Parenteral Vitamins and Minerals

Vitamins are organic compounds required in minute amounts for essential metabolic reactions in living organisms. Most vitamins are synthesized in the body in amounts insufficient for requirements. Therefore, they must be obtained from food, oral nutritional supplements or by injection.

Minerals are essential chemical elements required by living organisms. Most of the nutritional minerals are positive ions in solution and are listed as a salt on product labels, for example, potassium chloride

Osmolarity: Due to osmolarity differences between different pharmacies, it is always recommended that osmolarity values for each parenteral product be obtained from the supplier

IV Solution Physiology / Kinetics:

- When you infuse an IV you directly access the vascular (plasma) compartment
- You very quickly effect the ECF and then the ICF of most all cells
- Remembering the osmotic balances between these compartments is critical to proper IV therapy safety and outcomes

Classes of Vitamins

- Parenteral vitamins come in two general classifications, water-soluble and fat-soluble
- Water-soluble vitamins consist of all of the B vitamins and vitamin C.
  - The B vitamins and vitamin C are relatively non-toxic as they do not accumulate in the body
  - However, the patient may experience nausea when B vitamins are infused too quickly or given in higher doses

Points to remember

- IV protocols once mixed have a 4 hour "shelf life"
- Water soluble small molecules are going to go through the capillaries and be available to cells through normal uptake mechanisms.
  - Vitamin C will still favor the ECF and the cytosolic portion of the ICF
  - Lipid will still access the CM (vascular and cellular, and the lymphatics.)

MVI – Multi Vitamin Infusion

- Mixture of Vitamins:
  - Commercial Solution
    - **Ascorbic Acid** **200 mg**
    - **Vitamin A** **1 mg**
    - **Vitamin D** **5 mcg**
    - **B1: Thiamine HCl** **6 mg**
    - **B2: Riboflavin-5-phos-Na** **3.6 mg**
    - **B6: Pyridoxine HCl** **6 mg**
    - **B5: Dexpanthenol** **15 mg**
    - **B3: Niacinamide** **40 mg**
    - **Vitamin K** **150 mcg**
    - **Vitamin E** **10 mg**
    - **Biotin** **60 mcg**
    - **Folic Acid** **600 mcg**
    - **Cyanocobalamin** **5 mcg**
- Used in depleted patients as an additive nutrient mix
- Average IV dose: One vial

Pediatric Multivitamin Infusion

- Mixture of Vitamins – Commercial Product

Recommended Weight-Based Dosage of INFUVITE PEDIATRIC

	≥ 1 kg and < 3 kg	More than or equal to 3 kg
Daily Dosage Volume	3.25 mL	5 mL
Ascorbic acid (Vitamin C)	52 mg	80 mg
Vitamin A (as palmitate)	1495 IU (equals 0.5 mg)	2,300 IU (equals 0.7 mg)
Vitamin D_3 (cholecalciferol)	260 IU (equals 7 mcg)	400 IU (equals 10 mcg)
Thiamine (Vitamin B_1) (as the hydrochloride)	0.8 mg	12 mg
Riboflavin (Vitamin B_2) (as riboflavin 5-phosphate sodium)	0.9 mg	1.4 mg
Pyridoxine HCl (Vitamin B_6)	0.7 mg	1 mg
Niacinamide	11.1 mg	17 mg
Dexpanthenol (as J-pantothenyl alcohol)	3.3 mg	5 mg
Vitamin E (dl-a-tocopheryl acetate)	4.6 IU (equals 5 mg)	7 IU (equals 7 mg)
Vitamin K_1	0.1 mg	0.2 mg
Folic acid	91 mcg	140 mcg
Biotin	13 mcg	20 mcg
Vitamin B12 (cyanocobalamin)	0.7 mcg	1 mcg
contains no more than 30 mcg/L of aluminum		

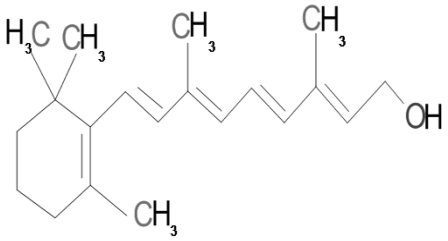
Pediatric Multivitamin Infusion

- Not to exceed single dose/day and daily doses are not to be given regularly without nutritional lab testing, in particular, fat soluble vitamin toxicity and Aluminum toxicity. Vit E toxicity is seen most frequently if not monitored.
- Not to be given to adults or children over 11 y.o., as effective dosing per weight, exceeds recommended aluminum dosage.
  - Patients with renal impairment, including premature neonates, who receive parenteral levels of aluminum at greater than 4 to 5 mcg/kg/day accumulate aluminum at levels associated with central nervous system and bone toxicity.
  - Plasma Aluminum levels greater than 100-150 mcg/L are at risk for aluminum toxicity. **Aluminum Toxicity in Infants and Children, American Association of Pediatrics**
- Not to be given IM. Diluted in a minimum of 100ml Saline or Dextrose. Light sensitive!
- Lab testing: May interfere with accurate readings of blood glucose and diagnosis of megaloblastic anemia
- Multiple drug interactions: See package inserts of particular commercial products.

Fat Soluble Vitamins

- The fat-soluble vitamins, including A, D, E, K and biotin are available in "water soluble" forms as stable emulsions
- The fat soluble vitamins can accumulate if given in too high dose over time and may result in toxicity

Vitamin A



Vitamin A

- Aquasol A, water-miscible vitamin A Palmitate
- Standard concentration is 50,000 IU/mL
- Labeled for I.M. use only.
- **DO NOT** give to patients with liver disease or liver cancer.
- Absolute contraindication if pregnant
- Concentrated vitamin A given i.v. may induce anaphylactoid or anaphylactic reactions and death

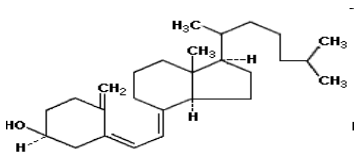
Vitamin A Functions

- Vitamin A effects
- gene expression
- is needed for normal vision(macular degeneration)
- essential for immune function
- effects fetal growth and development
- aids to differentiate stem cells to develop into red blood cells.

Vitamin A

- Pediatrics: MVI Pediatric, Infuvite
  - MVI products contain 2300 IU/5ml dose
  - Infant deaths with injectable Vitamin A:
    - 2,000 IU every two days x 28 days (14 injections total)
    - 4,000 IU every two days x 16 days (8 injections total)
    - 5,000-10,000 IU vitamin A three days weekly x 4 weeks
    - 15,000 IU vitamin A weekly for four weeks
    - Mayo Clinic
      - http://www.mayoclinic.org/drugs-supplements/vitamin-a/dosing/HRB-20060201

Vitamin D



Vitamin D

- Administration - IM:
  - Supplied in 1 mL ampules containing 500,000 IU/mL
    - Mayo clinic online (400,000 IU in elderly IM q 6-12 mos)
  - Calciferol In Oil Injection may be given undiluted deep IM
  - Compounded product is generally 10,000 to 50,000 IU / mL
- Adverse Reactions:
  - Generally seen only with excessive vitamin D administration
  - Early and late signs of overdose are hypercalcemia, which leads to weakness, muscle and bone pain, hypertension, cardiac arrhythmia and headache

IV Vitamin D

- Available as Calcitriol for injection, 1 mcg/ml (500 IU) or 2 mcg/ml single dose vials.
  - All other parenteral Vitamin D (in the US) is for IM use only.
- Dose recommended is 1 to 4 mcg (500 to 2000 IU) on the first dose, and 4 mcg or higher on successive doses.
  - Often dosed weekly. Check serum Ca, Vit. D and PTH if using long term.
  - Following the first dose, dose recommendations are 4 to 10 mcg weekly if needed.
    - On the high end: Muindi et. al. used 57 mcg weekly in a pharmacokinetic study with decadron in cancer patients.

IV Vitamin D

- Mix <u>without ionic additives</u> in D5W (normally 250 mL D5W run over 45 – 60 minutes to check patient tolerance.)
- Other IV formulas may be run either before or after.

Muindi JR, et. al. A phase I and pharmacokinetics study of intravenous calcitriol in combination with oral dexamethasone and gefitinib in patients with advanced solid tumors. Cancer Chemother Pharmacol. 2009 Dec;65(1):33-40. Epub 2009 Apr 26.

Vitamin D

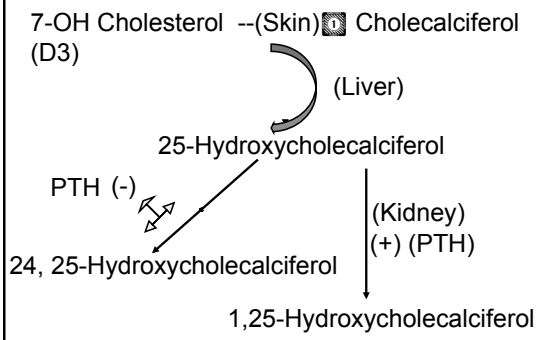
- Contraindications
  - Primary hyperparathyroidism
- Drug Interactions
  - Vitamin D levels are increased by: Estrogen, Isoniazid, Thiazide diuretics, Calcium channel blockers, sarcoidosis.
  - Vitamin D levels can be decreased by: Cholestyramine, Phenobarbital, phenytoin, mineral oil, Orlistat

Vitamin D

- Other effects
  - Vitamin D may enhance effects of cancer drug doxorubicin.
- Calcium levels should be followed closely if vitamin D is taken with digoxin
  - Vitamin D improves absorption of calcium, and in turn, can increase the likelihood of a toxic reaction from digoxin

Vitamin D

- Hormone effect:
- formed in the dermal layers (skin) by action of ultraviolet rays upon the precursors, 7-dehydrocholesterol and ergosterol, and acts on vitamin D receptors to regulate calcium in opposition to parathyroid hormone.
  - A vitamin that includes both CHOLECALCIFEROL and ERGOCALCIFEROL, have the common effect of preventing or curing rickets in animals.



