Review

MANAGING PREOPERATIVE USE OF HERBAL MEDICATIONS

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ABSTRACT

Herbal medicine is an increasingly common form of alternative therapy all over the world. Most herbal products are considered dietary supplements and thus are not regulated as medicines. During the preoperative evaluation, physicians should explicitly elicit and document a history of herbal medication use. Some herbal medications have potentially harmful side effects as well as adverse interactions with conventional drugs, especially before the preoperative conditions. Physicians should be familiar with the potential perioperative effects of the commonly used herbal medications to prevent, recognize, and treat potentially serious problems associated with their use and discontinuation. The purpose of this article was to review the recent literature on the potential risks of commonly used herbal medications: Echinacea, Ephedra, Garlic, Ginkgo Biloba, St. John's Wort, Ginseng, Kava, Valeriana, and bring focus to new molecular pharmacokinetic and pharmacodynamic evidence and mechanisms.

KEYWORDS: *herbal medicine, safety, preoperative assessment, risk interactions, echinacea, ephedra, garlic, ginkgo, ginseng, Kava, St. John's wort, Valerian*

INTRODUCTION

The power and the poisoning of medicinal plants have been known for centuries. Lately, there has been renewed interest in coniine's medical uses, particularly for pain relief without an addictive side effect. However, Socrates' death has almost always been attributed to his drinking an extract of poison hemlock, Conium maculatum (1). The use of complementary medicines is increasingly popular around the globe. Variously referred to as "herbals" or "supplements," numerous factors contribute to their resurgence; the most frequent among them is that because they are "natural," patients often hold the belief that these supplements are safer than prescription medications (2).

Morbidity and mortality associated with these may be more likely in the perioperative period because of the polypharmacy and physiological alterations. Such complications include myocardial infarction, stroke, bleeding, inadequate oral anticoagulation, prolonged or inadequate anesthesia, organ transplant rejection, and interference with medications indispensable for patient care (3).

Of the herbal medications (HMs) clinicians are likely to encounter, this review has identified the eight herbs that potentially pose the greatest impact on the care of patients undergoing surgery and proposed rational strategies for managing the preoperative use of these agents. These account for over 50% of all single herb preparations among the 1500-1800 HMs sold without prescription. Non herbal dietary supplements such as vitamins, minerals, amino acids, and

Received: 10 July 2024
Accepted: 7 August 2024

hormones are beyond the scope of this review. Some non-herbal dietary supplements that surgical patients are most likely to take, such as glucosamine and chondroitin for osteoarthritis, appear safe (4).

The prevention, recognition, and treatment of complications begin with explicitly eliciting and documenting a history of herbal medicine use. Familiarity with the scientific literature on HMs is necessary because the current regulatory mechanism for commercial herbal preparations sold does not necessarily protect against unpredictable or undesirable effects. The aim of this paper is to provide a framework for physicians practicing in the contemporary environment of widespread herbal medicine use (5). The most extensive surveys on complementary and alternative medicines worldwide revealed that approximately 32% of the population used HMs. Patients undergoing surgery appear to use HMs significantly more frequently than the general population. Over 70% of these patients fail to disclose their herbal medicine use during routine preoperative assessment. Explanations for this phenomenon include patient-held beliefs that physicians are unknowledgeable about HMs or prejudiced against their use (6). Some patients may fear admitting reliance on unconventional therapies to their physicians. Others may neglect to mention HMs when using them for reasons perceived as unrelated to their medical care. Still, others would not consider these substances to be medications and neglect to report them during routine questioning. For these reasons, it is necessary for physicians specifically to seek out a history of herbal medicine use in presurgical patients.

Regulation and safety of herbal medications

HMs were classified as dietary supplements in the Dietary Supplement Health and Education Act (DSHEA) of 1994. This exempts them from the proof of safety and efficacy required of prescription and over-the-counter drugs. The burden is shifted to the Food and Drug Administration (FDA) to prove a product unsafe before it can be removed from the market (7). Manufacturers are not required to conduct preclinical animal studies, premarketing controlled clinical trials, or post-marketing surveillance, and the inability to patent HMs discourages them from performing this costly research. Many studies have been recently addressed to assess their safety, efficacy, and regulation since they are getting growing attention in the market and research to clear the difference between them and other market-available food-derived products that claim beneficial effects on health.

