AANA Journal Course

Herbal Medications and Anesthesia Case Management

Timothy J. Donoghue, DNAP, CRNA

Herbal medicine use in the United States has increased substantially. Despite this upward trend, patients often fail to disclose use of these medicines to their healthcare provider. Currently, the US Food and Drug Administration (FDA) does not require preclinical animal studies, controlled clinical trials, or postmarket surveillance of herbal supplements. Lack of FDA oversight leads to product variation in quality, purity, efficacy, harvesting, and storage. Intentional or unintentional addition of contaminants to these products remains substantial. Because herbal medicines have the potential to adversely react with medications used in the perioperative period, anesthesia providers should be aware of the purported uses of common herbal supplements, potential drug interactions with these medicines or possible contaminants, and the anesthetic implications for patients who use these medicines.

Keywords: Anesthesia, herbal supplements, herb-drug interactions, perioperative complications, traditional Chinese herbal medicine.

Objectives

Upon completion of this course, the reader should be able to:

1. Define herbal medicine.
2. Discuss recent trends in herbal supplement use in the United States.
3. Describe indications for various herbal supplements, including St John's wort, echinacea, ginseng, Ginkgo biloba, ginger, garlic, kava, valerian, chamomile, and ephedra.
4. Differentiate potential adverse events caused by herbal supplements.
5. Examine anesthetic implications of a patient’s herbal supplement use.

Introduction

In 1992, increased public demand for complementary and alternative medicines led Congress to form the National Institutes of Health Office of Alternative Medicine. In 1998, this office became known as the National Center for Complementary and Integrative Health (NCCIH). The NCCIH objectives are to evaluate efficacy and safety of plant-based medicines. Complementary and alternative medicine (CAM) represents a multibillion dollar industry in the United States. Complementary and alternative medicine is defined as follows:

[A] broad domain of healing resources that encompasses all health systems, modalities, and practices and their accompanying theories and beliefs other than those intrinsic to the politically dominant health system of a particular society or culture in a given historical period. CAM includes all such practices and ideas self-defined by their users as preventing or treating illnesses or promoting health and well-being.1

Within the broad category of CAM, herbal medicine use has increased substantially over the past 20 years. Herbal medicines are plant-based remedies that do not fall under the practices of conventional Western medicine. According to the NCCIH's 2012 survey, 33.2% of US adults and 11.6% of children used complementary medicine in the previous year2 (Figure, key points 1). Despite a trend in increasing use, patients often fail to disclose herbal medicine use to their healthcare providers.3 Many patients believe products labeled natural are not medicines and are safe to use. Because patients do not view herbal supplements as medications, they are less likely to report taking them.3,4 The herbal supplement industry lacks manufacturing standardization, allowing for contaminants and fillers to find their way into products.5 There is also a lack of evidence-based research showing benefits in many available herbal supplements.3,5 Despite a lack of evidence regarding safety and efficacy, herbal medicines continue to grow in popularity.

Patients who use herbal remedies may be at an increased risk of intraoperative complications such as increased intraoperative bleeding and difficulty with intubation. Patients who are taking herbal supplements may be at an increased risk for bleeding during the perioperative period due to their potential to increase platelet dysfunction, inhibit the coagulation cascade, or alter the concentration of anticoagulants. Patients who are taking herbal supplements may also be at an increased risk for difficulty with intubation due to their potential to cause laryngospasm, bradycardia, or hypotension. It is important for anesthesia providers to be aware of the purported uses of common herbal supplements, potential drug interactions with these medicines or possible contaminants, and the anesthetic implications for patients who use these medicines.

Keywords: Anesthesia, herbal supplements, herb-drug interactions, perioperative complications, traditional Chinese herbal medicine.