Measuring Vitamin D Levels

- The preferred test for determining vitamin D
  - 25-hydroxyvitamin D (25(OH)D3)
  - Optimal levels upper 25 percentile of reference range
- Levels below 20 ng/mL indicate serious deficiency and will increase the risk of breast and prostate cancer, autoimmune diseases, and upper respiratory illness during winter months
  - ng/mL x 2.496 = nmol/L

Dawson-Hughes B, et al; Estimates of optimal vitamin D status. Osteoporos Int. 2005 Jul;16(7):713-6. Epub 2005 Mar 18.

- Vitamin D has captured attention as an important determinant of bone health, but there is no common definition of optimal vitamin D status.
- The opinions of the authors on the minimum level of serum 25(OH)D that is optimal for fracture prevention varied between 50 and 80 ng/mL. However, for five of the six authors, the minimum desirable 25(OH)D concentration clusters between 70 and 80 ng/mL
- The authors recognize that the average older man and woman will need intakes of at least 20 to 25 mcg (800 to 1,000 IU) per day of vitamin D (3) to reach a serum 25(OH)D level of 75 ng/mL.
- Based on the available evidence, we believe that if older men and women maintain serum levels of 25(OH)D that are higher than the consensus median threshold of 75 ng/mL, they will be at lower risk of fracture.

Vitamin E

- Vitamin E acetate, (check pharmacy availability)
- MVI – Multivitamin for injection, 1 mg/mL
- Administration and dose
  - ½-1 mL acetate (aqueous) in 500 mL solution
  - MVI 10 mL in 500 mL solution
  - IM admin leads to pain, swelling, tenderness at site
- CI side effects: No reports of harmful effect when physiologic doses are given

Vitamin K

- Essential cofactor for carboxylase, important clotting, will drive calcium into cells
- **WARNING** — INTRAVENOUS AND INTRAMUSCULAR USE Severe reactions, including fatalities, have occurred during and immediately after INTRAVENOUS injection of phytonadione, even when precautions have been taken to dilute the phytonadione and to avoid rapid infusion. Severe reactions, including fatalities, have also been reported following INTRAMUSCULAR administration. Typically these severe reactions have resembled hypersensitivity or anaphylaxis, including shock and cardiac and/or respiratory arrest. Some patients have exhibited these severe reactions on receiving phytonadione for the first time. Therefore the INTRAVENOUS and INTRAMUSCULAR routes should be restricted to those situations where the subcutaneous route is not feasible and the serious risk involved is considered justified.

Vitamin K

- Vitamin K1: Give **subcutaneous** whenever possible
- Protect from light at all times
- Can be diluted with Normal Saline, D5W or D5NS
- Should obtain preservative free form.
- Benzyl alcohol associated with toxicity in newborns.

The Anticancer Effects of Vitamin K (Lamson D and Plaza S. *Altern Med Rev* 2003;8(3):303-318)

Abstract
Vitamin K, an essential nutrient often associated with the clotting cascade, has been the focus of considerable research demonstrating an anticancer potential. Much of this research has focused on vitamin K3, although vitamins K2 and K1 have also been shown to have anticancer effects.
Early studies of vitamin K3 employed an oxidative model to explain the anticancer effects seen in both *in vitro* and *in vivo* studies; however, this model does not adequately address the action of vitamins K1 and K2.
Recent research has demonstrated the anticancer action of vitamin K may act at the level of tyrosine kinases and phosphatases.

Vitamin K

- Vitamin K3
- 250 mg to 1 gram K3
- Nausea is possible, many report severe but transient abdominal pain. You MUST warn patient of muscle spasms, abdominal cramping, masseter spasms.

Water Soluble Vitamins

- Water soluble vitamins, and vitamin like nutrients, generally are transported in plasma bound or attracted to plasma proteins.
- Their kinetics are complicated with respect to distribution and elimination, but are highly dependent upon hepatic uptake, plasma protein binding, renal transport effect, blood brain barrier physiology and many other factors which all come into play upon infusion.

Vitamin B1, Thiamine

- Supplied as Thiamine hydrochloride
- Standard concentration is 100 mg/mL
- Common dosing 100 – 300 mg.
- There is a thiamine disulfide (5 mg) + dextrose (200 mg)
- Can be administered i.m. or i.v. and should be diluted when given i.v., 30 mL minimum dilution

Thiamine

- Anaphylaxis has been rarely seen with thiamine HCl administered as a single agent
- An intradermal skin test may be used if a sensitivity to thiamine is suspected
- The risk of allergic reactions is very low when thiamine is given with other B-vitamins
- Doses up to 200 times the daily maintenance dose (1.5 mg/day) has not been associated with toxic effects

Vitamin B1, Thiamine

- Thiamine is a coenzyme in oxidative decarboxylation reactions
  -Deficiency slow function to HMP shunt and TCA cycle
- Important for reactions in energy metabolism, so requirement is related to energy intake in the form of carbohydrates
- Deficiency can be caused by digitalis and loop diuretics.

Vitamin B2: Riboflavin

- Low toxicity due to renal dumping of excess
- FMN (flavin mononucleotide)
- FAD (flavin adenine dinucleotide)
- Depressed B2 status leads to slow beta-oxidation of fats (1)
- Part of Glutathione Reductase & Synthase enzyme systems
  - Increase use with oxidative therapies
    - H2O2
    - Vit C
- Average IV dose 50 to 100 mg.

Vitamin B3: Niacin/Niacinamide

- Niacin converts to niacinamide
- Supports SEROTONIN synthesis
- Used in dehydrogenase reactions
- Dose: 100 mg/ml
  - Found in the B complex
  - Common dosage 100-1000 mg
- Deficiency: cholesterol, ht disease, pellagra
- Caution with Niacin leads to dermal flushing
- Niacinamide does not
- NAD is another form available and can be mixed 100-300 mg

Vitamin B5, Dexpanthenol

- Supplied as the alcohol form of pantothenic acid, Dexpanthenol
- Standard concentration is 250mg/mL
- Dose is 250-500 mg i.m., i.v. dose is up to 250 mg diluted in a push and 500 mg in a drip
- Physiologic doses are very safe
- Pharmacologic doses of 2500-3000 mg may prolong the effects of succinylcholine
- Consider in adrenal support, acylation reaction, NAT2 genomics support

Vitamin B5, Dexpanthenol

- Drug reactions:
  - Rare allergic reactions during use of parenteral dexpanthenol and some antibiotics, barbiturates and opiates when used concomitantly
- Pantothenic acid functions as a component of coenzyme A and as part of the acyl carrier protein for fatty acid synthetase
- Has major influences on the synthesis and breakdown of carbohydrates and fatty acids as well as the synthesis of steroid hormones and hemoglobin

Vitamin B6, Pyridoxine

- Supplied as Pyridoxine hydrochloride
- Standard concentration is 100 mg/mL
- Dose and administration
  - Prophylactic dose for i.m. or i.v. administration is 2-4 ml daily
  - Therapeutic dose is 10-15 mg one to three times daily (oral)
  - Nutritional protocols generally include 100 mg diluted in at least 30 mL carrier solution

Vitamin B6, Pyridoxine

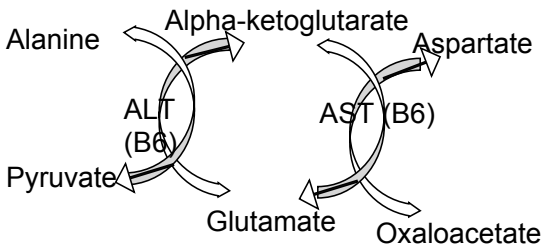
- Adverse Reactions:
- NAUSEA if given to fast or very toxic patient
- Drug Reactions: When given as undiluted i.v. injection may cause dizziness, faintness and irritation of tissue

– Doses higher than 5 mg daily can reverse the therapeutic effect of levodopa by increasing its metabolism in peripheral tissues. With a combination of carbidopa and levodopa(sinemet) this antagonistic effect is less noticeable

Vitamin B6, Pyridoxine

- Pyridoxine acts as a coenzyme in metabolic reactions for carbohydrate, lipid and amino acid metabolism
- B6 deficiency can be induced by malabsorption, malignancies, many diseases, long-term drug therapy as well as total parenteral nutrition (TPN).
- Ethanol increases the breakdown of pyridoxine

