PHARMACEUTICAL ADDITIVES, VETERINARY PRODUCTS, VITAMINS

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CORE CONTENT

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PHARMACEUTICAL ADDITIVES

- Pharmaceutical Additives
  - Benzalkonium chloride
  - Benzyl alcohol
  - Chlorbutanol
  - Diethylene glycol (DEG)
  - Diethylstilbestrol (DES)
  - Parabens
  - Polyethylene glycol
  - Propylene glycol
  - Sorbitol
  - Thalidomide
  - Thallium
  - Thimerosol
  - Thorotrust
  - Tryptophan
  - Vit E ferol

- Benzalkonium chloride
  - Most common ophthalmic preservative
  - Cytotoxic to corneal epithelium
  - Compromised cornea (keratoconjunctivitis)

- Gasping Syndrome
  - In 1981, 16 neonatal deaths occurred in a NICU
  - All were pre-term neonates < 2500 gm
  - Symptoms included severe anion gap metabolic acidosis, respiratory depression with gasping, and encephalopathy
  - All neonates had received bacteriostatic NaCl or water flushes containing 0.9% benzyl alcohol
    - Benzyl alcohol is normally oxidized rapidly to benzoic acid, conjugated with glycine in the liver, and excreted as hippuric acid
    - This metabolic pathway is not well developed in premature infants
    - The benzyl alcohol was metabolized to benzoic acid causing metabolic acidosis

- Chlorbutanol
  - Structure similar to trichloroethanol (chloral hydrate active metabolite)
  - IV thiamine preps in past
• **DEG**
  o **Sulfanilamide**
    ▪ September-October 1937
    ▪ S.E. Massengill Co., used DEG diluent in sulfanilamide elixir
    ▪ Vomiting, abdominal pain, anuria, seizures, coma
    ▪ 105 deaths in 15 states with 34 pediatric fatalities
      • Multiple other epidemics in Nigeria, Bangladesh, South Africa, Haiti
      • Hydropic tubular nephrosis
    ▪ Development of the Food, Drug, and Cosmetic Act
  o Oxidative metabolism by ADH/ALDH to hydroxethoxy acetic acid (HEAA)
  o Ether bond probably does not break
  o Renal biopsy typically reveals tubular necrosis and vacuolization
  o DEG has high fatality rate
  o Management with early hemodialysis in otherwise normal patients is still controversial

• **DES (Diethylstilbestrol)**
  o DES mothers – breast CA
  o DES daughters – vaginal clear cell adenoCA

• **Parabens**
  o Hypersensitivity reactions
  o 2nd most common ingredient (2nd to water) in medications

• **Polysorbate 80 and E-Ferol**
  o Polysorbate 80 = polyproblems
  o Released December 1983
  o IV form of a vitamin E preparation (E-Ferol)
  o Fatalities among low birth weight (< 1,500 g) and premature infants
  o 38 deaths and 43 cases of severe morbidity
    ▪ Thrombocytopenia
    ▪ Renal failure
    ▪ Cholestasis
    ▪ Ascites
  o Inhibitory effect by E-Ferol on the in vitro response of human lymphocytes to phytohemagglutinin

• **Propylene glycol**
  o IV preps pushed rapidly (> 50 mg/min for IV phenytoin (Dilantin) can result in toxicity
    ▪ Hypotension, bradycardia, asystole
  o Prolonged infusions
    ▪ Lactic acid production

• **Polyethylene glycol**
  o Toxicity concern with low MWs (< 400)
  o Risk of renal tubular necrosis

• **Sorbitol (D-glucitrol)**
  o Widely used as sweetening agent (activated charcoal)
Case reports of fatalities in patients with hereditary fructose intolerance (sorbitol metabolized to glucose and fructose) receiving IV formulation of sorbitol

• **Thalidomide**
  - Antiemetic (1960s)
  - 5,000 infants born with severe congenital abnormalities (phocomelia)

• **Koremlu (thallium acetate)**
  - 1920-1940 Koremlu was used topically as a treatment for ringworm (depilatory agent)
  - Patients were experiencing various aliments including losing all scalp hair, neuritis, myalgias, and arthralgias
  - Many of the nation’s leading department stores sold the product, and Vogue and Cosmopolitan carried its advertising
  - By 1934, 692 cases of thallium poisoning with 31 deaths

• **Eosinophilia Myalgia Syndrome (EMS)**
  - October 1989, the health department in New Mexico was notified of 3 patients with an unexplained acute illness
  - Characterized by intense myalgia, dyspnea, extremity edema, neuropathy, and peripheral blood eosinophilia
  - By July 1991, 1543 cases and 31 deaths were attributed to EMS
  - Some L-tryptophan may have been produced by a new bacteria causing an unknown bi-product
  - EMS Histology
    - Endothelial cell hyperplasia in the capillaries, with evidence of swelling and necrosis
    - Inflammatory cell infiltrate of predominantly monocytes, histiocytes, lymphocytes, macrophages, and plasma cells and occasionally eosinophils in nerve, muscle, and connective tissue, including the subdermal fascial layer (fasciitis)
    - Increased fibrosis, mostly in the fascia
  - EMS lead to the Dietary Supplement Health and Education Act of 1994