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blood loss, cardiac instability, prolongation of anesthesia, and adverse drug interactions.\textsuperscript{3-5} Anesthesia providers must remain vigilant during preoperative interviews, to determine whether a patient uses herbal remedies that could have adverse reactions with medications administered during the perioperative period.\textsuperscript{3,6-8} There remains little consensus regarding when surgical patients should stop using herbal medication before their operation. In general, it is advisable for patients to stop taking herbal medications 1 to 2 weeks before surgery to avoid potential cardiovascular, central nervous system (CNS), and bleeding effects.\textsuperscript{3-5} Although neither the American Society of Anesthesiologists (ASA) nor the American Association of Nurse Anesthetists (AANA) have formal guidelines regarding anesthesia management of patients who take herbal supplements, the patient education brochures for both organizations inform patients to stop taking herbal supplements before surgery.\textsuperscript{6,7} Unfortunately, the likelihood of an anesthesia provider seeing a patient 2 weeks before surgery is minimal. The anesthesia evaluation most often occurs in the presurgical holding area just before the patient is brought to the operating room, increasing the likelihood a patient has not stopped taking his or her herbal medications.

**Oversight by the Food and Drug Administration**

According to the Dietary Supplement Health and Education Act (DSHEA) of 1994, herbal medicines are excluded from regulation by the US Food and Drug Administration (FDA; Figure, key points 2). Manufacturers do not need to meet the same safety standards as the pharmaceutical industry, even though herbal medicines physically affect patients. These medications often contain contaminants and fillers that may diminish product purity and efficacy. Manufacturers are not required to prove efficacy, safety, or quality of their products. They are also not required to report postmarketing adverse events to any central agency. The DSHEA made the FDA responsible for proving an herbal supplement is unsafe, instead of requiring the manufacturer to prove it is safe.\textsuperscript{3}

Without industry standardization, manufacturing processes may differ greatly between companies, resulting in varying concentrations of herbal medicines. These differences make herbal supplements difficult to study. With more people using herbal medications as alternative means to treat physical ailments, the need for industry oversight and consumer protection has increased.\textsuperscript{8} In 2007, the FDA created policies for Good Manufacturing Practices (GMPs).\textsuperscript{9} These new rules required dietary supplements to be manufactured according to specific standards for personnel and equipment, properly labeled, and free of adulterants. Even with these GMP rules in place, no set standard for maximum concentration or dose limits have been established. There remains great variation in the quality, harvesting and storage conditions, processing, purity, efficacy, and accuracy of labeling in the United States (Figure, key points 3). These variations make herbal medicines potentially dangerous to patients.\textsuperscript{10} It is imperative that anesthesia providers familiarize themselves with commonly used herbal medicines and the potential adverse drug interactions that may be encountered.

**Unintentional and Deliberate Contaminants of Herbal Medications**

Misidentification of plants, drug substitution, and addition of heavy metals to herbal remedies result from the lack of standardization of herbal medicine manufacturing.\textsuperscript{3,5} Often, companies will substitute cheaper ingredients that may alter the supplement’s concentration. The addition of active drugs to increase the effects of herbal supplements may also occur.\textsuperscript{11} Pesticides, lead, mercury, and arsenic have been detected in herbal supplements, especially from China.\textsuperscript{12,13} Because the FDA does not regulate the herbal supplement industry with the same rigorous standards as it does the pharmaceutical industry, intentional and unintentional contamination of herbal supplements remains possible. This contamination is a problem with which anesthesia providers should familiarize themselves, because these additives could have adverse reactions with anesthetic agents.
Common Herbal Medicines

• **Echinacea.** Echinacea is a group of American wildflowers that typically grows in the Great Plains of North America. With 9 known species, echinacea is believed to improve immunologic activity and is used most commonly for the treatment of upper respiratory tract infections.³ However, there are few well-controlled studies showing efficacy. The active ingredients in this herbal medicine include echinacosides, caffeic acids, and alkylamides.⁴ There is debate regarding which of the active ingredients causes the medicinal effects. Echinacea may interact with simvastatin, lansoprazole, and losartan, increasing blood levels of these drugs.⁸ Some research has shown it to affect cytochrome P1A2 (CYP1A2) and P3A4 (CYP3A4), whereas other data conflict with these findings. Echinacea use should be cautioned in patients who take medications metabolized by cytochrome P enzymes such as antipsychotic and antidepressant drugs¹⁴,¹⁵ (Table ¹4,¹⁰,¹⁶,¹⁷).