Transaminase Reactions



BIOTIN

- Vitamin H or B7
- 5 mg/ml or 10 mg/ml
- Cofactor in the metabolism of fatty acids and amino acids/ leucine, and it plays a role in the citric acid cycle and gluconeogenesis.
- responsible for carbon dioxide transfer in several carboxylase enzymes

Signs of Biotin Deficiency

- appetite and growth decreased.
- Dermatologic symptoms:
  - Dermatitis, alopecia, achromotrichia (absence of loss of hair pigment) Perosis, Fatty liver and Kidney syndrome, hepatic steatosis, rash, seizures
- Neurologic symptoms: (adults)
  - depression, lethargy, hallucination, and numbness and tingling of the extremities.
  - hereditary disorders of biotin metabolism result in functional biotin deficiency generate impaired immune system function, with increased susceptibility to bacterial and fungal infections.
  - Long term TPN
  - MS
- Pregnant women tend to have high risk of biotin deficiency

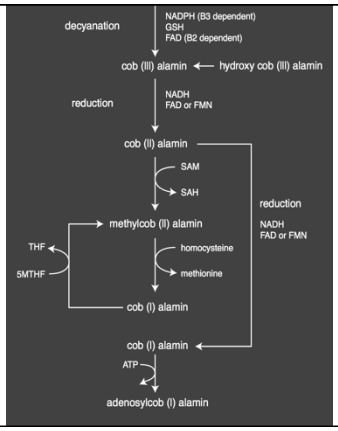
- High doses of biotin in chronic progressive multiple sclerosis: A pilot study
  Frédéric Sedel Caroline Papeix Agnès Bellanger Valérie Touitou Christine Lebrun-Frenay Damien Galanaud Olivier Gout, Olivier Lyon-Caen[1], Aymard Tourbah

Vitamin B12, Cobalamin

- Three types of parenteral B12 available
  - Cyanocobalamin, 100 mcg/mL, 1000 mcg/mL
  - Hydroxocobalamin, concentration as prescribed, compounded
  - Methylcobalamin, concentration as prescribed, compounded
- Dose and administration
  - 1000 mcg is common dose, but higher doses are very safe

Vitamin B12, Cobalamin

- Cyanocobalamin is best used i.m. as much of the dose is lost as blood circulates through the kidneys
- Hydroxocobalamin, also known as long acting B12, binds to serum proteins better than Cyano. Suitable for i.m. or i.v. use
  - Hydroxocobalamin is used as a treatment for cyanide poisoning, 5-10 g i.v.
- Methylcobalamin is a metabolically active form of B12, especially suited for neurological complaints



Credit to George Kelly, "On the synthesis of coenzyme forms of B12".

Vitamin B12, Cobalamin

- Methyl-B12 is required to convert homocysteine to methionine and to synthesize and maintain myelin sheaths on nerves
- Methionine is required for the metabolism of choline and betaine
- These facts help explain some of the neurological damage caused by B12 deficiency

Vitamin B12, Cobalamin

- Adverse reactions
  - Vitamin B12 has been shown to be nontoxic at doses that exceed daily requirements by 10,000 times
  - Preservative can result in hypersensitivity reactions but allergies to PF B12 are rare
- Drug reactions
  - Colchicine causes malabsorption of oral cobalamin

Folic Acid

- Folic Acid prefer Folinic or methyl folate
- 5mg/ml to 30 mg/ml
  - Compound as required or needed
- Dosage and Administration:
  - IM: up to 10 mg intermittent
  - Folate deficiency with megaloblastic anemia is treated with 0.5-1 mg/day i.m.
  - IV: 5-20 mg diluted in i.v. solution, intermittent
  - Mix in IV solution LAST (Precipitates easily!)

Folinic or methyl folate Acid

- Adverse Reactions and Toxicity
  - The toxicity of folic acid is very low
  - Adults showed no adverse effects after receiving 400 mg/day for five months or 10 mg/day for five years.
- Draw up in separate syringe and needle prior to insertion into bag of nutrients
- Add to bag at opposite order from magnesium
  - First or last

Folinic Acid, Leucovorin Calcium

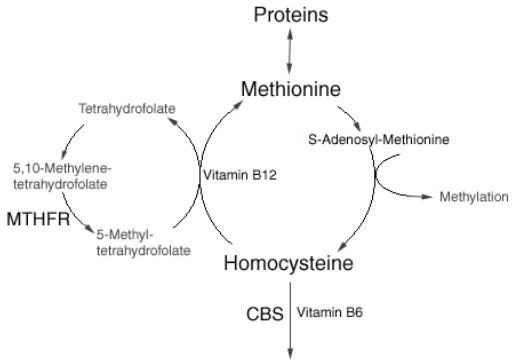
- Leucovorin Calcium Powder
  - 50 mg
    - Reconstitute with 5 mL Bacteriostatic Water for Injection, USP and use within 7 days, or with Sterile Water for Injection, USP and use immediately
    - Each mL of solution contains 10 mg Leucovorin.
  - Leucovorin Calcium Powder, 100 mg
  - Leucovorin Calcium Powder, 350 mg

Folinic Acid, Leucovorin Calcium

- Dosage and administration
  - 1-2 mL (10-20 mg)

MTHF (Methylene-tetrahydrofolate)

- Dosage and administration
  - 5 or 10 mg/ml doses
  - Dose at 1- 15 mg
  - Start low and work up, support collateral pathways first
  - Can precipitate easily if put in a syringe for IM delivery with other nutrients. (Best to give alone for IM)



- Succinyl CoA (TCA cycle)
- PAPS (Supports Dopamine production)
- Glutathione
- Taurine
- GABA
- Uric Acid

Vitamin B Complex

- B-complex 100 contains the following ingredients/mL:
  - Thiamine HCl 100 mg
  - Riboflavin-5-phosphate 2 mg
  - Niacinamide 100 mg
  - Dexpanthenol 2 mg
  - Pyridoxine 2 mg.
  - NOTE: SOME B-VITAMINS DO HAVE CORN IN THEM!!!

Vitamin B Complex

- Dosage and Administration:
- IM: 1 mL
- IV: 0.5-2.0 mL diluted in i.v. solution
  - One mL given as part of a 30 mL i.v. push (Myers Cocktail) has been administered countless times without adverse reaction
  - For doses higher than 1 mL it is recommended that B-complex be diluted in at least 100 mL i.v. solution

Vitamin B Complex

Life Sci. 2012 Dec 10;91(23-24):1187-95. doi: 10.1016/j.lfs.2012.08.025. Epub 2012 Aug 24.

- **B vitamins relieve neuropathic pain behaviors induced by infraorbital nerve constriction in rats.** Kopruszinski CM[1], Reis RC, Reis RC, Chichorro
  - suggest that B vitamins might constitute a relevant adjuvant to control some aspects of the pain afflicting patients suffering from trigeminal neuropathic pain

B Vitamins alleviate indices of neuropathic pain in diabetic rats.

- Jolivalt CG, Mizisin LM, Nelson A, Cunha JM, Ramos KM, Bonke D, Calcutt NA.
- Eur J Pharmacol. 2009 Jun 10;612(1-3):41-7. doi: 10.1016/j.ejphar.2009.04.028. Epub 2009 Apr 23.
- PMID: 19393643

B Complex

- Adverse reactions & toxicity
  - GI upset (nausea) is the most common complaint with oral preparations and can occur with too rapid i.v. infusions

Vitamin C, Ascorbic Acid

- Vitamin C is also available as Sodium Ascorbate. It is questionable that keeping this form in stock is worthwhile
  - Ascorbic acid solutions are buffered to a pH of 5.5-7.0 with sodium hydroxide or 8.4% sodium bicarbonate
  - Ascorbic acid and sodium hydroxide/bicarb react chemically, forming sodium ascorbate
  - So AA buffered to a physiologically tolerable pH is essentially sodium ascorbate
- So as Homer says -

Vitamin C

- L-Ascorbic acid is the metabolically active form
- Ascorbic acid functions as an antioxidant by donating electrons to free radicals
  - It is oxidized to dehydroascorbic acid by this process
- It is a cofactor for lysyl and prolyl hydroxylases in the production of collagen
  - Deficiency leads to the scorbutic manifestations of poor wound healing and bleeding.