The current regulatory mechanism provides little assurance that commercial preparations have predictable pharmacological effects and that product labels are accurate. The potency of HMs can vary from manufacturer to manufacturer and from lot to lot. Plants may be misidentified or deliberately replaced with cheaper or more readily available alternatives (8). Some herbal manufacturers have tried to standardize products to fixed concentrations of selected chemical constituents (9). However, the benefit of this effort is uncertain because many products achieve their effects through the combined or synergistic actions of different compounds. Even when advertised and labeled as standardized, potency can vary considerably. Because there is no mechanism for post-marketing events, which is unknown, empirical evidence from a long history of use supports the notion that most HMs are safe. Nevertheless, some have been associated with severe harm (10).

Adverse events are underreported, however, because there is no central mechanism for mandatory reporting as there is for conventional medications. Other factors that contribute to underreporting are that physicians do not recognize adverse events, and patients are reluctant to report and seek treatment for adverse reactions associated with HMs (11). This reluctance has been attributed to the belief that physicians cannot be consulted in the use of unconventional therapies and to patients' unwillingness to admit the use of these remedies to physicians. The deficiencies in monitoring adverse events mean that safety profiles are usually limited to animal studies, case reports, or predictions derived from known pharmacology.

Commonly used herbal medications

Despite many uncertainties in commercial preparations, HMs adhere to the principles of modern pharmacology. A single herbal medication may adversely impact the perioperative period through several different mechanisms. These are direct effects (intrinsic pharmacological effects), pharmacodynamic interactions (alteration of the action of conventional drugs at effector sites), and pharmacokinetic interactions (alteration of the absorption, distribution, metabolism, and elimination of conventional drugs).

Echinacea

Three species of echinacea, a member of the daisy family, are used to prevent and treat viral, bacterial, and fungal infections, particularly those of upper respiratory origins. Pharmacological activity cannot be attributed to a single compound, although the lipophilic fraction, which contains the alkylamides, polyacetylenes, and essential oils, appears to be more active than the hydrophilic fraction (12).

Echinacea had a few immunostimulatory effects in preclinical studies. At the same time, no studies specifically address interactions between echinacea and immunosuppressive drugs.

Expert opinion generally warns against the concomitant use of echinacea and these drugs, owing to the probability of diminished effectiveness. Therefore, patients who may require perioperative immunosuppression, such as those awaiting organ transplants, should be counseled to avoid echinacea. In contrast to the immunostimulatory effects with short-term use, long-term use of more than 8 weeks is accompanied by the potential for immunosuppression and a 'theoretically increased risk of certain post-surgical complications such as poor wound healing and opportunistic infections (13)

Echinacea has also been associated with allergic reactions, including one reported case of anaphylaxis. Therefore, echinacea should be used with caution in patients with asthma, atopy, or allergic rhinitis. Concerns of potential hepatoxicity have also been raised, although documented cases are lacking. In the absence of definitive information, patients with pre-existing liver dysfunction should be cautious using echinacea (14). Furthermore, since the pharmacokinetics of echinacea have not been studied, it may be prudent to discontinue this herb before surgery when compromises in hepatic function or blood flow are anticipated. These situations often occur secondary to concomitant administration or as an effect of surgical manipulation.

Ephedra

Ephedra, known as ma Huang in Chinese medicine, is a shrub native to central Asia. It promotes weight loss, increases energy, and treats respiratory conditions such as asthma and bronchitis. Ephedra contains alkaloids, including ephedrine, pseudoephedrine, norephedrine, methyl ephedrine, and pseudoephedrine (15). Ephedrine, the predominant active compound, is a non-catecholamine sympathomimetic that exhibits ßl and ß2 activity by acting directly at adrenergic receptors and 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 results in tachyphylaxis from depletion of endogenous catecholamine stores and may contribute to perioperative hemodynamic instability (16). 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. Heavy ephedra use has been also documented as a very rare cause of radiolucent kidney stones.

