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REVIEW

Herbal and alternative medicine: the impact on anesthesia

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The use of herbal and alternative therapies is increasing all over the developed as well as the developing world. As pharmacological data on drug interactions involving herbal therapies becomes available, it is important to be familiar with the challenges that concomitant use of these medications may present within the peri-operative period. This review aims to shed light on the more commonly used herbal drugs, and to discuss drug interactions and complications that may be expected in their use.

Keywords: anaesthesia, drug interactions, herbal medicine

The use of herbal therapies is fast becoming widespread in both developed as well as developing countries.[1] These "natural" therapies are considered beneficial, but more often than not their adverse effects and potential interaction with other drugs are not appreciated. Surveys in many developed countries have shown that the incidence of herbal medicine use ranges from 12% of the population in Australia[2] to 37% in the USA.[3] In South Africa it is estimated that as much as 27% of the population use herbal preparations as well as prescribed antihypertensive therapy to control their blood pressure.[4] It is thought that as much as one fifth of all patients on prescription medication also use herbal remedies, high dose dietary supplements, or both.[5] These figures may be as high as 80% or even higher when patients taking traditional herbal medication are included.[6–8]

A distinction needs to be made between herbal, alternative and traditional medicines since the setting is South Africa.

Herbal therapies are defined as plant-derived products that are indicated for medicinal or health purposes.[9] Herbal therapies have been part of human existence since the beginning of time.[10] They span the spectrum from home-brewed teas prepared from collected leaves and herbs to products with official approved status granted by drug-regulating authorities.

More than 122 distinct plant derived chemical entities with pharmacological action are known. About 25% of drugs listed in the pharmacopoeias of developed countries were isolated from plant origin, while another 25% are modifications of molecules first found in plants.

A recent survey suggests that as much as 51% of patients use herbal medication in the two weeks preceding surgery.[11] Of the drugs reported, 27% altered clotting, 30% had direct influence on cardiac rhythm, rate, blood pressure or serum electrolytes, and 20% would increase sedation.

The use of herbal medicines becomes problematic in the peri-operative setting for a number of reasons:

Disclosure of use to health care practitioner

- Herbal medicines are perceived as "natural" and therefore safe, and more than 70% of patients do not voluntarily disclose the use of these drugs to their physicians.[12] Inadequate knowledge of this nature may prove detrimental to peri-operative outcome.
- Physicians may not be familiar with the mechanism of action of a specific herb, and may well underestimate the clinical effect of the drug.

The influence on pharmacokinetics and –dynamics

- The degree of alteration in pharmacodynamics and –kinetics of concomitantly administered drugs are often unknown, making prediction of clinical and side effects impossible. Induction and inhibition of both hepatic and intestinal drug metabolising enzymes have been suggested in numerous studies.[13–15] Oral administration of herbs may alter gastric pH and motility and accelerate or impair drug delivery to the duodenum. Enterocytes are the first barrier that has to be crossed for absorption. These cells express high levels of CYP3A4 and P-glycoprotein, and the interplay of these are needed to determine bioavailability of many drugs. Modulation of these factors will determine enhanced or reduced bioavailability of co-administered substances.[16]
- Of concern to the anaesthetist is the effects these medications may have on hepatic metabolism. St John's wort is known to induce the CYP3A4 enzyme system, accelerating the metabolism of certain drugs such as amitriptyline.[17] Other herbal drugs compete for the same cytochrome pathway as commonly used anaesthetic agents (e.g. echinacea competes with lignocaine for clearance via the CYP3A4 system). This may slow down clearance of the anaesthetic drug, predisposing the patient to toxic effects because of elevated plasma concentrations.
- Drug interactions between herbal medicines and conventional drugs are often not appreciated. Examples include St John's wort and monoamine oxidase inhibitor interaction precipitating serotonin syndrome, or the additive effect on platelets that garlic and the nonsteroidal anti-inflammatory drugs have. This is dangerous especially when the conventional drug has a narrow therapeutic index (e.g. ginseng and warfarin), and relatively small alterations in concentration may have profound clinical consequences.[18]
- The nett result of interaction may not be predictable because interaction may take the form of synergism, antagonism, inhibition or even acceleration of metabolism of either product. This will lead to pharmacological chaos.[19]

