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2000 Student Writing Contest Honorable Mention

Herbal medicines and possible anesthesia interactions

Herbal medicines are biochemically active compounds that have the potential to interact with drugs used in anesthesia. Lack of herbal standardization makes definitive diagnosis of herb-anesthesia interaction difficult. However, identified herbal use and an understanding of possible interactions can alert the anesthesia provider and raise suspicion of possible herb-related complications.

In a recent survey, 22% of patients undergoing surgery reported herbal medicine use. Most patients using herbal remedies fail to report this use to their healthcare providers. Herbal medicine use is not routinely addressed during the preoperative interview. The interviewer should include open-ended questions such as: "What herbal or vitamin supplements do you currently take?"

The purpose of this review is to give an industry overview and look at commonly used herbal medicines, focusing on those with the greatest potential for anesthetic and operative complications.

Key words: **Anesthesia, drug interaction, herbs.**

Approximately 15 million Americans have reported using herbs and/or high-dose vitamins.[1] In a recent survey, 22% of patients reported using herbal remedies.[2] The most likely herbal consumers were women and adults aged 40 to 60 years.[2]

Most anesthesia providers do not include questions about herbal use in the preoperative interview.[3] Although 30% of prescription drugs are derived from botanical sources, many patients believe that herbals are harmless and do not identify them as drugs.[4,5] Many herbs are biochemically active and have the potential to interact with drugs in the anesthesia armamentarium.[1,6] The purpose of this review is to look at commonly used herbal medicines, focusing on those with the greatest potential for anesthetic interactions and operative complications.

The body of information relating to herbal medicine is largely anecdotal, with scattered empiric data.[7] There are many well-written texts on herbal medicine available. Respected scientists specializing in botanical medicine, such as Varro E. Tyler, PhD, of Purdue University School of Pharmacy, have produced a plethora of well-written, scientifically based herbal literature.[4] The majority of information found in his books and articles is based on the German Commission E monographs.[8,9] These monographs are analogous to prescription drug package inserts in the United States and are viewed as equally valid.[8-10]

Unfortunately, the average person is unable to distinguish between empiric data and corporate propaganda.[7] The general public views herbal medicines as harmless because they are "natural," with the implication that a chemical derived from a botanical source will elicit positive therapeutic actions without negative side effects.[5,11-13] This idea is perpetuated by a profit-driven, unregulated nutrition industry.[12] In addition, patients often seek healthcare advice from "pseudo-experts," many of whom may lack proper understanding of physiology, pathophysiology, and pharmacology.[4,11] There are countless pamphlets, books, and magazine articles written by modern day shamans, with the content taken as gospel by a misinformed public.[4,7,8,11] With a health food store clerk as his or her guide, the patient often does not make the connection that an herbal medicine may have an effect equivalent to a prescription drug.[5,7]

Regulation

In the United States, the Food and Drug Administration (FDA) classifies herbs as nutritional supplements through the Dietary Supplement Health and Education Act of 1994. This act defines herbal products, vitamins, minerals, and amino acids as dietary supplements. Although supplement labels are not permitted to make therapeutic claims, they may make claims regarding the supplement's effect on a function or structure of the body. For example, a label on a saw palmetto product is prohibited from stating that it provides a cure for benign prostatic hyperplasia. However, the label could state that saw palmetto "will improve urinary flow." A supplement label must also include the following disclaimers: "this statement has not been evaluated by the Food and Drug Administration" and "not intended to diagnose, treat, cure, or prevent any dis-

ease." The company must use the term dietary supplement and list each ingredient by name and quantity. The FDA does not police these companies or products, and the consumer must rely on corporate honesty.[4,5,8,11,14]

Herbal medicine is a part of mainstream healthcare in several European nations.[8,11,12,15] After receiving formal training in herbal medicine, 40% of German and French physicians use botanical therapies in their everyday practice.[8] In Germany, herbs are classified as drugs and regulated through the Commission E. This expert panel is comprised of physicians, pharmacists, pharmacologists, toxicologists, epidemiologists, and other scientists familiar with botanicals. The Commission E has developed approximately 300 monographs stating beneficial and adverse effects of botanicals.[15] Of the tested botanicals, 65% were found to be beneficial. The monographs are analogous to package inserts and provide accurate information on therapeutic effects, adverse effects, dosing, and pharmacology of herbal preparations. German herb manufacturers are required to follow specific monograph guidelines to assure quality and uniformity.[5,8-11,15]