• **Ephedra.** Ephedra (Ma huang) is an evergreen shrub plant that is native to Central Asia, Mongolia, and the Southwestern United States. The FDA banned the sale of commercial ephedra in 2004 because of adverse events. Ephedra was used as a weight loss supplement, to increase energy and athletic performance, and to treat asthma.³ Complications arising from ephedra intake include hypertension, myocardial infarction, arrhythmias, subarachnoid hemorrhage, increased blood glucose levels, and increased seizure intensity.⁴,¹⁸ Ephedra use may lead to neurotransmitter depletion, resulting in unexplained intraoperative hypotension.¹⁸ It interacts with monoamine oxidase inhibitors and CNS stimulants. Since being banned commercially by the FDA, ephedra is encountered less frequently in the United States.

• **Ginseng.** Throughout the world, ginseng is a widely used herbal medicine. Three main varieties exist, with *Panax ginseng* being the most readily available on the market.⁴ It has been used as a stimulant and a diuretic in Chinese medicine, and is used to improve cognitive and physical performance.⁴ It also has been used to improve glucose control in diabetes management, and the active ingredient is believed to be ginsenosides.¹⁹ These compounds have many heterogeneous and occasionally opposing effects. Ginsenosides inhibit platelet aggregation in vitro and prolong thrombin time in rats, but these results await confirmation in humans.²⁰ Ginseng theoretically may interact with warfarin. One case has been noted in which ginseng actually decreased the effect of warfarin.²¹ This contradiction in data demonstrates how little is known about the effects of ginseng. Data on concurrent use of ginseng and oral anticoagulants are sparse, but when they are taken together, an increased risk of bleeding complications may occur.¹³ Ginseng interacts adversely with monoamine oxidase inhibitors such as phenelzine, leading to possible hypertensive crisis¹⁶ (see Table ¹). Reported adverse events include hypertension, sleeplessness, anxiety, and rashes.⁴

• **Ginkgo biloba.** Ginkgo biloba is an herbal medicine used in the treatment of dementia. It is thought to diminish the side effects of dementia, enhance memory, and treat intermittent claudication.⁹ Other purported treatments are for asthma, Raynaud disease, and tinnitus.⁴ Ginkgo extract contains terpenoids and flavonoids thought to protect vascular walls and nerve cells.⁴ The mechanism of action is thought to be inhibition of platelet activating factor.²² Because Ginkgo biloba potentially increases blood flow while also decreasing blood viscosity, it has been used for treatment of peripheral vascular disease.²³ Potential additive effects could arise with concomitant use of acetaminophen, nonsteroidal inflammatory drugs, aspirin, or warfarin²⁰ (see Table ¹). Ginkgo biloba has antiplatelet and antithrombotic properties that might increase tendency to bleed in patients who consume it. There have been case reports of subarachnoid hemorrhage, subdural hematomas, and unexpected blood loss after surgery.²⁴,²⁵ One case of Ginkgo biloba–associated postoperative bleeding following laparoscopic cholecystectomy has been noted in the literature.²⁶

• **Garlic.** Garlic (*Allium sativum*), a close relative to onions and leeks, has been used for centuries as a seasoning agent as well as an herbal remedy. Garlic cells contain a compound called allin. When the cells are crushed, allin comes in contact with allinase, converting the allin to allicin. Allicin has potent antibiotic properties. Garlic is believed to reduce oxidative stress, inhibit 5-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase, and stimulate cellular immunity.²⁷ Some of the purported ben-
benefits of garlic consumption include lowered cholesterol and triglycerides, prevention of infection, improved diabetes mellitus management, and decreased blood pressure.  

