PRODUCT MONOGRAPH

MULTI-11
(Multiple Vitamins for Infusion)

Vitamin Supplement for Total Parenteral Nutrition

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PRODUCT MONOGRAPH

MULTI-11

(Multiple Vitamins for Infusion)

Vial 1

Ascorbic Acid	20 mg/mL
Vitamin A	660 I.U./mL
Thiamine (as hydrochloride)	0.6 mg/mL
Riboflavin (as phosphate)	0.72 mg/mL
Pyridoxine hydrochloride	0.8 mg/mL
Niacinamide	8.0 mg/mL
Pantothenyl alcohol (as D-Panthenol)	3.0 mg/mL
Vitamin E (as dl-alpha tocopheryl acetate)	2.0 I.U./mL

Vial 2

Biotin	12 µg/mL
Folic Acid	80 µg/mL
Vitamin B_{12} (cyanocobalamin)	1 µg/mL

Therapeutic Classification

Vitamin Supplement for Total Parenteral Nutrition

ACTION AND CLINICAL PHARMACOLOGY

Multi-11 is a multiple vitamin supplement for infusion containing the following vitamins:

Ascorbic acid is important in the synthesis of collagen, the matrix of tooth and bone, and the intercellular cement of the capillary endothelium. Its deficiency disease is scurvy.

Vitamin A is essential in the function of the retina, for growth and differentiation of epithelial tissue, for growth of bone, for reproduction and embryonic development, and in regulating membrane permeability. A deficiency leads to follicular hyperkeratosis, infections, night blindness, lack of bone growth, and CNS damage.

Thiamine is important in the metabolism of carbohydrates, and requirements increase with high carbohydrate diets such as occurs with total parenteral solutions. The deficiency disease is beriberi.

Riboflavin is important for maintenance of mucosal, epithelial and eye tissue.

Niacinamide is essential for tissue respiration. The deficiency disease is pellagra.

Pyridoxine acts as a coenzyme for a wide variety of metabolic transformations of amino acids. Deficiency affects the skin, nervous system, and erythropoiesis.

D-Panthenol is incorporated into coenzyme A, which serves as a cofactor in the metabolism of carbohydrates and fatty acids and the synthesis of sterols.

Vitamin E is an antioxidant that may play a role in the protection of erythrocyte membranes. A deficiency may lead to anemia due to hemolysis.

Biotin is a coenzyme for several carboxylation reactions. It is important in carbohydrate and fat metabolism, and in CO_2 fixation.

Folic acid is important for the synthesis of DNA in chromosomal replication. A deficiency results in megaloblastic anemia.

Cyanocobalamin is important in the conversion of folate derivatives. A deficiency of cyanocobalamin then leads to "trapping" of folate, and subsequent development of the folate deficiency symptom, megaloblastic anemia. Cyanocobalamin is also important in the metabolism of carbohydrates and lipids. Deficiency leads to neurological damage from demyelination and cell death.

INDICATIONS

Multi-11 is indicated for use as a supplement to parenteral nutrition for adults and children aged 11 and older. **Multi-11**, unlike Multi-12, does not contain Vitamin D. **Multi-11** is indicated specifically for patients requiring long-term multiple vitamin supplementation by the intravenous route in whom it has become necessary to limit or eliminate Vitamin D administration (for example, those exhibiting or at risk for hypercalcemia, metabolic bone disease, etc.). Administration of **Multi-11** helps to maintain plasma vitamin levels and helps to prevent depletion of endogenous stores of the vitamins and development of subsequent deficiency symptoms.

It is also indicated where there are increased requirements for vitamins due to stress situations such as surgery, extensive burns, fractures and other trauma, severe infectious diseases, and comatose states.

Vitamin therapy should be initiated before development of clinical signs of vitamin deficiency. Patients with multiple vitamin deficiencies or with markedly increased requirements may be given multiples of the daily dosage for two or more days as indicated by the clinical status.

CONTRAINDICATIONS

Multi-11 is contraindicated where there is a pre-existing hypervitaminosis, or a known sensitivity to any of the vitamins in this product.

Blood sampling for megaloblastic anemia should be done before administration of **Multi-11**, as folic acid and cyanocobalamin in the formula can mask serum deficits.

PRECAUTIONS

Some of the vitamins in **Multi-11** are incompatible with parenteral additives. The formulation is incompatible with alkaline solutions. Calcium ions are reported to reduce the availability of folic acid.

