HYPERVITAMINOSIS AND ANTIHISTAMINES

Introduction

- **VITAMIN** is an essential substance, needed in tiny amounts to facilitate normal metabolism
- Not synthesized in the body….must be ingested in the diet
- Not provide energy…..BUT….often act as **coenzyme in energy producing reactions**
- OTC
- large potential for misuse and toxicity……beliefs that megadoses of vitamins prevent or ameliorate the effects of aging and cancer
- Only **rarely** is an **acute vitamins** toxicity reaction reported, most cases involved chronic utilization

Introduction

- **Recommended Daily Allowance (RDA)**…..vit deficiency / hypervitaminosis

- **Megadosing**: a dose that is **10 or more** times the recommended daily allowance (RDA)

Vitamins

- **A**, **D**, E, K
- **Vitamin C**
- **Thiamine (B1)**
- Riboflavin(B2)
- **Niacin (B3)**
- **Pyridoxine (B6)**
- **Cyanocobalamin (B12)**
- Folic acid (B9)
- Biotin (B7)
- Pantothenic acid (B5)

Vitamin A….Retinoids

- First vitamin recognized
- ***RDA***: 3000IU

TOXICOKINETICS OF VITAMIN A

- More than **60,000** instances of vitamin toxicity are reported **annually to US** poison control centers
- **fat-soluble vitamins have a higher potential** for toxicity than do water-soluble vitamins (Owing to their ability to accumulate in the body).

VITAMIN A TOXICITY

- Acute ingestion >12,000 IU/kg. Chronic ingestion >25,000 IU/d for 2–3 weeks. **symptoms**:

- GI
  - Nausea , vomiting, gingivitis, mouth fissures, wt loss
- CNS
  - Drowsiness, Headache, irritability, increased intracranial pressure, vision changes, dizziness
- Skin
  - Dry, peeling skin, cheilosis, pruritis, alopecia
- Muscles and joints
  - Myalgia, arthralgia
- Other:
  - Hepatic enlargement, ascites, hepatocellular injury, elevated hepatic enzymes, hypercalcemia, bony changes

VITAMIN A TOXICITY

- **Teratogenicity:**
- The risk of infant malformations in the first trimester approaches 25-30%.....”retinoic acid dysmorphic syndrome”:.....
- **CNS defects, optic atrophy, cleft palate small or absent ears, thymic and congenital heart defects**

TREATMENT OF VITAMIN A TOXICITY

- Immediate discontinuation, most S&S will disappear within several weeks
- If very huge dose was taken……GI decontamination (administration of activated charcoal)
- High intracranial pressure treated with mannitol, hyperventilation

VITAMIN D TOXICITY

- Vit D acts to maintain serum **calcium** and **phosphate** concentration……increase Ca levels by acting on its absorption, excretion and bone resorption

- Manifestations of **vit D toxicity** are related to the effects of **hypercalcemia**

- Hypervitaminosis D & hypercalcemia in pregnant women may **suppress PTH function in the newborn**…..leading to **hypocalcemia**, **tetany** and **seizures**

VITAMIN D TOXICITY

- **4-5 times the RDA can cause toxicity (conc. >200pg/ml)**
- **Symptoms**
  - Hypercalcemia…..(polydipsia, polyuria, weakness, fatigue, anorexia, headache)
  - Altered mental status
  - GI upset
  - Renal tubular injury
  - Occasionally arrhythmias
  - Calcification of soft tissues (heart and lungs)

TREATMENT OF VITAMIN D TOXICITY

- Immediate discontinuation
- Reducing Ca intake by diet
- If cardiotoxicity due hypercalcemia…..fluids and diuretics
- Administration of glucocorticoids (prednisolone 20-40 mg), inhibit Ca absorption from the gut
- If Ca levels exceed 14mg/dl….Tx with calcitonin (i.m)

VITAMIN C-ASCORBIC ACID

- Supplements are available in 100 to 500mg doses and found in high concentrations in green tea

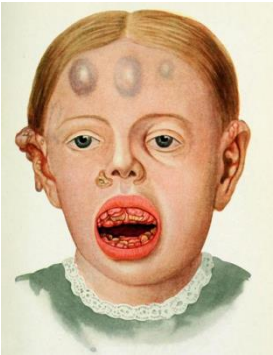
- **RDA** for ascorbic acid is 60mg/day

VITAMIN C-TOXICITY

- **WATER SOLUBLE VITAMIN….WHAT IS NOT UTILIZED WILL BE EXCRETED IN THE URINE…..**toxicity is rare
- Toxicity is related to the osmotic effects in the intestine…. **nausea and diarrhea**
- Chronic excessive use can produce **increased levels of the metabolite oxalic acid**
- Urinary acidification promotes **calcium oxalate crystal** formation…… nephroliathiasis and nephropathy