US clinicians and scientists working with herbal medicines have suggested the adoption of a Commission E program. This idea has been met with fierce opposition by herbal manufacturers and the nutrition industry.[4] With regulations in place, manufacturers would be forced to prove the quality and purity of their products.[11] This could result in decreased profits due to money spent on assay tests and more stringent manufacturing standards.[4,7,11,16] Industry analysts have speculated that stricter standards would likely put many companies out of business.[4]

Standardization

In the United States, prescription drugs go through rigorous testing to assure that quality, manufacturing, and dosage standards are maintained. Herbs are defined as food supplements with no legally required proof of efficacy, side effect warnings, or manufacturing standards.[4]

The part of the plant used, in conjunction with climate and soil conditions, greatly affects herbal potency.[4,5,11,17] Great differences in the quantity of active substances have been found between harvested herbs when subjected to batch analysis.[17] Factors affecting potency include the amount of time the plant is allowed to mature and the time elapsed before the harvested plant is processed.[11]

Independent analysis performed on herbal preparations has revealed significant discrepancies between the amounts of active ingredients found in different brands.[4,18] A 1995 *Consumer Reports* study found that the amount of the active ingredient ginsenosides varied widely between reputable brands of ginseng. This could potentially cause dose-related problems if a consumer were to change brands and consume what he or she thought was an equivalent dose.[4] Other studies have found minimal to absent levels of ginsenosides in commercially available ginseng products available in the United States.[7]

Mislabeling and questionable purity also have proved problematic.[4,5,13,17-21] Manufacturers are not required to assay their products, eliminating an important safety check. Herbs can be easily misidentified by the importer and labeled incorrectly. Unlisted prescription drug additives have been reported and may account for the pharmacological effect observed.[17] Heavy metals, pesticides, and the prescription drugs aminopyrine, corticosteroids, and benzodiazepines have been discovered in herbal preparations.[13,17,20,21] In one case report, 13 arthritic patients obtained herbal medications from Hong Kong via mail order. Abnormal bleeding, bone marrow depression, hypertension, and cardiac arrhythmias were observed. The herbal product they were using was analyzed and found to contain a corticosteroid, indomethacin, and lead.[17,20]

Without proper analysis and strict labeling laws, the patient is at risk. Lack of government enforcement places patient safety in the hands of the manufacturers. With the manufacturers' prime motivation being profit, the potential for patient harm is real.[11,17] The aforementioned problems have the potential to complicate the patient's anesthetic course and make differential diagnosis difficult.

Herbs with the most potential for anesthesia interactions

• *Ma Huang*. Also known as Ephedra sinica, Ma Huang contains more than 40 species of various alkaloids including ephedrine and pseudoephedrine.[10,22] Ephedra is indicated for the treatment of asthma and fatigue.[9,23] This herb is the active ingredient in many diet, antifatigue, and cold remedies.[4,24] Ephedra is also easily converted to methamphetamine for illicit use.[10,22] Misuse has been linked to 22 deaths, leading to a 1995 FDA warning.[10] Ephedrine is an indirect-acting sympathomimetic drug. Pharmacological effects are due to the release of presynaptic norepinephrine from sympathetic neurons. This sympathetic discharge results in $alpha_{1,2}$ and $beta_{1,2}$ receptor agonism.[10]

When administered orally, ephedra reaches peak effect in 1 hour with a half-life of 6 hours. The $alpha_{1,2}$ and $beta_1$ action can potentially lead to hypertension,

palpitations, arrhythmias, and tachycardia.[10] Arrhythmias have been reported with concurrent administration of cardiac glycoside drugs and halothane.[23] Neurological effects include headache, dizziness, and nervousness.[10,22,23] A potential beneficial effect of ephedra is $beta_2$ receptor–related bronchodilation.[9,10] Long-term use of Ma Huang may result in tachyphylaxis, making intraoperative administration of indirect-acting sympathomimetics less effective.[23]