The risk of systemic toxicity

- Another sinister complication refers to the ability of a herbal drug to enhance the organ toxicity of a concomitantly

administered drug. A herb such as echinacea increases the hepatotoxicity of drugs such as methotrexate and anabolic steroids,[20] while halothane will elicit severe dysrhythmias when the patient has been using ephedra.[21] Contaminants found in samples of herbal medication of questionable origin may include herbicides, pesticides, radio-isotopes, heavy metals and plant derived toxins, all adding to a confusing clinical picture when the patient become ill because of use of these drugs.[22]

Multiple adverse effects

- Adverse events may include increased bleeding, cardiovascular complications, prolonged sedation, suppression of the central nervous system, and liver or renal dysfunction with derangement of drug metabolism and elimination.[23]
- Adverse effects presenting peri-operatively due to the use of herbal medications may not be considered until late in the event process. And even when herbal therapies are considered in the aetiology of an adverse event, the response to standard emergency therapy (cardiovascular support drugs or haemostatic agents) may not be as expected.[24]
- Many herbal substances may have multiple actions on one physiological system – for example, decreased activation of clotting by inhibition of von Willebrand factor, and decreased platelet aggregation due to glycoprotein receptor interference – or, conversely, act on more than one system simultaneously, such as effects on both the cardiac contractility and haemostasis.

Manufacturing standards and regulatory challenges

- Because of poor regulation of herbal medicine manufacture, true content of different preparations vary greatly between different manufacturers.[25,26] Therefore estimation of total daily dose consumed is often very difficult to calculate.
- A single herb usually contains a number of bioactive components, each of which may contribute in varying degrees to the observed pharmacological effect and interactions. This, in turn, leads to difficulties in predicting and explaining possible mechanisms for herb–drug interactions.[27]
- Most clinical trials on the efficacy of herbal medication are of limited value because of poor study design, small sample size and poor quality control.[28]
- Legislation prohibits manufacturers of herbal medication claiming clinical indications for their products. However, they are not prohibited from stating physiological effects for herbal drugs.[29] Unfortunately, this leads to biased reporting where positive effects are overemphasised, while side effects are underreported and sometimes not even mentioned, perpetuating the notion that these drugs are safe, and their use has no negative consequences.

The systemic effects of herbal medication

An overview of clinical effects that commonly used herbal preparations have on different physiological systems is presented in Table 1.

Many plants are used in blood-related therapies, including as blood tonics, to prevent excessive bleeding and as wound dressings. The safety and efficacy of these therapies are not always scientifically defined, and as such may be associated with increased peri-operative blood loss.[30] The key is to understand whether the preparations have a direct effect on the coagulation system, or if disruption is due to drug interaction.

The main direct effect centres on decreased platelet activation and aggregation. Mechanisms to explain disaggregation include:

- Microtubule stabilization[31]
- Increased membrane fluidity
- Reduced tyrosine phosphorylation limiting calcium mobilization, arachidonic acid liberation[32]
- Decreased / inhibited activation of tissue factor,[33] thrombin,[34] plasminogen activator phospholipases, thromboxane A_2,[21] Co-enzyme A and HMG CoA reductase[35]
- Potentiation of heparin co-factor II[25]
- Increased fibrinolysis[36]

Increased aggregation or coagulation may be explained through:

- Increased network protein synthesis and
- Increased erythrocyte aggregation[37]
- Activation of several clotting factors or platelets due to glycoconjugates[38]

Recent literature reviews have attributed adverse coagulation effects due to drug–herb interaction in a number of specific herbal remedies,[41,42] The interaction of these preparations with warfarin especially seems to be of significance because of the narrow therapeutic index of warfarin. Of specific concern to the anaesthetist is the interaction between aloe vera and Sevoflurane.[43,44]