Vitamin C

- Vitamin C, with an osmolarity of 5.8 mOsm/ mL (typical), increases solution osmolarity of a solution significantly
- Even though pH is adjusted, it can cause discomfort in some people – buffer with:
  - Sodium bicarbonate, 8.4%, volume varies with vitamin C dose
  - Calcium gluconate or Calcium Chloride, 10%, is also useful, 5-20 mL depending on vitamin C dose

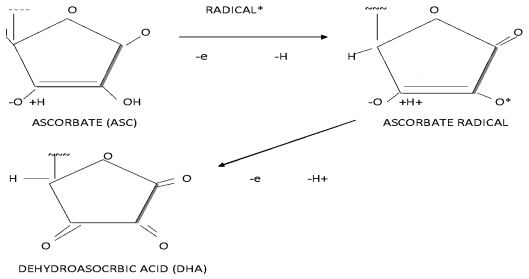
Vitamin C

- Vitamin C is a mild calcium chelator, calcium replacement is recommended
  - 1 mL 10% calcium gluconate for each 10 grams or
  - 1/3 mL 10% calcium chloride for each 10 grams of vitamin C alleviates this effect
  - Vitamin C is a hexose derivative, induces insulin, and will measure as glucose on a diabetic patient's glucose meter

Vitamin C

- Higher doses of vitamin C, 25-75 grams have:
  - Dehydrating effect, osmotic diuresis,
  - encourage pt. to drink (electrolyte) water
  - Hypoglycemic effect, pt. needs to snack
- Very high doses have potential to create a peroxide surge intracellularly, which provides the cytotoxic effect in cancer and virally infected cells
  - PET positive cancers would likely respond better due to their GLUT activity

Oxidation of Ascorbic Acid



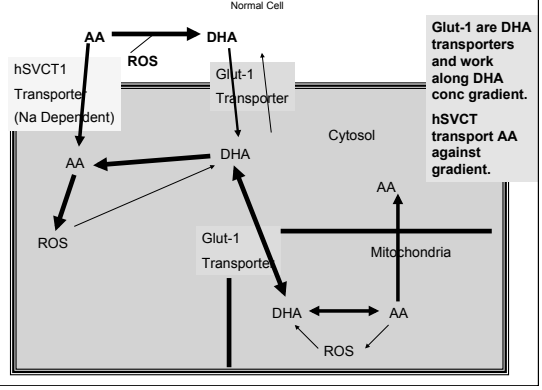
A Human Sodium-Dependent Vitamin C Transporter 2 Isoform Acts as a Dominant-Negative Inhibitor of Ascorbic Acid Transport

Eugene A. Lutsenko, Juan M. Carcamo, and David W. Golde*
Program in Molecular Pharmacology and Chemistry, Department of Medicine, and Department of Clinical Laboratories, Memorial Sloan-Kettering Cancer Center, New York, New York 10021
Received 11 July 2003/Returned for modification 18 September 2003/Accepted 16 January 2004

Vitamin C is transported as ascorbic acid (AA) through the sodium-ascorbate cotransporters (SVCT1 and-2) and as dehydroascorbic acid (DHA) through the facilitative glucose transporters. All cells have glucose transporters and take up DHA that is trapped intracellularly by reduction and accumulated as AA. SVCT2 is widely expressed in cells and tissues at the mRNA level; however, only specialized cells directly transport AA.

We undertook a molecular analysis of SVCT2 expression and discovered a transcript encoding a short form of human SVCT2 (hSVCT2-short) in which 345 bp is deleted without a frame shift. The deletion involves domains 5 and 6 and part of domain 4. cDNA encoding this isoform was isolated and expressed in 293T cells, where the protein was detected on the plasma membrane. Transport studies, however, revealed that hSVCT2-short gave rise to a nonfunctional transporter protein. hSVCT2-short arises by alternative splicing and encodes a protein that strongly inhibited the function of SVCT2 and, to a lesser extent, SVCT1 in a dominant-negative manner, probably by protein-protein interaction. The expression of hSVCT2-short varies among cells. PCR analysis of cDNA isolated from melanocytes capable of transporting AA revealed a predominance of the full-length isoform, while HL-60 cells, which express SVCT2 at the mRNA level and were incapable of transporting AA, showed a predominance of the short isoform. These findings suggest a mechanism of AA uptake regulation whereby an alternative SVCT2 gene product inhibits transport through the two known AA transporters.

Uptake of Ascorbate by Cells:



Mitochondrial recycling of ascorbate

Abstract:

Mitochondria are the major source of potentially damaging reactive oxygen species in most cells. Since ascorbic acid, or vitamin C, can protect against cellular oxidant stress, we studied the ability of mitochondria prepared from guinea pig skeletal muscle to recycle the vitamin from its oxidized forms. Although ascorbate concentrations in freshly prepared mitochondria were only about 0.2 mM, when provided with 6 mM succinate and 1 mM dehydroascorbate (the two-electron-oxidized form of the vitamin), mitochondria were able to generate and maintain concentrations as high as 4 mM, while releasing most of the ascorbate into the incubation medium. Mitochondrial reduction of dehydroascorbate was strongly inhibited by 1,3-bis(chloroethyl)-1-nitrosourea and by phenylarsine oxide. Despite existing evidence that mitochondrial ascorbate protects the organelle from oxidant damage, ascorbate failed to preserve mitochondrial α-tocopherol during prolonged incubation in oxygenated buffer. Nonetheless, the capacity for mitochondria to recycle ascorbate from its oxidized forms, measured as ascorbate-dependent ferricyanide reduction, was several-fold greater than total steady-state ascorbate concentrations. This, and the finding that more than half of the ascorbate recycled from dehydroascorbate escaped the mitochondrion, suggests that mitochondrial recycling of ascorbate might be an important mechanism for regenerating intracellular ascorbate.

Dr Paul Merik's Septic Shock Protocol

- **Vitamin C:** 1.5 g IV q 6 hourly for 4 days or until discharge from the ICU. Vitamin C is provided by the manufacturer as a 50 ml vial at a concentration of 500 mg/ml. Three (3) ml of vitamin C will be placed in a 100 ml bag of either dextrose 5% in water (D5W) or normal saline and infused over 60 minutes
- **Hydrocortisone:** 50 mg IV push q 6 hourly for 6 days or until discharge from the ICU. Taper is not required. Optional dosing strategy: Hydrocortisone 50 mg bolus, followed by a 24-hour continuous infusion of 200 mg for 4 days
- **Thiamine:** 200 mg IV q 12 hourly for 4 days or until discharge from the ICU. Intravenous thiamine (200 mg) was placed in a piggyback in 50 ml of either D5W or normal saline and administered as a 15-minute infusion

Protocol source: From the website: http://www.evms.edu/about_evms/administrative_offices/marketing_communications/publications/issue_9_4/sepsis.php#medical-professional. Accessed May 12, 2017.

Fowler, A. 3 year study of IV Ascorbic Acid and Sepsis, 2014 Virginia Commonwealth University.

Immune Netw.
Published online 2013 Apr 30. doi: 10.4110/in.2013.13.2.70

Vitamin C Is an Essential Factor on the Anti-viral Immune Responses through the Production of Interferon-α/β at the Initial Stage of Influenza A Virus (H3N2) Infection

Yejin Kim, Hyemin Kim, Seyeon Bae, Jiwon Choi, Sun Young Lim, Naeun Lee, Joo Myung Kong, Young-il Hwang, Jae Seung Kang, and Wang Jae Lee,
Immune Netw. 2013 Apr; 13(2): 70–74.
Published online 2013 Apr 30. doi: 10.4110/in.2013.13.2.70
PMCID: PMC3659258
PMID: 23700397

Abstract **(a mouse study)**

L-ascorbic acid (vitamin C) is one of the well-known antiviral agents, especially to influenza virus. Since the in vivo antiviral effect is still controversial, we investigated whether vitamin C could regulate influenza virus infection in vivo by using *Gulo* (-/-) mice, which cannot synthe
size vitamin C like humans. First, we found that vitamin C-insufficient *Gulo* (-/-) mice expired within 1 week after intranasal inoculation of influenza virus (H3N2/Hongkong). Viral titers in the lung of vitamin C-insufficient *Gulo* (-/-) mice were definitely increased but production of antiviral cytokine, interferon (IFN)-α/β, was decreased. On the contrary, the infiltration of inflammatory cells into the lung and production of pro-inflammatory cytokines, tumor necrosis factor (TNF)-α and interleukin (IL)-α/β, were increased in the lung. Taken together, vitamin C shows in vivo antiviral immune responses at the early time of infection, especially against influenza virus, through increased production of IFN-α/β

High-dose ascorbic acid increases intercourse frequency and improves mood: a randomized controlled clinical trial.

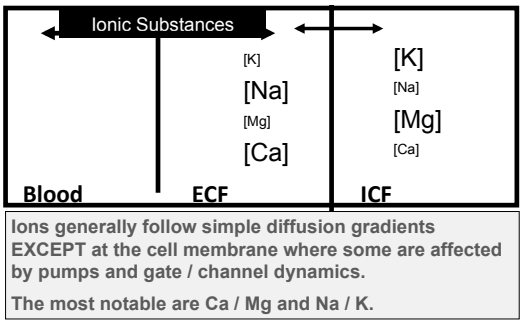
Brody S. **Journal** Biol Psychiatry. 2002 Aug 15;52(4):371-4.

Abstract
BACKGROUND: Ascorbic acid (AA) modulates catecholaminergic activity, decreases stress reactivity, approach anxiety and prolactin release, improves vascular function, and increases oxytocin release. These processes are relevant to sexual behavior and mood.
METHODS: In this randomized double-blind, placebo-controlled 14 day trial of sustained-release AA (42 healthy young adults; 3000 mg/day Cetebe) and placebo (39 healthy young adults), subjects with partners recorded penile-vaginal intercourse (FSI), noncoital partner sex, and masturbation in daily diaries, and also completed the Beck Depression Inventory before and after the trial.
RESULTS: The AA group reported greater FSI (but, as hypothesized, not other sexual behavior) frequency, an effect most prominent in subjects not cohabiting with their sexual partner, and in women. The AA but not placebo group also experienced a decrease in Beck Depression scores.
CONCLUSIONS: AA appears to increase FSI, and the differential benefit to non cohabitants suggests that a central activation or disinhibition, rather than peripheral mechanism may be responsible.

