33 Anesthetic Implications of Complementary and Alternative Therapies

SHIQIAN SHEN and LUCY LIN CHEN

KEY POINTS

- Herbal medication use has increased dramatically in the overall population and particularly in preoperative patients.
- Patients might not volunteer information unless they are queried specifically about herbal medication use.
- Although many commonly used herbs have side effects that affect drug metabolism, bleeding, and neuronal function, they are not subject to regulations on purity, safety, and efficacy.
- Knowledge of specific interactions and metabolism of herbs can provide practical guidelines to facilitate perioperative management.
- Other complementary therapies, including acupuncture and music therapy, have become increasingly popular and have shown positive results for certain pain conditions, albeit high-quality data are still lacking.
- Dietary supplements may influence gut microbiota, a consortium of diverse microorganisms residing in the gastrointestinal tract, which represents a new research frontier in perioperative medicine.

Complementary and alternative medicine (CAM) has implications for physicians in general, but has particular importance for the perioperative period because of specific complications associated with certain therapies. Complementary medicine is defined as the addition of nonconventional therapies to accepted treatments; alternative medicine describes the use of nonconventional therapies in lieu of accepted treatments. They have become an important part of contemporary health care. The more popular term of "integrative health or integrative medicine" is used when complementary approaches are incorporated into mainstream health care.

According to a 2012 U.S. National Health Interview Survey (NHIS), 33.2% of adults and 11.6% of children (4-17 years of age) have used CAM.[1,1a] Visits to CAM practitioners exceed those to American primary care physicians,[2] and CAM is even more widely used in Europe, where herbal medicines are prescribed more frequently than conventional drugs are. Furthermore, patients undergoing surgery appear to use CAM more than the general population does.[3] Aside from the widespread use of CAM, perioperative physicians have a special interest in CAM therapies for several reasons. First, several commonly used herbal medications exhibit direct effects on the cardiovascular and coagulation systems. Second, some CAMs can interfere with conventional medications that are commonly given in the postoperative period. Finally, the therapeutic potential of CAM in the perioperative period is increasingly being described in the literature for reducing postoperative nausea, vomiting, and pain.

Despite the public enthusiasm for CAM, scientific knowledge in this area is still incomplete and often confusing for practitioners and patients. One recent study confirmed poor knowledge of this subject among physicians.[4] Recommendations for clinicians are often based on small clinical trials, case reports, animal studies, predictions derived from known pharmacology, and expert opinion. Research is essential because CAM therapies are often widely adopted by the public before adequate data are available to support their safety and efficacy. In 1991, Congress established the Office of Alternative Medicine, which is now known as the National Center for Complementary and Integrative Health. It operates within the National Institutes of Health.

Based on the 2012 NHIS study, the most commonly used CAMs were natural products, deep breathing exercises, meditation, chiropractic or osteopathic manipulation, massage, and yoga. Interestingly, a 2017 NHIS survey noted increases in the use of yoga and meditation by both adults and children (https://nccih.nih.gov/research/statistics/NHIS, Accessed 11/13/2018/tg). CAM practices can be classified into three general categories (Box 33.1).[5] This chapter is not intended as a comprehensive review of CAM. Specific therapies relevant to anesthesia are discussed, with a focus primarily on herbal medicines. Nonherbal dietary supplements, acupuncture, and music are also considered because they are relevant to perioperative care.

BOX 33.1 Three Major Categories of Complementary and Alternative Medicine

1. Natural products: this group includes a variety of products, such as herbs (also known as botanicals),vitamins and minerals, and probiotics. They are widely marketed, readily available to consumers, and often sold as dietary supplements.
2. Mind-body practices: yoga, chiropractic and osteopathic manipulation, meditation, and massage therapy are among the most popular mind and body practices used by adults. Other mind and body practices include acupuncture, relaxation techniques (such as breathing exercises, guided imagery, and progressive muscle relaxation), tai chi, qi gong, and hypnotherapy.
3. Others: traditional healers, Ayurvedic medicine, traditional Chinese medicine, homeopathy, naturopathy, and functional medicine.

Modified from the National Center for Complementary and Integrative Health. https://nccih.nih.gov/health/integrative-health. Accessed April 11, 2018.

Herbal Medicines

Preoperative use of herbal medicines has been associated with adverse perioperative events.[6] Surveys estimate that 22% to 32% of patients undergoing surgery use herbal medications.[7-9] In a recent retrospective review, 23% of surgery patients indicated the use of natural products, and older patients preferred dietary supplements.[10]

Herbal medicines can affect the perioperative period through several classic mechanisms: direct effects (i.e., intrinsic pharmacologic effects), pharmacodynamic interactions (i.e., alteration of the action of conventional drugs at effector sites), and pharmacokinetic interactions (e.g., alteration of the absorption, distribution, metabolism, and elimination of conventional drugs). Because approximately 50% of herbal medicine users take multiple herbs concomitantly[7] and 25% of herbal medicine users take prescription drugs,[11] adverse effects are difficult to predict and attribute.

Herbal medicines are associated with unique problems not usually found with conventional drugs.[12] Many of the issues complicating the understanding of herbal medications derive from the fact that they are classified as dietary supplements under the Dietary Supplement Health and Education Act of 1994. As such, the introduction of herbal medications does not require animal studies, clinical trials, or postmarketing surveillance. Under current law, the burden is shifted to the U.S. Food and Drug Administration (FDA) to prove products unsafe before they can be withdrawn from the market, such as the withdrawal of intranasal Zicam (cold medicine) after more than 130 reports of persistent anosmia.[13] Commercial herbal medicine preparations can have unpredictable pharmacologic effects resulting from inaccurate labeling, misidentified plants, adulterants, variations in natural potency, and unstandardized processing methods.

Two of the major problems confronting herbal medicine research involve quality control and added adulterants. In a recent clinical trial to treat human H1N1 influenza, an herbal formulation containing 12 different Chinese herbal medicines including licorice (genus *Glycyrrhiza*) was used.[14] Some of the other botanicals in the formula were not accurately identified. There are three *Glycyrrhiza* species on the market that may show a twofold difference when the three species are compared.[15]

Labeled active ingredients can vary tenfold in different commercial preparations.[16] In June 2007, the FDA issued regulations for current good manufacturing practices (GMPs) for dietary supplements.[17] This rule requires that proper controls be in place so that dietary supplements are processed in a consistent manner and meet quality standards. Especially emphasized are the identity, purity, strength, and composition of the products. Dietary products adhering to GMPs undoubtedly reduce the potential risk in the use of herbal medicines. Because this rule is somewhat similar to that for prescription drug GMPs, many supplement manufacturers believe that it is not practical for botanicals.[18]

Beyond quality control is the inclusion of biologically active pharmacologic adulterants in herbal medications and supplements. There are clinical consequences when quality control is lacking or herbal preparations are adulterated, as found in a weight-loss remedy study that revealed one manufacturer's incorrect substitution of an herb for another when the carcinogen aristolochic acid led to an outbreak of nephropathy and urothelial carcinoma.[19] In another event, more than 14 million capsules of asexual enhancement supplement were recalled because the compound on the label did not actually exist and the supplement did contain an analogue of sildenafil, which has not been tested in humans.[20] In light of these events, in August 2016, the FDA proposed a new guidance to evaluate the safety of supplements based on their history of use, formulation, proposed daily dose, and recommended duration of use. Although the guidance represents only a fraction of what is necessary for a new drug application, it requires some testing for tolerability in animals, but not in humans,[21] when products are marketed for consumption at doses substantively greater than those historically ingested. Any ingredient formulated or prepared in a novel manner is considered a new ingredient.