Herbal drugs and the heart

Although epidemiological data support the cardiovascular benefits afforded by antioxidants and flavonoids[45] present in many herbal preparations, clinical trials with purified, single compound material have yet to show any benefit[46] In fact, botanical preparations are many times more likely to induce adverse cardiovascular effects including arrhythmias, hypertension[47] and sympathomimetic effects.[48] Reports of interference with coagulation, platelet activity and drug metabolism (especially where drugs with narrow therapeutic windows are used) exist almost exclusively as case reports, and it is well known that adverse events of this nature is vastly underreported.[49] Further effects include direct inhibition of contractility, interference with conduction (prolonged QT interval), additive effects to cardiac drugs used (especially cardiac glycosides) and vasoconstriction or –dilatation.[50] All of these may cause severe intra-operative complications.

Central nervous system effects of herbal preparations

Many herbal preparations are indicated for their sedating and anti-depressive effects.[51,52] Since their effects are mediated by GABA receptor activation or by serotonin re-uptake inhibition (amongst other mechanisms), there is great potential for interaction with anaesthetic agents.[53] Apart from prolonged sedation or the risk of serotonin syndrome, some of these drugs may also precipitate seizures[54] (due to direct inhibition of anti-convulsive therapy, accelerated anti-convulsive metabolism, or additive excitatory effects with mood stabilizers like trazondone, buspirone and fluoxetine). L-Dopa efficacy may be compromised, resulting in worsening symptoms of Parkinsonism.[55]

Hepatic effects of herbal medicines

As many as 60 herbal preparations are known to cause derangement of hepatic function.[56] This does not include hepatic damage attributed to contaminants, impurities, misidentified herbs and solvents used in extraction of the active ingredients. Herbal therapies may alter drug metabolism by the influence they exert on the glucuronidation process, the cytochrome p450 (CYP) and other hepatic enzyme systems. CYP inhibition will decrease

Table 1: Commonly used herbal drugs with indications, active ingredients and drug interactions[21,39,40]

