DRUG-SUPPLEMENT INTERACTIONS IN LYME DISEASE

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Interactions between prescription or over the counter drugs and nutritional supplements are common and often not well known. In creating the Drug-Nutrient Workshop (www.NutritionWorkshop.com), a professional database of interactions between drugs and dietary supplements, nutrients, and food or food components, I found that over 400 drugs commonly used in the U.S. deplete specific nutrients and almost 500 drugs have their efficacy or side effects influenced by various foods. I also identified about a thousand adverse interactions between drugs and dietary supplements and several hundred beneficial interactions, in which specific dietary supplements may enhance the efficacy or decrease the side effects of specific drugs.

People with Lyme and related diseases are usually administered prolonged therapy with antibiotics, often combined with Prilosec or other proton pump inhibitors (drugs that greatly reduce stomach acid), sometimes in conjunction with Plaquenyl (an immune modulator) or anti-parasitic drugs for treatment of babesiosis. Some potential interactions (negative and positive) between these drugs and dietary supplements are described below. Information on drug/food interactions is usually available from the pharmacist and included in the patient-package insert. This should be checked for each individual drug being taken, because the dosage form (sustained-release vs. regular, for example) may influence the effect of food on drug absorption. Patients with chronic tick-borne infections may also be taking antidepressants and pain relievers, each of which may have its own interactions with nutritional supplements and nutritional status.

Drugs may interact with food or supplements through the following mechanisms:

(1) The food or supplements may interfere with drug absorption. This is especially important for tetracycline or quinolone antibiotics. {Although quinolones like Levaquin are not used for Lyme disease, they are the primary drugs for treatment of bartonellosis, a common co-infection). Both groups of antibiotics form insoluble complexes with minerals, especially calcium, magnesium or iron. This process, called chelation, inhibits absorption of both the antibiotic and the mineral. Not only are most tetracyclines (with the sole exception of doxycycline) and all quinolones better absorbed away from food (especially mineral-rich foods like meat and dairy products), they must be taken several hours apart from any nutritional supplements containing minerals. Two hours of separation may not be enough. Several herbs, including fennel, dandelion, and Sanguisorba, have a high enough mineral content that their consumption has been shown to interfere with quinolone absorption.

Penicillins may have their oral absorption impaired by fiber or by food, although this is more likely for penicillin V and ampicillin that for amoxacillin. Food causes the drug to be retained in the stomach, where the presence of acid causes the drug to decompose. Psyllium has been shown to bind oral penicillin, decreasing its absorption.

(2) The drug may increase the requirement for certain nutrients, because it causes depletion of the nutrient from the body. The normal gastrointestinal bacterial flora synthesize B vitamins, biotin and vitamin K, which are absorbed and utilized by humans. Depletion of these bacteria by prolonged antibiotic therapy may produce vitamin deficits. Bleeding caused by vitamin K deficiency has occurred as a result of intravenous therapy with cephalosporin antibiotics[1], a group that includes Rocephin and Claforan. High dose penicillin therapy causes increased excretion of potassium by the kidneys[2]. When combined with antibiotic-induced diarrhea or poor appetite, this effect may cause potassium deficiency, with fatigue and muscle weakness as primary symptoms. Proton pump inhibitors like Prilosec, used to enhance antibiotic absorption and cellular penetration, decrease formation of stomach acid, permitting overgrowth of bacteria and/or yeast in the stomach and upper gastrointestinal tract. Microbial overgrowth may be associated with gastrointestinal symptoms like diarrhea and bloating[3] and may cause malabsorption of nutrients. Prolonged use of PPIs has been associated with decreased absorption of vitamin B12, zinc, and carotene and may create a need for supplementation[4].

(3) Drugs, supplements and food may interact by inhibition or stimulation of enzymes involved in drug transport or metabolism.

The **cytochrome P450 (CYP)** system is extensively involved in drug metabolism and may be strongly inhibited or stimulated by drugs, foods or dietary supplements. CYP enzymes are most active in the liver, intestines, lungs and kidneys. Humans have over 20 different CYP enzymes, all of which contain iron and which all use oxygen to change the structure and function of the drugs they metabolize. The most important CYP's for drug metabolism are designated CYP1A2, CYP2C9, CYP2C19, CYP2D6, CYP2E1 and CYP3A4. This classification system is not based upon biological function but upon similarity of amino acid sequences in the structure of the enzyme. CYP oxidation of drugs may produce metabolites that are less active or more active than the parent compound. The exact effect of inhibiting or stimulating any CYP enzyme will therefore depend upon the specific clinical circumstances and cannot necessarily be predicted from experiments done in a test tube.

