

Herbal Medicines: Anesthetic Concerns

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Introduction More than 20,000 herbal and related products are presently available in the United States. As many as 70% of patients do not reveal their use of these agents to treating anesthesiologists, considering nutraceuticals as “natural supplements” rather than a form of medicine. Hence, the patient presenting for emergency or elective surgery may pose a considerable challenge in terms of unexpected complications during preoperative care.

Definition and Use of Herbs:

Herbs are derived from flowers, shrubs, trees, algae, ferns, fungi, seaweeds and grasses. They are used not only to treat diseases but to improve the quality of life. All parts of plants are used. A belief held by many is that herbs are not drugs and are therefore safe. However the word “drug” is derived from an ancient word for “root” and thus, by definition, herbs are drugs. And, as many cases have proved, herbal use is not always safe and can even result in a fatal outcome. There has been a recent resurgence in the US in herbal reasons for many reasons, including efficacy, economic reasons, exposure to other cultures, ready availability and advertising.

It is estimated that approximately 20% of the adult population in the United States, take herbal medicines, megavitamins or both along with prescription drugs. Annual expenditures on herbal therapies alone have exceeded \$5 billion in recent years. It is important to understand the pharmacodynamics and pharmacokinetics of these self-prescribed formulations, and to be able to provide adjunctive therapy for treatment of unexpected drug-induced responses perioperatively. Also, 42% of adult Americans have used at least one alternative therapy in recent years. Relaxation techniques and herbs have been advocated to treat chronic medical conditions such as diabetes, cancer, arthritis or AIDS. Insurance plans and managed care organizations are beginning to offer reimbursement for alternative treatments. Coverage of chiropractic treatment is mandated by law in at least 45 states, acupuncture in 7 states and naturopathy in 2 states. Insurance plans that cover alternative health care often require physician referral for these services, highlighting the importance of physician awareness for less conventional therapies. Also, especially problematic for physicians is that up to 70% of patients who take herbal preparations do not tell their doctors of this practice believing it to be “safe” and “natural” and thus not “drug” related.

History of Herbal Medicine:

The history of herbal medicine is inextricably intertwined with that of modern medicine. Many drugs listed as conventional medications were originally derived from plants. Some herbs are of historic importance. For example, white willow bark, and meadowsweet plant are the basis for salicylic acid, a precursor of aspirin; foxglove plant is the basis for digitalis, cinchona bark is the precursor to quinine compounds, periwinkle provides the chemotherapeutic agent, vincristine. The most widely used narcotic, morphine is derived from the opium poppy

Drugs From Herbs:

Once scientific methods were developed to extract and synthesize the active ingredients from useful medicinal plants, pharmaceutical laboratories took over from the providers of medicinal herbs as producers of modern drugs. 30% of all modern conventional medicines are derived from plants. Some of the drugs, of importance in the perioperative period, derived from plants are listed below. (**Table 1**)

Plant	Drug
Atropa Belladonna	Atropine
Digitalis Purpurea	Digitalis
Papaver somniferum	Codeine
Cephaelis ipecaucuanha	Ipecac
Physostigma venunosum	Physostigmine
Ephedra sinica	Ephedrine
Erythroxyton coca	Cocaine
Datura fastuosa	Scopolamine

Government Regulation:

Several inconsistencies exist regarding manufacturing, promotion of health claims, potency and purity of compounding regarding herbal preparations. Herbal remedies are not held to the same standards and regulations as the FDA maintains for the pharmaceutical industry. Phased trials are not required though the FDA can “suggest” provision of scientific data to consumers. Herbs are not patented. However, recent regulation permits patenting of certain combinations of herbs. Although the Dietary Supplement Health and Education Act of 1994 places the burden of product safety assurance on the manufacture, the FDA assumes the responsibility to prove that a product is unsafe. Thus, only if the FDA has reason to believe that a herb is unsafe, can it remove the drug from the market. Nevertheless, as noted above, the FDA is not and cannot test all herbal preparations before they are available over the counter.

