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شبكة المعلومات الجامعية

التوثيق الالكتروني والميكروفيلم

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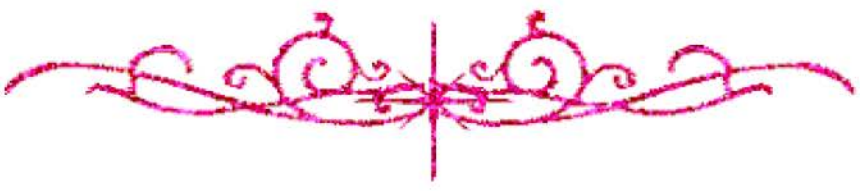

بالرسالة صفحات لم ترد بالأصل

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Protective Effect of Vitamin "E" Against Toxicity and Teratogenicity of Iron

Thesis

Submitted for partial fulfillment of
Master Degree in
Forensic Medicine and Clinical Toxicology

By

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To Whom I Love

To My Parents

To my brother

To my Lovely fiancé

Contents

Iron-dextran complex has been shown to be teratogenic in pregnant experimental animals. The most pronounced teratogenic effect after intraperitoneal administration of iron to experimental animals is exencephally **(Brigitte, 1982).**

Dietary alpha-tocopherol (vitamin E) supplementation has a protective and an antioxidant effect in vivo iron overload in experimental animals. Vitamin E has an important role in the prevention of nephrotoxicity and hepatotoxicity produced by iron **(Galleano and Puntarulo, 1997; Lawrence et al., 2002).**

Aim of the work:

The aim of the work is to study the effect of iron toxicity on different body organs (liver, kidney and heart) and its teratogenic effect. Also, to determine the protective effect of vitamin E in iron overload disorders.

Review of Literature

Although the incidence of iron exposures continued to increase in 1980, it became the leading cause of poisoning deaths in children younger than 6 years of age only in the last decade. This magic finding was publicized by a case series of fatalities involving 5 toddlers in Los Angeles in a 6-month period in 1992; all cases involved prenatal administration of vitamins with iron **(Weindlar et al., 1993).**

Iron has been used therapeutically for thousands of years, and continues to be available both with and without prescription for the prevention and treatment of iron-deficiency anemia in all ages. Despite this long history of use, the first reports of iron toxicity only occurred in the mid-20th century. Since then, numerous cases of iron poisoning and fatalities have been reported, many of them in children. In 1997, the Food and Drug Administration (FDA) mandated warning labels about the danger of pediatric iron poisoning on all iron-containing preparations **(Food and Drug Administration, 1997).**

Pharmacology of Iron

Iron Sources:

The best food sources of easily absorbed iron are animal products, which contain heme iron. Iron from vegetables, fruits...etc. is known non-heme iron, which is harder for the body to absorb. Although heme iron accounts for only 10-15 % of the iron in the diet, it may provide up to one third of total absorbed dietary iron. Absorption of heme iron is less influenced by other dietary factors than the non-heme iron (e.g. vitamin C, meat, etc) which enhance non-heme iron absorption **(Lynch, 1997; Steven, 2003).**

High iron foods are very important to enhance oxygen distribution throughout the body, keep the immune system of the body healthy and help the body to produce energy. There are many events that may indicate a need for more high-iron foods e.g. fatigue and weakness, decreased ability to concentrate, increased susceptibility to infections, hair loss, apathy, brittle nails and depression **(Lieu et al., 2001).**

It was found that chicken liver contains the highest concentration of heme iron (7.0 milligram) and the lowest concentration is present in shrimps (0.7 milligram). On the other hand, fortified cereals contain the highest concentration of non-heme iron (18 milligram) but raisins contain only 0.5 mg of non-heme iron. Other food sources of heme iron include red meat, poultry, tuna, salmon, turkey, eggs (especially egg yolk). While non-heme iron is also found in dried beans, soya beans, lentils, raisins and broccoli **(Steven, 2003)**

Physical Characters:

Iron is an essential element for life and, as a transition metal existing in both divalent (ferrous) and trivalent (ferric) forms. Most of the ferrous salts are freely soluble in water but the high reactivity of ferrous iron renders the solutions susceptible to oxidation at pH_7 **(Gabriela et al, 1999).**