• *Ginseng.* Ginseng (American and Korean) is described by the German Commission E as a "tonic for invigoration and fortification in times of fatigue and debility and for declining capacity to work and concentrate."[15,23] The lay press touts it as an "adaptogen," aphrodisiac, cholesterol reducer, tumor inhibitor, energy booster, antioxidant, and general cure-all.[9,22] The majority of literature is subjective and based on superstition.[22] A review by Tyler investigated 37 clinical trials of ginseng released between 1968 and 1990. Fifteen of the studies were controlled, with 8 being double-blinded. Results were mixed; however, some studies showed improved physical and intellectual performance, while others found improvement in mood. The design and statistical analysis of the studies were described as questionable.[22]

Excessive ginseng consumption has been reported to induce hypertension and central nervous system (CNS) stimulation, possibly increasing anesthetic requirements.[9]

• *Ginkgo biloba.* Ginkgo biloba has been advocated for the treatment of organic brain dysfunction, intermittent claudication, vertigo, and tinnitis.[15,23] There are many active components of ginkgo being investigated. Ginkgolides A, B, and bilobalide are thought to have neuroprotective properties. The flavanoid portion is an antioxidant.[15] Therapeutic action is due to vasodilatation of cerebral and peripheral arteries resulting in improved tissue perfusion.[4,9] Ginkgo is also theorized to inhibit age-related central cholinergic receptor reduction and increase choline uptake by the hippocampus, enhancing memory and concentration.[15,23]

Intraoperative considerations revolve around changes in cerebral blood flow and potential coagulopathies. An increased cerebral blood flow resulting in intracranial pressure elevation could be deleterious in certain patient populations.[25] Ginkgolide B inhibits platelet-activating factor and increases bleeding times.[23] Case studies have reported spontaneous subdural hematomas and synergistic bleeding with coadministration of nonsteroidal anti-inflammatory drugs.[10,24] Ineffective platelet aggregation can lead to excessive and unnecessary blood loss.[25]

• *Guarana.* Guarana, also known as Paullinia cupana, contains a high concentration of caffeine (1,3,7 trimethylxanthine) and is marketed as a CNS stimulant. This herb is found in many antifatigue products.[9] Seizures have been documented with excessive dosing of xanthines.[25]

Caffeine is a phosphodiesterase inhibitor. Inhibition of phosphodiesterase results in elevated cyclic adenosine monophosphate levels and enhanced $beta_{1,2}$ adrenergic responses. Bronchodilation is commonly seen due to increased efficacy with $beta_2$ stimulation. Administration of sympathomimetic drugs may lead to synergistic sympathetic activity, resulting in cardiac dysrhythmias and arrest. Dysrhythmias are commonly observed with concomitant caffeine and halothane administration.[25] Caffeine constricts cerebral vasculature, decreasing cerebral blood flow, which can be detrimental to certain patient populations.[23,25] Caffeine also potentiates the analgesia provided by nonprescription pain relievers by up to 40%. Guarana has also been shown to inhibit platelet aggregation and increase bleeding times.[9,26]

• *Yohimbe.* Yohimbe (active substance, yohimbine), is a selective presynaptic $alpha_2$ antagonist and weak monoamine oxidase (MAO) inhibitor.[22,27] The resultant rise in synaptic norepinephrine may increase volatile anesthetic needs and necessitate judicious use of sympathomimetic agents.[27] It is available by prescription, but also can be found in many over-the-counter impotence remedies and aphrodisiacs.[22] Yohimbe retailed at health food stores and sex shops has been shown to be of poor quality. Some brands may completely lack the active substance yohimbine. With the marketing of sildenafil (Viagra), pharmaceutical grade yohimbine is rarely prescribed.[22] The drug has been shown to be an effective treatment for men suffering from vascular, diabetic, and psychogenic impotence. Yohimbine readily crosses the blood-brain barrier and may cause tremor and increased skeletal muscle activity. Excessive doses may cause tachycardia, hypertension, paresthesias, and dissociative states.[27]

• *Kava kava.* Kava kava (*Piper methysticum*) is a CNS depressant used primarily as an anxiolytic and sedative. A few small, placebo-controlled, double-blind studies have shown that kavlactones (one of the active ingredients) were significantly better than a placebo in nonpsychotic anxiety disorders.[28] Volz and Kieser[29] studied the effects of kava in 101 outpatients with nonpsychotic anxiety disorders (criteria in the *Diagnostic and Statistical Manual of Mental Disorders*, *Third Edition*: agoraphobia, specific phobia, generalized anxiety disorder, and adjustment disorder with anxiety). A 25-week multicenter, randomized, placebo-controlled, double-blind trial was conducted using a 70% kava-

pyrone (another active ingredient) extract. The study showed that after 8 weeks, kava was significantly superior to placebo in the treatment of anxiety.[29]

