improve the health of the people of the US

**Center for Disease Control**

- 1946; Communicable Disease Center
- 1970; Center for Disease Control
- 1992; Congress added “and Prevention”

- **Evolution of focus**
  - ID (West Nile virus, pandemic flu, STDs...)
  - Chronic Dz, Disabilities, workplace hazards
  - Environmental threats & birth defects
  - Bioterrorism

**ATS DR**
Agency for Toxic Substances & Disease Registry

- Sister agency to the CDC
- Created by CERCLA (1980)
  - To perform specific functions concerning the effect on public health from haz subs in environ
- INCLUDED
  - Public health assessments of waste sites
  - Health consultations concerning specific haz subs
  - Health surveillance and registries
  - Emergency response to release of haz substances
  - Applied research in support of PH assessments, information development, and dissemination

Agency for Toxic Substances & Disease Registry

- Expand the knowledge base about health effects from exposure to haz substances
- Works closely with state legislatures, CDC, Dept of Toxic Subts Control, US Army corps of engineers, DOL, USAF, NASA, DOJ, and Dept of Homeland Security
- National Priorities List
  - With EPA
  - List of most sig potential threat found at facilities
  - Candidates for Toxicological Profile
World Health Organization

- Specialized agency of the UN
- A coordinating authority on international P.H.
- Established April 7, 1948 (Hqts = Geneva)
- Tasks
  - The attainment by all peoples of the highest possible level of health
  - To combat Dz, especially infectious Dz, & to promote the general health of the people of the world
- Smallpox, polio, malaria, AIDS, SARS

Regulatory/Legal Toxicology

- Occupational Safety & Health Administration (OSHA)
- National Institute for Occupational Safety & Health (NIOSH)
- American Conference of Governmental Industrial Hygienists (ACGIH)

Occupational Safety & Health Administration

OSHA
OSHA

- Occupational Safety and Health Act of 1970
  - This act mandated that employers provide safe work conditions for their employees
  - Specific exposure limits to toxic chemicals in the workplace were promulgated

OSHA

- Requires Monitoring (elf van)
  - Ethylene oxide
  - Lead
  - Formaldehyde
  - Vinyl Chloride
  - Asbestos
  - Noise

OSHA

- Under the “Department of Labor”
- Sets & enforces health and safety standards
- Empowered to investigate occ health and safety complaints and can inspect work sites and levy fines for violations of its standards
- Half of states = OSHA program implemented by a state agency
- Workers, unions, physicians can file complaint
OSHA

- Exposure Limits
  - Permissible Exposure Limit (PEL)
    - "Borrowed" from ACGIH's TLV-TWA
    - The airborne concentration of a substance to which workers can be continuously exposed in an occupational setting over an 8-hour period or 40-hour work week
    - Ex. CO = 50 ppm

National Institute for Occupational Safety & Health

NIOSH

- US Dept of Health & Human Services
- Part of the CDC
- Not a regulatory agency
- Responsibilities
  - Researching the causes of occupational disease and injury and methods for their prevention and control
  - Evaluation of workplace conditions
  - Recommending exposure limits to OSHA for standard setting
  - Training occupational health & safety professionals
NIOSH

- Responsibilities
  - Empowered to conduct on-site evaluations of health hazards in response to requests from employee representatives or employers
  - Post Evaluations
    - Immediately contacts OSHA, the employees, and the employer if they find that the workers are in imminent danger
  - Develops comprehensive documents that critically evaluates all scientific data on particular chemicals

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  - Develops comprehensive documents that critically evaluates all scientific data on particular chemicals
    - Criteria Documents
      - Review chemical properties, production methods, and workers at risk, studies of exposure (animal...)
    - Proposes methods of screening, surveill., control
    - Writes technical reports and reviews of hazards
    - Disseminates health hazard alerts
      - In conjunction with OSHA

NIOSH

- Exposure Limits
  - Recommended Exposure Limit (REL)
    - Highest allowable airborne concentration that is not expected to injure a worker; expressed as a ceiling limit or TWA for an 8 to 10 hour workday
      - Ex. CO = 35 ppm
  - Immediately dangerous to life & health (IDLH)
    - A maximum conc (in air) from which one could escape within 30 min w/o any escape-impairing symptoms or any irreversible health effects
      - Corrosives, asphyxiants, explosives, flammable
      - Ex. CO = 1500 ppm
American Conference of Governmental Industrial Hygienists

ACGIH

- Professional organization of industrial hygienists and practitioners of related professions
- Headquarters = Cin, OH
- Goal = Advance worker protection by providing timely, objective, scientific info to occupational and envir health professionals

ACGIH

- **Threshold Limit Values (TLV)**
  - The airborne conc of a substances and represents conditions under which it is believed that nearly all workers may be repeatedly exposed day after day w/o adverse effect
- **TLV-TWA**
  - The TWA conc for a normal 8 hour workday and a 40 hour workweek, to which nearly all workers may be repeatedly exposed, day after day, w/o adverse effect
  - Ex. CO = 25 ppm
Exposure Limits

