

Perioperative Implications

- The ASA recommends that all herbal medications be D/C 2–3 wk prior to elective surgery because it takes 5–6 half-lives for an agent to leave the body;

moreover, these substances lack uniform data regarding uptake, distribution, and elimination as they are not considered drugs by the USA FDA. Over 90 herbal products are associated with bleeding; this can be a specific problem intraop or when placement of

a regional anesthetic is being considered for postop pain management.

Phytosterols

Lee A. Fleisher

Uses

- Naturally occurring in human diet.
- Used as supplements, especially in margarines, to reduce cholesterol levels.
- May also possess anti-inflammatory, antipyretic, antineoplastic, and immune-modulating properties.
- Some recent evidence questions the beneficial effect of phytosterols and the potential for increased CV risk.

Perioperative Risks

- None known

Worry About

- Pts may be taking phytosterols because of hypercholesterolemia and occult CAD.

Overview/Pharmacology

- Phytosterols (including plant sterols and stanols) are natural components of edible vegetable oils such as

sunflower seed oil; as such, they are natural constituents of the human diet.

- It is difficult to incorporate free sterols into edible fats and/or oils because of their insolubility, whereas sterols esterified to fatty acids are more fat soluble.
- In the intestine, most sterol esters are hydrolyzed to free sterols as part of the normal digestive process.
- Plant stanols are hydrogenation products of the respective plant sterols (e.g., campestanol and/or campesterol, sitostanol and/or sitosterol) and are found in nature at very low levels.
- Enrichment of foods such as margarines with plant sterols and stanols is one of the recent developments in functional foods to enhance the cholesterol-lowering ability of traditional food products.
- May reduce the absorption of some fat-soluble vitamins. Randomized trials have shown that plant sterols and stanols lower blood concentrations of β -carotene by about 25%, concentrations of

α -carotene by 10%, and concentrations of vitamin E by 8%.

Drug Class/Usual Dose

- Consumption of plant sterols and stanols lowers blood cholesterol levels by inhibiting the absorption of dietary and endogenously produced cholesterol from the small intestine. Plant sterols and/or stanols are only very poorly absorbed themselves.
- This inhibition is related to the similarity in physicochemical properties of plant sterols and stanols and cholesterol and may be related to two mechanisms:
 - The greater the amount of plant sterols and/or stanols, the lower the solubility and perhaps the greater the amount of cholesterol precipitated. Cholesterol in the crystalline form cannot be absorbed.
 - Competition for space in mixed micelles.
- Being marketed in new margarine formulations.

Assessment Points

System	Effect	Assessment by Hx	PE	Test
CV	Hypercholesterolemia	CAD, angina	Chest pain	ECG
GI	Malabsorption of some vitamins			

Key References: Weingärtner O, Böhm M, Laufs U: Controversial role of plant sterol esters in the management of hypercholesterolaemia, *Eur Heart J* 30(4):404–409, 2009; Rocha VZ, Ras RT, Gagliardi AC, et al.: Effects of phytosterols on markers of inflammation: a systematic review and meta-analysis, *Atherosclerosis* 248:76–83, 2016.

Possible Drug Interactions

- No known drug interactions

Anticipated Problems/Concerns

- None known

Red Yeast Rice (Cholestin)

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Uses

- Chinese traditional medicine for therapy of pts with cardiovascular diseases
- Hypercholesterolemia
- Prevention of coronary events, stroke, and TIA
- Treatment of dyslipidemia in statin-intolerant pts
- Prostate and colon cancer
- Possible diabetes treatment

Perioperative Risks

- Obtain adequate Hx to determine indication for taking red yeast rice.

Worry About

- Chemical composition of red yeast rice is not controlled by the FDA and may vary by manufacturer.
- Relatively contraindicated in liver disease. Hepatotoxicity is worsened in combination with other hepatotoxic drugs.

Overview

- Prepared by growing red yeast (*Monascus purpureus*) on rice to produce a red product.

- Contains 10 mevinic acids include monacolin K, also known as lovastatin.
- Popular in Asian countries.
- Available in several preparations in USA.

Drug Class/Mechanism of Action/Usual Dose

- HMG-CoA reductase inhibitor, essentially a natural statin and its homologues, additionally contains unsaturated fatty acids, flavonoids, plant sterols, and other biologically active substances.
- Inhibits conversion of HMG-CoA to mevalonic acid, an early precursor of cholesterol.
- Usual dose is 600–2400 mg daily.
- Xuezhikang (from red yeast rice) reduces expression of mediators of oxidative stress induced in diabetes mellitus and protects pancreatic islet cells from hyperglycemic injury. Xuezhikang, which is purified from cholestin, has been shown to decrease blood glucose levels by improving glucose tolerance and insulin secretion in db/db mice. Xuezhikang has also been shown to protect islets from hyperglycemic injury with conserved β -cell content and

microenvironment. Xuezhikang potently inhibits the expression of key factors in oxidative stress and causes an upregulated expression of glucose-sensing tissue.

- Reduces matrix metalloproteinases 2 and 9 and CRP levels involved in vascular remodeling.
- Red yeast rice can significantly increase adiponectin and can significantly lower LDL-C and total cholesterol levels. Adiponectin correlates positively with HDL-C while serum leptin correlates negatively with triglycerides. Therefore red yeast rice has a potentially protective effect in obesity-related and cardiovascular diseases.
- Xuezhikang from red yeast rice has been shown to upregulate eNOS expression in vascular endothelium and RBCs, increasing plasma nitric oxide and improving abnormal hemorheology in high cholesterol diet–induced atherosclerotic rats. Therefore the elevated eNOS/NO and improved hemorheology may be beneficial in atherosclerosis.

