Kava

Amy O. Soleta

Uses

- Treatment of anxiety, stress, nervousness
- Treatment of insomnia
- Treatment of muscular aches and pains
- Traditionally used in the South Pacific during religious and cultural ceremonies to achieve relaxation and for medicinal purposes

Perioperative Risks

- No data exist to quantify risk of adverse effects
- ASA recommends stopping herbal supplements as long as 2 wk prior to elective procedures.

Worry About

- Risk of hepatotoxicity, especially when combined with other hepatotoxic drugs
- Oversedation when combined with ethanol or other sedative drugs
- Potential to affect hemodynamic stability and coagulation

Overview/Pharmacology

- Oral administration: Peak effect 1.8 h, elimination half-life 9 h, metabolized in liver by cytochrome P450.
- Effects on various ion channels leading to decreased excitability of CNS.
- Enhanced binding and regulation of GABA receptors, leading to anxiolysis, sedation, muscle relaxation, and anticonvulsive effects
- Inhibition of limbic system, leading to decreased emotional excitability and mood enhancement
- Weak Na channel antagonism, leading to potential anticonvulsant effects
- Inhibition of calcium channels, leading to inhibition of vascular smooth muscle
- Reduced reuptake of dopamine and norepinephrine
- Inhibition of COX, leading to antithrombotic, analgesic, and anti-inflammatory effects

Usual Dose

- Highly variable dosing based on growing and harvesting conditions, plant parts and extraction techniques used, and dosage form chosen by manufacturer
- Active compounds are kavapyrones
- Anxiolysis: 105–210 mg kavapyrones daily for 3-4 wk

Toxicity

- Risk of hepatotoxicity; caution with concomitant use of other hepatotoxic herbs
- Potentiation of sedation with ethanol, barbiturates, benzodiazepines, opioids
- Risk of MAOI toxicity if taken with MAOIs

Assessment Points

System	Effect	Assessment by Hx	PE	Test
CNS	Sedation	Headache, dizziness, dyskinesia	Mental status	Vital signs
CV	Hypotension	Lightheadedness, orthostasis	Decreased BP and HR	Vital signs
GI	Hepatotoxicity	Nausea, vomiting, abdominal pain, fatigue	Jaundice, ascites, edema	LFTs
RENAL	Decreased RBF	Oliguria, nausea	Peripheral edema, hypotension, tachycardia	Fluid challenge, BUN/Cr, lytes, urinalysis
HEME	Abnormal platelet aggregation	Use of other anticoagulants or antiplatelets, easy bruising, prolonged bleeding	Petechiae, hypovolemia	Elevated PT/INR, PTT, abnormal platelet function

Key References: Raduege KM, Kleshinski JF, Ryckman JV, et al.: Anesthetic considerations of the herbal, kava, *J Clin Anesth* 16(4):305–311, 2004; Horlocker TT, Wedel DJ, Rowlingson JC, et al.: Regional anesthesia in the patient receiving antithrombotic or thrombolytic therapy: American Society of Regional Anesthesia and Pain Medicine Evidence-Based Guidelines (Third Edition), *Reg Anesth Pain Med* 35(1):64–101, 2010.

Perioperative Implications

Preoperative Concerns

- Rely on pt self-report.
- Sedation.
- Consider preop LFTs, BUN/Cr, and coagulation studies if concern for concomitant disease.

Monitoring

- Standard

Regional Anesthesia

- No significant added risk, but use caution if combined with other anticoagulant/antiplatelet agents.

Emergence/Extubation

- Prolonged due to excess sedation

Postoperative Period

- Continue to monitor for increased sedation.
- Potential for prolonged bleeding.

Licorice *(Glycyrrhiza glabra)*

R. Blaine Easley

Uses

- One of the top 10 herbal medications utilized in USA.
- Historically used to improve immune function and treat a variety of conditions including PUD, duodenal ulcers, cough and/or bronchitis, atherosclerosis, chronic fatigue syndrome, various cancers, AIDS, and Addison disease. Most recently a study has demonstrated its effectiveness in relieving postop sore throat.

Perioperative Risks

- Unknown. Theoretical problems in pts with impaired renal function, Htn, chronic liver disease, cardiac arrhythmias, and hypertonia.
- Potential for drug interactions. Pseudohyperaldosteronism has been produced experimentally in healthy subjects taking >100 g/wk.