In this section, we discuss the preoperative assessment and management of patients who use herbal medicines and examine 11 herbal medicines that have the greatest effect on perioperative patient care: *Echinacea*, ephedra, garlic, ginger, *Ginkgo biloba*, ginseng, green tea, kava, saw palmetto, St. John's wort, and valerian (Table 33.1).

Preoperative Assessment and Management

Preoperative assessment should address the use of herbal medicines (see Table 33.1). One study found that 90% of anesthesia providers do not routinely ask about herbal medicine use.[22] Moreover, more than 70% of patients are not forthcoming about their herbal medicine use during routine preoperative assessment.[7] When a positive history of herbal medicine use is elicited, one in five patients is unable to properly identify the preparation being taken.[23] Asking patients to bring their herbal medicines

TABLE 33.1 Clinically Important Effects, Perioperative Concerns, and Recommendations for Perioperative Discontinuation of 11 Commonly Used Herbal Medicines

Herbs (Common Names)	Pharmacologic Effects	Perioperative Concerns	Discontinue Before Surgery
Echinacea (purple coneflower root)	Activation of cell-mediated immunity	Allergic reactions Decreases effectiveness of immunosuppressants Potential for immunosuppression with long-term use	No data
Ephedra (ma huang)	Increases heart rate and blood pressure through direct and indirect sympathomimetic effects	Risk of myocardial ischemia and stroke from tachycardia and hypertension Ventricular arrhythmias with halothane Long-term use depletes endogenous catecholamines and may cause intraoperative hemodynamic instability Life-threatening interaction with MAO inhibitors	24 h
Garlic (ajo)	Inhibits platelet aggregation (may be irreversible) Increases fibrinolysis Equivocal antihypertensive activity	May increase risk of bleeding, especially when combined with other medications that inhibit platelet aggregation	7 days
Ginger	Antiemetic Antiplatelet aggregation	May increase risk of bleeding	No data
Ginkgo (duck-foot tree, maidenhair tree, silver apricot)	Inhibits platelet-activating factor	May increase risk of bleeding, especially when combined with other medications that inhibit platelet aggregation	36 h
Ginseng (American ginseng, Asian ginseng, Chinese ginseng, Korean ginseng)	Lowers blood glucose Inhibits platelet aggregation (may be irreversible) Increased PT/PTT in animals	Hypoglycemia May increase risk of bleeding May decrease anticoagulant effect of warfarin	7 days
Green tea	Inhibits platelet aggregation Inhibits thromboxane A2 formation	May increase risk of bleeding May decrease anticoagulant effect of warfarin	7 days
Kava (awa, intoxicating pepper, kawa)	Sedation Anxiolysis	May increase sedative effect of anesthetics Increase in anesthetic requirements with long-term use unstudied	24 h
Saw palmetto (dwarf palm, *Sabal*)	Inhibits 5α-reductase Inhibits cyclooxygenase	May increase risk of bleeding	No data
St. John's wort (amber, goat weed, hardhay, hypericum, Klamath weed)	Inhibits neurotransmitter reuptake MAO inhibition unlikely	Induction of cytochrome P450 enzymes; affects cyclosporine, warfarin, steroids, and protease inhibitors; may affect benzodiazepines, calcium channel blockers, and many other drugs Decreased serum digoxin levels Delayed emergence	5 days
Valerian (all heal, garden heliotrope, vandal root)	Sedation	May increase sedative effect of anesthetics Benzodiazepine-like acute withdrawal May increase anesthetic requirements with long-term use	No data

MAO, Monoamine oxidase; *PT,* prothrombin time; *PTT,* partial thromboplastin time.

and other dietary supplements with them at the time of the preoperative evaluation would be helpful. A positive history of herbal medicine use should alert one to the presence of undiagnosed disorders causing symptoms leading to self-medication. Patients who use herbal medicines may be more likely to avoid conventional diagnosis and therapy.[24]

In general, herbal medicines should be discontinued preoperatively. Patients who require nonelective surgery are not evaluated until the day of surgery or are noncompliant with instructions to discontinue herbal medications preoperatively. In this situation, anesthesia can usually proceed safely at the discretion of the anesthesia provider, who should be familiar with commonly used herbal medicines. For example, recent use of herbal medicines that inhibit platelet function (e.g., garlic, ginseng, *G. biloba*) may warrant specific strategies for procedures with substantial intraoperative blood loss (e.g., platelet transfusion) and those that alter the risk-benefit ratio of using certain anesthetic techniques (e.g., neuraxial blockade).

Preoperative discontinuation of all herbal medicines might not eliminate complications related to their use. Withdrawal of some of the herbal medicines can increase morbidity and mortality after surgery similar to regular medications.[25,26] The danger of abstinence after long-term use may be similar with herbal medicines such as valerian, which can produce acute withdrawal after long-term use.

Although the American Society of Anesthesiologists has no official standard or guideline for the preoperative use of herbal medications, public and professional educational

information released by this organization suggests that herbals be discontinued at least 2 weeks before surgery.[25] Our review of the literature favors a more targeted approach. When pharmacokinetic data for the active constituents in an herbal medication are available, the timeframe for preoperative discontinuation can be tailored. Some herbal medications are eliminated quickly and may be discontinued near the time of surgery. For other herbal medicines, 2 weeks is recommended.[27]

Evidence-based estimates of herbal safety in the perioperative period are limited. One study of 601 patients who used traditional Chinese herbal medications suggested an infrequent rate of potential serious complications.[28] Clinicians should be familiar with commonly used herbal medications to recognize and treat any complications that might arise. Table 33.1 summarizes the clinically important effects, perioperative concerns, and recommendations for preoperative discontinuation of the 11 herbal medications that account for 30% of the dietary supplements sold in the United States.[29] The type of surgery and potential perioperative course should be considered in these clinical recommendations.

ECHINACEA

Three species of *Echinacea*, a member of the daisy family, are used for the prophylaxis and treatment of viral (decreasing the incidence and duration of the common cold), bacterial, and fungal infections, particularly those of upper respiratory origin, although its efficacy in fungal infections is doubtful.[30,31] The biological activity of *Echinacea* could be immunostimulatory, immunosuppressive, or antiinflammatory.[32] Although studies have not specifically addressed interactions between *Echinacea* and immunosuppressive drugs, experts generally warn against the concomitant use of *Echinacea* and these drugs because of the probability of diminished effectiveness.[33,34] In contrast to its immunostimulatory effects with short-term use, long-term use of more than 8 weeks is accompanied by the potential for immunosuppression[34] and a theoretically increased risk for postsurgical poor wound healing and opportunistic infections. A recent phytochemical study identified a potential immunosuppressant compound from *Echinacea*—cynarine.[35]

Information about Echinacea's pharmacokinetics is still limited.[36] *Echinacea* significantly reduced plasma concentrations of S-warfarin, but did not significantly affect warfarin pharmacodynamics and platelet aggregation in healthy subjects.[37] However, this herb should be discontinued as far in advance of surgery as possible when compromises in hepatic function or blood flow are anticipated.[38] In the absence of definitive information, patients with preexisting liver dysfunction should be cautious in using *Echinacea*.