Name	Indications	Active constituents	Drug interactions
Aloe vera *(Aloe vera)*	Oral – laxatives Topical – creams	Polysaccharides Acytelated mannans Inhibits arachidonic acid synthesis	**Additive to sevoflurane effect on platelets** - inhibition of GPIIb/IIIa receptors on platelet - inhibition of GPIa interaction with intercanalicular system - inhibition of von Willebrand – platelet – fibrinogen interaction Poor platelet plug formation – increased risk of haemorrhage
Chamomile, German *(Matricaria recutita)*	Restlessness Insomnia Gastrointestinal upset	Azulene constituents, Sesquiterpene, bisabolol and coumarin constituents	**Central nervous system depressants** (e.g. opioids, benzodiazepines) – increased sedation **Warfarin, aspirin and NSAIDs** – increased risk of bleeding from presence of coumarin in chamomile
Echinacea *(Echinacea. angustifolia, E. purpurea,* and *E. pallida)*	Oral – prevent and treat common cold and upper respiratory tract infections, immunostimulant Topical – wound healing, burns, abscesses, eczema, herpes simplex virus	Chicoric, echinacosides, polysaccharides polyacetylenic compounds ketoalkenes and ketoalkynes	**Immunosuppressants** (e.g. cyclosporine, prednisone, azathioprine) – decreased immunosuppressant effects due to possible immunostimulation **Hepatotoxic agents** (e.g. acetaminophen, methotrexate, amiodarone) – additive hepatotoxicity resulting from glutathione depletion **Inhibition of CYP3A4 and CYP1A2** increasing levels of drugs metabolized by these enzymes
Evening primrose oil *(Oenothera biennis)*	Premenstrual syndrome (PMS) Menopausal symptoms Atopic eczema Rheumatoid arthritis Raynaud's syndrome Multiple sclerosis Hypercholesterolemia Diabetic neuropathy	Gamma-linolenic acid (GLA) – rapidly metabolized to Dihomogammalinolenic acid (DGLA) Linoleic acid	**Anticonvulsants** – risk of seizure **Anticoagulants and antiplatelet agents** – increased risk of bleeding **Anaesthetics**– risk of seizure **Phenothiazines** – report of seizures with concomitant use
Feverfew *(Tanacetum parthenium)*	Oral – prevent migraine used for fever, arthritis, tinnitus and vertigo Topical – toothache and insect bites	Parthenolide – a sesquiterpene lactone	**Anticoagulants, antiplatelet agents, and NSAIDs** – inhibition of platelet aggregation and risk of bleeding
Garlic *(Allium sativum)*	Hypertension Hyperlipidemia Coronary heart disease Bacterial and fungal infections Prevention of atherosclerosis	Powdered extract - 1.3% alliin Fresh garlic contains 1% alliin, allicin, and other organosulfur constituents	**Protease inhibitors** – decreased levels - treatment failure, risk of viral resistance **Non-nucleoside reverse transcriptase inhibitors (NNRTI)** – decrease serum levels - treatment failure, risk of viral resistance **Cyclosporine** – decrease levels, risk of transplant rejection **Anticoagulants and antiplatelet agents** – increased risk of bleeding **Insulin and antihyperglycemics** – enhanced hypoglycaemic action **Oral contraceptives** – possible contraceptive failure
Ginger *(Zingiber officinale)*	Nausea Arthritis	Gingerols Gingerdione Galanolactone Zingerone	**Antacids, H2 antagonists, proton pump inhibitors** – ginger increases stomach acid while these medications suppress it **Anticoagulants, antiplatelet medications, NSAIDs** – increased risk of bleeding **Sedatives, barbiturates, benzodiazepines, alcohol** – enhanced effect **Blood pressure medications** – ginger alters blood pressure and interferes with therapy **Cardiac glycosides** – inotropic effect; can alter contractility **Diabetes medications** – additive hypoglycaemic effect
Ginkgo *(Ginkgo biloba)*	Oral – memory loss, Alzheimer's disease, circulatory disorders, intermittent claudication and tinnitus Topical – frostbite and wound dressings	Terpene lactones, Ginkgo flavone glycosides Isorhamnetin, quercetin, kaempferol, and proanthocyanidins Bilobalide Primary terpenoids are ginkgolides A, B, C, M, and J	**Thiazide diuretics** – increased blood pressure **Anticoagulants, antiplatelet agents, NSAIDS** – increased risk of bleeding **Buspirone and fluoxetine** – possibility of hypomania **Trazodone** – associated with coma **Insulin** – altered insulin secretion, leading to altered blood glucose levels **Anticonvulsants** – decreased efficacy **Mild inhibitor of CYP3A**
Ginseng *(Panax quinquefolius)*	Enhanced stamina, concentration, energy, immune response, and stress response Antidepressant Diuretic Acute respiratory illness Diabetes Impotence	Ginsenosides – Rb-1 Panaxosides	**Digoxin** – increased effects **Anticoagulants** – decreased efficacy **Monoamine oxidase inhibito** – insomnia, headache, tremor, agitation, and worsening of depression **Diabetes medications** – increased risk of hypoglycaemia **Opioids** – decreased analgesic effect **Oestrogen** – additive estrogenic effect
Kava *(Piper methysticum)*	Oral – anxiety, insomnia, restlessness, muscle pain, headaches Topical – wound healing	Kava-lactones and -pyrones, Kawain, dihydrokawain, Methysticin, dihydromethysticin, Vangonin	**Benzodiazepines** – increased lethargy and disorientation **Levodopa** – decreased effectiveness **CNS depressants, alcohol** – additive drowsiness, and depression of motor reflexes

(*Continued*)

Table 1: (*Continued*)