Minerals

- Ionic substances (Na, Ca, K…) act the same way they do in normal physiology!
  - So, what if you infuse a high volume of an ion normally found in the ICF?

Compartment Dynamics



Ions generally follow simple diffusion gradients EXCEPT at the cell membrane where some are affected by pumps and gate / channel dynamics.

The most notable are Ca / Mg and Na / K.

Calcium

- 10% Calcium gluconate, 100 mg/ml
- 10% Calcium chloride, 100 mg/ml
- 10%Calcium glycerophosphate (Calphosan), contains 50 mg calcium glycerophosphate and 50 mg calcium lactate
- Dosage and administration
  - Gluconate 100-2000 mg (0.465-9.3 mEq) i.v.
  - Chloride 100- 700 mg (13.6 mEq)
    - Infusion rate never greater than 1 mEq/min.

Calcium

- Calcium salts administered i.m. can cause local necrosis and abscess
- Calcium added to lipid emulsions has resulted in non-visible precipitates, patient deaths
- NEVER mix calcium and Bicarbonate in the same syringe. Will get cloudy precipitate due to very close interactions which will not be seen in larger space provided in bag.
- Storage – room temperature to avoid precipitation

Calcium

- Adverse reactions: hypotension, bradycardia, arrhythmia, tingling sensations, syncope, cardiac arrest
- Calcium gluconate possible shellfish allergy.
- Parenteral effects are mainly on nerve conduction and muscle contraction

Calcium

May have increased requirement for Ca in IV's under some circumstances such as:

- Chelation remineralization
- Hypocalcemic patients
- High dose IV – Vitamin C

Calcium

- Hypocalcemia: **(Life threatening complication: laryngospasm)**
  - Causes:
    - Hypoparathyroidism / Mg. & Vit. D. deficiency
    - Diarrhea / Infection / Trauma / Burns
  - Effects: **(All effects aggravated by High K and low Mg.)**
    - Cramping (See next 2 slides), Neurological sx's
    - **Prolonged Q-T interval**

Calcium deficit: Chovestek's sign

FIG. 4–5. Positive Chvostek's sign, which occurs after tapping the facial nerve approximately 2 cm anterior to the earlobe. Unilateral twitching of the facial muscle occurs in some patients with hypocalcemia or hypomagnesemia.

Calcium deficit: Trousseau's sign

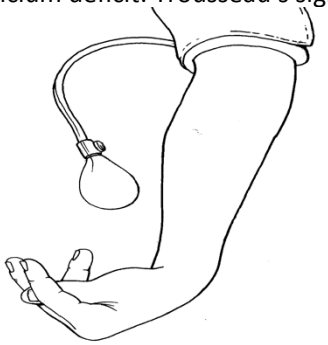


FIG. 4–4. Positive Trousseau's sign. Carpopedal attitude of the hand when blood pressure cuff is place on the arm and inflated above systolic pressure for 3 minutes. A positive reaction is the development of carpal spasm.

Magnesium

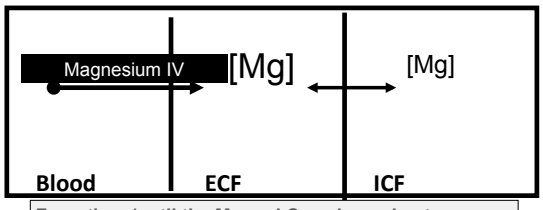
- Dosage & Administration
  - IM: Up to 3 mL 50% adults
    - 1-3 mL 20% pediatric
  - IV: given normal renal function, up to 50 mEq over 4-6 hours (12.5 mL 50% Mg Sulfate)
  - Clinical use
    - Up to 3 mL 50% over 20-30 min, watch for O.D. Sx
    - Up to 6 mL 50% over 2 hours in drip

Magnesium – Clinical

Using Mg Salt in appropriate protocols

- 50% Mg Sulfate: Asthma, muscle cramps, migraine
  - 3 mL in push to 6 mL drip
- 20% Mg Chloride: Arrhythmia
  - 10 mL in drip with other mineral chloride salts
- Many (most likely most) patients are Mg deficient and benefit from an appropriate degree of Mg replacement during IVMT

Compartment Dynamics: Magnesium Administration



For a time (until the Mg and Ca+ channel gates can equilibrate) The abnormally high ECF Mg will cause a dampening of the normally high Ca ECF and High Mg ICF gradient. The membrane will thus lose some (or all) excitability!

**** This is why Mg is a functional Ca-Channel blocker.**

Magnesium

- **Hypermagnesemia:**
  - **Tx: Cal. Gluconate 10% or Cal Chloride 1 to 10 mL IV**
  - Causes: Mg antacids, Renal failure
  - Effects: **Lethargy, Hypotension, Slow/weak pulse, flushing/sweating, muscle weakness, decreased DTR's, Heart block, Cardiac Arrest, Coma/Death**

The therapeutic use of magnesium in anesthesiology, intensive care and emergency medicine: a review:

[L'usage therapeutique du magnesium en anesthesiologie, reanimation et medecine d'urgence].

Dube L, Granry JC.
Department of Anesthesiology, University Hospital, Angers, France. Can J Anaesth. 2003 Aug-Sep;50(7): 732-46.

==========

PURPOSE: To review current knowledge concerning the use of magnesium in anesthesiology, intensive care and emergency medicine.

METHODS: References were obtained from Medline(R) (1995 to 2002). All categories of articles (clinical trials, reviews, or meta-analyses) on this topic were selected. The key words used were magnesium, anesthesia, analgesia, emergency medicine, intensive care, surgery, physiology, pharmacology, eclampsia, pheochromocytoma, asthma, and acute myocardial infarction.

Can J Anaesth. 2003 Aug-Sep;50(7):732-46. (Continued)

Principal findings:

- Hypomagnesemia is **frequent postoperatively and in the intensive care** and needs to be detected and corrected to prevent increased morbidity and mortality.
- Magnesium **reduces catecholamine release** and thus allows better control of adrenergic response during intubation or pheochromocytoma surgery.
- It also **decreases the frequency of postoperative rhythm disorders in cardiac surgery as well as convulsive seizures in preeclampsia and their recurrence in eclampsia**.
- The use of **adjuvant magnesium during perioperative analgesia may be beneficial for its antagonist effects on N-methyl-D-aspartate receptors**.
- The precise role of magnesium in the treatment of asthmatic attacks and myocardial infarction in emergency conditions needs to be determined.

CONCLUSIONS: Magnesium has many known indications in anesthesiology and intensive care, and others have been suggested by recent publications. Because of its interactions with drugs used in anesthesia, anesthesiologists and intensive care specialists need to have a clear understanding of the role of this important cation.

PMID: 12944451 [PubMed - in process]

I.V. Mg Research-Migraines

Bigal, M. E., C. A. Bordini, et al. (2002). "Intravenous magnesium sulfate in the acute treatment of migraine without aura and migraine with aura. A randomized, double-blind, placebo-controlled study." Cephalalgia 22(5): 345-53.

- Sixty patients in each group were assigned at random to receive magnesium sulfate, 1000 mg intravenously, or 0.9% physiological saline, 10 ml. We used seven parameters of analgesic evaluation and an analogue scale to assess nausea, photophobia and phonophobia. Mg sulfate can be used for the treatment of all sxs in migraine with aura, or as an adjuvant therapy for associated symptoms in patients with migraine without aura.

- 2001 Feb;41(2):171-7.
- **Efficacy of intravenous magnesium sulfate in the treatment of acute migraine attacks.**
- http://nyheadache.com/educational-materials/magnesium-and-headaches/

I.V. Mg Research-Bronchial Hyper-reactivity

Schenk, P., K. Vonbank, et al. (2001). "Intravenous magnesium sulfate for bronchial hyperreactivity: a randomized, controlled, double-blind study." Clin Pharmacol Ther 69(5): 365-71.

- In the magnesium group, 30% of the subjects reached a normal PC(20) or decrease of FEV in 1 second by 20% compared with 10% in the placebo group. We conclude that intravenous magnesium sulfate significantly improved bronchial hyperreactivity and may serve as an adjunct to standard treatment.