EPHEDRA

Ephedra, known as *ma huang* in Chinese medicine, is a shrub native to central Asia. It is used to promote weight loss, increase energy, and treat respiratory conditions such as asthma and bronchitis. Ephedra contains alkaloids, including ephedrine, pseudoephedrine, norephedrine, methylephedrine, and norpseudoephedrine.[25] Commercial preparations can be standardized to a fixed ephedrine content. Publicity about adverse reactions to this herb prompted the FDA to bar its sale in 2004, but ephedra is still widely available via the Internet.

Ephedra causes dose-dependent increases in arterial blood pressure and heart rate. Ephedrine, the predominant active compound, is a noncatecholamine sympathomimetic that exhibits α_1, β_1, and β_2 activity indirectly by releasing endogenous norepinephrine (noradrenaline). These sympathomimetic effects have been associated with more than 1070 reported adverse events, including fatal cardiac and central nervous system complications.[39] Vasoconstriction and, in some cases, vasospasm of coronary and cerebral arteries can cause myocardial infarction and thrombotic stroke.[40] Ephedra can also affect cardiovascular function by causing hypersensitivity myocarditis, characterized by cardiomyopathy with myocardial lymphocyte and eosinophil infiltration.[41] Long-term use results in tachyphylaxis from depletion of endogenous catecholamine stores and can contribute to perioperative hemodynamic instability. In these situations, direct-acting sympathomimetics may be preferred as first-line therapy for intraoperative hypotension and bradycardia. Concomitant use of ephedra and monoamine oxidase inhibitors can result in life-threatening hyperpyrexia, hypertension, and coma. Finally, continuous ephedra is a rare cause of radiolucent kidney stones.[42] Recently, there was a case report describing acute angle-closure glaucoma caused by ephedra.[42a]

The pharmacokinetics of ephedrine have been studied in humans.[43,44] Ephedrine has an elimination half-life of 5.2 hours, with 70% to 80% of the compound excreted unchanged in urine. Based on the pharmacokinetic data and the known cardiovascular risks associated with ephedra, including myocardial infarction, stroke, and cardiovascular collapse from catecholamine depletion, this herb should be discontinued at least 24 hours before surgery.

GARLIC

Garlic is one of the most extensively researched medicinal plants. It has the potential to modify the risk for atherosclerosis by reducing arterial blood pressure, thrombus formation, and serum lipid and cholesterol concentrations.[45] These effects are primarily attributed to its sulfur-containing compounds, particularly allicin and its transformation products. Commercial garlic preparations can be standardized to a fixed alliin and allicin content.

Garlic inhibits platelet aggregation in vivo in a concentration-dependent fashion. The effect of one of its constituents, ajoene, is irreversible and can enhance the effect of other platelet inhibitors such as prostacyclin, forskolin, indomethacin, and dipyridamole.[46] Although the effects are not consistently demonstrated in volunteers, there is one case described in an 80 year old who had a spontaneous epidural hematoma develop that was attributed to continuous garlic use.[47] Garlic has interacted with warfarin, resulting in an increased international normalized ratio (INR).[48]

In addition to bleeding concerns, garlic can decrease systemic and pulmonary vascular resistance in laboratory animals, but this effect is marginal in humans.[49] Although there are insufficient pharmacokinetic data on garlic's constituents, the potential for irreversible inhibition of platelet function may warrant discontinuation of garlic at least 7 days before surgery, especially if postoperative bleeding is a particular concern or other anticoagulants are given. Additionally, garlic's pharmacokinetics should be considered when a risk-benefit analysis is made for neuraxial techniques.

GINGER

Ginger (*Zingiber officinale*) is a popular spice with a long history of use in Chinese, Indian, Arabic, and Greco-Roman herbal medicines. Ginger has a wide range of reported health benefits for those with arthritis, rheumatism, sprains, muscular aches, pains, sore throats, cramps, constipation, indigestion, nausea, vomiting, hypertension, dementia, fever, infectious diseases, and helminthiasis.[50] Ginger contains up to 3% volatile oil, mostly monoterpenoids and sesquiterpenoids.[51] Gingerols are representative compounds in ginger.[52]

Ginger is an antiemetic and has been used to treat motion sickness and to prevent nausea after laparoscopy.[53] The number of postoperative antiemetic medications was significantly reduced after aromatherapy with essential oil of ginger.[54] In another recent trial, ginger supplementation reduced the severity of acute chemotherapy-induced nausea in adult cancer patients and compared favorably to conventional antiemetics.[55]

In an in vitro study, gingerols and related analogues inhibited arachidonic acid–induced human platelet serotonin release and aggregation, with a potency similar to that of aspirin.[52] In another in vitro study, the antiplatelet effects of 20 ginger constituents were evaluated. Five constituents showed antiplatelet activities at relatively low concentrations. One of the ginger compounds (8-paradol) was the most potent cyclooxygenase-1 inhibitor and antiplatelet aggregation drug.[56] In a case report, a ginger-phenprocoumon combination resulted in an increased INR and epistaxis.[57] Although the sample size was relatively small, the platelet inhibition potential of ginger has been suggested in a pilot clinical study.[58] This result may warrant the discontinuation of ginger at least 2 weeks before surgery,

GINKGO

Ginkgo is derived from the leaf of *G. biloba* and has been used for cognitive disorders, peripheral vascular disease, age-related macular degeneration, vertigo, tinnitus, erectile dysfunction, and altitude sickness. Studies have suggested that ginkgo can stabilize or improve cognitive performance in patients with Alzheimer disease and multiinfarct dementia,[59] but not in healthy geriatric patients.[60] The compounds that might be responsible for its pharmacologic effects are the terpenoids and flavonoids. The two ginkgo extracts used in clinical trials are standardized to ginkgoflavone glycosides and terpenoids.

Ginkgo alters vasoregulation, acts as an antioxidant, modulates neurotransmitter and receptor activity, and inhibits platelet-activating factor. Of these effects, inhibition of platelet-activating factor is of primary concern for the perioperative period. Although bleeding complications have not occurred in clinical trials, four cases of spontaneous intracranial bleeding,[61-63] one case of spontaneous hyphema,[64] and one case of postoperative bleeding after laparoscopic cholecystectomy[65] have been described when ginkgo was being taken.

Terpene trilactones are highly bioavailable when administered orally. The elimination half-lives of the terpene trilactones after oral administration are between 3 and 10 hours. For ginkgolide B, a dosage of 40 mg twice daily resulted in a higher area under the curve, and a longer half-life and residence time, than after a single 80-mg dose. A once daily dose of 80 mg guaranteed a larger maximum concentration peak (T_{max}) that was reached 2 to 3 hours after administration.[66] The pharmacokinetics of terpene trilactones in three different ginkgo preparations in human plasma[67] indicate that ginkgo should be discontinued at least 2 weeks before surgery to avoid bleeding.[38]

GINSENG

Among the several species of ginseng used for their pharmacologic effects, Asian ginseng *(Panax ginseng)* and American ginseng *(Panax quinquefolius)* are the most commonly described.[68] Ginseng has been labeled an "adaptogen" because it reputedly protects the body against stress and restores homeostasis.[69] Because its pharmacologic actions are attributed to the ginsenosides, a group of compounds known as *steroidal saponins,* many commercially available ginseng preparations have been standardized to ginsenoside content.[68,70]

The many heterogeneous and sometimes opposing effects of different ginsenosides[71,72] give ginseng a broad but incompletely understood pharmacologic profile including general health, fatigue, immune function, cancer, cardiovascular disease, diabetes mellitus, cognitive function, viral infections, sexual function, and athletic performance.[69] The underlying mechanism is similar to that classically described for steroid hormones. This herb decreases postprandial blood glucose in both healthy and type 2 diabetes patients,[73] an effect that can create unintended hypoglycemia in patients who have fasted before surgery.