CLINICAL MANIFESTATIONS

- **Toxic doses???.....**
- Acute IV doses >1.5 g OR chronic ingestion >4 g/d have produced nephropathy
- Decrease abs of vit B12
- **MANAGEMENT:**
- Abrupt withdrawal not recommended….rebound deficiency (**scurvy**) following prolonged administration of megadose
- So…..gradual withdrawal



THIAMINE (Vit **B1**)

- "Antiberiberi".....Vit B1.....Thiamine
- **Source**: rice bran extracts, yeast extracts
- **RDA** of thiamine is 1.5mg/day.....Most exceed RDA in diet
- **Deficiency** results from **poor dietary intake** or more commonly from excess alcohol intake??!!
  - *Alcohol interfere with gastric absorption of vit B1 and its conversion to the active form*

THIAMINE (B1) TOXICITY

- Pain on injection and contact dermatitis
- Anaphylactic reaction after i.v administration
- Transient vasodilation
- Hypotension……vascular collapse
- **MANAGEMENT:**
  - Administration of **epinephrine and antihistamines**
  - Pressor agent may be necessary in extreme cases

VITAMIN B_{12} TOXICITY

- Vitamin B12 is non toxic unless very huge quantities are ingested
- Rare instances of allergic reactions…..pruritis, urticaria, anaphylaxis
- Contact dermatitis
- **Management**: discontinuation

Anti Histamine Classification

- H_1 antagonists are divided into 1st and 2nd generation;
- **1st generation** has strong sedative effects (enter the CNS) and can block autonomic receptors
- **2nd generation**: incomplete distribution to CNS→ less sedation

H_1 Receptor Antagonists

- **Competitive antagonists** of H1 receptor found in many OTC and prescription medication alone or in combined formulation

- **Major therapeutic uses:**

1. **motion sickness,**
2. **control of allergy-related itching,**
3. **cough and cold palliation**
4. **and used as sleep aids**

Toxicity:

- H1 antagonists are rarely ingested for suicidal purposes and have a **high therapeutic/toxic ratio**
- **Wide spectrum of side effects**
- **Sedation**, **antimuscarinic action** → most common undesirable actions

Toxicity:

- **Toxic dose.** The estimated fatal oral dose of diphenhydramine is 20–40 mg/kg
- In general, toxicity occurs after ingestion of 3–5 times the usual daily dose
- **Children** are **more sensitive** to the toxic effects of antihistamines than are adults
- The non-sedating agents are associated with less toxicity

Toxicity:

- CNS: sedation (most common with 1st generation), coma, delirium, hallucinations, psychomotor agitation (myoclonic or choreoathetoid movements), or convulsions

- Anticholinergic effects: hyperpyrexia, tachycardia, HTN, urinary retention, dilated pupils, dry mouth

- Reports of cholinergic toxicity upon stopping taking the drug

Toxicity:

- **CV effects**: massive diphenhydramine overdose has been reported to cause **myocardial depression** and QRS widening….similar to TCAs overdose

- Overdosage of **astemizole or terfenadine** may induce cardiac arrhythmias through QT prolongation (removed from the US market)

Drug Interactions:

- **Arrhythmia** occur particularly **when taken with P450 inhibitor** (erythromycin, ketoconazole, grapefruit juice….)

- Significant **sedation** when taken with **alcohol**, **benzodiazepines** → C/I while driving or operating machinery

Treatment

- **Treatment is supportive….stabilization and reduce amount absorbable**

1. Maintain an open airway and assist ventilation if necessary

2. Treat coma, seizures, hyperthermia, and atypical ventricular tachycardia if they occur

3. Monitor the patient for at least 6–8 hours after ingestion.

Treatment

- **Decontamination**:
  - Administer activated charcoal orally
  - Gastric lavage not necessary
  - N.B: GI decontamination helpful even in late-presenting patients because of slowed GI motility
- **Enhanced elimination**
  - Hemodialysis, hemoperfusion, peritoneal dialysis, and repeat-dose activated charcoal are **not effective** in removing antihistamines

Treatment

- There is **no specific antidote** for antihistamine overdose
- **Physostigmine** used for the treatment of **severe delirium** or **tachycardia**
- Not recommended routinely! may cause toxic effects as seizures, bronchoconstriction, bradycardia, asystole (may need to be reversed by atropine)