• **Thorotrast (thorium dioxide 25%)**
  - IV radiocontrast medium (1928-1955)
  - Delayed hepatic angiosarcoma
  - Leukemia and skeletal sarcomas (thorotrastomas at sites of extravasation)

### VETERINARY PRODUCTS

• **Xylazine**
  - Animal sedative with central alpha-agonist and imidazoline properties similar to clonidine
  - CNS depression, miosis, respiratory depression, bradycardia symptoms

• **Ivermectin:**
  - Antiparasitic drug that potentiates GABA release

• **4-aminopyridine**
  - Avian pesticide
Potassium channel blocker and enhances release of ACh from nerve endings
- Marketed in humans as Fampridine and Neurelan
  - Multiple sclerosis therapy
  - Shown to reverse tetrodotoxin toxicity in animal models
- Seizures: probably the only drug-induced seizures that respond to phenytoin

**VITAMINS**

- **Fat soluble = A, D, E, K**
- **Vitamin A**
  - Binds retinal binding proteins to maintain vision, epithelial cell integrity
  - Deficiency: night blindness, Bitot spots on conjunctiva with corneal drying (xerosis)
  - Acute toxicity defined > 12,000 IU/kg, chronic toxicity > 25,000 IU/day for 2-3 weeks
    - Pseudotumor cerebri (IHH): also consider tetracycline, steroids, OCPs
    - Hepatotoxicity – uptake into Ito cells, cirrhosis, alcohol may potential
    - Teratogenic – facial and ear deformities, rare CNS/CV
    - Misc – dry skin, alopecia, premature epiphyseal closure in infants
- **Vitamin D**
  - Ca/Phos intestinal absorption, bone development, parathyroid gland function
  - Deficiency: adults - osteomalacia, peds – rickets (craniotabes, rachitic rosary, genu varum)
  - Toxicity
    - Acute: hypercalcemia, muscle weakness
    - Chronic: nephrocalcinosis, renal failure
- **Vitamin E**
  - Antioxidant
  - Deficiency: preterm infants have large requirement (↓ ROP, BPD, IVH, hemolytic anemia)
  - Review polysorbate 80 and E-Ferol in Pharmaceutical additives
  - Toxicity
    - Antagonizes epoxidation of vitamin K (anticoagulant effect)
    - Muscle weakness, nausea, diarrhea, headache
- **Vitamin K₁**
  - Vitamin K₁ = phytonadione (vitamin K₃ is not clinically relevant)
  - Essential cofactor in hepatic synthesis of coagulation factors II, VII, IX, X, protein C
  - Deficiency: rare except in newborns (bleeding episodes)
    - Hemorrhagic disease of the newborn occurs if vit K₁ is not given at birth
  - Toxicity
• Jaundice in premature infants, elevated levels could impair effects of anticoagulants
• IV preps uncommonly cause anaphylaxis, IM preps hematomas

Vitamin B₁ (Thiamine)
  o Coenzyme (TTP) in oxidative metabolism of glucose and ketoacid decarboxylation
  o Deficiency:
    ▪ Wet beriberi – high output cardiac failure
    ▪ Dry beriberi – Wernicke-Korsakoff syndrome: oculomotor changes, ataxia, global confusion. Seen in malnourished such as alcoholism and gastric bypass
  o Toxicity: antiquated literature reported anaphylactoid reactions with IV dosing. May be due to previous formulations containing chlorbutanol

Vitamin B₂ (Riboflavin)
  o FAD coenzyme in oxidative-reduction reactions
  o Deficiency: anorexia, mucositis, cheilosis, nasolabial seborrhea
  o Toxicity: Yellow urine. Increased riboflavin excretion with boric acid toxicity (blue-green vomit, boiled lobster appearance). No evidence that riboflavin is useful in the treatment of boric acid toxicity.

Vitamin B₃ (Niacin or Nicotinic acid)
  o NAD coenzyme for oxidative-reduction reactions
  o Deficiency: pellagra (4 Ds: diarrhea, dermatitis, dementia, death)
  o Toxicity:
    ▪ Niacin flush (skin flush, headache, pruritis, vasodilation). Mediated by prostaglandins, not histamine. Use aspirin to treat.
    ▪ Used by some young adults to adulterate urine to “beat” drug tests
  o Vacor (PNU) antidote

Vitamin B₆ (Pyridoxine)
  o Cofactor for GAD in GABA synthesis. Converted to active form pyridoxal phosphate by pyridoxine phosphokinas
  o Deficiency: Seizures
    ▪ Isoniazid, Gyromitra esculenta (false morel), hydrazine rocket fuel
  o Toxicity: peripheral sensory neuropathy with excessive chronic dosing or large acute ingestions
  o Antidote: INH, G. esculenta, hydrazines, ethylene glycol poisoning