Kava is thought to work at the γ-aminobutyric acid receptor and potentiate barbiturate and benzodiazepine effects. It also has been shown to have potent muscle relaxant properties. The mechanism of action involves inhibition of neuronal voltage–gated sodium channels. Toxic doses have produced dose-dependent, reversible ataxia, muscle weakness, and ascending paralysis without loss of consciousness. No neuromuscular junction curarelike effects have been observed. Kava is thought to be a dopamine antagonist. A few case studies have reported decreased effectiveness of levodopa therapy in people with Parkinson disease. The effects of dopamine antagonist antiemetics and antipsychotics may be potentiated.[28]

• *Valerian.* Valerian (*Valeriana officinalis*) is a CNS depressant with sedative and hypnotic effects. Valerinic acid inhibits the enzyme responsible for the breakdown of γ-aminobutyric acid. This can potentiate the sedative effects of benzodiazepines, barbiturates, and opiates.[24] The drug also exhibits antispasmodic effects on the gastrointestinal tract.[9] The German Commission E indicates valerian for treatment of insomnia and restlessness.[15]

• *St John's wort.* St John's wort (*Hypericum perforatum*) is indicated by the German Commission E for treatment of depression and anxiety. The drug is a first-line therapy in Germany for treatment of mild to moderate depression.[15] Anti-inflammatory and sedative activity also have been reported. Originally, the mechanism of action was thought to be MAO inhibition.[24] However, some recent research has indicated little to no MAO activity.[15] The other proposed mechanism involves inhibition of serotonin reuptake from the synaptic cleft.[24]

To err on the side of safety, the same precautions should be taken as if treating a patient taking a prescription MAO inhibitor or selective serotonin reuptake inhibitor.[24] MAO inhibitors are known to cause hepatic enzyme inhibition and exaggerate CNS depressant effects produced by opioids and barbiturates. Hepatic production of plasma cholinesterase also may be decreased, necessitating reduced succinylcholine dosing.[30] Exaggerated blood pressure responses to sympathomimetic drugs are possible. Direct-acting agents at a decreased dose are recommended over indirect-acting agents.[30]

• *Garlic.* Garlic (*Allium sativum*) has proposed antibacterial, antimycotic, and lipid-lowering effects. The Commission E indicates use in the treatment of the common cold, arteriosclerosis, and bronchitis. Surgical considerations stem from the drug's ability to inhibit platelet aggregation and enhance fibrinolytic activity. This can result in excessive intraoperative blood loss.[23]

• *Licorice.* Licorice *(Glycyrrhiza glabra)* is used as an expectorant, cough suppressant, and peptic ulcer remedy.[9,15] Licorice increases prostaglandin production in the stomach, protecting the gastric mucosa and allowing peptic ulcers to heal. This herb is generally viewed as unsafe due to its side effect profile.[9]

High doses of licorice increase glucocorticoid concentrations in tissues responsive to mineralocorticoids, resulting in pseudoaldosteronism. Sodium and water retention result in hypertension. Hypokalemia can be significant and lead to potentially fatal cardiac arrhythmias if undiagnosed. Licorice is contraindicated in patients taking cardiac glycosides and potassium-excreting diuretics.[9]

Discussion

Possible herb-anesthesia interactions should not be overlooked when forming a differential diagnoses in the perioperative setting. Preoperative history should be inclusive of herbal medications the patient is currently using. The healthcare provider performing a preoperative interview should include open-ended questions such as: "What herbal or vitamin supplements do you currently take?" The follow-up questions should be similar to those used when inquiring about prescription drug use.[11,31] The lack of herbal medicine standardization limits the ability to conceptualize dose-response relationships. We cannot assume that 900 mg of brand Y garlic is therapeutically equivalent to 900 mg of brand X garlic.[4] However, identified herbal use can alert the anesthesia provider and raise suspicion of possible herb-anesthesia interactions. For example, if the surgeon reports excessive bleeding, it may be the daily garlic dose the patient failed to stop taking preoperatively.[23] The addition of herbal use to the preoperative interview and an understanding of the possible ramifications of each compound can provide a more complete patient picture. This information can then be used as an additional component of a finely tailored anesthetic plan.

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