Possible Leukopenia Associated with Long-term Use of Echinacea

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Americans spend between $3.5 and $5 billion annually on herbal treatments,[1] and nearly 50 million individuals currently report use of botanical supplements.[2] With so many herbal products on the market, it is imperative that physicians thoroughly question patients with regard to supplement use. Physicians must understand the benefits and risks associated with medicinal herbs and counsel patients as to their safety. Echinacea is one such supplement that has gained popularity in recent years. A member of the daisy family—Asteraceae (Compositae)—*Echinacea purpurea* is believed to have properties that protect against upper respiratory tract infections such as the common cold. In 1998, retail sales of the product worldwide totaled $69,702,144, and in Germany more than 2 million prescriptions for echinacea were filled each year.[3]

Animal studies show echinacea affects the immune system by increasing the number of circulating white blood cells,[4] promoting phagocytosis, and stimulating the production of cytokines.[5] Echinacea is also found to improve wound healing by inhibiting tissue and bacterial hyaluronidase[6]; its extracts could potentially inhibit replication of some viruses directly.[7]

According to German Commission E monographs, arguably the best compilation of clinical information about herbs, chronic use (longer than 6 to 8 weeks' duration) is generally discouraged because of reported cases of immune suppression.[1,8] For this reason echinacea is contraindicated in patients with acquired immunodeficiency syndrome and other disorders in which immune suppression would be detrimental. Because echinacea is an immune stimulant when administered short term both in vivo and in vitro, it is contraindicated in patients with autoimmune disorders, multiple sclerosis, tuberculosis, and those on immunosuppressant therapy.[4,8]

We describe a case in which chronic use of echinacea resulted in an asymptomatic leukopenia. We believe this case might be the first in the English literature to confirm the German Commission E reports that chronic use indeed results in immune suppression.

Case Report

A 51-year-old woman visited her physician for her yearly physical examination.. She had no complaints, and her only known medication allergy was to sulfa drugs, which precipitated a rash. According to the patient's medical history, she was taking bupropion (Wellbutrin SR) for depression; her hay fever was not being treated with any over-the-counter or prescription drugs. She appeared healthy from all aspects with the exception that her white cell count had decreased from 5,800/μL the preceding year to 3,300/μL (normal range 4,000–11.0/μL). The only change found was an increased use of herbal remedies and vitamin supplements. The patient's only medication was a stable dose of bupropion 300 mg/d that she had been taking for 18 months.

For the past 8 weeks she had been taking vitamins C, E, and B complex, along with echinacea, ginkgo biloba, and calcium. She initially began taking echinacea when family members became ill with upper respiratory tract infections. The patient believed echinacea had prevented her from getting a cold and thus continued to take 450-mg capsules of the herb, three times daily for 2 months. This dose is typically recommended by manufactures and European physicians, but generally for only up to 6 weeks or less.

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A hematologist recommended testing again after the patient discontinued echinacea, ginkgo biloba, and bupropion. The patient refused to discontinue taking bupropion but agreed to stop echinacea and gingko biloba. One month later her white cell count had increased slightly to 3,700/μL and maintained that level for 3 months. An anemia profile, electrolyte count, thyroid-stimulating hormone level, and a differential blood count were normal.

The patient's next visit was 1 year later for a routine examination. The patient had continued taking bupropion at the same dose, but for the previous 2 months had resumed taking echinacea at 450 mg three times daily. She also took the recommended calcium and multivitamin but had not resumed taking gingko biloba. Her white cell count was 2,880/μL and on repeated testing the same day was 3,000/μL. Other normal laboratory findings included an anemia profile, urinalysis, electrolytes, lipid profile, urine monoclonal protein analysis, total urine protein, thyroid-stimulating hormone, acute phase reactants, serum monoclonal protein analysis, antinuclear antibodies, rheumatoid factor, hepatitis panel, urine electrophoresis, and serum electrophoresis. Although the differential blood count was interpreted as normal, neutrophil counts were slightly less than normal while lymphocyte and monocyte counts were slightly increased. Tests for human immunodeficiency virus (HIV) infection were negative. The patient agreed to stop taking echinacea and to have a bone marrow aspiration if her white cell count did not return to normal.