Multi-11 may not be compatible with other drugs. Pyridoxine enhances the peripheral metabolism of levodopa, thus decreasing its efficacy in treatment of parkinsonism.

Some of the vitamins are unstable in the presence of vitamin K bisulfite or sodium bisulfite; if bisulfite solutions are necessary, patients should be monitored for thiamine deficiency.

Concomitant use of a retinoid can lead to additive adverse effects of vitamin A.

ADVERSE REACTIONS

Prolonged IV administration of low doses of vitamin A has been reported to result in hypervitaminosis A.

Severe allergic reactions have been reported for thiamine or other vitamins in the formulation.

SYMPTOMS AND TREATMENT OF OVERDOSAGE

The fat-soluble vitamins A and E can accumulate to harmful levels. Water-soluble vitamins, however, are readily excreted in the urine. Treatment of vitamin overdosage usually consists of withdrawal of the vitamin.

DOSAGE AND ADMINISTRATION

For administration to adults and children aged 11 and older, for intravenous feeding, add one daily dose (5 ml of Vial 1 and 5 ml of Vial 2) directly to not less than 500 mL, preferably 1,000 mL of dextrose 5% or NaCl 0.9% solution. The mixed solution should be stored in a refrigerator (4°C) and used within 24 hours. The solution should be protected from light as some of the vitamins are light-sensitive.

Multi-11 should not be injected without dilution, as dizziness, faintness, and possible tissue irritation may develop.

PHARMACEUTICAL INFORMATION

DRUG SUBSTANCE

Ascorbic Acid

Proper Name:	Ascorbic acid or vitamin C
Chemical Name:	l-ascorbic acid
Molecular Formula:	$C_6 H_8 O_6$
Molecular Weight:	176.13
Description:	White or slightly yellow crystals or powder. On exposure to light it gradually darkens. In the dry state, is reasonably stable in air, but in solutions rapidly oxidizes. Melts at about 190°C-192°C with some decomposition.
Solubility:	Freely soluble in water, sparingly soluble in alcohol; insoluble in chloroform, and in ether.

Vitamin A

Proper Name:	Vitamin A
Chemical Name:	3,7-dimethyl-9-(2,6,6,-trimethyl-1-cyclohexen-1-yl)-2,4,6,8-nonate-tetraen-1-ol.
Molecular Formula:	$C_{20} H_{30} O$
Molecular Weight:	286.5
Description:	In liquid form, a light-yellow to red oil that may solidify upon refrigeration. In solid form, has the appearance of any diluent that has been added. May be practically odourless or may have a mild fishy odour, but has no rancid odour. Is unstable to air and light.

Solubility:	In liquid form, insoluble in water and in glycerin; very soluble in chloroform and in ether; soluble in absolute alcohol and vegetable oils. In solid form, may be dispersible in water.

Thiamine

Proper Name:	Thiamine, thiamine hydrochloride or vitamin B1
Chemical Name:	Thiazolium,3-[4-amino-2-methyl-5-pyrimidinyl)methyl]-5-(2-hydroxyethyl)-4-methyl-, chloride, monohydrochloride.
Molecular Formula:	$C_{12}\ H_{17}\ CIN_4\ OS.\ HCl$
Molecular Weight:	337.27
Description:	White crystals or crystalline powder, usually having a slight, characteristic odour. When exposed to air, the anhydrous product rapidly absorbs about 4% of water. Melts at about 248°C, with some decomposition.
Solubility:	Freely soluble in water; soluble in glycerine; slightly soluble in alcohol; insoluble in ether.

Riboflavin

Proper Name:	Riboflavine or vitamin B_2
Chemical Name:	7,8-dimethyl-10-(D-ribo-2,3,4,5-tetrahydroxypentyl) isoalloxazine
Molecular Formula:	$C_{17}\ H_{20}\ N_4\ O_6$
Molecular Weight:	376.37
Description:	Fine, orange-yellow, crystalline powder having a slight odour. Melts at about 278°C-282°C. Its saturated solution is neutral to litmus.

When dry, is not appreciably affected by diffused light, but when in solution, light induced quite rapid deterioration, especially in the presence of alkalies.

Solubility: Very slightly soluble in water, in alcohol, and in isotonic sodium chloride solution; very soluble in dilute solutions of alkalies; insoluble in ether and in chloroform.

