Dietary Supplement and Medication Interactions: *An Introduction*

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BACKGROUND

For thousands of years, cultures worldwide have turned to nature to address problems of illness and disease. However, as synthetic drugs were developed and found to have larger pharmacologic effects, they increasingly replaced herbal therapies.[1] In recent decades, we have seen a revival in the use of natural products in the United States. As reported by data from the 2007 National Health Interview Survey (NHIS), almost 4 in 10 Americans used complementary and alternative medicine (CAM) therapies in the previous year, with non-vitamin, non-mineral, natural products being the most commonly used (17.7% of adults).[2]

With this rise in interest and use of supplements, it is imperative that medical providers become aware of their potential to affect physiology and interact with medications including those used for anesthesia. Practitioners should also be comfortable with asking patients about their supplement use.

Table 1
Selected dietary supplements with notable pharmacological effects in patients undergoing anesthesia

Notable pharmacological effect	Dietary supplements[a]
Antiplatelet/anticoagulant	Andrographis, black tea, boldo, chondroitin, danshen, dong quai, fenugreek, fish oil, garlic, ginger, ginkgo, glucosamine, green tea, guarana, horse chestnut, policosanol, resveratrol, saw palmetto, turmeric, vitamin E, willow bark
CNS depression	Chamomile, hops, kava, L-tryptophan, lavender, lemon balm, melatonin, passionflower, skullcap, theanine, valerian
Hypoglycemic effects	Agaricus mushroom, alpha-lipoic acid, American ginseng, banaba, bitter mellon, cinnamon, chromium, fenugreek, glucomannan, gymnema, panax ginseng, prickly pear cactus, vanadium
Blood pressure effects	Andrographis, casein peptides, coenzyme Q10, horny goat weed, garlic, L-arginine, licorice, pycnogenol, theanine
Stimulant effects	Bitter orange, dimethylamylamine (DMAA), ephedra, higenamine, raspberry ketone, yohimbe
Serotonergic effects	5-HTP, L-tryptophan, phosphatidylserine, SAMe, St. John's wort, theanine

[a] Not a complete list.

Table 1. Source: "Perioperative Analgesia and the Effects of Dietary Supplements," Andrew Abe, PharmD; Alan David Kaye, MD, PhD; Karina Gritsenko, MD; Richard D. Urman, MD, MBA; Adam Marc Kaye, PharmD, Best Practice & Research Clinical Anaesthesiology 2014; 28: 183-189

PHARMACOLOGY

According to the United States Food and Drug Administration, a dietary supplement is any product which contains a dietary ingredient, such as a vitamin, mineral, or herb and intends to supplement the diet.[3] Patients may view dietary supplements as natural and harmless and may not mention their use to the practitioners involved in their care. They may not be aware of the risk of interaction with medications or may worry about the practitioners' reaction to the use of the supplement. This omission could negatively impact their health.

Dietary supplements interact with medications through the same mechanisms as other drug-drug interactions. These interactions fall into one of two major classifications, pharmacokinetic or pharmacodynamic.[4] Pharmacokinetic interactions are those that impact the movement of a compound within the body, such as absorption, distribution, metabolism, or excretion. These interactions tend to involve various isoenzymes and have the potential to be more extreme because their magnitude of effect may be manifold.[4] On the other hand, pharmacodynamic interactions modulate the effect of a compound on the body producing either an additive or oppositional pharmacological effect.[4] These can often be predicted based on the pharmacological effects of the dietary supplements.[4]

Of the pharmacokinetic interactions, the most common involve the cytochrome P450 pathway. Greater than half of all marketed drugs are metabolized to some degree by CYP450 isoenzyme 3A4 (CYP3A4), making dietary supplements which inhibit or induce CYP3A4 of significant concern.[4] Commonly used supplements that affect this isoenzyme include garlic, St. John's wort, and feverfew. Both garlic and St. John's wort are inducers. In the case of St John's wort, its interaction with cyclosporine can decrease levels by as much as 60%, potentially leading to sub-therapeutic cyclosporine levels and organ rejection.[5]

The more significant and applicable interactions to be aware of in pharmacodynamic interactions are those which affect blood clotting, central nervous system depression, glycemic balance, blood pressure, and serotonin levels.[4] For example, omega-3 fatty acids, in

amounts of three grams per day or greater, may increase the risk of bleeding.[6] Omega-3 fatty acids are found in foods such as fish and canola oil, and walnuts. According to 2007 NHIS data, fish oil is the natural product most commonly used by adults.[2] Another example is valerian. Primarily used in the treatment of insomnia, valerian may potentiate barbiturates. Its effects are mediated through GABA neurotransmitters and use with sedatives and anxiolytics is contraindicated.[7]

DISCONTINUING AND RESTARTING SUPPLEMENTS

The American Society of Anesthesiologists recommends discontinuing dietary supplements at least two weeks prior to any procedure. "For the majority of dietary supplements, abrupt discontinuations poses little to no harm."[4] However, there are some notable exceptions including feverfew and valerian. Feverfew is primarily used for migraine relief.[7] Those who discontinue feverfew without a taper have a 10% risk of developing postfeverfew syndrome "...symptoms include rebound headaches, insomnia, muscle stiffness, joint pain, fatigue, nervousness, and tension."[6] It is recommended that it be tapered over two weeks and then discontinued completely for two weeks prior to surgery.[6] The withdrawal effects of valerian are unknown and long-term use should not be discontinued abruptly. There is a case report of presumed withdrawal after long term consumption resulting in delirium and cardiac failure during emergence from anesthesia.[6]

There are no comprehensive recommendations on when to restart supplements. A review of the literature suggests it would be reasonable to stop all supplements until medications with potential interactions have been discontinued for a duration of at least five half-lives of the discontinued medication.[4] Approximately 97% of the drug should be eliminated by that time and interactions would be less likely to occur.[4]

OTHER CONSIDERATIONS

More studies are needed to determine the translatability of in vitro effects of supplements to humans. As complementary and alternative medicine becomes more popular, there are attempts to research their effectiveness. Currently, however, there is little research on the interaction between dietary supplements and medications. This is due to a number of reasons including funding and concerns about quality of research.

This is not to say that patients should be encouraged to discontinue all supplements indefinitely. Many people find them helpful. However, preparations with pharmacologic activity can positively and negatively impact health. Their use with conventional medication should be discussed with a knowledgeable provider. When assessing use multiple terms describing supplements should be use to aid patients in recognizing and identify supplements. Terms may include "dietary supplement," "herbal tea," "natural products," and "vitamins."[4] Practitioners should also have the patient bring in their supplements, as there are many dietary supplements that combine herbal preparations. As many of us see on a daily basis, open communication can go a long way toward strengthening the practitioner-patient relationship and patient safety.

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