Safety and health claim practices continued to be concerning and on April 29, 1998 the FDA put forth the “Regulations on Statements Made for Dietary Supplements Concerning the Effects of the Product on the Structure of Function of the Body.” These regulations state that “under the proposal dietary supplements that expressly or implicitly claim to diagnose, treat, prevent or cure a disease continue to be regarded as drugs and have to meet the safety and effectiveness standards for drugs under the Food, Drug and Cosmetic Act.” The definition of disease is “any deviation from, Impairment of, or interruption of the normal structure of function of any part, organ or system of the body that is manifested by a characteristic set of one or more signs or symptoms...”. This definition allows the claim “promotes vascular health” while disallowing the statement “decreases blood pressure.” In response to the regulations, herbal manufactures now add information that their product “ is not intended to diagnose, treat, cure or prevent any disease” and thus is not subject to the FDA drug regulations.

Both the American Society of Anesthesiologists (ASA) and the New York State Society of Anesthesiologists (NYSSA) have addressed the seriousness of drug interactions with herbal preparations and anesthetics. The ASA has produced a pamphlet (Considerations for Anesthesiologists: What you should know about your patients’ use of Herbal Medicines: available from the ASA, 520 N.. Northeast Highway, Park Ridge, IL 60068-2573, WWW.ASAhq.org, 1999). The NYSSA issued a warning in the form of an edition of the newsletter, Monitor (Herbal Medicines Can Have a Significant Impact During Surgery, Monitor, Spring 1999; available from the NYSSA, 360 Lexington Ave, Suite 1800, New York, NY 10017, WWW.nyssa.pga.org).

Commonly used Herbs

A recent survey of 163 health food retail stores in the United States revealed that the top 10 selling herbs were, Echinacea (*Echinacea purpurea*, *Echinacea pallida* and *angustifolia*), garlic, goldenseal (*Hydrastis canadensis*), ginseng (*Asian Panax ginseng* and *American Panax quinquefolius*), ginkgo (*Ginkgo biloba*), saw palmetto (*Serenoa repens*), aloe (*Aloe species*), ma huang (*Ephedra sinica*), siberian ginseng (*Eleutherococcus senticosus*) and cranberry (*Vaccinium macrocarpon*). Current trends suggest St. John’s wort (*Hypericum perforatum*), valerian (*Valeriana officinalis*) and feverfew (*Tanacetum parthenium*) are likely soon to be listed among the top 10 herbal agents.

Echinacea The Echinacea are members of the daisy family and grow widely throughout North America. Alkylamide and polysaccharide constituents of echinacea possess significant *in vitro* and *in vivo* immunostimulation properties due to enhanced phagocytosis and nonspecific T-cell stimulation. In a randomized, double-blind, placebo-controlled study involving 302 volunteers taking *E. angustifolia* and *E. purpurea* roots versus placebo, the two echinacea compounds had subjective beneficial effects with regard to upper respiratory infection (rates of infection were- 36.7% in placebo group, 32% in *E. angustifolia* group and 29.3% in the *E. purpurea* group. However, the observations failed to achieve statistical significance. The herb has also been used to aid in wound healing.

The most common side effect, after oral administration, is an unpleasant taste sensation. A prolonged use of echinacea (more than 8 weeks) can cause tachyphylaxis, albeit through an unknown mechanism. There is a possibility of anaphylaxis even with a single dose of the herb, as it can cross-react with other allergens, especially with members of the sunflower family (asteraceae) This herb can be potentially hepatotoxic if used with other hepatotoxic agents (e.g. anabolic steroids, amiodarone, methotrexate and ketoconazole. Flavinoids from *E. purpurea* are known to inhibit the hepatic cytochrome P-450 3A4 and sulfotransferas. Use of Echinacea is contraindicated in systemic and autoimmune disorders.

Drug Interactions: The immunostimulatory effects of echinacea may offset the immunosuppressive actions of corticosteroids and cyclosporine. Since the herb is known to cause inhibition of the hepatic microsomal enzymes, its concomitant use with drugs e.g. phenytoin, rifampin, phenobarbital, which are metabolized by the hepatic microsomal enzymes, should be avoided as such a combination can precipitate toxicity of these drugs.