Recently, the pharmacokinetics of ephedrine have been studied in humans. Ephedrine has an elimination half-life of 5.2 h, with 70-80% of the compound excreted unchanged in the urine. Based on the pharmacokinetic data and the known cardiovascular risks of ephedra, including myocardial infarction, stroke, and cardiovascular collapse from catecholamine depletion, this herb should be discontinued for complications (17). Although ephedrine is widely used as first-line therapy for intraoperative hypotension and bradycardia, the unsupervised preoperative use of ephedra raises particular concerns. Vasoconstriction and, in some cases, vasospasm of coronary and cerebral arteries may cause myocardial infarction and thrombotic stroke. Patients who have consumed ephedra and are later anesthetized with halothane may be at risk of developing intraoperative ventricular arrhythmias because halothane sensitizes the myocardium to ventricular arrhythmias caused by exogenous catecholamines (18). Ephedra may also affect cardiovascular function by causing hypersensitivity myocarditis, characterized by cardiomyopathy with myocardial lymphocyte and eosinophil infiltration. Is important to highlight that this herb should be discontinued at least 24 h prior to surgery (19).

Garlic

One of the most widely used medicinal plants in traditional medicine is garlic. Allium sativum L. belongs to the Amaryllidaceae family and has pronounced nutritional and medicinal properties. It has the potential to modify the risk of developing atherosclerosis by reducing blood pressure, thrombus formation, and serum lipid and cholesterol levels. These effects are primarily attributed to the sulfur-containing compounds, particularly allicin and its transformation products. Commercial garlic preparations may be standardized to a fixed alliin and allicin content (20). According to various studies that have proven the drug interaction of this valuable plant with chemical drugs, the simultaneous use of garlic with chemical medications should be used attentively to prevent different side effects (21, 22).

Garlic inhibits platelet aggregation in vivo in a dose-dependent range. The effect of one of its constituents, ajoene, appears to be irreversible and may potentiate the effect of other platelet inhibitors such as prostacyclin, forskolin, indomethacin, and dipyridamole. Although these effects have not been consistently demonstrated in volunteers, there is one case in the literature of an octogenarian who developed a spontaneous epidural hematoma that was attributed to heavy

garlic use (23). In addition to bleeding concerns, garlic has the potential to lower blood pressure. Allicin decreased systemic and pulmonary vascular resistance and reduced blood pressure in laboratory animals.

Although there are insufficient pharmacokinetic data on garlic's constituents, the potential for irreversible inhibition of platelet function may warrant the discontinuation of garlic at least 7 days prior to su rgery, especially if postoperative bleeding is a particular concern or other platelet inhibitors are given (24).

Ginkgo

Ginkgo is derived from the leaf of *Ginkgo biloba*. It 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 may stabilize or improve cognitive performance in patients with Alzheimer's disease and multi-infarct dementia (25). The compounds believed responsible for their pharmacological effects are terpenoids and trials are standardized for ginkgo-flavone glycosides and terpenoids (26).

Ginkgo appears to alter circulation, act as an antioxidant, modulate neurotransmitter and receptor activity, and inhibit platelet-activating factor (PAF). Of these effects, the inhibition of PAF raises the most significant concern for the perioperative period since platelet function may be altered. Clinical trials in a small number of patients have not demonstrated bleeding complications, but recently, four reported cases of spontaneous intracranial bleeding, one case of spontaneous hyphemia, and one case of postoperative bleeding following laparoscopic cholecystectomy have been associated with ginkgo use (26, 27).

The elimination half-lives of the terpenoids after oral administration are between 3 and 10. Based on the pharmacokinetic data and the risk of bleeding, particularly in the surgical population, ginkgo should be discontinued at least 36 h prior to surgery (28).

Ginseng

Panax ginseng is a beneficial herb consumed for a long time by people in East Asian countries. Consumption of ginseng-based products, such as red ginseng (RG), as a health food, has rapidly increased worldwide in recent years. Generally, saponins in ginseng, called ginsenosides, are regarded as the primary active components of ginseng with multiple pharmacological activities. Ginseng has been labeled an 'adaptogen' since it reputedly protects the body against stress and restores homeostasis. Commercially available ginseng preparations may be standardized to ginsenoside content (29).