Magnesium

- Magnesium sulfate 500 mg/mL (50%)
  - Preg. Category D (FDA changed from Cat A 2013)
    - Pregnancy Category D means there is positive evidence of human fetal risk, but the potential benefits from using the drug in pregnant women may be acceptable.
    - Changed from Category A due to studies of long term use (5-7 days) in to low fetal blood Ca levels . Lab values were normal a few days after birth.
- **FDA Recommends Against Prolonged Use of Magnesium Sulfate to Stop Pre-term Labor Due to Bone Changes in Exposed Babies Safety Announcement [5-30-2013]**
- Magnesium chloride, 200 mg/mL (20%)
  - Pregnancy Category C
    - Magnesium chloride should be given to a pregnant woman only when it out ways the risks , or if there is clear need.
    - Can be used in pregnancy; preferred over Category D

Hypertensive with Low Magnesium

- **The effect of lowering blood pressure by magnesium supplementation in diabetic hypertensive adults with low serum magnesium levels: a randomized, double-blind, placebo-controlled clinical trial.**
- Guerrero-Romero F, Rodriguez-Morán M.
- **Abstract**
- To test the blood pressure (BP)-lowering effect of oral magnesium supplementation (that is, magnesium chloride (MgCl(2)) solution) in diabetic hypertensive adults with hypomagnesaemia not on diuretic treatment but receiving concurrent captopril, we conducted a double-blind, placebo-controlled trial. Eighty-two subjects between 40 and 75 years of age were randomly enrolled. Over 4 months, subjects in the intervention group received 2.5 g of MgCl(2) (50 ml of a solution containing 50 g of MgCl(2) per 1000 ml of solution) equivalent to 450 mg of elemental magnesium, and control subjects inert placebo. The primary trial endpoint was a reduction in systolic (SBP) and diastolic (DBP) blood pressure. Complete follow-up was achieved for 79 of the 82 randomized subjects. SBP (-20.4+/-15.9 versus -4.7 +/- 12.7 mm Hg, P=0.03) and DBP (-8.7+/-16.3 versus -1.2+/-12.6 mm Hg, P=0.02) showed significant decreases, and high-density lipoprotein-cholesterol (0.1+/-0.6 versus -0.1+/-0.7 mmol l(-1), P=0.04) a significant increase in the magnesium group compared to the placebo group. The adjusted odds ratio between serum magnesium and BP was 2.8 (95%CI: 1.4-6.9). **Oral magnesium supplementation with MgCl (2) significantly reduces SBP and DBP in diabetic hypertensive adults with hypomagnesaemia.**
- J Hum Hypertens. 2009 Apr;23(4):245-51. doi: 10.1038/jhh.2008.129. Epub 2008 Nov 20.
- PMID: 19020533 [PubMed - indexed for MEDLINE]

Calcium and Magnesium IV Products

- Between 'salt' forms calculating mg / mL based on product concentration may not yield an equivalent dose of the electrolyte in the IV solution.
- Example:
  - Calcium in the chloride and gluconate forms are both 10% solutions (100 mg/mL).
  - 10 mL Calcium gluconate (1000 mg) yields 4.65 mEq Ca++
  - 10 mL Calcium chloride (1000 mg) yields 13.6 mEq Ca ++

Calcium and Magnesium IV Products

Product	Percent	mg/mL	mEq / mL
Calcium Gluconate	10%	100	0.465
Calcium Chloride	10%	100	1.36
Magnesium Sulfate	50%	500	4.06
Magnesium Chloride	20%	200	1.97

Calcium and Magnesium IV Products

- Therefore on an equivalent ionic basis:
  - 1 mL Calcium chloride is equal to 2.92 mL Calcium gluconate
  - 1 mL Calcium gluconate is equal to 0.34 mL Calcium chloride
  - 1 mL Magnesium sulfate is equal to 2.06 mL magnesium chloride
  - 1 mL Magnesium chloride is equal to 0.49 mL Magnesium sulfate

Potassium

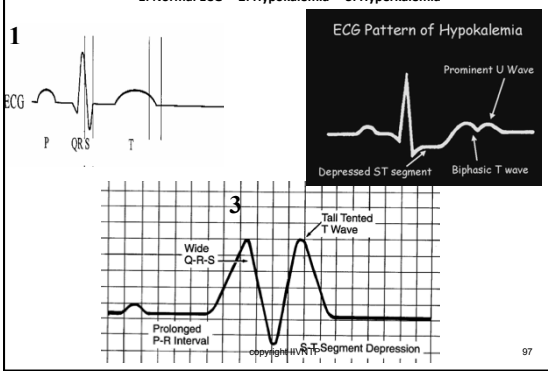
- Potassium chloride, 2 mEq/mL is principle form used in IVMT
  - Potassium phosphate and acetate are available
- Dose and administration
  - Not for i.m. use
  - Never add potassium to an i.v. push
  - Always dilute appropriately prior to infusion
  - K administration in IVMT is intended to improve mineral balance, NOT for K repletion

Potassium - Clinical

- Typical IVMT dose is 2-5 mL in drip of 200-500 mL given over 1-3 hours
- It is useful to include potassium
- When giving high dose vitamin C
- When infusing solutions using D5W as carrier
- Both of these treatments induce insulin and when insulin moves either glucose or vitamin C into cells potassium is required

ECG Changes and Potassium

1: Normal ECG 2: Hypokalemia 3: Hyperkalemia



NEVER GIVE POTASSIUM IM OR SQ !!!!!

CRITICAL GUIDELINES FOR ADMINISTRATION OF POTASSIUM

Never give a potassium I.V. push.

Potassium chloride (KCl) should be added to a nondextrose solution such as isotonic saline to treat severe hypokalemia because administration of KCl in a dextrose solution may cause a small reduction in the serum potassium level.

Never administer concentrated potassium solutions without first diluting them as directed.

KCl preparations greater than 60 mEq/L **should not** be given in a peripheral vein. Concentrations greater than 8 mEq/100 mL can cause pain and irritation of peripheral veins and lead to postinfusion phlebitis (Rapp, 1987).

When adding KCl to infusion solutions, especially plastic systems, make sure the KCl mixes with the solution thoroughly. Invert and agitate the container to ensure mixing. ***Do not add KCl to a hanging container!***

For patients with any degree of renal insufficiency or heart block, Zull (1989) recommends reducing the infusion by 50 percent. For example, 5 to 10 mEq/h rather than 10 to 20 mEq/h.

Administer potassium at a rate not to exceed 10 mEq/h through peripheral veins (Kokko & Tannen, 1990; Gahart, 1994).

For patients with extreme hypokalemia, rates should be no more than 40 mEq/h while ECG is constantly monitored (Kokko & Tannen, 1990).

If KCl is administered into the subcutaneous tissue (infiltration), it is extremely irritating and can cause severe tissue loss. Use extravasation protocol in this situation.

Chromium

- Chromium 4 mcg/mL
- Chromium 200 mcg/mL
- Dosage
  - 20 – 200 mcg per infusion (250mL or 500mL)
- Uses for insulin resistance
  - Hypoglycemia/Hyperglycemia
  - Diabetes

Chromium infusion reverses extreme insulin resistance in a cardiothoracic ICU patient.

Via M Scurlock C, Raikhelkar J, Di Luozzo G, Mechanick JI

Abstract

Insulin resistance is common and often multifactorial in acutely critically ill patients. At our institution, glycemic control is achieved in these patients using an intravenous insulin protocol. The authors present a case in which a patient developed severe insulin resistance following surgical repair of a thoracic aorta aneurysm. Postoperatively, the patient required 2110 units of insulin over 40 hours while receiving pressors and glucocorticoids. After the administration of intravenous chromium at 3 microg/h, the blood sugar normalized and insulin therapy was discontinued. This case represents a unique approach using intravenous chromium to achieve glycemic control in a patient with extreme insulin resistance and acute critical illness. Prospective clinical trials using intravenous chromium may provide the means to optimize intensive insulin therapy for critically ill patients.

Nutr Clin Pract. 2008 Jun-Jul;23(3):325-8. doi: 10.1177/0884533608318676

• PMID: 18595867

Copper

- Copper sulfate, 0.4 mg/mL
- Copper chloride, 0.4 mg/mL

- Dosage and administration
  - IV: 1-2 mL as part of a drip infusion
- Caution: cholestasis, cirrhosis, Wilson's disease (copper storage disease)
- Indicated for depigmentation of hair, microcytic hypochromic anemia, neutropenia, skin pallor, skeletal demineralization

Manganese

- Manganese chloride 2 mg/ml
- Dose and Administration
  - IM: Contraindicated
  - IV: Sulfate form is preferred
  - Adults 0.15-0.8 mg (NOTE THIS DOSAGE!!!!)
  - Children 2-10 mcg/kg

- Adverse reactions: manganese excretion is primarily though bile, toxicity may result in patient experiencing cholestasis

Manganese

- Manganese can cause neuropsychiatric symptoms; irritability, excitement, compulsive behavior, Parkinson Disease like symptoms (Google Groote Syndrome)
- Caution in Fe anemia
- Essential nutrient, serves as enzyme activator as in H202 ; Mn-SOD, pyruvate carboxylase, cholinesterase
  - H_20_2 + Mn ⟶ H_20 + Mn0

Molybdenum

- Ammonium molybdate, 25 mcg/mL
- Dose and administration
  - IV: 5 mL as part of mineral replacement protocols
  - 5-10 mL for patients deficient in liver phase II sulfation detoxification pathway

Molybdenum

Beneficial in copper toxicity

- more than 0.5 mcg/mL blood levels leads copper excretion to

Cautions:

- aggravates copper deficiency
- avoid in pregnancy
  - fetus can't excrete trace mineral sufficiently

Molybdenum

Observational and experimental studies have shown an association between low molybdenum and bipolar disorder (1).

There is also strong evidence for the neuroprotective role of molybdenum (2,3,4).