Garlic:Garlic (*Allium sativum*) has been used for centuries. The most active ingredient alliin (contains sulfur, and combined with breakdown products, gives garlic its characteristic smell). Crushing the garlic clove activates the enzyme allinase which converts allin to alliin. Recent studies have targeted its vasodilator and hypocholesterolemic activity. Garlic derivatives are also frequently used for antiplatelet, antioxidant and fibrinolytic effects. The evidence supporting the use of garlic for hypertension is less substantial, with a few clinical trials showing modest decreases in systolic and diastolic blood pressure with the use of garlic supplements. Decreased platelet aggregation has been noted. There is a reported case of spontaneous spinal/epidural hematoma in a 87 year-old male, with associated platelet dysfunction related to excessive garlic ingestion.

Drug Interactions:

Garlic may augment the effects of warfarin, heparin, non-steroidal anti-inflammatory agents (NSAID's), aspirin and may result in an abnormal bleeding time that may increase the risk of perioperative bleeding. Awareness of this action is especially important for chronic pain patients who not frequently have tried many different types of therapy and now may present for neuraxial block.

Ginger:Ginger (*Zingiber officinale*) has been described as an effective adjuvant against nausea, vomiting, motion sickness and vertigo. Anti-vertigo effects of ginger have been observed. In comparing the effect of diphenhydriate and ginger in the treatment of motion sickness, results demonstrated that ginger exerted a superior anti-motion sickness response. These studies further concluded that ginger exerts a gastric mechanism unlike diphenhydriate, which has a central nervous system mechanism. Ginger has been found to be effective in controlling the symptoms in hyperemesis gravidarum. However, two recent clinical trials, concluded that ginger was ineffective in reducing the incidence of postoperative nausea and vomiting in patients undergoing gynecologic laparoscopic surgery. Ginger has been found to be a potent inhibitor of thromboxane synthetase enzyme, which can prolong bleeding time. The root may also be used as seasoning and as a taste enhancer with other less palatable herbs.

Drug Interactions:

Use of ginger may increase bleeding time; therefore, its use should be avoided in patients on anticoagulants like warfarin and heparin or drugs such as NSAIDs and aspirin. The caveat about neuraxial blocks as noted above also applies.

Ginkgo biloba: Also known as Maidenhair-tree, the extracts from the leaves of the *Ginkgo biloba* tree have long been used in traditional Chinese medicine. The use of ginkgo biloba is on the rise in the United States. In 1997, it was one of the best selling herbs on the United States market, with sales in excess of \$240 million. The most important components are flavinoids, terpenoids, and organic acids. Metabolic pathways vary. Thus far, four preparations of ginkgo have been used in clinical trials, namely tebonin, tanakan, rokan and kaveri. The extract from the first three forms has been classified as EGB761.

The herb is used as an antioxidant, circulatory stimulant, and for the treatment of intermittent claudication, tinnitus, vertigo, memory enhancement, and sexual dysfunction. A recent large placebo-controlled, double-blind, randomized trial concluded that ginkgo extract was capable of stabilizing and modestly improving cognitive performance and social functioning ability. Also the herb has the potential to improve symptoms of intermittent claudication and can inhibit platelet-activating factor, modulate nitric oxide, and has an anti-inflammatory effect. Ginkgo biloba is considered to be relatively safe with few side effects, limited to mild gastrointestinal upset and headache. However, a few disturbing case reports have been published. Ginkgo biloba-induced spontaneous hyphema (bleeding from the iris in the anterior chamber of the eye), subarachnoid hemorrhage, and spontaneous bilateral subdural hematomas have been described. Of additional concern is the ginkgo toxin which is neurotoxic.

Drug Interactions: Although there have been no placebo-controlled double-blind studies regarding potential ginkgo-induced abnormal bleeding, concomitant use with aspirin, or any NSAIDs and anticoagulants such as warfarin and heparin, is not recommended as ginkgo may increase the potential to bleed. Concomitant use with anticonvulsant drugs (e.g. carbamazepine, phenytoin, phenobarbital) is also not recommended as it may decrease the effectiveness of these highly useful drugs. In addition, it has been suggested that ginkgo should be avoided in patients taking tricyclic antidepressant agents, as the herb might increase the seizure threshold lowering the efficacy of these agents.

