

Vitamin B2 – Riboflavin

Overview of interactions:

- nutrient affected by drug: Doxorubicin
- nutrient affected by drug: Oral Contraceptives
- nutrient affected by drug: Tetracyclines
- nutrient affected by drug: Tricyclic Antidepressants

Chemistry:

- Stable to heat, oxidation, and acid, riboflavin is somewhat soluble in water.
- Light and alkali destroy it.
- It should be noted that bottled milk (which has a relatively large amount of B2) loses a significant amount of B2 if it is left in the sunlight.

Metabolism:

- Absorption occurs mainly in the upper GI tract. 60% of a 30mg dose is absorbed when taken with meals compared to 15% when taken separately.
- Synthetic thyroid medication decreases absorption, but thyroid in general increases the absorption.
- It should be noted that gastric acid is responsible for releasing B-2 from non-covalent bonding in foods so that it may be absorbed.
- Riboflavin is stored to some extent in the liver. However, when supplies are low the liver will only go down to 50% of its maximum storage.
- Riboflavin is also found in high amounts in the retina of the eye.

Function:

- Riboflavin is involved with production of FMN and FAD, both of which are involved in redox reactions.
- Riboflavin causes the activation of vitamin B6.
- Riboflavin is involved in the conversion of tryptophan to niacin.
- Riboflavin is involved in the conversion of folate to its coenzymes.
- Riboflavin aids in Beta oxidation in fat metabolism.
- Riboflavin is involved as a coenzyme component of the dehydrogenases in the first step in glucose metabolism.
- Riboflavin is needed for the production of corticosteroids; erythropoiesis; gluconeogenesis; and thyroid enzyme regulation.

Dietary sources:

Milk, liver, meat, fish, eggs, cereal products, green leafy vegetables, whole grains, brewer's yeast, torula yeast, wheat germ, almonds, sunflower seeds.

Deficiency:

- A deficiency of riboflavin usually occurs in concert with other B vitamin deficiencies. However, clinical signs are less dramatic than other deficiencies. Cheilosis and glossitis are classic deficiency symptoms. Dry and scaly skin (seborrheic dermatitis) along with itchy eyes and sensitivity to light are also common. In animals riboflavin deficiencies cause alopecia, anemia, neuropathy, corneal vascularization (precataracts) and congenital malformations.
- Alcoholics are at increased risk for vitamin B2 deficiency.
- Research indicates that individuals with cataracts and sickle cell anemia are more likely to demonstrate a vitamin B2 deficiency pattern than others.

Known or potential therapeutic uses:

Acne rosacea, anemia (rare), athletic performance, cataracts, depression, migraine headaches.

Maintenance dose: 30 mg per day.

Therapeutic dose: 10-100 mg per day.

Note: Vitamin B2 should be taken as part of a B-complex formula because it works in combination with vitamins B1, B3, and B6.

Side effects: None known to date.

Toxicity: No toxicities have been reported or suspected as being associated with vitamin B2 at typical dietary and supplemental levels. However, large doses may result in increased urinary excretion of other B vitamins, leading to imbalances

Contraindications: None known to date.

Insufficient intake of vitamin A, riboflavin, ascorbate, and folate is associated with an increased risk of cervical dysplasia. The effect of certain drugs on nutrient metabolism is discussed. Antituberculous drugs such as INH and cycloserine interfere with vitamin B6 metabolism and may produce a secondary niacin deficiency. Oral contraceptives interfere with the metabolism of folic acid and ascorbic acid, and in cases of deficient nutrition, they also seem to interfere with riboflavin. Anticonvulsants can act as folate antagonists and precipitate folic acid deficiency. Therefore, in some cases, supplementation with folate has been recommended simultaneously with anticonvulsant therapy. Cholestyramine therapy has been associated with malabsorption of vitamins; several reports suggest that cholestyramine affects absorption of the fat-soluble vitamins K and D and, in addition, may alter water-soluble vitamins, including folic acid. The study of the interaction of drugs and nutrients is an area that deserves a greater attention in the future, especially in groups where nutrient deficiencies may be prevalent.