Ferrous salts have many different types such as ferrous sulfate (20% of elemental iron), ferrous gluconate dihydrate (12% of elemental iron), ferrous fumarate (33% of elemental iron), ferrous lactate (19% of elemental iron), ferrous succinate tetrahydrate, ferrous carbonate, ferrous oxalate, ferrous chloride (28% of elemental iron) and ferrous aspartate **(James and Anne, 1982).**

Ferric iron salts are available in complexes such as iron sorbitol complex, iron phosphate complex and iron dextran complex which is a sterile, dark brown, slightly viscous and colloidal solution. It contains a complex of ferric hydroxide with low molecular weight dextran (5000-7500) in the presence of Nacl for intramuscular and intravenous administration. It may contain 0.5% of phenol as a preservative. PH is between 5.2 and 6.5. It is sterilized by autoclaving or filteration. Its molecular weight is 73000. Iron sorbitol complex is smaller in diameter than iron dextran complex & the difference in size might affect the distribution of the complexes in the body after injection. Compared with iron dextran, absorption from the site of injection is quicker, diffusion similar, and excretion is more rapid. The increased rate of absorption is due to its molecular weight **(Hershko et al., 1988).**

Pharmacokinetics:

Absorption:

Iron is an essential component of hemoglobin, myoglobin and many enzymes in the body and thus an important nutrient in a well-balanced diet. An adult can absorb approximately 1-2mg of dietary iron each day. Ferric iron is enzymetically reduced in the proximal small intestine to ferrous iron by ferrireductase enzyme. The divalent metal transporter 1(DMT-1) enables this iron to be transported into the enterocytes of the villus tips of duodenum, which is the major site of iron absorption **(Denise, 2002).**

Iron absorption is regulated by three mechanisms. The first one is dietary regulator, in which a short-term increase in dietary iron is not absorbed as the mucosal cells have accumulated iron and block additional uptake. The second mechanism is stores regulator in which if body iron stores fall, the mucosa is signalled to moderately increase absorption. The last one is erythropoietic regulator; in response to anemia, the erythroid cells will signal the mucosa to increase iron absorption more significantly **(Steinberg et al., 2001).**

Robert (2001) demonstrated that some dietary factors bind with non-heme iron enhances its absorption. These factors include meat, fish and poultry, although these factors contain the highly bioavailable heme iron, but also they can promote the absorption of non-heme iron from other foods eaten with them. Vitamin C (ascorbic acid) enhances the absorption of non-heme iron by reducing dietary ferric iron to ferrous iron and forming an absorbable

iron-ascorbic acid complex. Other factors that enhance absorption include copper, manganese and organic acids e.g. citric, lactic acids from foods by stimulating the secretion of hydrochloric acid in the stomach. Other factors inhibit absorption of non-heme iron as phytates and fibers in cereals and nuts. Also calcium and phosphorus in milk supplements inhibit the absorption of iron. Recent studies reveal that soya protein, may inhibit iron absorption that is independent of its phytic acid content.

Metabolism and Fate:

Iron is oxidized to ferric iron in the enterocytes by hephaestin (which is a transmembrane-bound ferroxidase that bears a 50% identity with ceruloplasmin and it does not localize to the basolateral membrane) and either stored in the enterocytes as ferritin which is the major storage form of iron, or transported into the circulation by the transport protein Ireg 1. In serum, the absorbed ferric iron is bound to transferrin. The diferric transferrin (FeTf) then binds to a transferrin receptor (TFR) on the cellular plasma membranes of peripheral cells and endocytosis of FeTf- TFR-complex takes place **(Denise, 2002).**

The result of endocytosis, is the release of iron from the endocytotic vesicle to a labile intracellular iron pool (LIP). Iron from the LIP is either utilized for the immediate metabolic needs of the cell (heme proteins, cytochromes, mitochondrial enzymes, etc.) or stored in the iron-storage protein ferritin (Ft). The metabolic needs of an iron-deficient mammalian cell