St. John's Wort : Known colloquially as St. John's Wort, *hypericum perforatum*, is approved in Europe for the treatment of anxiety, depression sleep related disorders and vitiligo among many other ailments. Active compounds include, naphthadihydrodianthrones, particularly hypericin and pseudohypericin; flavinoids including quercitrin, rutin and hyperin.

The mechanism of action of this herb is controversial. Hypericum extract inhibits isoforms of monoamine oxidase *in vitro*, but this has not been observed in *in-vivo* experiments. *In-vitro* studies have shown inhibition of GABA receptors by hypericum, which suggests a mode of action for the antidepressant effect of the herb. According to some researchers, serotonin receptor inhibition may be the underlying mechanism responsible for the antidepressant action.

Side effects include dry mouth, dizziness, fatigue, constipation and nausea. The most prominent adverse effect, attributed to its hypericin component, is photosensitivity. There have been no reports of any adverse effects on cardiac conduction although if used concomitantly with a selective serotonin reuptake inhibitor (SSRI) e.g. fluoxetine or paroxetine, it can cause a serotonergic syndrome, characterized by tremors, hypertonicity, myoclonus, autonomic dysfunction, hallucinosis, hyperthermia and even death.

Drug Interactions:

Concomitant use of St. John's wort is currently not recommended with photosensitization drugs (e.g. piroxicam and tetracycline hydrochloride), monoamine oxidase inhibitors (e.g. phenelzine),

-sympathomimetic amines (e.g. ma huang, pseudoephedrine hydrochloride or SSRIs (e.g. fluoxetine or paroxetine).

Ginseng: There is a wide variation in the components of this herb. The active compound in panax ginseng is ginsenoside. The herb has been used as an aphrodisiac, anti-aging and energy-boosting tonic. It is also used by modern day athletes, to increase their “energy levels” and is used as an antioxidant. It has been labeled as an adaptogenic, augmenting adrenal steroidogenesis via a centrally mediated mechanism. Ginseng’s immunomodulatory effects have been described and studies have shown a ginseng-induced hypoglycemic effect, attributed to ginsenoside Rb2 and panaxans I, J, K, and L.

Adverse effects include hypertension, insomnia, headache, vomiting, and epistaxis. Stevens-Johnson syndrome, postmenopausal vaginal bleeding, mastalgia and diffuse breast nodularity have been associated with the use of this herb. Ginseng should be avoided in pregnancy, in children, lactating women, and in patients with cardiovascular disease. One fatality associated with ginseng laced with ma huang has been described. The herb may interact with warfarin with clinically relevant coagulation modulation due to antiplatelet components.

Drug Interactions:

The use of ginseng should be avoided in patients on drugs like warfarin, heparin, NSAIDs and aspirin. Since ginseng can cause hypertension, attention should focus on perioperative hemodynamic variation as these patients are often volume depleted and since many anesthetic agents can cause generalized vasodilatory effects intraoperative hypotension may result. Concomitant use of ginseng with monoamine oxidase inhibitors (e.g. phenelzine sulphate), should be avoided as manic episodes have been reported with routine use of ginseng. Ginseng should be used cautiously in patients on hypoglycemic medications. Also, blood glucose levels should be monitored perioperatively in patients at risk. (e.g. neurosurgical patients receiving steroids, patients with diabetic and stage renal disease.

Piper methysticum (Kava kava): Kava-kava is commonly used for its anxiolytic properties. The herb has been attributed with anesthetic, analgesic, anti-convulsive, anti-fungal, sleep inducing and spasmolytic properties. Kava-kava can cause visual alterations, ichthyosiform dermatopathy, and hallucinations. Antinociceptive effects produced by kava-kava may be similar to local anesthetic responses. The inhibition of noradrenaline may contribute to the psychotropic qualities of the herb.

Drug Interactions:

Ethanol can increase the hypnotic effect of Kava-kava and it should be avoided in patients with endogenous depression as it increases the risk of suicide. Kava-kava can potentiate the effects of barbiturates and benzodiazepines and can cause excessive sedation.