Niacinamide

Proper Name: Niacinamide or nicotinamide

Chemical Name: 3-pyridinecarboxamide

Molecular Formula: $C_6 H_6 N_2 O$

Molecular Weight: 122.13

Description: White, crystalline powder. Is odourless or practically so. Its solutions are neutral to litmus. Melts at about 128°C-131°C.

Solubility: Freely soluble in water and in alcohol; soluble in glycerine.

Pyridoxine

Proper Name: Pyridoxine, pyridoxine hydrochloride, or vitamin B_6

Chemical Name: 3,4-pyridinedimethanol,5-hydroxy-6-methyl-, hydrochloride.

Molecular Formula: $C_8 H_{11} NO_3 . HCl$

Molecular Weight: 205.64

Description: White to practically white crystals or crystalline powder. Is stable in air, and is slowly affected by sunlight. Its solutions have a pH of about 3. Melts at about 202°C-206°C with some decomposition.

Solubility:	Freely soluble in water; slightly soluble in alcohol; insoluble in ether.

D-Panthenol

Proper Name:	Pantothenyl alcohol
Chemical Name:	Butanamide, 2,4-dihydroxy-*N*-(3-hydroxypropyl)-3,3-dimethyl-, (R)-
Molecular Formula:	$C_9 H_{19} NO_4$
Molecular Weight:	205.25
Description:	Clear, viscous liquid with a slight characteristic odour. Slightly hygroscopic.
Solubility:	Freely soluble in water and alcohol.

Vitamin E

Proper Name:	Vitamin E
Chemical Name:	d or dl-alpha tocopheryl acetate
Molecular Formula:	$C_{31} H_{52} O_3$
Molecular Weight:	472.8
Description:	Clear, yellow to greenish yellow viscous oils. Pratically odourless. The solid forms are white to tan-white granular powders.
Solubility:	Vitamin E preparations- The liquid forms are insoluble in water; soluble in alcohol; and miscible with ether, with acetone, with vegetable oils, and with chloroform. The solid forms disperse in water to give cloudy suspensions.

Biotin

Proper Name:	Biotin

Chemical Name:	1H-thieno[3,4-d]imidazole-4-pentanoic acid,hexahydro-2-oxo-, [3aS-(3aα,4β,6aα)]-
Molecular Formula:	$C_{10}\ H_{16}\ N_2O_3\ S$
Molecular Weight:	244.31
Description:	A practically white, crystalline powder. Melts at about 232°C-233°C
Solubility:	Very slightly soluble in water and in alcohol; insoluble in other common organic solvents.

Folic Acid

Proper Name:	Folic acid
Chemical Name:	L-glutamic acid, N-[4-[[(2-amino-1,4-dihydro-4-oxo-6-pteridiniyl)methyl]amino] benzoyl]
Molecular Formula:	$C_{19}\ H_{19}\ N_7O_6$
Molecular Weight:	441.40
Description:	Yellow, yellow-brownish, or yellowish orange, odourless, crystalline powder. No melting point, darkens and chars at about 250°C.
Solubility:	Very slightly soluble in water; insoluble in alcohol, in acetone, in chloroform, and in ether; readily dissolves in dilute solutions of alkali hydroxides and carbonates, and is soluble in hot, 3N hydrochloric acid and in hot, 2N sulfuric acid. Soluble in hydrochloric acid and in sulfuric acid, yielding very pale yellow solutions.

Cyanocobalamin

Proper Name:	cyanocobalamin or vitamin B_{12}
Chemical Name:	cyanocobalamin
Molecular Formula:	$C_{63}\ H_{88}\ Co\ N_{14}\ O_{14}\ P$
Molecular Weight:	1355.38
Description:	Dark red crystals or amorphous or crystalline red powder. In the anhydrous form, it is very hygroscopic and when exposed to air it may absorb about 12% of water. Not melted at 300°C.
Solubility:	Sparingly soluble in water; soluble in alcohol; insoluble in acetone, in chloroform, and in ether.

Composition:

Vial 1

Concentration per mL:	Ascorbic Acid	20 mg
	Vitamin A	660 I.U.
	Thiamine (as hydrochloride)	0.6 mg
	Riboflavin (as phosphate)	0.72 mg
	Pyridoxine hydrochloride	0.8 mg
	Niacinamide	8.0 mg
	Pantothenyl alcohol (as d-Panthenol)	3.0 mg
	Vitamin E (as dl-alpha tocopheryl acetate)	2.0 I.U.