Another important aspect of drug metabolism is transport into and out of cells. Some drugs are ejected from cells by a transport system referred to as **P-glycoprotein** (P-gp). In the intestine, P-gp limits the absorption of a variety of unrelated drugs, many of which are also metabolized by the intestinal form of CYP3A4. Inhibition of P-gp and/or CYP3A4 by grapefruit juice or other natural substances can increase absorption of drugs that are P-gp or CYP3A4 substrates, raising their concentration in blood. This effect is only important for drugs that are slowly absorbed in the intestine to begin with. Drugs that pass through the intestinal lining rapidly are absorbed too quickly for inhibition of CYP or P-gp enzymes in the intestine to affect drugs levels. St. John's wort is one of the few products that stimulate intestinal P-gp and CYP3A4. Taking St. John’s wort can decrease the plasma concentration of those same drugs and underlies many of the adverse drug interactions reported for this herb.

Some important interaction of drugs used in treating tick-borne diseases and the CYP system are listed below:

CYP2C9 is increased by rifampin (an antibiotic sometimes used to treat Bartonella) and inhibited by fluconazole (Diflucan, an anti-fungal).

CYP2C19 is increased by rifampin and artemisin (a derivative of the herb *Artemisia annua*, a natural anti-malarial herb that may be used in the treatment of Babesiosis). CYP2C19 is decreased by Prilosec and ketoconazole (Nizoral, an anti-fungal).

CYP3A4 is increased by St. John's wort and rifampin and inhibited by grapefruit juice, Seville orange juice, the anti-fungal drugs ketoconazole (Nizoral) and itraconazole (Sporanox), and the macrolide antibiotics azithromycin (Zithromax), clarithromycin (Biaxin) and telithromycin (Ketek). The effect of grapefruit juice occurs only in the intestines, not in the liver, so it can--at high levels of consumption--increase absorption of some drugs without affecting their internal metabolism. Artemisinin is metabolized by intestinal CYP3A4, and its absorption appears to be enhanced by grapefruit juice[5]. The herb *Echinacea*, used for immune stimulation, inhibits intestinal CYP3A4 but stimulates the liver's CYP3A4, so it may increase or decrease the levels of a co-administered drug, depending upon the drug's rate of absorption and the extent to which it is metabolized by CYP3A4.

Milk thistle, an herb used to support liver function, contains a group of bioflavonoids called silymarin. Silymarin may inhibit intestinal P-gp and liver CYP3A4. Surprisingly, concomitant administration of milk thistle significantly decreased the absorption of metronidazole (a drug used to treat the spore form of Borrelia).[6] This interaction could not have been predicted from knowledge of the herb's effects on drug metabolizing enzymes. Moreover, vitamin C (500 mg/day) and vitamin E (400 units/day) decreased the effectiveness of metronidazole in treating H. pylori infection of the stomach.[7] The mechanism of this interaction is unknown but suggests that anti-oxidants should not be used with metronidazole therapy.

Quercetin, a bioflavonoid used as an anti-oxidant and for relief of allergic symptoms, competes with quinolone antibiotics for binding sites on bacteria. No interaction between quercetin and antibiotics has yet been demonstrated outside a test tube, but it would be prudent for people taking quinolone antibiotics to refrain from the use of quercetin and perhaps other bioflavonoids.

Beneficial effects of dietary supplements for people taking antibiotics have been described. The most consistent benefits have been demonstrated for probiotics (living organisms) that can counter the gastrointestinal side effects of antibiotics. The best

studied are *Saccharomyces boulardii* (a yeast, dubbed "yeast against yeast" in France)[8], *Lactobacillus rhamnosis* GG[9], *Lactobacillus plantarum* and *Lactobacillus sporogenes*[10].

Proteases are enzymes that digest protein. When taken by mouth on an empty stomach some of the preparation is absorbed intact and may be active in the body. Oral proteases have been shown to relieve pain and inflammation in patients with arthritis[11], may break down circulating complexes of antigen and antibody (these have been described in so-called "post-Lyme syndrome") and may breakdown blood clots that form as a result of inflammation. Although research on proteases as adjuncts to antibiotic therapy is minimal, a study done in animals found that bromelain (a protease-containing extract of pineapple stem), increased penetration of tetracyclines into the tissues[12].

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