Chrysanthemum (Tanacetum) Parthenium (Feverfew): Introduced to the Americas as an ornamental medical herb, it is used as an insecticide in Mexico and was also advocated as an alternative for aspirin. The most common use now is for migraine headaches. Parthenolide is the active compound. The word feverfew is derived from the Latin word, febrifugia, meaning, “fever reducer”. Feverfew inhibits serotonin release from aggregating platelets possibly related to inhibition of the release of arachidonic acid via a phospholipase-linked mechanism. The herb has been found to reduce prostaglandin production by 86% to 88% without inhibiting the cyclooxygenase.

Adverse effects include aphthous ulcers, and gastrointestinal irritability. Rebound headache may be associated with cessation of use. Feverfew is not recommended for children, pregnant patients or nursing mothers. Post feverfew syndrome is characterized by nervousness, headaches, insomnia, arthralgias, joint stiffness and fatigue.

Drug Interactions:

Feverfew can inhibit platelet activity and its use should be avoided in patients taking medications such as, heparin, warfarin, NSAIDs, aspirin and vitamin E . Tannin-containing herbs like feverfew, can interact with iron preparations, thereby reducing their bioavailability.

Ephedra sinica (Ma huang): The herb is traditionally used for treatment of the common cold, flu, various allergic symptoms, bronchitis, low blood pressure, fever, asthma, arthritis and fluid retention. Native-Americans have used ephedra as an external application for sore healing. It acts as a sympathomimetic agent, and has positive inotropic and chronotropic responses. Ephedra also has bacteriostatic and antitussive actions. It is a cardiovascular stimulant (acts as an α or β -adrenergic agonist) and is a potent bronchodilator. Because it increases metabolic rate, ephedra is contained in many over-the-counter “slimming preparations”.

Adverse effects of this herb include hypertension, tachycardia, cardiomyopathy, cardiac dysrhythmias, myocardial infarction, cardiovascular accidents, seizures, psychosis and/or death. Numerous fatalities, due mainly to myocardial infarction or cerebrovascular accidents have been linked to its use have been attributed to a lack of standardization in formulation.

Drug Interactions:

Ephedra can interact with volatile general anesthetic agents (e.g. halothane) and cardiac glycosides (e.g. digitalis) to cause cardiac dysrhythmias. Patients on ephedra, under general anesthesia, can have severe hypotension that can be controlled with phenylephrine instead of ephedrine. Use of ephedra with phenelzine or other monoamine oxidase inhibitors may result in insomnia, headache, and tremulousness. Concomitant use with oxytocin, can cause hypertension

Other commonly used herbs:

Several herbs are used that may or may not have perioperative implications. Goldenseal is used as a mild laxative and to reduce inflammation. It may increase hypertension. It is widely used for intestinal problems, and may increase blood pressure or cause electrolyte imbalance from diarrhea. Saw Palmetto, given for urinary difficulties may interact with other hormone therapies. Valerian, used for its sedative and muscle relaxant effects, may increase the effectiveness of antiseizure medications and prolong action of other sedatives.

Anesthesia and Herbal Medicine (Table 2)

Only a small number of case reports relate to herbal medicine/anesthesia interactions, substantiating the need for well-designed scientific studies to elaborate the anesthetic responses in patients taking over-the-counter herbs. In a recent case report, a male patient had a cardiac arrest, 20 minutes after receiving epidural anesthesia. Blood samples revealed low plasma renin and aldosterone levels. The patient was taking an herbal medicine containing ethoxybenzamide, which is a NSAID, for one and a half years. The cardiac arrest was believed to be related to NSAID-induced hyporeninemic hypoaldosteronism, superimposed on epidural anesthesia-induced sympathectomy.

Rarer agents have also been studied. A traditional Chinese herbal medicine, Huatuo reconstructive pill (HRTP) used for thousands of years for cerebral palsy, has been studied in anesthetized animals. Carotid blood flow was selectively increased (up to 173%) without changing vascular resistance of the hind limb. A positive inotropic action was demonstrated by an increase in left ventricular pressure and cardiac output without changes in heart rate, blood pressure, electroencephalogram, electrocardiogram, or respiration.