Each mL of vial 1 also contains polysorbate 80 1.4%, sodium hydroxide to adjust pH and water for injection.

Vial 2

Concentration per mL:	Biotin	12 µg
	Folic Acid	80 µg
	Vitamin B_{12} (cyanocobalamin)	1 µg

Each mL of vial 2 also contains propylene glycol 30%, citric acid and/or sodium citrate to adjust pH with and water for injection.

Stability and Storage Recommendations:

Store the vials in the refrigerator between 2° and 8°C. Single use vial. Discard unused portion. Protect from light. Do not freeze.

Dilution For Intravenous Use:

Aseptic addition of **Multi-11** to Dextrose Injection 5% or Sodium Chloride Injection 0.9% solution is recommended. Dilution may be made in glass containers or PVC plastic. Diluted solutions should be stored for no more than 24 hours under refrigeration.

As with all parenteral drug products, intravenous admixtures should be inspected visually for clarity, particulate matter, precipitate, discolouration and leakage prior to administration whenever solution and container permit. Solutions showing haziness, particulate matter, precipitate, discolouration or leakage should not be used. Discard unused portion.

AVAILABILITY OF DOSAGE FORMS

Multi-11, 5 mL single dose vial is available in boxes of 2, containing 1 x Vial 1 and 1 x Vial 2. The use of 5 mL of Vial 1 and 5 mL of Vial 2 constitutes a 10 mL single dose of **Multi-11**.

PHARMACOLOGY

Ascorbic Acid:

Ascorbic acid is a six-carbon compound structurally related to glucose. It is reversibly oxidized in the body to dehydroascorbic acid, which possesses full vitamin C activity. Only the L isomer has antiscorbutic activity. Ascorbic acid functions in a number of oxidation reactions. It plays an important role in the synthesis of collagen, the matrix of tooth and bone, and the intercellular cement of the capillary endothelium. Thus, its deficiency disease, scurvy, is associated with failure of wounds to heal, defects in tooth formation, and in the rupture of capillaries. Psycholocical disturbances have also been noted. Secondary symptoms may include anemia, infections, and metabolic disturbances. Symptoms of deficiency appear 60 to 90 days after cessation of intake.

Ascorbic acid is also required for the transport of iron from blood plasma to its storage form in the liver.

Ascorbic acid is readily absorbed into the circulation from the intestine. It is present in the plasma and is ubiquitously distributed in the cells of the body. Concentrations of the vitamin in leukocytes are taken to represent those in the tissues, and is normally 27 μg of ascorbic acid per 10^8 cells. The concentration in plasma varies with intake, and is normally 0.5 mg/dL; concentrations of 0.15 mg/dL are seen in cases of frank scurvy. The renal threshold is 1.5 mg/dL of plasma, and increasing amounts are excreted when the daily intake exceeds 100 mg.

The half-life of ascorbate is 16 days. Metabolites and unchanged ascorbic acid are excreted in the urine.

Vitamin A:

In the average diet, about half the vitamin A is available as the preformed vitamin and the rest as the plant pigment carotene. Interconversion between isomers readily takes place in the body, with *trans*-retinol and its aldehyde, retinal, exhibiting the greatest biological potency.

Vitamin A plays an essential role in the function of the retina. With deficiency, there is a gradual diminishing of ability for dark adaptation in the rods. When the supply of retinal is depleted, opsin decays and there is irreversible damage to the rods.

It is apparently essential for growth and differentiation of epithelial tissue. Deficiency leads to keratinization of the alimentary canal, glandular ducts, conjunctiva, cornea, and kidney medulla.

The vitamin is required for growth of bone, reproduction, and embryonic development. It also has a stabilizing effect on various membranes and acts to regulate membrane permeability. Respiratory tract infections, lack of bone growth, and CNS damage can result from a deficiency.

Signs of mild deficiency are skin lesions, such as follicular hyperkeratosis and infections, and night blindness.

Deficiency of vitamin A is thought to enhance susceptibility to carcinogenesis.

Lack of dietary lipid and malabsorption states such as steatorrhea may limit absorption of vitamin A in the diet. Carotenoids are converted to vitamin A in the intestinal tract. Vitamin A then passes through the intestinal wall into the lymph system and is transported to the liver dissolved in the blood lipids. From the liver it is transported to target tissues as needed.