Ginseng can alter coagulation pathways. The antiplatelet activity of panaxynol, a constituent of ginseng, may be irreversible in humans.[74] Ginseng extract and ginsenosides inhibit platelet aggregation in vitro[75,76] and prolong thrombin time and activated partial thromboplastin time in in vivo animal models.[77,78]

The clinical evidence implicating ginseng as a cause of bleeding is weak and based on only a few case reports.[79] Although ginseng may inhibit the coagulation cascade, one case associated its use with a significant decrease in warfarin anticoagulation.[80] Subsequently, a study in volunteers showed that American ginseng interfered with warfarin-induced anticoagulation,[81] reducing its anticoagulant effect. When prescribing warfarin, clinicians

should specifically ask about ginseng use. In another clinical trial, warfarin's clearance was moderately increased with Asian ginseng.[82] Because warfarin is often used after orthopedic or vascular procedures, this herbal drug interaction can affect perioperative management in many patients.

In rats, the elimination half-lives are different after an intravenous infusion of ginseng, with ginsenosides Re and Rg1 between 0.7 and 4 hours, and ginsenosides Rb1 and Rd between 19 and 22 hours.[83] After oral administration of ginseng, ginsenoside Rb1 reached the maximum plasma concentration at approximately 4 hours with a prolonged half-life.[84,85] These data suggest that ginseng should be discontinued at least 48 hours before surgery. Because platelet inhibition by ginseng may be irreversible, ginseng use should be stopped at least 2 weeks before surgery.[38]

GREEN TEA

Tea from the *Camellia sinensis* is one of the most ancient and the second most widely consumed beverage in the world.[86,87] Tea can be classified into different types, such as green, oolong, and black. Green tea, which is not fermented and is derived directly from drying and steaming fresh tea leaves, contains polyphenolic compounds. Catechins in green tea account for 16% to 30% of its dry weight. Epigallocatechin-3-gallate (EGCG), the most predominant catechin in green tea, is responsible for much of the biologic activity mediated by green tea.[86]

In an early in vitro and in vivo study, both green tea and EGCG significantly prolonged mouse tail bleeding time in conscious mice. They inhibited adenosine diphosphate- and collagen-induced rat platelet aggregation in a dose-dependent manner.[88] The antiplatelet activity can result from the inhibition of thromboxane A2 formation by preventing arachidonic acid liberation and thromboxane A2 synthase.[89,90] Regarding a possible adverse effect of green tea on platelets, one case reported thrombotic thrombocytopenic purpura developed after a patient consumed a weight-loss product containing green tea.[91] On the other hand, drinking green tea could antagonize the anticoagulant effects of warfarin because green tea contains vitamin K.[92]

The half-life for EGCG in one study was between 1.9 and 4.6 hours[93] and in another study was observed to be between 2.2 and 3.4 hours.[94] Based on pharmacokinetic data and possible antiplatelet activity, green tea should be discontinued at least 7 days before surgery.

KAVA

Kava is derived from the dried root of the pepper plant *Piper methysticum*. Kava has gained widespread popularity as an anxiolytic and sedative. The kavalactones appear to be the source of kava's pharmacologic activity.[95]

Because of its psychomotor effects, kava was one of the first herbal medications expected to interact with anesthetics. The kavalactones can have many effects such as: (1) dose-dependent effects on the central nervous system, including antiepileptic, neuroprotective, and local anesthetic properties; (2) act as a sedative-hypnotic by potentiating inhibitory neurotransmission of γ-aminobutyric acid (GABA); (3) increased barbiturate sleep time in laboratory animals,[96] which might explain the mechanism of a coma attributed to an alprazolam-kava interaction[97]; (4) abuse potential, whether long-term use can result in addiction, tolerance, and acute withdrawal after abstinence is unknown; (5) increased γ-glutamyl transpeptidase levels with potential risk of hepatotoxicity[98]; and (6) produces "kava dermopathy," characterized by reversible scaly cutaneous eruptions.[99]

In an in vitro investigation, a kava compound (+)-kavain suppressed the aggregation of human platelets. Kava inhibits cyclooxygenase with the potential to decrease renal blood flow and to interfere with platelet aggregation. Consumption of kava has potential cardiovascular effects that could manifest in the perioperative period.[100,101] Although kava has been banned in Europe since 2002, it is available in North America and many countries in the Pacific region. A concentration-based response relationship can occur with hepatotoxicity, even leading to numerous cases of liver transplantation.[102-104]

Peak plasma levels occur 1.8 hours after an oral dose, and the elimination half-life of kavalactones is 9 hours.[105] Unchanged kavalactones and their metabolites undergo renal and fecal elimination.[106] Pharmacokinetic data and the possibility for enhancement of the sedative effects from anesthetics suggest that kava should be discontinued at least 24 hours before surgery. Earlier discontinuation probably should be considered when surgical procedures are expected to compromise hepatic function or blood flow.

SAW PALMETTO

Saw palmetto, which is used by more than 2 million men in the United States to treat symptoms associated with benign prostatic hypertrophy, is of questionable efficacy for this purpose.[107] The major constituents of saw palmetto are fatty acids and their glycerides (i.e., triacylglycerides and monoacylglycerides), carbohydrates, steroids, flavonoids, resin, pigment, tannin, and volatile oil. The pharmacologic activity of saw palmetto has not been attributed to a single compound.

Although the mechanism of action of saw palmetto is not known, multiple mechanisms have been proposed.[108] Saw palmetto extract, like finasteride, inhibits 5α-reductase in vitro; however, results of in vivo studies have been inconsistent.[109] Other proposed mechanisms are inhibition of estrogen and androgen receptors, binding of autonomic receptors, blocking of prolactin receptor signal transduction, interference with fibroblast proliferation, induction of apoptosis, inhibition of α_1-adrenergic receptors, and antiinflammatory effects.

In a patient undergoing craniotomy, saw palmetto was associated with excessive intraoperative bleeding that required termination of the procedure.[109] Another case of hematuria and coagulopathy in a patient who used saw palmetto was reported.[110] This complication was attributed to saw palmetto's antiinflammatory effects, specifically the inhibition of cyclooxygenase and subsequent platelet dysfunction. Because there are no pharmacokinetic or clinical data for saw palmetto, specific recommendations for preoperative discontinuation cannot be made.

ST. JOHN'S WORT

St. John's wort is the common name for *Hypericum perforatum,* and has been used for mental health and depression conditions. A multicenter clinical trial concluded that St. John's wort is not effective in the treatment of major depression.[111] The compounds believed to be responsible for its pharmacologic activity are hypericin and hyperforin.[112] Commercial preparations are often standardized to a fixed hypericin content of 0.3%.