The American Society of Anesthesiologists (ASA) recommends that all herbal medications should be discontinued 2-3 weeks prior to an elective surgical procedure. If the patient is not sure of the contents of the herbal medicine, he/she should be urged to bring the container so that an attempt can be made to review the contents of the preparation. While such an action holds some promise

in the elective setting, emergency care should be based on a thorough drug-intake history from the patient or a relative, if possible.

Medical research and medical literature in general has not addressed this new group of health supplements, despite the fact that many of these herbs have the potential to cause serious health problems and drug interactions. Clinical trials are needed to study the anesthetic drug responses to commonly used nutraceutical agents.

Table-2

Herb	Adverse effects	Anesthetic Considerations
Echinacea	Unpleasant taste sensation, tachyphylaxis, potential-hepatotoxicity.	May potentiate barbiturate toxicity.
Garlic	Halitosis, prolongation of Bleeding time, hypotension.	Increased risk of Intraoperative hemodynamic instability.
Ginger	Prolongation of bleeding time	Increased risk of Intraoperative hemodynamic instability.
Gingko biloba	Platelet dysfunction	Increased intraoperative/postoperative bleeding tendencies. May decrease effectiveness of I/V barbiturates.
St. John's wort	Dry mouth, dizziness, constipation, nausea.	Pseudoephedrine, MAOI's, SSRI's should be avoided.
Ginseng	Hypertension, Insomnia, headache, vomiting, epistaxis, prolonged bleeding time, hypoglycemia	Increased risk of Intraoperative hemodynamic instability.
Kava kava	Characteristic Ichthyosiform dermatopathy	May potentiate effect of barbiturates/benzodiazepines, thereby causing excessive sedation.
Feverfew	Aphthous ulcers, Gastrointestinal irritability, headache.	Increased risk of intraoperative hemodynamic instability.
Ephedra	Hypertension, tachycardia, cardiomyopathy, CVA, cardiac arrhythmias.	May interact with volatile anesthetic agents e.g. Halothane and fatal cardiac dysrhythmias. Profound intraoperative hypotension controlled with phenylephrine and NOT pseudoephedrine.

Some of the more commonly used herbs and their side effects are shown.

Select the single correct answer

1. How many patients in the United States are estimated to take herbs, megavitamins or both along with prescription drugs?

- a) 20%
- b) 40%
- c) 60%
- d) 80%

2. Approximate expenditure on the herbal therapies in US in the year 1997, was in excess of;

- a) \$ 10 million
- b) \$ 20 million
- c) \$ 5 billion
- d) Unknown

3. The least likely reason for the recent Herbal Renaissance is:

- a) Safety
- b) Herbs often work
- c) Decreased meat diets are recommended
- d) Increased awareness and exposure to other cultures

4. Herbs are derived from:

- a) Fungi
- b) Seaweed
- c) Algae
- d) All of the above

5. Chiropractic treatment:

- a) Is not covered by insurance
- b) Often requires physician referral for these services
- c) Cannot be considered as an alternative therapy
- d) Is often effective for first line therapy in diabetes

6. Patients who take herbal preparations are most likely to:
- a) Tell their physicians
 - b) Do not confide this practice
 - c) Believe that they are “doing drugs” and should keep it a secret
 - d) None of the above
7. Paulus Aegineta:
- a) Consolidated the medical knowledge of the ancient Greeks, Romans and Arabians into a 7 volume compendium
 - b) Gave a description of herbs and their uses that has changed little for 1500 years
 - c) Lived probably in the early 7th century
 - d) All of the above
8. The foxglove:
- a) Was discovered by William Withering in 1785
 - b) Was known to the Greeks
 - c) Proved to be successful for all illnesses common in the 18th century
 - d) Probably resulted in death in many cases at first because of overdose
9. Which of the following statements is true?
- a) Atropine is derived from the poppy
 - b) Digitalis is extracted from the foxglove
 - c) Codeine is part of the belladonna plant
 - d) Scopolamine is a synthetic compound
10. The Dietary Supplement Health and Education Act::
- a) Ensures governmental supervision of all medical preparations
 - b) Requires that manufacturers of all medicinals perform large case studies
 - c) Places the burden of product safety assurance on the manufacturer
 - d) Requires nothing of the FDA

Answers:

1. a
2. c
3. a
4. d
5. b
6. b
7. d
8. d
9. b
10. c