- 1. Naylor GJ, Smith AH, Bryce-Smith D, Ward NI. Trace elements in manic depressive psychosis. J Affect Disord. 1985 Mar-Apr; 8(2): 131-6.
- 2. Woo WH, Yang H, Wong KP, Halliwell B. Sulphite oxidase gene expression in human brain and in other human and rat tissues. Biochem Biophys Res Commun. 2003 Jun 6; 305(3): 619-23.
- 3. Johnson JL, Rajagopalan KV. The oxidation of sulphite in animals systems. Ciba Found Symp. 1979; (72): 119-33.
- 4. Yamamoto T, Moriwaki Y, Takahashi S, Tsutsumi Z, Tuneyoshi K, Matsui K, Cheng J, Hada T. Identification of a new point mutation in the human molybdenum cofactor sulfurase gene that is responsible for xanthinuria type II. Metabolism. 2003 Nov; 52(11): 1501-4.

ROLE OF MOLYBDENUM HYDROXYLASES IN DISEASES

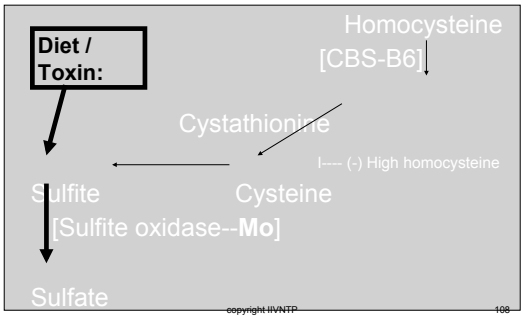
Mohamed A. Al-Omar*, Hussein I. El-Subbagh, Christine Beedhamand John Smith

Saudi Pharmaceutical Journal, Vol. 13, No. 1 January 2005

- The role of molybdenum-containing enzymes, aldehyde oxidase and xanthine oxidase in the production of reactive oxygen species has been discussed in term of mechanism of action. Unlike cytochrome P450 and other monooxygenase systems, **the molybdenum hydroxylases carry out their reactions using water** rather than molecular oxygen as the source of the oxygen atom incorporated into the product, and **generated rather than consumed electrons**. Aldehyde oxidase and xanthine oxidase differ in their substrates and inhibitor specificity. While aldehyde oxidase is a predominant oxidase, xanthine oxidase can undergo inter-conversion between oxidase/ dehydrogenase forms under pathological conditions such as ischaemia. Nevertheless, the wide range of drugs, xenobiotics and endogenous chemicals that interact with these enzymes, particularly aldehyde oxidase, highlight the importance of these enzymes in drug oxidation, detoxification and activation. Aldehyde oxidase and xanthine oxidase have been linked to some diseases such as neurodegenerative and ischaemiadisorders, respectively. In vivo, oxidation of aldehyde oxidase-substrates such as ethanol-derived acetaldehyde, retinal and NADH may alter the balance of ROS production by this enzyme leading to neurological disorders, such as amyotrophic lateral sclerosis, Parkinson's disease and schizophrenia. In addition, aldehyde oxidase has been implicated in pathophysiology of alcohol liver injury, visual processes, synthesis of retinoic acid and reperfusion tissue injury. Under pathological conditions, such as ischaemia-reperfusion injury, both enzymes may participate.

- 1 Department of Pharmaceutical Chemistry, College of Pharmacy, King Saud University, P.O. Box 2457, Riyadh 11451, Saudi Arabia. .
- 2 Clinical Sciences,School of Life Sciences, University of Bradford, Bradford, BD7 1DP, West Yorkshire, UK.
- 3Department of Pharmaceutical Chemistry, University of Bradford, Bradford, BD7 1DP, West Yorkshire, UK

Catalytic role of Molybdenum in Sulfite clearance



Selenium

- Selenium trace element, 40 mcg/mL
- Selenium trace element (compounded), most commonly 100 and 200 mcg/mL
- Dose and administration
  - IV: 200-800 mcg in drip protocol
- Contraindications/cautions: pregnancy, infants
- Caution renal disease, decreased excretion
- Avoid exposing solution to sun, degradation

Selenium - Se

- Selenium is incorporated into proteins to make selenoproteins, which are important antioxidant enzymes
  - Other selenoproteins help regulate thyroid function and play a role in the immune system
- Selenium is often depleted in mercury toxic patients

Zinc

- Zinc chloride, 5-10 mg/mL mEq: .08
- Zinc sulfate, 5-10 mg/mL mEq: .15
- 5 mg/mL (concentrate)
  - Can be compounded in higher concentrations
- Dose and administration
  - IV: sulfate is best due to better solubility and stability characteristics
  - Concentration of zinc in infusates should not be greater than 10 mg/mL
    - If the patient's parenteral requirement is greater than 30 mg, this 10 mg/L limit may be increased
  - Doses of 50-100 mg/day can be tolerated if infused steadily over 24 hours in zinc deficiency

Zinc

- Adverse and allergic reactions do not occur
- Toxic reactions to parenteral overdose range from mild to lethal
  - An error resulting in 23 mg in infusate lead to asymptomatic hyperamylasemia
  - 9.8 mg over one hour caused flushing, blurred vision, sweating
  - 1.6 gram error lead to death
- Clinical: lowered immunity, impaired wound healing, impaired smell/taste, depression, infertility

Does zinc supplementation enhance the clinical efficacy of chloroquine/hydroxychloroquine to win today's battle against COVID-19?

Abstract

•Currently, drug repurposing is an alternative to novel drug development for the treatment of COVID-19 patients. The antimalarial drug chloroquine (CQ) and its metabolite hydroxychloroquine (HCQ) are currently being tested in several clinical studies as potential candidates to limit SARS-CoV-2-mediated morbidity and mortality. CQ and HCQ (CQ/HCQ) inhibit pH-dependent steps of SARS-CoV-2 replication by increasing pH in intracellular vesicles and interfere with virus particle delivery into host cells. Besides direct antiviral effects, CQ/HCQ specifically target extracellular zinc to intracellular lysosomes where it interferes with RNA-dependent RNA polymerase activity and coronavirus replication

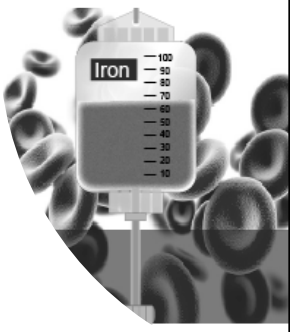
•As zinc deficiency frequently occurs in elderly patients and in those with cardiovascular disease, chronic pulmonary disease, or diabetes, we hypothesize that CQ/HCQ plus zinc supplementation may be more effective in reducing COVID-19 morbidity and mortality than CQ or HCQ in monotherapy. Therefore, CQ/HCQ in combination with zinc should be considered as additional study arm for COVID-19 clinical trials.

R. Derwanda,1, M. Scholzb,1,⁎aAlexion Pharma Ge. mbH, Landsberger Str. 300, 80687 Munich, GermanybLEUKOCARE AG, Am Klopferspitz 19, Martinsried, Munich, Germany. ScienceDirect Medical Hypotheses journal homepage:www.elsevier.com/locate/mehy 9.2020

Stock Element Formulas:

Additive:	MTE-4	MTE-4 Conc.	MTE-5	MTE-5 Conc.
Zinc	1 mg	5 mg	1 mg	5 mg
Copper	0.4 mg	1 mg	0.4 mg	1 mg
Manganese	0.1 mg	0.5 mg	0.1 mg	0.5 mg
Chromium	4 mcg	10 mcg	4 mcg	10 mcg
Selenium	None	None	20 mcg	60 mcg

Parenteral Iron



115

Iron Indications

- Iron deficiency in patients where oral iron supplementation is ineffective or not tolerated.
- Severely impaired oral absorption of iron such as gastric surgery.
- Other malabsorption syndromes
- Very low ferritin and iron markers. <15 ferritin
- Iron replacement following significant blood loss.
- Iron deficiency anemia in patients with end-stage renal disease undergoing hemodialysis or receiving epoetin therapy.

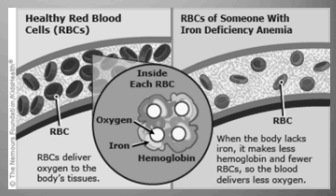
116

Clinically

- Used Most often in:
  - Malabsorption conditions
  - Chronically ill and / or heavy menses
  - Rare but after treatment for low iron:
  - Differential diagnosis Chronic Virus "stealing".
- Must TREAT CAUSE of Low IRON/Ferritin NOT just replete!

117

Clinically



- Providing a lot of iron to patients with oxygen and nutrient depleted tissues puts a lot of oxidative stress on their body. It is common to have severe side effects of oxidative stress for up to 72 hours, such a severe fatigue, brain fog and headaches.
- Giving a nutrient infusion and/or a strong anti-oxidant such as **1g Glutathione** prior to infusing Iron will avoid much of the oxidative load and stress to the patient.