Garlic also decreases platelet aggregation, thereby potentiating anticoagulation effects of medicines such as aspirin and warfarin. (Table 2). There has been one case report concerning spontaneous epidural hematoma in a patient who consumed excessive amounts of garlic.

- **St John’s Wort.** St John’s wort (*Hypericum perforatum*) has been in use for thousands of years. It is a yellow flower containing hypericin, pseudohypericin, protohypericin, quercetin, rutin, luteolin, flavonoids, xanthones, and hyperforin. As an herbal remedy, St John’s wort is thought to have antidepressant characteristics. Hypericin is believed to be the active ingredient responsible for these mood effects by modulating serotonin, norepinephrine, and dopamine levels. Hypericin inhibits serotonin synaptic reuptake, inhibits monoamine oxidase A and B, and inhibits norepinephrine and dopamine reuptake. St John’s wort has also been used for treating insomnia, obsessive-compulsive disorder, and attention-deficit/hyperactivity disorder. Research has failed to show any efficacy for treating these disorders with St John’s wort.

St John’s wort induces cytochrome P450. It increases metabolism of protease inhibitors, cyclosporine, oral contraceptives, warfarin, and digoxin. St John’s wort increases the clearance rate of these medications. It may interfere with statin cholesterol-lowering medications, calcium channel blocking agents, and irinotecan. Multiple case reports about St John’s wort reducing blood concentration of cyclosporine have been noted in the literature (Table 2). Serotonin syndrome may occur when St John’s wort is used in conjunction with drugs affecting 5HT serotonin receptors, namely selective serotonin reuptake inhibitors (SSRIs). There have been case reports of serotonin syndrome in patients taking St John’s wort concomitantly with SSRIs. Precipitation of opiate withdrawal in patients taking St John’s wort have also been noted.

St John’s wort has also been noted to decrease alprazolam and oxycodone blood concentrations.

- **Ginger.** Ginger (*Zingiber officinale*) is a flowering plant whose root is used as a spice and an herbal medicine. It belongs to the same family as turmeric and cardamom. Uses include treatment of gastrointestinal discomfort, nausea, motion sickness, drug withdrawal symptoms, rheumatoid arthritis, and osteoarthritis. It is thought that ginger competitively antagonizes serotonin 5HT3 receptors and prostaglandins. Active ingredients include shogaol, gingerol, and galanolactone. Ginger has the potential to interact with warfarin, thereby increasing potency and the tendency for bleeding. Because of antiplatelet characteristics, ginger may adversely interact with diclofenac and ibuprofen (see Table 2).

- **Chamomile.** Chamomile is one of the oldest medicinal herbs known. It is found in 2 common varieties, German chamomile (*Chamomilla recutita*) and Roman chamomile (*Chamaemelum nobile*). The active ingredients are terpenoids and flavonoids. Chamomile has been used as an antiseptic, an anti-inflammatory, and an antioxidant. It has mild sedative and digestive relaxing effects. Other uses include treatment of insomnia, gastric disturbances, colic, gout, eczema, sciatica, and mucositis. When used topically, chamomile may inhibit Lipopolysaccharide prostaglandin E2 release which attenuates cyclooxygenase (COX-2) activity. Chamomile has been shown to cause apoptosis of cancer cells and may have benefits in the treatment of prostate, breast, skin, and ovarian cancer. The FDA recognizes chamomile as generally safe for consumption. A theoretical increasing of the anticoagulant effects of warfarin may occur because chamomile contains coumarin (see Table 2).