St. John's wort exerts its effects by inhibiting reuptake of serotonin, norepinephrine, and dopamine.[113] Concomitant use of this herb with or without serotonin reuptake inhibitors can create a syndrome of central serotonin excess.[114] Although early in vitro data implicated monoamine oxidase inhibition as a possible mechanism of action, a number of later investigations have demonstrated that monoamine oxidase inhibition is insignificant in vivo.[115]

Use of St. John's wort can significantly increase the metabolism of many concomitantly administered drugs, some of which are vital to the perioperative care of certain patients. There is induction of the cytochrome P450 3A4 isoform,[116] and interactions with substrates of the 3A4 isoform, including indinavir sulfate,[117] ethinylestradiol,[118] and cyclosporine,[119] have been documented. There are important clinical consequences of this metabolic effect, particularly in transplant patients. In two case reports of heart transplant patients, after taking St. John's wort the patients' plasma cyclosporine concentrations became subtherapeutic and acute transplant rejection resulted. After stopping St. John's wort, plasma cyclosporine remained within the therapeutic range with no further episodes of rejection (Fig. 33.1).[120] In one series of 45 organ transplant patients, St. John's wort was associated with an average 49% decrease in blood cyclosporine levels.[121] Other P450 3A4 substrates commonly used in the perioperative period include alfentanil, midazolam, lidocaine, calcium channel blockers, and 5-hydroxytryptamine receptor antagonists. In addition, the cytochrome P450 2C9 isoform also may be induced, which results in decreased anticoagulant effect of warfarin, a substrate of the 2C9 isoform, in seven reported cases.[118] Other 2C9 substrates include the nonsteroidal antiinflammatory drugs. Furthermore, the enzyme induction caused by St. John's wort may be more pronounced when other enzyme inducers, which could include other herbal medications, are taken concomitantly. St. John's wort also affects digoxin pharmacokinetics.[115]

The single-dose and steady-state pharmacokinetics of hypericin, pseudohypericin, and hyperforin have been determined in humans.[122,123] After oral administration, peak plasma levels of hypericin and hyperforin are achieved in 6.0 and 3.5 hours, respectively, and their median elimination half-lives are 43.1 and 9.0 hours, respectively. Long half-life and altered metabolism of many drugs make concomitant use of St. John's wort a particular risk in the perioperative setting. Pharmacokinetic data suggest that this herbal medication should be discontinued at least 5 days before surgery. Discontinuation is especially important in patients awaiting organ transplantation or in those who might require oral anticoagulation postoperatively. Moreover, these patients should be advised to avoid taking St. John's wort postoperatively.

VALERIAN

Valerian *(Valeriana officinalis)* is an herb that is native to temperate regions of the Americas, Europe, and Asia. It is used as a sedative, particularly in the treatment of insomnia, and virtually all herbal sleep aids contain valerian.[124] Valerian contains many compounds acting synergistically, but the sesquiterpenes are the primary source of valerian's pharmacologic effects. Commercially available preparations may be standardized to valerenic acid.

Valerian produces dose-dependent sedation and hypnosis.[125] These effects are probably mediated through modulation of GABA neurotransmission and receptor function.[126] Valerian increased barbiturate sleep time in experimental animals.[127] In several randomized, placebo-controlled trials in humans, there was a mild subjective improvement in sleep with valerian, especially when used for 2 weeks or more.[128,129] Objective tests have had less consistent results, with little or no improvement in sleep noted.[130] In one patient, valerian withdrawal appeared to mimic an acute benzodiazepine withdrawal syndrome characterized by

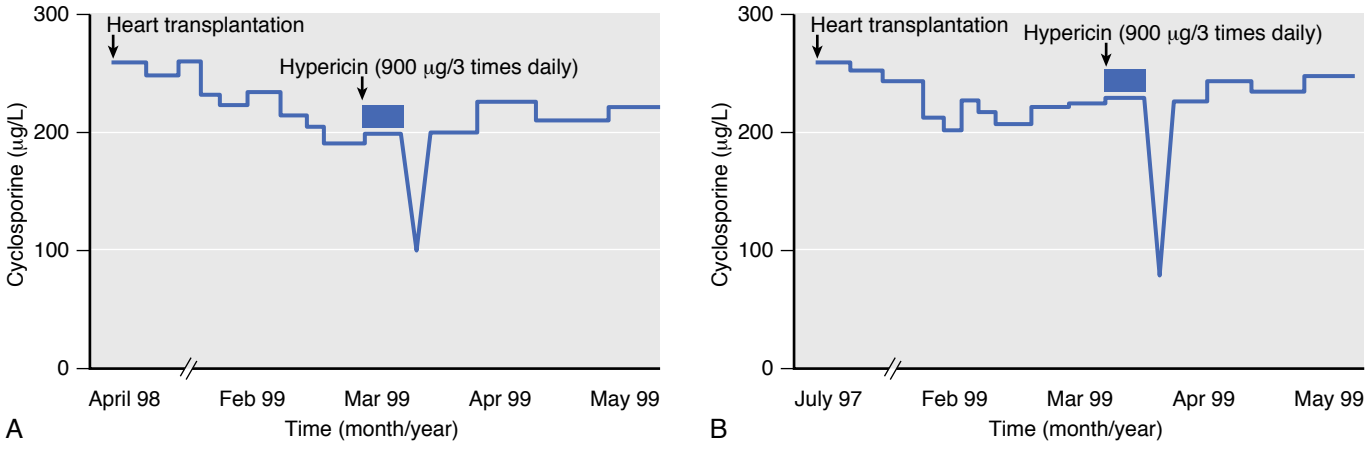

Fig. 33.1 Cyclosporine concentrations in two patients (A and B) after heart transplantation. Treatment with St. John's wort extract containing 900 μg of hypericin was associated with a drop in cyclosporine values below the therapeutic range and acute transplant rejection. (From Breidenbach T, Hoffmann MW, Becker T, et al. Drug interaction of St John's wort with cyclosporine. *Lancet*. 2000;355:1912.)

delirium, cardiac complications after surgery, and attenuation of the symptoms by administration of a benzodiazepine.[131] Based on these findings, valerian should potentiate the sedative effects of anesthetics and adjuvants that act at the GABA receptor, such as midazolam.

The pharmacokinetics of valerian's constituents have not been studied, although their effects may be short-lived. Abrupt discontinuation in patients who may be physically dependent on valerian risks benzodiazepine-like withdrawal. In these individuals, this herbal medication should be gradually decreased with close medical supervision over the course of several weeks before surgery. If such tapering is not feasible, physicians can advise patients to continue taking valerian until the day of surgery. Based on the mechanism of action and a reported case of efficacy,[131] benzodiazepines can treat withdrawal symptoms should they develop in the postoperative period.

OTHER HERBAL MEDICINES

In a survey conducted in 2007,[1] the top 10 herbal medicines also included soy isoflavones, grape seed extract, and milk thistle. There are no reports of adverse effects or perioperative risks from these herbs.

Although boldo *(Peumus boldus)*, Danshen *(Salvia miltiorrhiza)*, Dong quai *(Angelica sinensis)*, and papaya *(Carica papaya)* are encountered less frequently, it may be prudent to discontinue their use 2 weeks before surgery because they have shown antiplatelet aggregation activity and herb-drug interactions.[132]

COMMON DIETARY SUPPLEMENTS

Herbal medicines fall into the broader category of dietary supplements that also includes vitamins, minerals, amino acids, enzymes, animal extracts, prebiotics, and probiotics. Data on the safety of these agents in the perioperative period are scant. High-dose vitamin use, particularly of the fat-soluble vitamins (i.e., A, D, E, and K), can be associated with acute and chronic toxicity. Drug interactions for coenzyme Q_{10}, glucosamine, chondroitin, sulphate, and fish oil have been sufficiently documented to merit inclusion in this chapter. Prebiotics and probiotics have become increasingly popular in research, in the context of the rapidly evolving field of gut microbiome, adding to the current knowledge of perioperative medicine.