The normal level of vitamin A in plasma is 30 to 70 μg/dL. Low plasma values indicate that hepatic storage may be exhausted. Symptoms of deficiency appear when the plasma concentration falls below 10 to 20 μg/dL.

The half-life of vitamin A is weeks or months. Retinol is oxidized in the liver to retinal, retinoic acids and other water-soluble metabolites, which are excreted in the urine and feces. Sixty percent or more of the metabolites appear in the bile.

Thiamine:

Thiamine pyrophosphate, the physiologically active form of thiamine, functions in carbohydrate metabolism as a coenzyme in the decarboxylation of a-keto acids such as

pyruvate and a-ketoglutarate. In thiamine deficiency, the oxidation of a-keto acids is impaired, and there is an increase in the concentration of pyruvate in the blood. Measurement of transketolase activity in erythrocytes is used as a diagnostic test of deficiency.

The requirement for thiamine is related to metabolic rate and is increased with high carbohydrate diets such as total parenteral solutions, where the calories are in the form of dextrose. Thiamine deficiency can occur during pregnancy, where the diet is poor or in patients with hyperemesis gravidarum. A deficiency can also develop from the consumption of large amounts of thiaminase in raw fish, or from consumption of thiamine antagonist in large quantities of tea.

Symptoms of mild thiamine deficiency include loss of appetite, muscular weakness, pain and parethesias in the extremities, edema, decreased blood pressure, and low body temperature.

Severe thiamine deficiency leads to beriberi. Neurological signs and symptoms of dry beriberi include sensory disturbances in the extremities with local hyperesthesia or anesthesis, loss of muscle strength or paralysis, personality disturbances, depression, lack of initiative and poor memory.

Cardiovascular symptoms of wet beriberi include dyspnea on exertion, palpitation, tachycardia, abnormal ECG, extensive edema, and cardiac failure of the high-output type.

Gastrointestinal symptoms include loss of appetite and subsequent constipation, ulcerative colitis, gastrointestinal hypotonia, and chronic diarrhea.

Absorption from the intestine occurs by sodium-dependent active transport.

Normal blood levels are 1.3 μg/100 mL free base in serum, and 3-11 μg/100 ml cocarboxylase in blood cells.

When intake exceeds the minimal daily requirement of 1 mg, tissue stores are first saturated, then excess appears quantitatively in the urine as intact thiamine or as pyrimidine.

Riboflavin:

Riboflavin is converted to flavin mononucleotide (FMN) and flavin adenine dinucleotide (FAD), which are coenzymes for a wide variety of respiratory flavoproteins. Riboflavin is important for growth and development in the fetus, and for maintenance of mucosal, epithelial and eye tissue.

Initial symptoms of riboflavin deficiency are sore throat and angular stomatitis. Later symptoms are glositis, chilosis, seborrheic dermatitis, anemia, neuropathy, corneal vascularization and cataract formation.

Riboflavin is readily absorbed from the intestine by a transport mechanism. Here, and in other tissues, it is phosphorylated to FMN by flavokinase. The vitamin is distributed to all tissues, but little is stored.

Blood levels are not of much diagnostic value. The normal blood level is 6.6 μg/100 mL, but decreases with age. Urinary excretion of less than 50 μg/day is indicative of riboflavin deficiency.

There is some secretion into the intestinal tract via the bile. Riboflavin is present in the feces from synthesis by intestinal flora; however, this is not absorbed.

Niacinamide:

Niacin, or nicotinic acid, is converted to two active forms, either nicotinamide adenine dinucleotide (NAD) or nicotinamide adenine dinucleotide phosphate (NADP). These serve a vital role as coenzymes for a wide variety of proteins that catalyze oxidation-reduction reactions essential for tissue respiration. Tryptophan in the diet is an important source of additional nicotinic acid and deficiencies have occurred when diets have been deficient in tryptophan while supplying otherwise adequate amounts of niacin. Deficiencies may occur in Hartnup's disease, in which there is a defect in the absorption of tryptophan, and in patients with carcinoid tumor, which may divert large amounts of tryptophan from nicotinic acid synthesis.

The deficiency disease, pellagra, is characterized by changes in the skin, gastrointestinal tract, and central nervous system. Erythematous eruptions, first resembling sunburn, appear on the back of the hands and other areas exposed to light. They are symmetrical and may darken, desquamate, and scar.