- **Kava.** Kava (*Piper methysticum*) is a member of the pepper family native to the South Pacific Islands. It has anxiolytic effects similar to benzodiazepines that promote relaxation. The active ingredient in kava is believed to be kavalactones. These compounds cause dose dependent effects on the CNS such as sedation by

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**Table 2. Indications, Evidence, and Adverse Effects of Herbal Medicines**

<table>
<thead>
<tr>
<th>Herbal medicine</th>
<th>Indication</th>
<th>Evidence</th>
<th>Adverse effects</th>
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<tbody>
<tr>
<td>Garlic (<em>Allium sativum</em>)</td>
<td>Hypercholesterolemia</td>
<td>Possibly effective</td>
<td>Platelet dysfunction</td>
</tr>
<tr>
<td>Ginger (<em>Zingiber officinale</em>)</td>
<td>Food flavoring, upper gastrointestinal tract discomfort, nausea, motion sickness, rheumatoid arthritis</td>
<td>Inconclusive</td>
<td>Antiplatelet properties</td>
</tr>
<tr>
<td>Chamomile (<em>Chamomilla recutita, Chamaemelum nobile</em>)</td>
<td>Sleep promotion, gastrointestinal tract discomfort, antiseptic, anti-inflammatory</td>
<td>Inconclusive</td>
<td>Contains coumarin, potentiates warfarin</td>
</tr>
<tr>
<td>Kava (<em>Piper methysticum</em>)</td>
<td>Anxiety, promotes relaxation</td>
<td>Possibly effective</td>
<td>Inhibits cytochrome P450; hepatic dysfunction; renal dysfunction; enhanced acetaminophen-induced cytotoxicity; impaired platelet function</td>
</tr>
<tr>
<td>Valerian (<em>Valeriana officinalis</em>)</td>
<td>Insomnia, anxiety</td>
<td>Possibly effective</td>
<td>Hepatotoxicity, acute pancreatitis, potentiation of benzodiazepines</td>
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enhancing γ-aminobutyric acid (GABA)–mediated neurotransmission inhibition.4 Kavalolactones may possess neuroprotective and antiepileptic properties. Kava inhibits cytochromes P450 and 2E1 and could affect the metabolism of acetaminophen.30 It potentially enhances acetaminophen-induced cytotoxicity increasing glutathione depletion and cell death leading to hepatotoxicity, renal dysfunction, and impaired platelet function.14,31,45 Kava may have synergistic effects when taken with benzodiazepines and barbiturates46 (see Table 2).

• Valerian. Valerian (Valeriana officinalis) is a plant native to Europe and Asia. The root is used to treat insomnia and anxiety.47 It may also be used to treat nervousness, trembling, heart palpitations, and headaches.3 Although there is no scientific agreement regarding the active components of valerian, the effect is likely from multiple compounds acting independently or synergistically.3 The volatile oils and iridoids seem to cause the sedative effects of this herb. Valerian may increase GABA concentrations at the synaptic cleft.7 Valerian may adversely potentiate benzodiazepines, barbiturates, and haloperidol.48,49 Some cases of hepatotoxicity and acute pancreatitis have been previously reported.

### Anesthetic Implications of Herbal Medicines

There is a steadily increasing number of herbal medications for sale in the United States, and no industry standardization for manufacturing these agents. The use of herbal medicines is further complicated by the potential for contaminant and filler introduction during the manufacturing process. A wide variety of mechanisms of action for each herb also exists; unfortunately, many of these actions are unknown. Evidence based research remains difficult to perform on herbal medicines due to their lack of standard concentrations and manufacture by companies. Double-blinded, placebo-controlled trials addressing herbal medicine interaction with anesthesia are currently lacking in the literature, but consideration of side effects and potential drug interactions of herbal medicines is warranted.

Impaired coagulation is a significant concern. Garlic, ginseng, and Ginkgo biloba may affect platelet aggregation.18 Chamomile contains coumarin compounds that may interact negatively with warfarin.41 Increased bleeding effects may only be noted during serious blood loss. All of these potential side effects should be considered preoperatively.

Some herbs contain anxiolytic and sedative properties. These remedies have the potential to increase CNS depression. Concomitant use with benzodiazepines and opioids may lead to synergistic effects and prolonged anesthesia. Valerian and kava represent 2 herbs that possess these properties. Caution is warranted when using anesthesia drugs such as benzodiazepines, opioids, and sedative-hypnotics in patients with a reported use of kava or valerian.