Coenzyme Q_{10}

Coenzyme Q_{10} (CoQ_{10}), or ubidecarenone, is a single-constituent antioxidant compound that is structurally related to vitamin K. It is widely promoted as an antioxidant. Endogenous CoQ_{10} can prevent the membrane transition pore from opening, because it counteracts several apoptotic events, such as DNA fragmentation, cytochrome c release, and membrane potential depolarization.[52]

Of importance, this compound interacts with warfarin and was investigated in rats.[133] Following oral administration of 1.5 mg/kg of racemic warfarin to rats during an 8-day oral regimen of CoQ_{10} (10 mg/kg daily), no apparent effect was observed on serum protein binding of warfarin enantiomers. Treatment with CoQ_{10} did not affect the absorption and distribution of the S- and R-enantiomers of warfarin, but it increased total serum clearance of both R- and S-warfarin. The increased clearance values are likely due to acceleration of certain metabolic pathways and renal excretion of the warfarin enantiomers.

An in vitro study showed a predicted 32% and 17% increase in the total clearance of S- and R-warfarin respectively with co-administration of 100 mg CoQ_{10}.[134] CoQ_{10} may decrease the effects of warfarin,[135] but results were inconsistent in another controlled, clinical trial.[136] In 171 patients, co-administration of CoQ_{10} with warfarin appeared to increase the risk of bleeding.[137] Based on the clinical information regarding drug interaction and reported prolonged elimination half-life (38-92 hours) after a single oral dose,[138] CoQ_{10} should be discontinued at least 2 weeks before surgery.

GLUCOSAMINE AND CHONDROITIN SULFATE

Glucosamine and chondroitin sulfate are widely used for joint disorders by many patients undergoing orthopedic procedures. Although their mode of action may be complex, glucosamine and chondroitin sulfate have been widely accepted as supplements in the management of osteoarthritis (OA) because they are the essential components of proteoglycan in normal cartilage.[139] When a large-scale trial evaluated glucosamine and chondroitin sulfate alone or in combination, pain was not reduced in a group of patients with OA of the knee. Exploratory analyses suggested that the two in combination might be effective in a subgroup of patients with moderate-to-severe knee pain.[140]

Long-term clinical data regarding the safety of glucosamine and chondroitin sulfate alone or in combination are limited. Use of chondroitin sulfate alone is well tolerated and without significant adverse drug interaction.[139] One concern regarding the use of glucosamine is its potential to cause or worsen diabetes in animal models[141]; this effect is supported by clinical studies.[142] In a report from the FDA MedWatch database, there were 20 cases of complications involving glucosamine or glucosamine-chondroitin sulfate use with warfarin. Coagulation was altered as manifested by increased INR or increased bleeding or bruising.[143]

When glucosamine is taken orally, 90% is absorbed. Because of extensive first-pass metabolism, only 25% bioavailability is achieved by oral administration compared with bioactivity of 96% with intravenous administration.[144] Peak plasma levels occurred 4 hours after an oral dose and declined to baseline after about 48 hours.[145] Chondroitin sulfate was absorbed slowly after oral ingestion with a plasma peak at 8.7 hours and decline to baseline at about 24 hours.[146] Considering the reported interaction between glucosamine-chondroitin and warfarin, these supplements should be discontinued 2 weeks before surgery, especially if warfarin will be given during the perioperative period.

FISH OIL

Intake of fish oil supplements containing omega-3 fatty acids (eicosapentaenoic acid and docosahexaenoic acid) reduces the incidence of many chronic diseases that involve

inflammatory processes, including cardiovascular diseases, inflammatory bowel disease, cancer, rheumatoid arthritis, and neurodegenerative illnesses.[147] However, omega-3 fatty acid did not reduce the rate of death in patients with cardiovascular risk in one study.[148] A metaanalysis of efficacy also concluded that omega-3 polyunsaturated fatty acid supplementation does not decrease the risk of all-cause mortality, cardiac death, sudden death, myocardial infarction, or stroke based on relative and absolute measures of association.[149] This article included many studies of patients with complex risk factors.

Omega-3 fatty acids, however, can inhibit platelet aggregation and increase bleeding risk by the following studies: (1) In vitro experiments have demonstrated an antiplatelet aggregate effect,[150] and inhibition correlated with platelet cyclic adenosine monophosphate levels.[151] (2) In vivo studies have showed decreased platelet aggregation but do not influence bleeding time.[152,153] (3) The inhibition of platelet aggregation was gender specific in a clinical study.[154]

Although evidence for significant bleeding concerns is not found in clinical trials,[155,156] several case reports have illustrated a possible interaction between warfarin and omega-3 fatty acids.[157] Extremely elevated INR associated with warfarin in combination with omega-3 fatty acids was found in two cases.[158,159] These reports suggest that fish oil be discontinued 2 weeks before surgery, especially for patients taking large doses.

PREBIOTICS AND PROBIOTICS

A prebiotic is a nondigestible food ingredient that beneficially affects the host by selectively stimulating the growth and activity of one or a limited number of bacteria in the colon that has the potential to improve host health. A probiotic is a live microbial feed supplement that beneficially affects the host by improving its intestinal microbial balance.[159a] Both prebiotics and probiotics can perturbate the gut microbiota, a consortium of diverse microorganisms residing in the gastrointestinal tract, with significant influence in energy metabolism, immune system development, neurologic function, and behaviors. Research on gut microbiota has made significant progress in recent years owing to the technological advancement of next-generation DNA sequencing and high-throughput data processing.

Targeting gut microbiota using fecal transplantation or fecal capsules to treat recurrent *Clostrisium difficile* infection is under intense investigation, with a few trials indicating promising results.[159b] However, a recent trial comparing oral probiotics with oral antibiotics for elective colorectal surgery showed that conventional oral antibiotics preparation in addition to mechanical bowel preparation is better than oral probiotics with mechanical bowel preparation.[159c] Studies have implicated gut microbiota in visceral hypersensitivity (irritable bowel syndrome), inflammatory pain, and more recently, neuropathic pain.[159d-159f] Moreover, gut microbiota have been shown to modulate the central nervous system function, including anxiety/depression and cognition. Despite the rapidly evolving field of gut microbiome, data on perioperative use of prebiotics and probiotics are scarce. Future research is warranted to investigate potential roles of prebiotics and probiotics in the perioperative setting, particularly in volatile anesthetics sensitivity, postoperative pain control, and postoperative cognitive dysfunction.

Other Dietary Supplements

Other top 10 dietary supplements include flaxseed oil, fiber or psyllium, cranberry, melatonin, methylsulfonylmethane, and lutein.[1] No special concerns have been published associated with bleeding or other perioperative risks from the use of these supplements.

Summary

Commonly used herbal medications can have direct and indirect effects in the perioperative period. Although there is little direct evidence for discontinuation timing, emerging knowledge of the underlying biology of these medications and review of case reports suggest that herbal medications should be considered in the perioperative plan.