Gastrointestinal symptoms include stomatitis, enteritis, diarrhea, ulcerated tongue, excessive salivary secretion, salivary gland enlargement, nausea, vomiting, and gastric achylia.

Symptoms of the CNS are headache, dizziness, insomnia, depression, impairment of memory, delusions, hallucinations, dementia, and motor and sensory disturbances of the peripheral nerves.

In some cases, macrocytic anemia develops.

Both niacin and niacinamide are readily absorbed from all portions of the intestinal tract, into the circulation.

The vitamin is stored in the liver, heart, and muscle. Normal blood levels are 0.42 to 0.84 mg/100 mL. 33% of the intake is excreted in 24 hours.

When therapeutic doses of niacin or niacinamide are administered, only small amounts of unchanged vitamin appear in the urine; when high doses are given, the unchanged vitamin represents the major urinary component.

Pyridoxine:

Pyridoxine is converted to its active form, pyridoxal phosphate, which serves as a coenzyme for a wide variety of metabolic transformations of amino acids, including decarboxylation, transamination, and racemization, as well as for enzymatic steps in the metabolism of tryptophan, sulfur-containing amino acids, and hydroxy-amino acids. When there is a pyridoxine deficiency, large quantities of tryptophan metabolites are excreted in the urine, particularly xanthurenic acid; thus, tryptophan loading tests have been used to test for pyridoxine deficiency.

Deficiency of pyridoxine affects the skin, nervous system, and erythropoiesis. Sebborrhea-like skin lesions appear about the eyes, nose, and mouth, accompanied by glossitis and stomatitis. There may be peripheral neuritis associated with synovial swelling and tenderness, especially of the carpal synovia (carpal tunnel disease).

Fifteen to twenty per cent of women taking oral contraceptives containing estrogen may be pyridoxine deficient.

Genetically determined pyridoxine dependency results in pyridoxine-responsive anemia, pyridoxine-responsive seizure disorder in infants, and abnormalities characterized by xanthurenic aciduria, primary cystathioniuria, or homocystinuria. These symptoms respond to administration of large amounts of the vitamin.

Convulsions in the newborn may occur with mothers on a pyridoxine deficient diet.

Pyridoxine is absorbed from the lumen of the small intestine, by simple diffusion. The normal blood level is 11.2 μg/100 mL. The vitamin is stored in the liver, with small amounts stored in the skeletal muscle.

Fifty-seven per cent of the ingested dose is excreted per day. The principle excretory product is 4-pyridoxic acid, formed from free pyridoxal by hepatic aldehyde oxidase. 3-4 mg of 4-pyridoxic acid and 0.2-0.3 mg pyridoxal are excreted per day in the urine. The feces contain 0.5-0.8 mg per day.

D-Panthenol:

Only the *d* isomer of panthenol or pantothenyl alcohol is biologically active, and functions in the body following its incorporation into coenzyme A. Coenzyme A serves as a cofactor for a variety of enzyme-catalyzed reactions involving transfer of acetyl groups. Such reactions are important in the oxidative metabolism of carbohydrates, gluconeogenesis, synthesis and degradation of fatty acids, and the synthesis of sterols, steroid hormones, and porphyrins.

Symptoms of deficiency include fatigue, headache, sleep disturbances, nausea, abdominal cramps, occasional vomiting, flatulence, paresthesias in the extremities, muscle cramps, impaired coordination, loss of eosinopenic response to ACTH, and increased sensitivity to insulin. "Burning foot" syndrome responds favorably to administration of the vitamin.

It is readily absorbed from the intestine into the circulation, and is present in all tissues.

Normal blood levels are 19-32 μg/100 mL. It is stored in the liver, heart and kidney in small amounts.

It seems not to be metabolized in the body, as the intake equals that excreted. About 70% is excreted in the urine. This can be 1-7 mg/day. The amount excreted in the feces is variable.

Vitamin E:

Of the eight naturally occurring tocopherols with vitamin E activity, alpha-tocopherol comprises about 90 % of the tocopherols in animal tissues and displays the greatest biological activity. The *d* isomers are more active than the *l* forms. Alpha-tocopherol is structurally similar to coenzyme Q_4, with which it shares biological activity in several systems.

Tocopherols are antioxidants that form reversible oxidation-reduction systems.

Although there are many signs and symptoms of vitamin E deficiency in animals, there is little evidence that vitamin E is of nutritional significance in man or of any value in therapy.

