

Clinical pharmacology

Possible herbal medicine-drug interactions in the perioperative period

Complementary and alternative medicines and dietary supplements are not regulated by the Food and Drug Administration (FDA) or the Medicine Control Council as rigorously as conventional prescription and over-the-counter drugs. Although not permitted to market unsafe products, the manufacturers of herbal medicines currently do not have to prove that their products are safe and effective. In the USA, once dietary supplements are marketed, they can only be removed from the market if proven to be unsafe. There is growing popularity to use herbal medicines among the public worldwide. These medicines are regarded as natural and therefore 'safe', devoid of adverse effects or interactions.

This assumption leads to the unwary use of these medicines in special risk groups, e.g. children, the elderly, pregnant/lactating women, and patients with liver and kidney failure. The herbal medicines are used in pregnant women as it is believed that they are natural and safe for the unborn child.

The use of herbal medicines extends to children who present for 'day-case' anaesthesia, especially those with chronic conditions, e.g. asthma or eczema or those perceived by caregivers to be 'sickly' and in need of immune or energy boosters. Increasingly, the herbal medicines are used by HIV-positive patients and cancer patients in combination with their prescribed drugs.

As the public perceive the medicines as natural products, they neglect to mention

their use. Alternatively, they deliberately hide the fact that they use herbal or 'traditional' medicines as they think that their medical practitioners may be prejudiced against their use. In the perioperative period, several agents may be given in a short period of time and anaesthetists may not be aware that their patients are taking herbal medicines. These herbal medicines can have clinically significant interactions with conventional drugs.

Modern medical practice allows for patients to be seen on the day of their surgery. This review article will address potential herb-drug interactions between commonly used herbal medicines and drugs used in the perioperative period. The aim is to create an awareness of these potential interactions.

Potential herbal medicine-drug interaction and possible mechanisms

Herbal medicines have pharmacokinetic and pharmacodynamic interactions with conventional drugs. Pharmacokinetic interactions involve drug absorption, distribution, metabolism and excretion. Most herbal medicines and conventional drugs are orally administered. Most orally administered drugs are lipophilic and need to be transformed into water-soluble compounds. The liver is the principal site for drug biotransformation. Phase I reactions such as oxidation, reduction and hydrolysis transform drugs into inactive or active metabolites. Typically, these metabolites are then conjugated by phase II reactions such as glucuronidation, sulphation or methylation to form less toxic, water-soluble metabolites which are more readily excreted in bile and urine.

Phase I metabolism occurs mainly via the cytochrome P450 (CYP450) mixed oxidase enzyme system. CYP450 is a large family of isoenzymes found mainly in the liver (can also be found elsewhere, e.g. gut). Conventional drugs and herbal medicines can be substrates, inhibitors or inducers of the CYP450 enzyme system. The CYP3A isoenzyme metabolises more than half of drug metabolised by the CYP450 enzyme system. Inhibitors increase the bioavailability of the substrate, which can result in toxicity. The inducers, on the other hand, increase their metabolism, leading to decreased efficacy and therapeutic failure.

An important site for pharmacokinetic interaction is the drug transporter P glycoprotein. P glycoprotein is an energy-dependent efflux pump expressed in cell membranes found in the gastrointestinal tract and sites of excretion (e.g. liver and kidney, blood-brain barrier). In the gut, it pumps xenobiotics (including herbal medicines or drugs) back into the lumen. It enhances drug elimination at the excretion sites. Conventional drug and herbal medicines can be substrates, inducers or inhibitors. Inhibitors result in increased bioavailability and decreased excretion of substrates while inducers result in decreased bioavailability and increased excretion.

Pharmacodynamic interactions involve biochemical and physiological effects (therapeutic or adverse) of the co-administered drugs on the body. The interactions can either be synergistic or antagonistic. These can be herb-

Table I. Indications for herbal medicines with clinical implications in the perioperative period

Herbal medicine (common name)	Commercial use
Echinacea purpura (echinacea)	Common colds and flu
Ephedra sinica (ma huang)	Weight loss, energy booster, asthma and bronchitis
Allium sativum (garlic)	Immune booster, lipid lowering and prevention of atherosclerosis
Ginkgo biloba (gingko)	Peripheral vascular diseases, cognitive disorders, macular degeneration, intermittent claudication
Panax ginseng (ginseng)	Diabetes, protection against stress
Piper methysticum (kava)	Anxiolysis and sedation
Hypericum perforatum (St John's wort)	Clinical depression
Valeriana officinalis (valerian)	Sedation and hypnosis



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Table II. Clinically important effects and perioperative concerns of 8 herbal medicines and recommendations for discontinuation of use