Acupuncture

MECHANISM AND GENERAL PRACTICE

Although acupuncture can reduce preoperative anxiolysis, intraoperative anesthetic requirements, and postoperative ileus, and can support cardiovascular function, it has been most widely studied to control postoperative pain and to prevent or treat nausea and vomiting.[160]

Acupuncture has been used in China for more than 3000 years, and in the 1970s, it gained international attention as a treatment for a variety of diseases. In 1974, Dr. Bonica became the first pain physician invited by the Chinese government as a member of an American medical delegation to assess the utility of acupuncture in surgical procedures. He witnessed more than 28 surgeries personally and spoke with a large number of surgeons as well as anesthesia providers. In the report subsequently published in JAMA,[160a] he pointed out, "it (acupuncture) may prove extremely useful in relieving postoperative pain thus obviating the depressant effects of narcotics usually employed for this purpose." Traditional Chinese medicine (TCM) is the basis for acupuncture practice. According to TCM, the human body operates on 12 bilaterally distributed channels (6 yin channels and 6 yang channels) in conjunction with two midline channels in the ventral and dorsal aspects of the body, respectively. Acupuncture is the stimulation of anatomic locations on the skin by a variety of techniques that can be classified as invasive (e.g., needles, injections) or noninvasive (e.g., transcutaneous electrical stimulation, pressure, laser). Needles inserted into the skin can be stimulated by manual manipulation, moxibustion (i.e., burning a substance to produce heat), pressure, laser, and electricity. A scientific basis may exist for acupuncture. Acupuncture stimulates high-threshold, small-diameter nerves that activate the spinal cord, brainstem (i.e., periaqueductal gray area), and hypothalamic (i.e., arcuate) neurons, which trigger endogenous opioid mechanisms.[161] The effect of

acupuncture analgesia can be reversed by administration of naloxone.[162] Other mechanisms such as modulation of immune function,[163] inhibition of the inflammatory response,[164] regulation of neuropeptide gene expression,[165] and alteration in hormonal levels[166] have been proposed. The development of neuroimaging tools, such as positron emission tomography[167] and functional magnetic resonance imaging (fMRI),[168,169] make noninvasive studies of acupuncture's effects on human brain activity possible. Studies using positron emission tomography have demonstrated that the thalamic asymmetry present in patients suffering from chronic pain was reduced after acupuncture treatment. Other studies using fMRI have pointed to relationships between particular acupoints and activation of the visual cortex.[170] Using a noninvasive imaging technique called Bi-Digital O-Ring Test, researchers found that each meridian is connected to a representative area in the cerebral cortex, suggesting that the meridian system defined in the theories of Chinese medicine may overlap with distinct supraspinal regions.[170a] Electroacupuncture, particularly at low frequency, is associated with widespread fMRI signal increases in the anterior insula area, limb, and paralimbic structures. These humoral and neuronal changes induced by acupuncture form the basis for its clinical use.

According to the Centers for Disease Control and Prevention, more than 50 million procedures are performed each year in the United States, including more than 1 million hip and knee replacements. Most surgical procedures are associated with postoperative pain, for which opioids are the mainstay of treatment. However, opioid usage is associated with a high incidence of side effects including respiratory depression, reduced gastrointestinal motility, sedation, and itching. Chronic exposure to high-dose opioids can also induce opioid tolerance and dependence. It is therefore highly desirable to develop alternative therapies that provide adequate postoperative pain relief with minimal side effects. In this context, acupuncture for acute postoperative pain control has gained significant interest, including its use for oral-maxillofacial and neck surgeries, sternotomy/thoracotomy, abdominal/pelvic surgeries, and orthopedic and spine surgeries. Studies have shown that acupuncture can lead to improved pain scores or reduced opioid requirements postoperatively. Lao and associates carried out a randomized, double-blinded, and placebo-controlled trial on postoperative dental pain ($N = 39$).[170b] The acupuncture group received acupuncture for about 20 minutes with intermittent manual manipulation to trigger "De Qi" sensation—a sensation of numbness, distension, or electrical tingling at the needling site. The control group underwent placebo acupuncture treatment at the identical acupuncture points to the acupuncture group but without needle insertion into the skin. Mean pain-free postoperative time was significantly longer in the acupuncture group (172.9 minutes) than in the placebo group (93.8 minutes). Pain medication requirements were significantly less in the acupuncture group than in the control group. Of note, this study also ruled out psychological variables as confounders for their observed benefits of acupuncture.

It is important to note that many of the studies on clinical applications of acupuncture have insufficient sample size, high dropout rates, inadequate follow-up, and poorly defined illnesses, enrollment criteria, and outcome measures.[161] Additionally, many of the clinical trials are single center studies, which could potentially demonstrate larger treatment effects than multicenter studies.[170c]

Side effects of acupuncture treatments include bruising or bleeding at the needle insertion site, transient vasovagal response, infection, dermatitis, and retained needle fragments. The occurrence of adverse events during acupuncture treatment is considered extremely low. In a survey that included 34,407 acupuncture treatments, there were no reported events of serious side effects and only 43 cases of significant mild side effects were noted, such as nausea, fainting, and bruising.[170d,e] Recently, the safety of acupuncture was confirmed in a cohort of cancer patients with thrombocytopenia.[170f]

ACUPUNCTURE FOR POSTOPERATIVE NAUSEA AND VOMITING

One of the most promising indications for acupuncture is to prevent postoperative nausea and vomiting (PONV). PONV results in patient dissatisfaction, delayed discharge, unanticipated hospital admission, and the use of resources. Drugs have been the mainstay of management, however these have limited effectiveness, are associated with adverse effects, and can be costly. Acupuncture prevents PONV compared with sham acupuncture or no treatment.[160] In two early controlled trials, acupuncture prevented PONV in the pediatric population[171,172]; however, one literature review of 10 research studies examining the use of acupressure and acupuncture in adults concluded that it is not effective in preventing and managing PONV.[173] Other clinical studies have found that acupuncture prevents PONV and results in a greater degree of adult patient satisfaction.[174,175] For many of the trials in both adults and children, the PONV acupuncture point was P6 or PC6 (i.e., Nei guan or Pericardium 6).[173,176] The P6 acupuncture point is located between the palmaris longus and flexor carpi radialis muscle tendons, 4 cm proximal to the distal wrist crease and 1 cm below the skin (Fig. 33.2). Intraoperative stimulation of the P6 acupuncture point reduced the incidence of PONV, and its efficacy was similar to that of antiemetic drugs.[177] Stimulation of the acupuncture point should be initiated before induction of anesthesia.[178] Postoperative stimulation may be just as or more effective.[179] In children, stimulation immediately before emergence and in the recovery room has been effective. A recent metaanalysis for pediatric tonsillectomy indicated that acupuncture at the P6 acupuncture point is effective in preventing PONV.[179a] Some anesthesiologists anecdotally report tapping a small needle cap or other piece of smooth plastic over the P6 point as an effective means of acupressure stimulation.

Studies often differ in acupuncture method: duration and timing of stimulation, unilateral versus bilateral stimulation, and type of stimulation (i.e., needles with or without additional stimulation, acupressure, transcutaneous electrical stimulation, cutaneous laser stimulation, injection of a 50% dextrose solution, or capsicum plaster). Data to compare the effectiveness, safety, and costs of different methods of stimulation are inadequate.