117

Calculation of Total Dose

Calculate total dose using equations based on LBW then give 2ml i.m. (100mg) daily until calculated dose is given – OR, give IV infusion of total dose at once

Dose(ml) = 0.0442(desired Hgb – observed x LBW + (0.26 x LBW)

119

Forms of Injectable Iron

Dexferrum, InFeD -- Iron Dextran
Feraheme – Ferumoxytol
Ferrlecit – Sodium Ferric Gluconate
Venofer – Iron Sucrose
Injectafer – Ferric carboxymaltose

120

Dexferrum, InFeD – Iron Dextran
- Supplied as 100 mg/2 ml SDV
- 100 mg or less given on daily basis
- Delivered over 1 hour, even longer
- Don't advise PUSH

***Ferrlecit – Sodium Ferric Gluconate**
- Supplied as 62.5 mg/5 ml SDV
- Max dose not to exceed 125 mg per dose, 1000 mg total cumulative
- Delivered over at least 1 hour

***Venofer – Iron Sucrose**
- Supplied as 50 mg/2.5 ml SDV, 100 mg/5 ml SDV, 200 mg/10 ml, 400 mg/ml SDV
- 100 – 400 mg can be given in single delivery, 1000 mg total cumulative
- Deliver in 15 minutes to 2.5 hours depending on dose

***Injectafer – Ferric carboxymaltose**
- Supplied as 750 mg/15 ml SDV
- Not to exceed 750 mg per dose, 1500 mg total cumulative
- Delivered in at least 15 minutes

Feraheme – Ferumoxytol
- Supplied as 510 mg/17 ml SDV
- Not to exceed 510 mg per dose, 1020 mg total cumulative
- Delivered in at least 15 minutes
- NEVER PUSH

*Preferred infusion forms due to safety and less reactivity

Ferrous Gluconate Dosing

- 62.5 mg in 100cc NS or D5W
- 125 mg in 100cc NS or D5W
- Initial infusion start with lower amount
- Minimum infusion time for both = **1-1 ½ hour**, longer often required due to better tolerance.

Ferrous Sucrose Dosing

- 100 mg in 100cc NS or D5W
- 200 mg in 250cc NS or D5W
- 400 mg is max (advise 500cc NS or D5W)
- Initial infusion start with lower amount
- Minimum infusion time for both = 15 min, we highly advise 1 hour or more.

Ferric carboxymaltose Dosing

- 1st infusion 750 mg in 100cc -250 NS or D5W
- 2nd infusion 750 mg in 100cc – 250 NS or D5W
- Done with 2 infusions to reach max 1500 mg.
- Minimum infusion time= 15 min, we highly advise 1 hour or more.
- SPENDY!! Around $1200+ per vial wholesale cost

NEVER MIX ANYTHING IN THE SAME BAG WITH IRON!!

You may run other nutrients in the same day or a series of infusions.

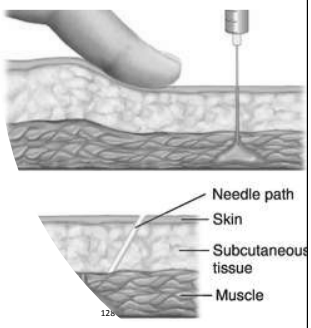
Make sure to change tubing or flush the line between iron and the nutrients.

Iron Intramuscular Delivery

- Iron Administration for IM
  - Lay patient prone for iron administration i.m.
  - If using Dextran always give test dose of 0.5ml must be given over 30 seconds, wait 1 hour, then give remainder at 1ml (50mg) per minute
  - IM administration MUST be give deep i.m. using Z-track technique. Aspirate with syringe prior to injection

Z-Track

•Source: http://medical-dictionary.thefreedictionary.com/Z-track+injection

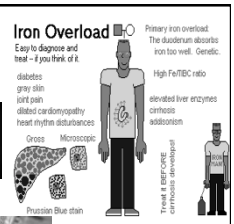


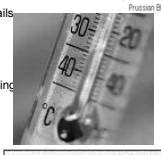
Monitoring Iron Levels

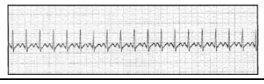
1. Serum iron may not be meaningful for 3 weeks
2. Serum ferritin peaks after about 7 to 9 days and slowly returns to baseline after 3 weeks
   - Labs of iron status
   - ferritin, TIBC:total iron binding capacity, & transferrin saturation and red blood cell
3. checked every 3 weeks to 3 months to reevaluate the patient's need for additional iron supplementation

Iron overdose

Early symptoms of iron overdose
-Diarrhea (may contain blood)
-Fever; nausea
-Stomach pain or cramping (sharp);
-Vomiting, severe (may contain blood)
Late symptoms of iron overdose
Cyanosis: Bluish-colored lips, fingernails, and palms of hands
-Convulsions (seizures)
-Drowsiness
- Pale, clammy skin
-Tachypnea: shallow and rapid breathing
-Unusual tiredness or weakness
-Tachycardia:weak and fast heartbeat







Treatment for Iron Overdose

- **Desferrioxamine** is a chelating agent which forms with iron
  - Oral to bind oral overdoses
  - Injectable and IV delivery for iron overdoses

  Consider if:
  - Serum iron > 90 mmol/l or >500 mcg/dL
  - Symptomatic patient with worsening symptoms.
- **Deferiprone**
  - Absorbed and approved for transfusion iron overload with thalassemia

Iron Safety (MUST HAVE)

Some choose to pretreat with Diphenhydramine and/or steroids.

If doing Iron IV or IM you MUST HAVE resuscitation drugs on hand

Iron Contraindications

- Hypersensitivity or allergy to iron or sugars bound
- Early pregnancy (first trimester)
- liver disease
- acute renal failure
- Parenteral iron should not be administered to patients with ferritin > 800 ng/mL or transferrin saturation > 50%.
- IV iron therapy becomes progressively less successful in patients with higher pretreatment ferritins and is predictably unsuccessful when the pretreatment ferritin exceeds 500 ng/m
- Manganese inhibits Iron absorption
- Large doses Vit C can lead to iron overload

Iron Adverse Side Effects

YOU MUST WARN PATIENTS BEFORE TREATMENT

–Dose related: arthralgia, backache, chills, dizziness, moderate to high fever, headache, malaise, myalgia, nausea and vomiting

–Increased incidence of these effects with total dose infusions

–Onset is 24-48 hours after administration

–Effects subside within 3-7 days

Conclusion For IV/IM Iron

Use either iron gluconate or iron sucrose or ferric carboxymaltose (AVOID iron dextran)

Plan on a series of 8-10 IV's at 1X a week (1 Amp of Fe in 150-250 mL NS or D5W) OR 200 mg in 4-5 weeks

After the 8-10 IV Fe visit 3-4 weeks and re-run the CBC, Ferritin, TIBC

You need to be ready for allergic reactions with IV or IM Iron

35 year old female (Fatigue/Depression)

- 1 year after giving birth to her first child comes to see me
- Has been dealing with 1 year of fatigue and postpartum depression
- Has been put on antidepressants which didn't change anything
- Next move by her other physician was to add Levothyroxine and double antidepressant.
- Her TSH was around 7 and her other physicians wanted to put her on thyroid.
- 12/2016----Presented to me with TSH 7, Free T4 0.8, Free T3 3.4, Reverse T3 16,
- AM Cortisol 7.
- Vitamin D 35.0, Iron 58, Ferritin 8, reactivated EBV, digestion overall no complaints.
- Did 3 IV iron sucrose infusions, then went to oral iron.
- 2/2017 ----TSH 3.63, Free T3 3.5, Free T4 0.6, Reverse T3 10, Vitamin D 51.8, Cortisol 5.5,
- Iron 85, Ferritin 36.5
- Put on oral iron, started addressing HPA axis disorder and EBV reactivation (continuing to address this) Then got busy with life didn't see her until 12/2017.
- Have continued to address EBV and HPA axis.
- Nov 2018: Ferritin 44, Iron 90 (Uses oral iron around menses only)

45 year old female (Fatigue/Abdominal pain)

- Hx of generalized pain in the RUQ region post cholecystectomy.
- The fatigue and abdominal pain different. Exhaustion easily and generalized abdominal pain.
- Anti-Gliadin marker high on stool profile. Eliminated gluten.
- Some improvement in abdominal pain
- Initial labs: Sept. 2018. Vitamin D: 25.6, Iron 41, Ferritin 12.
  - Denies any bleeds or heavy menstrual issues.
- Started with 100 mg Iron Sucrose x 8 (1 of them we tried 200 mg and she reported too much adverse side effects).
- Repeat labs: Dec 31, 2018. Vitamin D: 22.7 (decided not to take supplement). Iron: 82, Ferritin 78.5
- Abdominal pain resolved. Fatigue improved by 60%

References

- *Van Wyck DB, Cavallo G, Spinowitz BS et al. Safety and efficacy of iron sucrose in patients sensitive to iron dextran: North American Clinical Trial. Am J Kidney Dis2000; 36: 88–97*
  - Iron sucrose at a dose of 100 mg can be administered safely and effectively by i.v. push (5 min) or infusion (15–30 min) without a test dose [].
- *Hoigne R, Breymann C, Kunzi UP, Brunner F. Parenteral iron therapy: problems and possible solutions. Schweiz Med Wochenschr1998; 128: 528–535*
- Auerbach, M and Macdougall, I. Safety of intravenous iron formulations: facts and folklore. Blood Transfus. 2014 Jul. 12(3): 296-300.

Websites:

- https://www.medscape.com/viewarticle/807081 http://www.rxlist.com/ferrlecit-d_drug.htm
- http://www.drugs.com/cdi/sodium-ferric-gluconate.html
- http://www.medscape.com/viewarticle/478589
- http://products.sanofi-aventis.us/ferrlecit/ferrlecit.html
- Uptodate: Treatment of Iron Deficiency anemia in adults