Vitamin B₁₂ (Cyanocobalamin)
  o Coenzyme for 5-methyltetrahydrofolate formation, DNA synthesis, myelin
  o Deficiency: megaloblastic anemia with peripheral neuropathy (post/lat columns, foot drop)
  o Toxicity: probably none
  o Nitrous oxide abusers (dentists): bone marrow suppression, and pernicious anemia. Histochemistry reveals inactive cobalt and inhibition of methionine synthetase
  o Antidote: CN – Hydroxycobalamin (synthetic B₁₂) exchanges hydroxyl group with free CN to produce cyanocobalamin (renally excreted)
• Vitamin C
  o Reducing agent and antioxidant, \( Cr^{6+} \rightarrow Cr^{3+} \), collagen metabolism
  o Deficiency: scurvy (poor wound healing, bleeding gums, bone pain)
  o Toxicity: > 1.5 grams IV or chronic oral intake > 4 grams/day
    ▪ Calcium oxalate with ARF (urinary acidification), chronic nephropathy
    ▪ G6PD hemolysis
    ▪ Gouty arthritis due to ↓ urate excretion
    ▪ ↑ Fe absorption leading to hemochromatosis
  o Antidote: congenital methemoglobinemia

FOOD ADDITIVES

• Regulated by FDA and categorized into 5 groups
  o Enhance texture
  o Improve nutritional value (ie, vitamins)
  o Maintain freshness/safety
    ▪ Sulfites (red wines): hypersensitivity reactions
    ▪ Nitrates
      ▪ Hypotension (hotdog syndrome)
      ▪ Infants convert nitrates to nitrites – methemoglobinemia
  o Regulate acidity
    ▪ NaOH and KOH: skin, mucous membrane irritation
  o Provide flavoring/coloring
    ▪ MSG: “Chinese restaurant syndrome” – flushing, headache, chest pain, vomiting, rare angioedema, bronchospasm
    ▪ Yellow dye #5: hypersensitivity reactions
    ▪ Aspartame: three metabolites – aspartic acid, phenylalanine, methanol (minute). Patients with PKU unlikely to accumulate toxic levels of phenylalanine
    ▪ Saccharin: bladder CA in animals
QUESTIONS

1. The structure of chlorobutanol most closely resembles which of the following compounds?
   A. Chloral hydrate
   B. Dibromochloropropane
   C. Hexachlorobenzene
   D. Hydroxyethoxy acetic acid
   E. Trichloroethanol

   The structure of chlorobutanol most closely resembles trichloroethanol, the metabolite of chloral hydrate. Hydroxyethoxy acetic acid is the metabolite of DEG. The other choices are not related to chlorobutanol. Dibromochloropropane is a pesticide that causes sterility and altered sex ratio in offspring. Hexachlorobenzene is a fungicide associated with porphyria, pemba yara, and spongiform encephalopathy.

2. Which of the following statements best describes the pathophysiology of the neonatal “gasping” syndrome?
   A. Benzy1 alcohol metabolized to benzoic acid resulting in metabolic acidosis
   B. Chlorobutanol in thiamine preparation resulting in coma
   C. Diethylene glycol metabolized to HEAA resulting in renal failure
   D. Hydrogen peroxide in the dialysate resulting in severe hemolysis
   E. Propylene glycol infusions producing hypotension, bradycardia, asystole

   The gasping syndrome in 1981 was due to bacteriostatic NaCl or water flushes containing 0.9% benzyl alcohol. The benzyl alcohol was metabolized to benzoic acid resulting in severe metabolic acidosis.

3. Propylene glycol is metabolized by alcohol dehydrogenase to which of the following?
   A. Acetone
   B. Ethylene glycol
   C. Lactic acid
   D. Oxalic acid
   E. Trichloroethanol

   Propylene glycol is metabolized to lactic acid in a complex metabolic pathway. This is most likely to be of clinical importance during prolonged infusions. Oxalic acid is the metabolite of ethylene glycol. Trichloroethanol is the metabolite of chloral hydrate. Acetone is the metabolite of isopropyl alcohol.
4. Which of the following toxicological disasters lead to the Dietary Supplement Health and Education Act of 1994?
   A. Diethylstilbestrol clear cell adenocarcinoma
   B. Eosinophilia Myalgia Syndrome
   C. Gasping syndrome
   D. Sulfanilamide and DEG
   E. Vitamin E-Ferol-induced renal failure

   Eosinophilia Myalgia Syndrome was caused by L-tryptophan and lead to the Dietary Supplement Health and Education Act of 1994. The sulfanilamide disaster with DEG lead to the development of the Food, Drug, and Cosmetic Act. Gasping syndrome, vitamin E-ferol and diethylstilbestrol were tragic toxicologic events but did not lead to any national legislation.

5. Which of the following pharmaceutical additives is second only to water as the most common ingredient in medications?
   A. Benzalkonium chloride
   B. Parabens
   C. Polyethylene glycol
   D. Propylene glycol
   E. Sorbitol

   The parabens are very common ingredients in medications and cosmetics. They probably have little toxicity other than allergic reactions.

1E 2A 3C 4B 5B