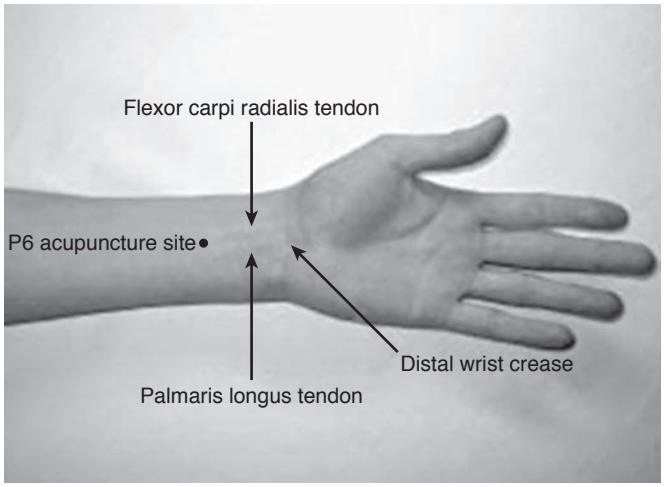

Fig. 33.2 The P6 acupuncture point is located between the palmaris longus and flexor carpi radialis muscle tendons, 4 cm proximal to the distal wrist crease and 1 cm below the skin.

DEEP BREATHING

Deep breathing exercises are performed as part of a relaxation technique. With this method, a subject consciously slows breathing and focuses on taking deep breaths.[180] Deep breathing can help reduce abdominal and surgical pain.[181,182]

Studies of postoperative pain relief with breath control were reported in the 1970s.[183,184] Since then, many studies have reported its efficacy against postoperative pain in adult patients[181,185]; prevented postoperative pulmonary complications[186]; and decreased pain in pediatric patients.[199]

Fast or forced deep breathing can also increase postoperative pain.[187] Thus, those who assist patients in postoperative pain management should encourage deep breathing exercises that are performed slowly, smoothly, and gently. Slow, deep breathing relaxation exercises have been used successfully as an adjunct to opioids for postoperative pain management in patients who had coronary bypass surgery[188]; however, after abdominal surgery, deep breathing was ineffective for pain reduction in older patients because pulmonary complications developed postoperatively.[189] Most patients who receive deep breathing education think it is useful, and the exercise was effective in increasing their feelings of rapport with staff and intention to follow their doctor's directives.[190] Results from a recent trial demonstrated that slow, deep breathing had analgesic effects with increased vagal cardiac activity.[191] Slow, deep breathing relaxation can also decrease the sensation of postoperative nausea.[192,193]

Music Therapy

Music therapy is the clinical, evidence-based use of music interventions to accomplish individualized therapeutic goals. Because music can be used for diverse applications, music therapists practice in a variety of healthcare and education settings.[194] Music for pain relief benefits individuals experiencing a low to moderate amount of pain more than those experiencing a high degree of pain.[195] A patient's preferred music should be considered when it is used for pain relief. The increase of endogenous opioids through music may be the reason for pain relief.[194]

Perioperatively, music can decrease preoperative anxiety, reduce intraoperative sedative and analgesic requirements, and increase patient satisfaction. Patient-selected music can reduce patient-controlled sedative requirements during spinal anesthesia and analgesic requirements during lithotripsy.[196] Music in the preoperative setting can reduce anxiety without affecting physiologic measures of stress.[197,198] Music can also increase patient satisfaction and reduce systolic blood pressure during cataract surgery after retrobulbar block.[199] Perioperative music can reduce arterial pressure, anxiety, and pain among women undergoing mastectomy for breast cancer.[200] As a noninvasive intervention, the low sensory stimulation of music reduced anxiety and increased cooperation in children undergoing induction of anesthesia.[201]

Music therapy interventions that have targeted nausea, both anticipatory or after treatment, have had conflicting results.[194] One study showed that a patient's preferred music for listening during chemotherapy infusion was effective in decreasing the onset and occasion of nausea.[202] In another study, listening to music with a personal message from the physician yielded no difference in chemotherapy-induced side effects compared with not listening to music during chemotherapy.[203] Some studies have found no effect on PONV from music therapy,[204,205] yet PONV was reduced in hospitalized transplant patients postoperatively.[206] Although the exact mechanism is not well understood, music therapy has been an alternative option to mainstream therapies in healthcare settings to reduce patient pain, anxiety, and perioperative stress.[207] Another use of music is in the intensive care unit. A recent clinical trial observed that among patients in the intensive care unit who received acute ventilator support for respiratory failure, patient-directed music intervention resulted in more reduction in anxiety and sedation frequency and intensity compared with usual care.[208] In addition, music can attenuate cardiovascular variability and nociceptive effects.[209,210]

Conclusion

One of the fastest changing aspects of health care is the growing public and scientific interest in CAM. An increasing number of patients and physicians have combined integrative medicine into their treatment plans. Because of the significant increase in demand for CAM therapies, most U.S. medical schools have added coursework on integrative medicine. Anesthesiologists are the physicians to manage these patients perioperatively, and therefore should have updated knowledge for the modalities of complementary and integrative medicine. To manage herbal medications in the perioperative period, their possible direct and indirect effects should be recognized based on an understanding of the underlying pharmacology. Surgery and anesthesia can usually proceed safely if potential complications are anticipated and can be minimized. As CAM therapies

TABLE 33.2 Printed and World Wide Web Sources of Herbal Medicine Information

Source	Comments
Physicians' Desk Reference for Herbal Medicines	
Encyclopedia of Dietary Supplements	
Commission E Monographs	Safety and efficacy information on herbs and phyto-medicinals; published in German, translated to English, 1998
Center for Food Safety and Applied Nutrition, Food and Drug Administration: https://www.fda.gov/AboutFDA/CentersOffices/OfficeofFoods/CFSAN/default.htm	Clinicians should use this site to report adverse events associated with herbal medicines and other dietary supplements. Sections also contain safety, industry, and regulatory information
National Center for Complementary and Alternative Medicine, National Institutes of Health: http://nccam.nih.gov/	This site contains fact sheets about alternative therapies, consensus reports, and databases
Agricultural Research Service, U.S. Department of Agriculture https://www.ars.usda.gov/	The site contains an extensive phytochemical database with search capabilities
Quackwatch: http://www.quackwatch.com	Although this site addresses all aspects of health care, there is a considerable amount of information covering complementary and herbal therapies
National Council Against Health Fraud: http://www.ncahf.org	This site focuses on health fraud with a position paper on over-the-counter herbal remedies
HerbMed: http://www.herbmed.org	This site contains information on numerous herbal medications, with evidence for activity, warnings, preparations, mixtures, and mechanisms of action. There are short summaries of important research publications with Medline links.
ConsumerLab: http://www.consumerlab.com	This site is maintained by a corporation that conducts independent laboratory investigations of dietary supplements and other health products

gain popularity in the United States, patients are likely to accept some alternative modalities during the perioperative period, such as acupuncture, deep breathing, and musical intervention. These modalities are easy to administer, have a rapid onset of action, are cost effective, and produce minimal side effects. Based on preliminary studies, perioperative use of CAM therapies may be an adjunct for management of multiple symptoms including pain, anxiety, and nausea and vomiting, among others. Additional large, well-designed trials are required to verify current observations on the effectiveness of CAM and to answer the concerns of possible side effects. Although medical schools are beginning to incorporate CAM into their curricula, it is important for anesthesiologists to stay informed about CAM therapies (Table 33.2).

Acknowledgment

The editors and publisher would like to thank Drs. Chong-Zhi Wang, Chun-Su Yuan, and Jonathan Moss for contributing a chapter on this topic in the prior edition of this work. It has served as the foundation for the current chapter.

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