On the basis of animal studies, vitamin E has been used to treat various reproductive disorders, muscular dystrophy, and cardiovascular disorders in man; however, there is no conclusive evidence that the vitamin is beneficial to man in these conditions.

In man and in animals, vitamin E deficiency does seem to produce alpha-tocopherol-responsive anemia. Presumably, tocopherol protects the lipids in the erythrocyte membrane from peroxidation, which results in membrane destruction and hemolysis.

Vitamin E is absorbed from the lumen of the gastrointestinal tract by passive diffusion. It enters the blood stream by way of the lymph, and is distributed to all tissues, where it is stored for a long time. Excessive adipose tissue may compete with target tissues that require vitamin E. Small amounts are also stored in muscle tissue.

Plasma concentrations vary among individuals and appear to be related to dietary intake and defects in intestinal absorption of fat. The normal blood level is 1.11 mg/100 mL serum.

Sixty to seventy per cent of the daily ingested dose is excreted by the liver in the feces. The balance appears as metabolites in the urine. The CO_2 produced by the metabolism of vitamin E is excreted through the lungs.

Biotin:

Biotin is an organic acid, the *d* isomer being biologically active. Biotin is a coenzyme for several enzyme-catalyzed carboxylation reactions, and is important in CO_2 fixation. Biotin is a cofactor for pyruvate carboxylase and acetyl-CoA carboxylase, and, thus, is important in carbohydrate and fat metabolism.

Biotin antagonists include biotin sulfone, desthiobiotin, and imicazolidone carboxylic acids. Avidin, present in raw egg white, binds with biotin, preventing its absorption.

Signs and symptoms of deficiency are dermatitis, atrophic glossitis, hyperesthesia, muscle pain, lassitude, anorexia, slight anemia, and changes in the ECG.

Much of the biotin is derived from bacterial synthesis in the intestine. Absorption occurs by passive diffusion from the upper intestine into the blood, where it circulates bound to plasma proteins.

Normal blood levels average 1.23 mg/100 mL. Biotin is stored in the liver, and 3 to 4 weeks are required to produce a deficiency with its antagonist, avidin.

Biotin appears in the urine predominantly as intact biotin, and in lesser amounts as metabolites *bis*-norbiotin and biotin sulfoxide. The urine contains 0.4 g/kg/day of biotin and metabolites, and the feces contain 2.5 times the dietary intake due to bacterial synthesis.

Folic Acid:

Folic acid is a family of pteroylglutamic acids which are reduced in the body to tetrahydrofolic acid, which, in turn, accepts a number of one-carbon units. The forms that are synthesized by these reactions play specific roles in intracellular metabolism, such as: conversion of homocystein to methionine utilizing vitamin B_{12} as a cofactor; conversion of serine to glycine utilizing pyridoxal phosphate as a cofactor; synthesis of thymidylate - a rate-limiting step in DNA synthesis; in histidine metabolism as an acceptor of a formimino group in the conversion of formiminoglutamic acid to glutamic acid; synthesis of purines; and utilization or generation of formate.

Folate deficiency is common where disease of the small intestine or toxic effects of alcohol on the hepatic parenchymal cells interferes with absorption from the diet and recirculation of the vitamin. Drugs that interfere with the absorption and storage of folate, such as methotrexate, trimethoprim, anticonvulsants and oral contraceptives, are capable of producing folate deficiency.

Since the hematopoietic system has the greatest rate of cell turnover, it is especially sensitive to a deficiency of folic acid, and megaloblastic anemia will develop. Maturation of red cells is highly abnormal, and a major ity die within the marrow. Many cell fragments, poikilocytes, and hyperchromic macrocytes appear in the peripheral blood.

Normal folate concentrations in plasma range from 4 to 20 ng/mL. A deficiency state may exist when the value is below 4 ng/mL. Since plasma concentration is sensitive to dietary

intake and presence of inhibitors, measurement of folate in red cells or lymphocytes will better reveal a long-standing deficiency of folic acid.

Folate is actively absorbed by the proximal portion of the small intestine, and folate deficiency can occur when there is pathology of the jejunum, such as nontropical and tropical sprue. Once absorbed, the folate is rapidly transported to tissues.

Supplies of folate are maintained both by food and by an enterohepatic cycle. Folate is reduced and methylated in the liver, transported in the bile, reabsorbed by the gut, and delivered to the tissues. This pathway may provide as much as 200 μg or more of folate each day for recirculation.