Herb: common name(s)	Relevant pharmacological effects	Perioperative concerns	Preoperative discontinuation
Echinacea: purple cone-flower root	Activation of cell-activated immunity	Allergic reactions; decreased effectiveness of immunosuppressants, potential for immunosuppression with long-term use	No data
Ephedra: ma huang	Increased heart rate and blood pressure through direct and indirect sympathomimetic effects	Risk of myocardial ischaemia and stroke from tachycardia and hypertension, ventricular arrhythmias with halothane; long-term use depletes endogenous catecholamines and may cause intraoperative haemodynamic instability, life-threatening interactions with monoamine oxidase inhibitors	At least 24 hours before surgery
Garlic	Inhibition of platelet aggregation (may be irreversible); increased fibrinolysis; equivocal antihypertensive effects	Potential to increase risk of bleeding, especially when combined with other medications that inhibit platelet aggregation	At least 7 days before surgery
Ginkgo: duck foot tree, maiden hair tree, silver apricot	Inhibition of platelet-activating factor	Potential to increase risk of bleeding, especially when combined with other medications that inhibit platelet aggregation	At least 36 hours before
Ginseng: american, asian, chinese, korean ginseng	Lowers blood glucose; inhibition of platelet aggregation (may be irreversible); increased prothrombin time/partial thromboplastin time in animals; many other diverse effects	Hypoglycaemia; potential to increase risk of bleeding; potential to decrease anticoagulation effect of warfarin	At least 7 days before surgery
Kava: awa, intoxicating pepper, kawa	Sedation, anxiolysis	Potential to increase sedative effects of anaesthetics, potential for addiction, tolerance withdrawal after abstinence unstudied	At least 24 hours before surgery
St John's wort: amber, goat weed, hardhay, hypericum, kalamathe weed	Inhibition of neurotransmitter reuptake, monoamine oxidase inhibition unlikely	Induction of cytochrome P450 enzymes, affecting cyclosporine, warfarin, steroids, protease inhibitors, and possibly benzodiazepines, calcium channel blockers, and many other drugs; decreased digoxin levels	At least 5 days before surgery
Valerian: all heal, garden heliotrope, vandal root	Sedation	Potential to increase sedative effect of anaesthetics; benzodiazepine-like withdrawal; potential to increase anaesthetic requirements with long-term use	No data

drug or herb-herb interactions, as some commercially available formulations contain more than one herb.

Herbal medicines with clinical implications in the perioperative period

Herbal medicines are usually used for curing diseases or as dietary supplements, alone or in combination with conventional medicines. The indications for their use vary from treatment of common colds or flu, pain relief, depression, to treatment of serious diseases like cancer or HIV/AIDS-related illnesses.

Table I lists indications for herbal medicines with clinical implications in the perioperative period. *In vivo* data are lacking, and most data come from *in vitro* and animal studies. The limited clinical data come from case reports rather than randomised controlled trials.

St John's wort is one of the few herbal remedies that has been tested *in vitro*, and pharmacokinetic and clinical studies have shown that it reduces drug concentrations of midazolam, alprazolam, cyclosporin, tacrolimus, amitriptyline, selective serotonin re-uptake inhibitors (SSRIs), digoxin, warfarin, theophylline, dextromethorphan, simvastatin, anti-convulsants, chemotherapy, some anti-retrovirals, oral contraceptives, etc. This is due to potent induction of cytochrome P450. It is important to note that when combined with SSRIs, it increases the risk of the potentially fatal serotonin syndrome. Other drugs that may increase this risk in combination with St John's wort are the commonly used analgesics tramadol and pethidine.

Garlic, most commonly used in HIV patients as a dietary supplement, has been reported to increase bleeding tendency

due to a direct anticoagulation activity. The active compound allicin inhibits platelet aggregation.

Ginkgo biloba has antiplatelet effects and has been reported to cause spontaneous bleeding. It may interact with non-steroidal anti-inflammatory drugs, e.g. ibuprofen. Combination with warfarin may increase the risk of spontaneous bleeding. Ginseng has been reported to cause hypoglycaemia. Ginseng lowers glucose levels by increasing the number of insulin receptors and enhancing insulin release. This is especially important in diabetic patients who are fasted preoperatively. It also inhibits platelet aggregation and therefore increases the risk of bleeding.

Kava kava and valerian are used for anxiolysis and sedation and may cause prolonged sedation when combined with benzodiazepines, anaesthetic agents and the analgesics.

Ephedra contains alkaloids including ephedrine, pseudoephedrine, norephedrine, methylephedrine and norpseudoephedrine. Ephedrine is the predominant active component and is usually found in stimulants and diet pills. It causes dose-dependent tachycardia and hypertension and potentiates arrhythmias and uncontrolled hypertension when combined with halothane and other sympathomimetics respectively. This could lead to fatal cardiovascular events, e.g. myocardial infarction and cerebrovascular accidents.

Table II lists the commonly used herbal medicines that have clinical interactions in the perioperative period and recommendations regarding discontinuation. However, as there is lack of clinical data regarding discontinuation of these medicines, the conservative approach by the American Society of Anaesthesiologists suggests discontinuation 2 weeks before elective surgery. This may be challenging as most patients are preoperatively assessed the day before or on the day of surgery. What is required is collaboration between attending clinicians and anaesthesiologists as to whether patients are using herbal remedies, as well as awareness of these potentially harmful interactions.

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Further reading

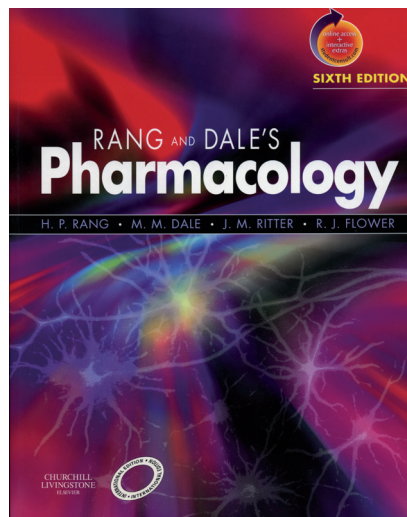
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