Worry About

- Pseudohyperaldosteronism: Documented mineralocorticoid effects that result in fluid retention, hypernatremia, hypokalemia, and edema.
- Hypertension: Direct effects on vascular smooth muscle tone independent of mineralocorticoid properties.
- Vasospasm and/or headache: Recent case reports of cerebral artery spasm causing severe headache, visual disturbances, and potential ischemia.
- Hypokalemia and/or muscle weakness: Chronic usage related to hypokalemic myopathies, muscle cramps, and skeletal muscle spasms.
- Arrhythmias: Rare side effect but more worrisome in pts with Hx of arrhythmias requiring medication (e.g., digoxin).
- Paresthesias: Numbness in extremities may be a sign of licorice toxicity.

Overview/Pharmacology

- Licorice is the common name given to various substances derived from the plant root *Glycyrrhiza glabra*, also known as Spanish licorice. This plant is a perennial that grows 3–7 feet high and originated in Europe and Asia. Also called sweet root and licorice root.
- Glycyrrhizin and/or glycyrrhizic acid (the glucoside form) and glycyrrhetinic acid (the glycoside form) are the most important substances or metabolites found in licorice. The roots also contain coumarins, flavonoids, volatile oils, and plant sterols.
- Licorice and its components are metabolized and excreted by the liver and kidneys.
- Mineralocorticoid effects of licorice, via glycyrrhetinic acid, result from the inhibition of 11-β-hydroxysteroid dehydrogenase (an enzyme that normally inactivates cortisol by converting its C11 alcohol to a ketone). Excess glucocorticoids then bind to mineralocorticoid receptors and produce a mineralocorticoid response, as evidenced by increased sodium retention and Htn. Thus licorice ingestion creates a syndrome of hyperaldosteronism characterized by hypernatremia, Htn, hypokalemia, and suppression of the renin-angiotensin system.
- Glycyrrhetinic acid also inhibits 15-hydroxy-prostaglandin dehydrogenase and prostaglandin reductase. These two enzymes are important in the metabolism of prostaglandin E and F_2, perhaps explaining licorice's immunologic benefits, effects on reducing cough and/or bronchospasm, protection of gastric mucosa, and benefit by decreased platelet aggregation.
- Glabridin has antioxidant and potential wound/ulcer healing properties.

Drug Class/Usual Dose

- Made from peeled and unpeeled dried root compounded and sold as a powder, dry extract, and liquid extract. In some preparations, such as DGL, harmful

components have been removed. Unfortunately preparation and advertising of these compounds is unregulated by the FDA.
- Licorice is taken in the following manner
  - Dried root: 1–5 g PO 3 times daily up to 6 wk (indication: general use).
  - Extract: (1:1 preparation) 2–5 mL PO 3 times daily up to 6 wk (indication: general use)
  - DGL extract: 1.5–3 g/d for peptic ulcer
  - DGL extract: 380–760 mg PO 20 min before meals for peptic ulcer

Assessment Points

System	Effect	Assessment by Hx	PE	Test
CNS	Headache Visual changes Paresthesias	Exposure/use of licorice	Visual acuity Sensory exam	Neurologic consult, possible MRI
CV	Hypovolemia Hypervolemia Htn Arrhythmia	Exposure/use of licorice	BP/HR, consider orthostatics	ECG rhythm strip
GI	Black stools (rare) Laxative effect	Report of loose dark stool	Abdominal exam	Stool guaiac
HEME	Decreased clotting (rare)	Bleeding problems	Plts, PT/PTT	
ENDO	Hyperglycemia Hypernatremia Hypokalemia	Exposure/use of licorice Weight gain, increased urination		Serum chemistries

Key References: Kaye AD, Clarke RC, Sabar R, et al.: Herbal medicines: current trends in anesthesiology practice—a hospital survey, *J Clin Anesth* 12(6):468–471, 2000; Ruetzler K, Fleck M, Nabecker S, et al.: A randomized, double-blind comparison of licorice versus sugar-water gargle for prevention of postoperative sore throat and postextubation coughing, *Anesth Analg* 117(3):614–621, 2013.