If there is a deficiency of vitamin B_{12}, folic acid will be "trapped" by the lack of sufficient B_{12} to continue its metabolism, and megaloblastic anemia will result even though adequate folates are present.

Cyanocobalamin:

Intracellular vitamin B_{12} is maintained as two active coenzymes: deoxyadenosylcobalamin is a coenzyme important in carbohydrate and lipid metabolism; methylcobalamin acts as a methyl-group donor for the conversion of homocysteine to methionine. Of greater importance is the interaction of vitamin B_{12} in the conversion of folate derivatives, and all subsequent steps that require folate are then deprived of substrate, even though folates are

present. This, then, leads to development of a folic acid deficiency state and subsequent development of megaloblastic anemia.

Vitamin B_{12} deficiency can also result in neurological damage, with progressive swelling of myelinated neurons, demyelination, and cell death in the spinal column and cerebral cortex. This causes symptoms such as paresthesias of the hands and feet, diminution of sensation of vibration and position, decreased deep-tendon reflexes, loss of memory, confusion, moodiness, loss of central vision, delusions, hallucinations, and overt psychosis. If only folic acid is administered to overcome being "trapped" by lack of B_{12}, then symptoms of anemia will disappear, but neurological damage will continue.

Dietary B_{12}, in the presence of gastric acid, is released from proteins to which it is bound and is then bound to gastric intrinsic factor. The vitamin-intrinsic factor complex is absorbed from the ileum, into the circulation. Classic Addisonian pernicious anemia is caused by a failure of gastric parietal cells to produce intrinsic factor. Gastric achlorhydria, antibodies to the intrinsic factor, bacterial overgrowth, intestinal parasites, and damage to the ileal mucosal cells by disease or surgery can interfere with this process.

Once absorbed, the vitamin is rapidly cleared from plasma and stored in the liver. Approximately 3 to 8 μg of the vitamin is secreted into bile each day, and is normally

reabsorbed. Previously mentioned interference with reabsorption can result in a continuous depletion of hepatic stores, and deficiency may develop within 3 to 4 years.

Normal plasma concentrations are 200 to 900 pg/mL, while values below 200 pg/mL indicate a deficiency state. The correlation is excellent except when the concentrations of transcobalamin I and III, forms of the vitamin relatively unavailable to the tissues, increase as a result of hepatic disease or myeloproliferative disorder, and result in normal or high concentration of vitamin in the plasma.

REFERENCES

1. Gilman AG, Goodman LS, Gilman A, ed. Goodman and Gilman's the pharmacological basis of therapeutics. 6th ed. New York, MacMillan, 1980: 1331-46, 1538-1601.

2. Kutsky RJ. Handbook of vitamins and hormones. New York, Van Norstrand Reinhold, 1973: 8-31, 38-111.

3. Ferrari RA. The vitamins. In: Verderame M, ed. CRC handbook of hormones, vitamins, and radiopaques. Boca Raton, Florida, CRC Press, Inc., 1986: 245-307.

4. Shils ME, Baker H, Frank O. Blood vitamin levels of long-term adult home total parenteral nutrition patients: the efficacy of the AMA-FDA parenteral multivitamin formulation. J Parenter Enteral Nutr, 1985: 9(2): 179-88.

5. Ladefoged K, Jarnum S. Metabolic complications to total parenteral nutrition. Acta Anaesthesiol Scand, 1985: 29: 89-94.

6. Ruberg RL. Role of nutrition in wound healing. Surg Clin North Am. 1984: 64(4): 705-14.

7. McEvoy G, ed. Vitamins. In AHFS Drug Information. Bethesda, MD. American Society of Hospital Pharmacists, Inc., 1989: 2036-58.

8. Trissel LA. Multivitamins. In: ASHP Handbook of Injectable Drugs. 4th ed. Bethesda, MD, American Society of Hospital Pharmacists, 1988: 388-93.

9. Trissel LA. Folic acid. In: ASHP Handbook of Injectable Drugs. 4th ed. Bethesda, MD, American Society of Hospital Pharmacists, 1988: 250-2.

10. Phillips GD, Odgers CL. Parenteral nutrition: current status and concepts. Drugs, 1982: 23:276-323.

11. Myhr K. Addition of drugs to infusion fluids: Pharmaceutical considerations on preparation and use. Acta Anaesthesiol Scand 1985: 29: 71-5.