Name	Indications	Active constituents	Drug interactions
			Antihistamines – increased risk of sedation **Tricyclic antidepressants** – increased adverse effects and decreased effectiveness **Hepatotoxic drugs** (e.g. paracetamol) – additive hepatotoxicity and increased risk of liver damage
Liquorice *(Glycyrrhiza glabra)*	Oral – ulcers, chronic gastritis, arthritis, inflammation and bronchitis Topical (shampoo) – treatment of excessive oil production	Glycyrrhizin Glycyrrhetinic acid (Potent inhibitor of 11-β hydroxysteroid dehydrogenase – increased cortisol levels exerting mineralocorticoid effect – Conn syndrome picture)	**Corticosteroids** – prolonged duration of effect **Digoxin** – increased risk of toxicity resulting from potassium depletion **Potassium-depleting diuretics** – enhanced effects **Antihypertensives** – risk of hypertension resulting from sodium and water retention **Insulin** – potentiates hypokalaemia and sodium retention **Furosemide** – enhanced mineralocorticoid effects
St John's wort *(Hypericum perforatum)*	Oral – mild to moderate depression, anxiety, exhaustion, menopause related mood disturbances, muscle pain, fatigue, insomnia and viral infections Topical – analgesia and wound healing	Hypericin, hyperforin, adhyperforin, and pseudohypericin	**Cyclosporine** – decreased levels and possible transplant rejection **Digoxin** – decreased levels **Protease inhibitors** – decreased levels – treatment failure, increased viral resistance **Tacrolimus** – decreased levels **Methadone** – decreased serum concentration **Antidepressants** – Serotonin-syndrome **Oral contraceptives** – decreased levels, treatment failure **Theophylline** – decreased levels **Warfarin** – decreased International Normalised Ratio **5-hydroxytryptamine 1 agonists** – serotonin syndrome. **Potentially induce CYP3A4, CYP2D6 and CYP1A2**
Valerian *(Valeriana officinalis)*	Insomnia Anxiety Restlessness Tension	Valepotriates, berneol valerenic acid, valerenone, and kessyl glycol	**Barbiturates, benzodiazepines, and alcohol** – increased CNS depression and side effects **Inhibition of CYP3A4**

Notes: CNS: central nervous system, NSAID: nonsteroidal anti-inflammatory drug

metabolism of competing drugs dependant on the specific enzyme, whereas induction of the CYP enzyme will accelerate metabolism in a similar fashion (e.g. St John's wort and amitrypteline[57]). Some therapies (on their own or additive to other hepatotoxins) may cause direct hepatocellular damage,[58] while others are known to protect against hepatotoxicity by inhibiting enzymes responsible for metabolism of a compound into a toxic metabolite (garlic protecting against paracetamol toxicity).[59]

Herbal effects on the immune system

Many so called immune boosters have yet to be proven effective in clinical trials. Most of these drugs only decrease the severity of the symptoms, but do not in fact alter the duration of the disease.[60] Important to note is the fact that these drugs interact with immune modulating agents in a way that poses significant danger to the patient.[61] Alteration in CYP metabolism leads to may lead to a decrease in the efficacy of immunosuppressant drugs like cyclosporine (narrow therapeutic window), increasing the risk for rejection in organ transplant patients.[62,63] Furthermore, a herb such as garlic decrease the bioavailability of anti-retroviral drugs such as sequinavir and ritonavir, thus rendering therapy ineffective and increasing the risk of viral resistance.[10]

Endocrine and electrolyte effects of herbal preparations

The effects on the endocrine system are varied and specific to relevant herbs,[16] and include hyper- and hypoglycaemia,[64] oral contraception failure with some preparations,[65] impaired corticosteroid synthesis[66] and hypokalaemia.[67]

Conclusion

Herbal medicine usage is very common. The anaesthetist will be confronted more and more with patients using these drugs. It is true that our knowledge of the clinical effects of many of the preparations is still incomplete. However, there is a growing body of evidence regarding drug interactions and side-effects concerning these drugs. Specific enquiry during history taking may alert and prepare the peri-operative physician for the most likely adverse events. Where unexpected complications occur, one must have a high index of suspicion that the patient omitted to reveal the usage of herbal medication. No guidelines from scientific societies have been published as yet, but most authorities agree that all herbal supplements and drugs be stopped at least 2 weeks prior to surgery.[68]

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