Ginseng has varied effects that need consideration. It has been shown to decrease blood glucose.17 Additionally, ginseng interacts adversely with monoamine oxidase inhibitors such as phenelzine leading to possible hypertensive crisis.20 Patients who take ginseng may experience a decrease in the anticoagulant effects of warfarin, which may make these patients more susceptible to blood clotting.19 These interactions make patients who use ginseng potentially difficult to care for intraoperatively.

To date, no official guidelines regarding the perioperative management of patients who take herbal medicines have been set forth by the ASA or the AANA. The American Society of Regional Anesthesia and Pain Medicine says that since the risk of spinal hematoma with epidural or spinal neuraxial anesthesia is extremely low, patients should not stop taking herbal medicines before surgery nor should patient consumption of herbal medicines preclude the placement of neuraxial blocks.50 Guidelines from the American Society of Regional Anesthesia and Pain Medicine50 are based on research from 1969 to 2001. It is important to note that, although the ASA and AANA have no formal guidelines, the patient education brochures from both societies recommend patients stop taking herbal supplements at least 1 week before surgery.6,7 High-quality data concerning herbal supplement pharmacokinetics, metabolism, and

<table>
<thead>
<tr>
<th>Drug class or medication</th>
<th>Interaction with St John’s wort</th>
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<tbody>
<tr>
<td>Antidepressants: SSRIs and MAOIs</td>
<td>Serotonin syndrome</td>
</tr>
<tr>
<td>Warfarin</td>
<td>Decreased efficacy</td>
</tr>
<tr>
<td>Digoxin</td>
<td>Decreased efficacy</td>
</tr>
<tr>
<td>Anticonvulsants: phenytoin and carbamazepine</td>
<td>Decreased efficacy</td>
</tr>
<tr>
<td>Antiretroviral drugs: indinavir, efavirenz, saquinavir</td>
<td>Decreased efficacy</td>
</tr>
<tr>
<td>Cyclosporine</td>
<td>Decreased serum concentration leading to rejection of transplanted organ</td>
</tr>
<tr>
<td>Sumatriptan</td>
<td>Additive serotonin effects</td>
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</table>

Table 3. Drug Interactions With St John’s Wort4,36-41

Abbreviations: MAOI, monoamine oxidase inhibitor; SSRI, selective serotonin reuptake inhibitor.
drug interactions is currently lacking in the literature with much of the information being greater than 10 years old and based on anecdotal case reports. With only a few anecdotal case reports in the literature about herb-drug or herb-anesthesia interactions, determining exact cause of adverse events has been difficult. Because of the lack of randomized controlled clinical studies, unknown active ingredients, and unregulated herbal supplement concentrations, the overall risk of continuing herbal medications through surgery is unknown.

It is important that anesthesia providers ask patients directly in the preoperative period about the medications they take because patients do not often disclose the use of natural remedies. Specifically, anesthetists must consider the potential for cardiovascular instability, herb-drug interactions, and potential adverse reactions with anesthetic agents before surgery start. Impaired coagulation, prolongation of anesthesia, and immunosuppression represent a few of the potential perioperative problems anesthesia providers may face when caring for patients who take herbal medications.

Conclusion
The rapid growth in herbal supplement use in the United States over the past 20 years poses problems for anesthesia providers. Herbal medicines are not regulated in the same manner as pharmaceutical drugs, thus manufacturing standards, and drug concentration are highly variable. This leads to wide variation of supplement concentration, efficacy, and product labeling. Companies are not responsible for complete premarket safety testing of their product. Determining what patients are actually taking is difficult because of this lack of uniformity of concentration, and because patients often do not report herbal supplement use to their healthcare provider. Anesthesia providers must remain vigilant when interviewing patients preoperatively, and be aware of potential side effects, drug interactions, and complications that may arise with the use of herbal supplements.

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