VITAMIN A TOXICITY

Background

1. Definition: **Hypervitaminosis A** (Vitamin A Toxicity)- effects of excessive vitamin A (specifically retinoid) intake
2. Dietary vitamin A obtained from preformed vitamin A found in animal foods (liver, milk, kidney, and fish oil), fortified foods, and drug supplements.
    - Also available in plant sources as provitamin A carotenoids.

Pathophysiology

1. Vitamin A fat-soluble and stored in body to variable degree.
2. Storage makes it more likely to cause toxicity when taken in excess amounts.
3. Metabolism of beta carotene highly regulated, so excessive ingestion of this form rarely causes toxicity.
4. Toxicity mainly caused by preformed Vitamin A ingestion.
5. Cofactor for biologic processes: isoretinoin
    - Beta-carotene converted to retinol, but not rapidly enough for acute toxicity.
6. Kinetics
    - T½: 9hr
    - Acute toxic dose: 25,000 IU/kg.
    - Chronic toxic dose: 4,000 IU/kg q Daily x6-15mos.
7. Morbidity/mortality
    - Mortality rare from vitamin A toxicity.
    - Morbidity mainly caused by side-effects and complications of excess ingestion.

Diagnostics

1. History
    - Carotenemia caused by excessive ingestion of vitamin A containing foods, mainly carrots
        - Manifested by yellow-orange coloring of skin, in palms of hands and soles of feet.
    - Signs/Symptoms of acute toxicity[1]
        - GI - Nausea, Vomiting, Anorexia, Abdominal pain
        - Neurological - Headache , Irritability, Drowsiness, Altered mental status, Blurred vision
        - Musculoskeletal - Muscle pain with weakness.
    - Signs/Symptoms of Chronic toxicity[1]
        - Acute toxicity signs/symptoms plus:
            - Eye – Nystagmus, Papilledema, Diplopia.
            - GI - Abdominal pain, Hepatosplenomegaly, Liver cirrhosis.
            - GU- Polyuria, Hypomenorrhea.
            - Musculoskeletal - Joint pain, Bone tenderness, bulging fontanelle in infants, craniotabes in children.
            - Dermatological - Pruritus , skin dryness, dermatitis, palmar and plantar peeling, alopecia.

2. Physical Examination:
    - Acute
        - Muscle and bone tenderness, especially over long bones of upper and lower extremities.
        - Neurologic manifestations with signs of increased intracranial pressure (e.g., children may have bulging fontanelles).
    - Chronic
        - Papilledema (increased intracranial pressure/ICP), hepatomegaly, ascites, erythematous dermatitis
        - Bulging fontanelle in infants, fever, yellow pigmentation/jaundice
3. Diagnostic testing[2]
    - Labs
        - Lytes: hypercalcemia[3], elevated BUN/Cr
        - CBC: normochromic, macrocytic anemia, leucopenia, thrombocytopenia.
        - Elevated Creatine Kinase/myoglobin (rhabdomyalysis)
        - LFTs, coags: coagulopathy, low prothrombin
        - Serum Vitamin A levels
            - Normal: 20-60 mcg/dL
            - Toxic: >60-100 mcg/dL
    - Radiologic
        - Skeletal X-rays: R/O calcifications in chronic toxicity, hand x-ray for periosteal calcifications
        - CT scan if neurologic abnormalities
        - Bone mineral density to evaluate potential osteopenia/osteoporosis from long term toxicity [4]
    - Other diagnostic testing
        - Lumbar Puncture: In the presence of increased ICP (cautious about cerebral herniation).
        - EKG:
            - In the presence of abnormal heart rhythm
            - In the presence of hypercalcemia which causes short QT interval and widened T wave.

Therapeutics

1. Acute treatment
    - ABCs, IV, O2, monitor
    - Decrease absorption
        - Gastric lavage/emesis if >12,000 U/kg (children); >840,000 U (adults).
        - Activated charcoal.1 gm/kg administered by mouth or NG tube Within one hour of ingestion
    - Stop vitamin A supplements.
2. Further management
    - In the presence of increased ICP:
        - Daily therapeutic LPs
        - Diuretics Furosemide 0.5-1 mg/kg Intravenously

- Steroids Dexamethasone (0.25-0.5 mg/kg) administered every 6 hrs with maximum dose of 16 mg per day.
- Mannitol 0.25 -1 g/kg IV bolus; repeat doses can be administered every 6-8 hrs.
- Intra venous Hypertonic saline; 3 percent saline administered as an initial bolus of 2 to 6 mL/kg. Continuous infusion of 3 percent saline at rates of 0.1 to 1 mL/kg per hour adjusted to maintain ICP <20 mmHg.

Follow-Up

1. Return to Office
    - Follow-up with primary care physician in 1-2 weeks.
2. Refer to Specialist
    - Neurosurgery consult: In the presence of elevated ICP or MS changes.
    - Dermatology consult: In the presence of serious skin reactions.
3. Admit to Hospital
    - Admit patients to the hospital in the presence of the following symptoms:
        - Altered mental status
        - Severe dehydration
        - Neurologic deficits
        - Metabolic derangements
        - Liver toxicity
        - Significant hypercalcemia
4. Discharge asymptomatic patients within 4-8 hrs post-ingestion

Prognosis

1. Prognosis for vitamin A intoxication is good.

Evidence-Based Recommendations

1. Pregnant women in industrialized countries should limit vitamin A intake to less than 5,000 IU per day. High dietary intake of vitamin A (i.e., more than 10,000 IU per day) associated with cranial-neural crest defects. (SOR:B)[5]
2. Liver and liver products should be eaten in moderation. Excessive consumption could cause vitamin A toxicity (SOR:C)[5]
3. The U.S. Preventive Services Task Force (USPSTF) concludes that evidence is insufficient to recommend for or against use of: vitamins A, C, or E supplements; multivitamins with folic acid; or antioxidant combinations for prevention of cancer or cardiovascular disease (Grade: I Statement)[6]
4. The USPSTF recommends against use of beta-carotene supplements, either alone or in combination, for prevention of cancer or cardiovascular disease (Grade: D Recommendation)[6]

References

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3. Bhalla K, Ennis DM, Ennis ED. Hypercalcemia caused by iatrogenic hypervitaminosis A. *J Am Diet Assoc*. 2005;105:119-121.
4. Genaro Pde S, Martini LA. Vitamin A supplementation and risk of skeletal fracture. *Nutr Rev*. Feb 2004;62(2):65-7.
5. Kirkham MD, Harris MD, Grzybowski MD, Am Fam Physician 2005, April 1, 71 (7) - http://www.aafp.org/afp/2005/0401/p1307.html.
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