The combined use of CoQ10 with adriamycin has been recommended for reduction of the cardio toxicity that occurs during

cancer chemotherapy. Vitamin B2-butyrate was also investigated in order to determine anti-oxidative effects on adriamycin cardio toxicity. This vitamin analysis prevented enhanced lipid peroxidation and rectified the respiratory disorders of heart mitochondria induced by adriamycin, however, the deficiency of the CoQ10-pool was not rectified. The combined approach of using CoQ10 for rectifying the deficiency of this component and of using B2-butyrate for reducing lipid peroxidation was indicated for adriamycin cancer chemotherapy. The effects of various vitamins on lipid peroxidation and the suppression of DNA synthesis induced by adriamycin (ADR) in vitro using Ehrlich ascites carcinoma (EAC) cells were studied. ADR produced a concentration-dependent stimulation of lipid peroxidation in EAC cells. alpha-Tocopherol and coenzyme Q10 inhibited ADR-induced lipid peroxidation to about the same extent and these effects were the greatest for all antioxidants added. The inhibitory effect of riboflavin 2',3',4',5'-tetrabutryrate was greater than that of riboflavin 5'-phosphate. On measuring incorporation of [3H] thymidine into EAC cells, these vitamins did not alter appreciably the magnitude of the ADR-induced suppression of DNA synthesis in EAC cells.

Previous studies in rats have demonstrated that 1) aldosterone enhances biosynthesis of renal flavin coenzymes; 2) riboflavin analogs inhibit the synthesis of aldosterone; and 3) adriamycin inhibits flavin coenzyme biosynthesis. In their entirety, these findings suggest that both diminished flavin coenzyme biosynthesis induced by adriamycin and a dietary riboflavin deficiency would result in decreased formation of aldosterone. The present study examined the effects of adriamycin treatment on serum aldosterone in rats consuming either a diet adequate in riboflavin or a riboflavin-deficient diet. Groups of rats fed specially prepared diets were injected for 3 days with adriamycin (cumulative dose range, 6-24 mg/kg BW). Pair-fed controls were given saline. After death, adrenal glands were excised, and blood samples were analyzed for aldosterone levels. No changes in adrenal weights or protein and potassium concentrations were observed after adriamycin treatment.

In contrast to initial predictions, in riboflavin-sufficient rats, serum aldosterone levels were markedly enhanced by adriamycin in a dose-related manner. Riboflavin-deficient animals had lower basal aldosterone levels and markedly attenuated responses to adriamycin than did riboflavin-sufficient rats. In separate groups of adriamycin-treated rats fed a normal chow diet, serum aldosterone levels increased, and serum corticosterone levels showed a small but significant decline. In addition, adriamycin treatment caused an increase in urinary potassium excretion and a decrease in sodium excretion. These results suggest that flavins play a decisive role in regulating the levels of aldosterone and raise the possibility that the adriamycin-induced increase in serum aldosterone may be part of the pathogenetic mechanisms of cardiovascular toxicity and overall muscular weakness.

Chlorpromazine, imipramine and amitriptyline, drugs structurally related to riboflavin, each inhibited the formation in vivo of flavin adenine dinucleotide (FAD) from riboflavin in rat heart at 2-5 mg/kg body weight, doses comparable on a weight basis to those used clinically. All three drugs inhibited FAD formation in heart within 5 hr after a single dose of 25 mg/kg. Chlorpromazine under these conditions also inhibited FAD formation in liver, cerebrum and cerebellum. A series of psychoactive agents structurally unrelated to riboflavin did not inhibit flavin formation in the organs tested. These findings indicate that the inhibitory effects of the drugs studied have organ specificity with respect to FAD formation.

A deficit of mitochondrial energy metabolism may play a role in migraine pathogenesis. We found in a previous open study that high-dose riboflavin was effective in migraine prophylaxis. We now compared riboflavin (400 mg) and placebo in 55 patients with migraine in a randomized trial of 3 months duration. Using an intention-to-treat analysis, riboflavin was superior to placebo in reducing attack frequency ($p = 0.005$) and headache days ($p = 0.012$). Regarding the latter, the proportion of patients who improved by at least 50%, i.e. “responders,” was 15% for placebo and 59% for

riboflavin ($p = 0.002$) and the number-needed-to-treat for effectiveness was 2.3. Three minor adverse events occurred, two in the riboflavin group (diarrhea and polyuria) and one in the placebo group (abdominal cramps). None was serious. Because of its high efficacy, excellent tolerability, and low cost, riboflavin is an interesting option for migraine prophylaxis and a candidate for a comparative trial with an established prophylactic drug.

Reports concerning the interaction between steroidal contraceptives (the combined pill) and vitamins indicate that in users the mean serum-vitamin-A level is raised and the mean serum-vitamin-B2 (riboflavin), vitamin-B6 (pyridoxine), vitamin-C, folic-acid, and vitamin-B12 levels are reduced. Other vitamins have been insufficiently studied for comment. Biochemical evidence of co-enzyme deficiency has been reported for vitamin B2, vitamin B6, and folic acid. Clinical effects due to vitamin deficiency have been described for vitamin B6--namely, depression and impaired glucose tolerance. Folic-acid deficiency with megaloblastic anaemia has been reported in only 21 cases.