Possible Drug Interactions

Preoperative Period

- Multiple adverse drug interactions reported in pts using licorice preparations and prescription medications. Licorice can interfere with the function of hormone supplements (e.g., birth control pills), oral hypoglycemic agents, and corticosteroids. Lyte imbalances and GI symptoms can be worsened by usage of licorice with diuretics and laxatives. Digoxin usage and licorice-induced hypokalemia can be potentially arrhythmogenic.
- Lyte abnormalities of hypokalemia, hypernatremia, and metabolic alkalosis should be sought and corrected before surgery in high-dose frequent users.
- Pt should be instructed to discontinue use of the herbal medicine approx 2 wk before elective surgery.

Induction/Maintenance

- No known interactions with licorice metabolites. However, pseudohyperaldosteronism should be considered and anesthetic management directed at the problems of hypokalemia, Htn, and fluid status. Placement of an arterial line and/or central venous line should be considered in symptomatic pts. (See Hyperaldosteronism, Secondary.)

Adjuvants/Regional Anesthesia/Reversal

- No known interactions. Consider pros and cons of NSAID use intraop, especially if no assessment of renal function. Careful attention to neurologic exam and/or paresthesias before initiation of regional technique.

Emergence/Extubation

- No known interactions. Acute topical preop and postop administration (by gargle) has been used without adverse effect to prevent postop sore throat. However, hypokalemia with or without a Hx of muscle weakness could potentially modify response to nondepolarizing muscle relaxants.

Postoperative Concerns

- Failure of resolution of preop symptoms attributed to licorice use with D/C of licorice-containing compound should prompt investigation of other causes.
- Continued monitoring of fluid and lyte status. If problems with hypokalemia continue despite potassium supplementation, consider potassium-sparing diuretics (e.g., triamterene) or a competitive aldosterone antagonist (e.g., spironolactone); investigate other possible causes.

Melatonin (*N*-Acetyl-5-Methoxytryptamine, Bevitamel, Vitamist, Melatonex)

Ori Gottlieb

Uses

- Regulates sleep-wake cycles.
- Prescribed for jet lag, shift work, depression.
- Use as antineoplastic, antidelirium, and anticonvulsant is under investigation.
- Questionable benefit in treating breast cancer and migraines.
- Categorized as a nutraceutical (unregulated).

Risks

- Not controlled by FDA; therefore quality and potency may vary.
- May interact with other CNS-acting medications such as hypnotics, sedatives, or psychotropics.
- Not recommended in children or pregnant/breast-feeding women owing to insufficient data
- May cause excessive somnolence.
- Use of animal-source melatonin products is not recommended because of risk of viral contamination or infection.

Overview/Pharmacology

- Secretion modulated by hypothalamic enzymes in response to a dark environment.
- Exogenous routes of administration: Oral tablets, capsules, lozenges, teas, sprays.
- Unlike endogenous melatonin, oral doses undergo first-pass hepatic metabolism with a bioavailability of 30–50%.
- Crosses the blood-brain barrier.
- Mean elimination half-life is 45 min. Only 0.01% of melatonin is excreted unchanged in urine.
- Pharmacologic tolerance to melatonin has not been described.
- Alcohol may potentiate side effects.

Usual Dose

- Taken 1–2 h before usual sleep time.
- Significant individual dose variation.
  - Insomnia: 1–4 mg PO in evening.
  - Insomnia with depression: 5–10 mg PO in evening.
  - Jet lag: 3–6 mg PO in evening on the destination's sleep schedule; may require up to 5 nights to become effective.
  - Tinnitus: 3 mg PO in evening.
  - Circadian disruption/blindness
  - Adults: 5–7 mg PO in evening.
  - Children: 2.5–7.5 mg PO in evening.

Endogenous Actions

- Secreted by the pineal gland in response to the absence of photic stimuli (known as the "darkness hormone").
- Reduces the body's core temperature in preparation for sleep.
- Secretion peaks during the pediatric years and decreases with age.
- Is involved in some way with reproductive function. Receptors have been found in reproductive tissues.
- Endogenously produced melatonin may have a significant role in deferring a number of free radical–related diseases and some pathophysiologic changes associated with aging.

Exogenous Actions

- Resets the body to the environmental clock and allows pts to normalize physiologic and behavioral sleep patterns.
- Used commonly as a preventive and therapeutic agent against jet lag.
- Useful in individuals with poor circadian synchrony, such as the visually impaired.