Ginseng has a broad but incompletely understood pharmacological profile because of the many heterogeneous and sometimes opposing effects of different ginsenosides. The underlying mechanism appears to be like that classically described for steroid hormones. A potential therapeutic use for this herb has to do with its ability to lower postprandial blood glucose in both type 2 diabetics and non-diabetics, but this effect may create unintended hypoglycemia, particularly in patients who have fasted before surgery (30).

There is a concern about ginseng's effect on coagulation pathways. Ginsenosides inhibit platelet aggregation in vitro and prolong both thrombin time and activated partial thromboplastin time in rats. One early study suggested that the antiplatelet activity of panaxynol, a constituent of ginseng, may be irreversible in humans. Although ginseng may inhibit the coagulation cascade, ginseng use was associated with a significant decrease in warfarin anticoagulation in one reported case (31, 32). The pharmacokinetics of ginsenosides Rgl, Re, and Rb2 have been investigated in rabbits, with elimination half-life between 0.8 and 7.4. This data suggests that ginseng should be discontinued at least 24h prior to surgery (33). However, because ginseng platelet inhibition may be irreversible, it is probably prudent to discontinue ginseng use at least 7 days prior to surgery (34).

Kava

Kava is derived from the dried root of the pepper plant *Piper methysticum*. Kava has gained widespread popularity as an anxiolytic and sedative medical plant. The kavalactones appear to be the source of kava's pharmacological activity, and clinical trials suggest therapeutic potential in the symptomatic treatment of anxiety, which is attributed to these phytochemical compounds (35).

Because of its psychomotor effects, kava was one of the first HMs expected to interact with anesthetics (36). The kavalactones have dose-dependent effects on the central nervous system, including antiepileptic, neuroprotective, and local anesthetic properties. Kava may act as a sedative/hypnotic by potentiating inhibitory neurotransmission of y-aminobutyric acid (GABA). The kavalactones increase barbiturate sleep time in laboratory animals. This effect may explain the mechanism underlying the report of a coma attributed to an alprazolam-kava interaction (37). Although kava has abuse potential, whether long-term use can result in addiction, tolerance, and acute withdrawal after abstinence has

not been satisfactorily investigated. With heavy use, kava produces 'kava dermopathy', characterized by reversible scaly cutaneous eruptions.

Peak plasma levels occur 1.8 h after an oral dose, and the elimination half-life of kavalactones is 9 h. Unchanged kavalactones and their metabolites undergo renal and fecal elimination (38). The pharmacokinetic data and possibility for the potentiation of the sedative effects of anesthetics suggest that this herbal medication should be discontinued at least 24 h prior to surgery.

St John's wort

St John's wort is the common name for *Hypericum perforatum*. Several clinical trials have reported efficacy in the short-term treatment of mild-to-moderate depression. The compounds believed to be responsible for pharmacological activity are hypericin and hyperforin. Commercial preparations are often standardized to a fixed hypericin content of 0.3% (39).

St John's wort exerts its effects by inhibiting serotonin, norepinephrine, and dopamine reuptake. Concomitant use of this herb with or without serotonin reuptake inhibitors may create a syndrome of central serotonin excess (40).

The 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 specific patients. The long half-life and alterations in the metabolism of many drugs make concomitant use of St John's wort a particular risk in the perioperative setting. The pharmacokinetic data suggest that this herbal medication should be discontinued at least 5 days prior to surgery (41).

The cytochrome P450 3A4 isoform is induced, approximately doubling its metabolic activity. Interactions with substrates of the 3A4 isoform, including indinavir sulfate, ethinylestradiol, and cyclosporin, have been documented. In one series of 45 organ transplant patients, St John's wort was associated with an average decrease of 49% in blood cyclosporin levels. Huppertz et al. reported two cases of acute heart transplant rejection associated with this pharmacokinetic interaction (42). Other P450 3A4 substrates commonly used in the perioperative period include fentanyl, midazolam, lidocaine, calcium channel blockers, and 5-hydroxytryptamine (HT)3 receptor antagonists. St John's wort also affects digoxin pharmacokinetics; in addition to the 3A4 isoform, the cytochrome P450 2C9 isoform may also be induced (43). The anticoagulant effect of warfarin, a substrate of the 2C9 isoform, was reduced in seven reported cases. Other 2C9 substrates include non-steroidal anti-inflammatory drugs. Furthermore, the enzyme induction caused by St John's wort may be more pronounced when other enzyme inducers, including other HMs, are taken concomitantly (44).

