Pharmaceutical Additives

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Some (most) material plundered from various mentors and other talented toxicologists, with permission
 MENU

- 2.1.12 Pharmaceutical Additives
- 2.1.13 Veterinary Products
- 2.1.14 Vitamins
Pharmaceutical Additives

- Propylene glycol
- Polyethylene glycol
- Benzyl alcohol
- Vit E ferol
- Benzalkonium chloride
- Thimerosal
- Tryptophan
- Sorbitol
- Chlorbutanol
- Parabens
- Diethylene glycol
- Thallium
- Thorotrast
- Thalidomide
- DES
Pharmaceutical Additives

- Propylene glycol
  - IV preps pushed rapidly
    - Hypotension, bradycardia, asystole
  - Prolonged infusions
    - Lactic acid production

- Polyethylene glycol
  - Toxicity concern with low MWs (< 400)
  - Risk of renal tubular necrosis
Gasping Syndrome

- In 1981 16 neonatal deaths occurred in a NICU
- All were pre-term neonates < 2500 gm
- Symptoms included severe AGMA, respiratory depression with gasping, and encephalopathy
- All neonates had received bacteriostatic NaCl or water flushes containing 0.9% benzyl alcohol
Gasping Syndrome

- **Benzyl alcohol** is normally oxidized rapidly to benzoic acid, conjugated with glycine in the liver, and excreted as **hippuric acid**.

- This metabolic pathway is well developed in **premature infants**.

- The benzyl alcohol was metabolized to benzoic acid causing metabolic acidosis.
DEG and 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
  - 34 children
- Hydropic tubular nephrosis
- Development of the Food, Drug, and Cosmetic Act
Polysorbate 80 and E-Ferol

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

- 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.
- Syndrome resembled Toxic Oil Syndrome (rapeseed oil).
Pharmaceutical Additives

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

- Chlorbutanol
  - Structure similar to trichloroethanol
  - Chloral hydrate active metabolite
  - IV thiamine preps
Pharmaceutical Additives

- **Thorotrast** (thorium dioxide 25%)
  - IV radiocontrast medium (1928-1955)
  - Delayed hepatic angiosarcoma

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

- **DES (Diethylstilbestrol)**
  - DES mothers – breast CA
  - DES daughters – vaginal clear cell adenoCA
Question

Which of the following pharmaceutical additives is associated with acute renal dysfunction?

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B. Polysorbate 80
C. Thimerosol
D. Vit E ferol
E. Xylitol
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Vitamins
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 (IIH):
  - Hepatotoxicity potential
  - Teratogenic
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)
- Recall 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)
- Synthesis of 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
  - IV preps associated with anaphylaxis
Vitamin B1 (Thiamine)

- Coenzyme (TTP) in oxidative metabolism of glucose and ketoacid decarboxylation

- Deficiency:
  - Wet beriberi – high output cardiac failure
  - Dry beriberi – Wernicke-Korsakoff syndrome: oculomotor changes, ataxis, global confusion. Seen in malnourished such as alcoholism and gastric bypass

- Toxicity: antiquated literature reported anaphylactoid reactions with IV dosing. May be due to previous formulations containing chlorbutanol
Vitamin B2 (Riboflavin)

- **FAD coenzyme in oxidative-reduction reactions**
- **Deficiency:** anorexia, mucositis, cheilosis, nasolabial seborrhea
- **Toxicity:**
  - Yellow urine
  - Increased riboflavin excretion with boric acid toxicity (blue-green vomit, boiled lobster appearance)
Vitamin B3
(Niacin or Nicotinic acid)

- NAD coenzyme for oxidative-reduction reactions
- Deficiency: pellagra (4 Ds: diarrhea, dermatitis, dementia, death)
- 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
- Vacor (PNU) antidote
Vitamin B6 (Pyridoxine)

- Cofactor for GAD in GABA synthesis
  - Converted to active form pyridoxal phosphate by pyridoxine phosphokinase
- Deficiency: Seizures
  - Isoniazid, *Gyromitra esculenta* (false morel), hydrazines (high output fuels)
- Toxicity: peripheral sensory neuropathy with excessive chronic dosing or large acute ingestions
- Antidote: INH, *G. esculenta*, hydrazines, ethylene glycol poisoning
Vitamin B12 (Cyanocobalamin)

- Coenzyme for 5-methyltetrahydrofolate formation, DNA synthesis, myelin
- Deficiency: megaloblastic anemia with peripheral neuropathy (post/lat columns, foot drop)
- Toxicity: probably none
- Nitrous oxide abusers (dentists): bone marrow suppression, and pernicious anemia. Histochemistry reveals inactive cobalt and inhibition of methionine synthetase
- Antidote: CN – Hydroxycobalamin (synthetic B12)
Vitamin C

- Reducing agent and antioxidant, Cr6+ → Cr3+, collagen metabolism
- Deficiency: scurvy (poor wound healing, bleeding gums, bone pain)
- 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 decreased urate excretion
  - h Fe absorption leading to hemochromatosis
- Antidote: congenital methemoglobinemia
Question

Which of the following clinical manifestations is associated with excessive vitamin C use?

A. Esophagitis
B. Flushing of the skin
C. Megaloblastic anemia
D. Nephrolithiasis
E. Peripheral neuropathy
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Food Additives
Food Additives

- Regulated by FDA and categorized into 5 groups
  - Enhance texture
  - Improve nutritional value (ie, vitamins)
  - Maintain freshness/safety
  - Regulate acidity
  - Provide flavoring/coloring
Food Additives

- Sulfites (red wines): hypersensitivity reactions
- Nitrates
  - Hypotension (hotdog syndrome)
  - Infants convert nitrates to nitrites – methemoglobinemia
- NaOH and KOH: skin, mucous membrane irritation
Food Additives

- 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
A young boy presents to the hospital with acute urticaria after eating lemon cake. What was the likely food additive to which he is allergic?

A. Aspartame  
B. Metabisulfite  
C. Monosodium glutamate  
D. Saccharin  
E. Tartrazine
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D. Saccharin
E. Tartrazine (Yellow dye #5)
Questions?

Good Luck!!