Two months after discontinuing echinacea, her white cell count was 3,440/μL and 7 months later rose to 4,320/μL. It remains within normal range, and she has not resumed using echinacea.

Discussion

Although we cannot be absolutely certain that echinacea caused the decrease in white cell count, it is noteworthy that stopping this herbal remedy led to gradual improvement. The patient described did not have atopy, HIV, or an autoimmune disorder, yet the possibility of a type IV allergic response with a delay in observation of the reduced white cell count after weeks of echinacea is also worth consideration. Although we could find no journal articles, there is drug company literature that describes leukopenia secondary to bupropion.[9] It is possible that bupropion exacerbated the response to echinacea, but when echinacea was discontinued and bupropion continued, the white cell count increased, lending less support to the role of bupropion.

The dose ingested by this patient, 1,350 mg/d for 8 weeks, is not large and, in fact, was lower than many others. During a recent pharmacy visit, we found bottles listing echinacea in various doses ranging from 380 mg to 1,200 mg and schedules from 3 to 6 times per day.* The totals ranged from 2,500 mg to 3,600 mg daily to "stimulate the body's own defenses." Four of five bottles recommended 8 weeks regular use with a 2-week hiatus before restarting, whereas one bottle did not. Four of five bottles recommended that persons with known autoimmune disorders not ingest echinacea, but one did not. One brand also recommended against use in persons with severe systemic illness, tuberculosis, muscular sclerosis, or allergy to sunflowers.

Echinacea is a popular herbal remedy taken by many to treat upper respiratory tract infections and a variety of other disorders. In assessing the therapeutic merit of echinacea, we found a review of 5 trials enrolling 1,272 subjects that tested echinacea in the prevention of upper respiratory tract infections. The incidence of upper respiratory tract infections was lower in the treatment branches of all 5 studies, with 2 trial results being statistically significant.[10] A systematic review of the Cochrane database found a total of 26 trials that studied echinacea, with 8 addressing its effect on respiratory tract infections. Six of 8 trials showed a beneficial effect with use of the herbal supplement.[11] Because the reviews on its effectiveness are mixed, larger studies with improved methods might clarify its value.

In the meantime, many patients continue to take this product, believing it is a natural and therefore safe remedy. Even patients without known autoimmune disorder or allergies to plants in the daisy family might be at risk for side effects. Echinacea is categorized as "generally regarded as safe for consumption" (GRAS) by the Food and Drug Administration (FDA) based on popular, widespread use and no serious side effects. Recent reports, how-

*Nature's Way Products, Inc, Springville, Utah (echinacea, 1200 mg); Nature's Bounty, Inc, Bohemia, NY (echinacea alone, 500 mg liquid; echinacea with goldenseal, 500 mg); CVS brand, Woonsocket, RI (echinacea, 380 mg: 1,140 mg).

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ever, name echinacea as a possible cause of erythema nodosum,[12] life-threatening anaphylaxis,[13] and possible hepatotoxicity in combination with other drugs metabolized by the liver such as amiodarone, ketoconazole, and methotrexate.[14] Although short-term use can be beneficial when a cold begins, some formulations of echinacea alone or with goldenseal, carry labels implying it can be used chronically to fend off colds—a potentially harmful recommendation. Because the Dietary Supplement Health and Education Act of 1994 states that herbal remedies are dietary supplements, they are not required to undergo premarket testing for safety and efficacy and are not regulated for quality by the FDA.

Physicians must remind patients that herb-drug interactions do occur, and because of the lack of standardization, variability in herb content and efficacy often exist among different manufacturers.[15] Physicians should offer advice based on available knowledge while making recommendations in a manner compatible with the patient's personal beliefs and needs. One author has proposed a step-by-step strategy that physicians can use to discuss use or avoidance of alternative therapies, emphasizing patient safety, need for documentation in the patient record, and importance of collective decision making.[16] Another author has proposed a set of 12 guidelines physicians should follow when advising patients about herbal therapies.[17] Physicians should ask patients about herbal use and should include these agents when considering side effects or drug interaction in the differential diagnosis for newly discovered signs such as leukopenia. Only through continued documentation of unusual findings with herbal consumption can physicians safely and accurately counsel patients on the subject of herbal therapy.

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