Valerian

Valerian is an herb native to the Americas, Europe, and Asia temperate areas. Valerian contains many compounds acting synergistically, but the sesquiterpenes are the primary source of valerian's pharmacological effects (45). It is used as a sedative, particularly in the treatment of insomnia, and virtually all herbal sleep aids contain valerian.

Valerian produces dose-dependent sedation and hypnosis. These effects appear to be mediated through modulation of GABA neurotransmission and receptor function (46). Valerian increases barbiturate sleep time in experimental animals. In one case, valerian withdrawal appeared to mimic an acute benzodiazepine withdrawal syndrome after the patient presented with delirium and cardiac complications following surgery, and his symptoms were attenuated by benzodiazepine administration (47). Based upon these findings, valerian should be expected to potentiate the sedative effects of anesthetics and adjuvants, such as midazolam, that act at the GABA receptor.

The pharmacokinetics of valerian's constituents have not been studied, although their effects are thought to be short-lived. Caution should be used with abrupt discontinuation in patients who may be physically dependent upon valerian, owing to the risk of benzodiazepine-like withdrawal. In these individuals, it may be prudent to taper this herbal medication with close medical supervision over several weeks before surgery (48). If this is not feasible, physicians can advise patients to continue taking valerian until surgery. Based on the mechanism of action and a reported case of efficacy, benzodiazepines can be used to treat withdrawal symptoms should they develop in the postoperative period (38).

DISCUSSION

The task of caring perioperatively for patients who use HMs is an evolving challenge. Because most patients may not volunteer this information in the preoperative evaluation, physicians should specifically elicit and document a history of herbal medication use. Obtaining such a history may be difficult. Written questionnaires for information on herbal medication use have not proved to be beneficial in identifying patients taking these remedies since half of the patients who use alternative therapies fail to report this information unless questioned in person. An oral history, however, can also be inadequate today. Unless this information is directly solicited, patients may not be forthcoming. Even when a

positive history of herbal medication use is obtained, one in five patients is unable to correctly identify the preparation they are taking (49). Therefore, patients should be asked to bring their HMs and other dietary supplements during the preoperative evaluation.

Patients who use HMs may be more likely than those who do not avoid conventional diagnosis and therapy. Hence, a history of herbal medicine use should prompt physicians to suspect the presence of undiagnosed disorders causing symptoms that may lead to self-medication. These recommendations also apply to pediatric patients because caretakers may treat children with HMs without medical supervision since one in six parents reported giving dietary supplements to their children.

Although there are no existing official standards or guidelines on the preoperative use of HMs, public and professional education suggests that they be discontinued at least 2-3 weeks before surgery. Our review of the literature favors a more targeted approach. Pharmacokinetic data on selected active constituents indicate that some HMs are eliminated quickly and may be discontinued closer to surgery. Moreover, some patients require non-elective surgery or are non-compliant with instructions to discontinue HMs preoperatively. These factors and the high frequency of herbal medicine use may mean that many patients will take HMs until the time of surgery. Therefore, clinicians should be familiar with commonly used HMs to recognize and treat complications that may arise.

Clinicians should also recognize that presurgical discontinuation of all HMs may not free a patient from risk. Withdrawal of regular medication is associated with increased morbidity and mortality after surgery. In alcoholics, preoperative abstinence may result in poorer postoperative outcomes than continued preoperative drinking (50).

CONCLUSIONS

Because this field is rapidly evolving, sources for reliable and updated information are important in helping physicians stay abreast of new discoveries about the effects of HMs and other dietary supplements. This information is necessary to prevent, recognize, and treat potentially serious problems associated with herbal medicines, whether alone or in conjunction with conventional medications.

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