- Ex. CO
  - OSHA; PEL = 50 ppm
  - NIOSH; REL = 35 ppm
  - ACGIH; TLV = 25 ppm

Bottomline: *Not always in agreement*

Regulatory/Legal Toxicology

- Food & Drug Administration (FDA)
- Health Resources & Services Administration (HRSA)
- Consumer Product Safety Commission (CPSC)
- Poison Prevention Packaging Act (PPPA)
- No Observed & Lowest Observed Adverse Effect Levels (NOAEL, LOAEL)

Food & Drug Administration

**FDA**
FDA

- Agency: US Dept of Health & Human Services
- Regulates & Supervises safety of
  - Foods
  - Dietary supplements
  - Drugs
  - Vaccines
  - Biological medical products
  - Blood products
  - Medical devices
  - Radiation-emitting devices
  - Veterinary products
  - Cosmetics

FDA

- To Protect & Promote the Nation's Health
- Headquarters = Silver Spring, MD (1906)
- Organized into major subdivisions
- Collaborates with other Federal agencies
  - Dept of Agriculture
  - CPSC
  - DEA

FDA

- Big Cash
  - Regulates more than $1 trillion worth of goods
  - Budget over $2 billion

- Most Federal Laws concerning FDA = part of
  - Food Drug & Cosmetic Act (1938)
    - Required toxicity testing (animal) of pharmaceuticals prior to marketing
  - Elixir of Sulfanilamide tragedy – 1937
    - > 150 deaths
    - 72% diethylene glycol as vehicle
    - Renal failure, death
FDA

- Pursuant to the DSHEA (1994)
  - Dietary Supplement Health & Education Act
  - FDA regulates “dietary supplements” as food, and NOT as drugs
    - Permitted dietary supplements, including many herbal preparations, to bypass FDA pre-market safety scrutiny
    - Vitamins, minerals, herbs, amino acids
    - “New category” (Not a drug or conv food & label = dietary supplement)
    - Increased incidence of toxicity!!

Health Resources & Services Administration

HRSA

- Agency: US Dept of Health & Human Services
- Envisions
  - Optimal health for all
  - Uninsured
  - Isolated
  - Medically vulnerable
- Funding
  - $7 Billion budget, 23 million people
  - Community-based clinics
  - HIV Meds
  - Poison Centers
Consumer Product Safety Commission

CPSC

- Independent agency of US govt (1972)
- “Consumer Product Safety Act”
  - Protect against unreasonable risks of injuries associated with consumer products
- Authority to
  - Regulate sale & manufacture of > 15000 diff consumer products (cribs, ATVs, grills, pools...)

CPSC

- Bans dangerous consumer products
- Issues recalls on products already on market
- Researches potential hazards

- Hotline, Website, ER (National Electronic Injury Surveillance or NEISS)
- Ex. The Lead-Free Toys Act
  - A chemical regulation that requires the CPSC to ban children’s products containing > trace amount of Pb
POISON PREVENTION PACKAGING ACT

PPP Act (1970)

- **Goal**: To reduce poisonings in children
- Certain products must be sold in safety pack.
  - ASA
  - Oral Rx drugs
  - Furniture polish
  - Oil of wintergreen
  - Antifreeze
  - Cleaners (drain, ovens)

PPP Act (1970)

- Safety packaging must
  - Be designed so that "most" kids <5 y.o. can't open
  - >80% of kids can't open, >90% adults can open
  - i.e. child-resistant tops
    - ASA!!
    - CPSC involved
No Observed & Lowest Observed Adverse Effect Levels

**NOAEL & LOAEL**

**NOAELs & LOAELs**

- **Threshold Dose**
  - There is "some dose" below which an organism’s repair mechanisms can prevent the onset of AEs
  - Often used as a point for setting regulatory limits on exposures to environmental toxins
  - **NOAELs & (LOAELs (ie. the next highest dose))**
    - **Benchmarks** for establishing acceptable contaminant levels in drinking H2O, soil, foods, air
    - Divided by one or more "uncertainty factors" to account for interspecies & interindividual variability

**NOAELs & LOAELs**

- **Reference Doses (RfDs)**
  - Exposure limits for noncancer endpoints through the oral route of exposure (mg/m³)
  - **EPA uses** to quantify risk assessment
    - ID a safe exposure level that does not cause any adverse effects on human health
    - Formally known as **acceptable daily intake**
    - mg/kg/day
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Program Objectives:
• Present study content specifically designed for the medical toxicology subspecialty exam offered jointly by ABEM, ABP, and ABPM
• Present a comprehensive review of medical toxicology
• Allow attendees to gain new insight into current clinical issues

Target Audience: Physicians preparing for the biennial certification and recertification examination in Medical Toxicology, and others with an interest in medical toxicology.