Assessment Points

System	Effect	Test
CV	Reduces VLDL, LDL, and triglyceride levels Reduces matrix metalloproteinases and CRP involved in vascular remodeling Increases adiponectin levels Reduces eNOS regulatory factor Increases expression of eNOS.	VLDL, LDL, HDL, triglycerides Matrix metalloproteinases 2 and 9 and CRP Adiponectin, LDL-C, HDL, triglycerides, leptin
HEPAT	Rare hepatocellular damage and cholestasis	AST, ALT
MS	Rare myopathy, myalgia, and rhabdomyolysis	CPK
ENDO	Reduces pancreatic B-cell destruction and oxidative stress	Pancreatic B-cell numbers

Key References: Becker DJ, Gordon RY, Halbert SC, et al.: Red yeast rice for dyslipidemia in statin-intolerant patients. A randomized trial, *Ann Intern Med* 150(12):830–839, 2009; Cicero AF, Derosa G, Parini A, et al.: Red yeast rice improves lipid pattern, high-sensitivity C-reactive protein, and vascular remodeling parameters in moderately hypercholesterolemic Italian subjects, *Nutr Res* 33(8):622–628, 2013.

Perioperative Implications

Preoperative Concerns

- Lovastatin has been designated as pregnancy category X by the FDA. Thus red yeast rice should be avoided in pregnancy and lactation.

Preinduction/Induction

- Succinylcholine is contraindicated in myopathies associated with elevated serum CPK values.

S-Adenosyl-L-Methionine

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Uses

- As an antiaging, antidisease therapeutic agent.
- May protect against the hepatotoxic effect of certain drugs (e.g., alcohol, acetaminophen, phenobarbital, and steroids).
- Depression, mild to moderate and adolescent.
- Anxiety, PMS.
- Heart disease.
- Liver disease, cirrhosis, intrahepatic cholestasis, disorders of porphyrin, and bilirubin metabolism.
- Osteoarthritis, tendinitis, bursitis, chronic low back pain.
- Dementia, Alzheimer disease, Parkinson disease.
- MS, migraine, seizure, spinal cord injury.
- Chronic lead poisoning.
- Disorder of porphyrin and bilirubin metabolism.
- Chronic fatigue syndrome.
- Intellectual enhancement, ADHD.
- Postop SAME therapy can benefit residual liver function of pts with cirrhosis, especially pts suffering marked ischemia reperfusion injury.
- SAME supplementation restores hepatic antioxidant glutathione (GSH) deposits. Depleted glutathione is associated with alcoholism, acetaminophen toxicity, Alzheimer disease, Crohn disease, diabetes, heart disease, and stroke.

Perioperative Risks

- N/V, flatulence, diarrhea, irregular or accelerated HR
- Anxiety

Overview/Pharmacology

- SAME is produced endogenously by ATP activation of methionine, which is produced by the body from dietary protein.

- SAME is required in numerous transmethylation reactions involving nucleic acids, proteins, phospholipids, amines, and other neurotransmitters. The synthesis of SAME is linked with folate and cyanocobalamin metabolism; deficiencies of both these vitamins have been found to reduce SAME concentrations in the CNS.
- May improve methylation by different mechanisms in several neurologic and psychiatric disorders.
- Is well tolerated with oral use and free of serious side effects. The oral supplement was developed in the 1970s and has been touted as a multipurpose treatment ever since.
- Exogenously administered SAME has a low bioavailability due to rapid first-pass metabolism by the liver.
- Peak plasma concentration reached in 3–5 h.
- Half-life of 100 min.
- Excreted in urine and feces.
- Crosses the blood-brain barrier.
- Metabolized to homocysteine; remethylated to form methionine, which can form more SAME.
- Tosylate salt has 1% oral bioavailability.
- Butane disulfonate salt has 5% oral bioavailability.

Mechanism of Action

- Contributes to the synthesis, activation, and metabolism of hormones, neurotransmitters, nucleic acid, proteins, phospholipids, and some drugs.
- SAME crosses the blood-brain barrier and is involved in transmethylation and folate and monoamine metabolism as well as in membrane function and neurotransmission.
- SAME plays a role in more than 100 biochemical reactions: increases levels of serotonin, dopamine, norepinephrine, phosphatides, and proteoglycans.

- Improves intrahepatic cholestasis. SAME supplementation seems to improve hepatic function and reverse imbalances of various enzymes. In liver disease, deficiencies of MAP often lead to reductions in cysteine and choline, which can lead to depletion of glutathione. SAME restores levels of glutathione, decreases inflammation, and increases methylation of DNA.
- Stimulates growth of articular cartilage.
- Relieves joint pain, possibly owing to analgesic or anti-inflammatory effects. May stimulate articular cartilage growth and repair as a result of chondrocyte proteoglycan synthesis. May antagonize TNF-alpha, which may be beneficial in arthritic pts.
- Antidepressant effect is probably due to increased serotonin turnover and elevated dopamine and norepinephrine levels or alterations in cellular membrane fluidity, which would facilitate signal transduction across membranes and increase the efficiency of receptor-effector coupling.
- In liver disease, restores depleted biochemical factors.
- In myelopathy of AIDS, replenishes depleted endogenous SAME.

Usual Dose

- For depression, 400–1600 mg daily PO or 200–400 mg daily IV to speed onset of action of tricyclic antidepressants.
- Addition of betaine to SAME counteracts high levels of homocysteine; combination more effective than SAME alone for treatment of depression.
- For osteoarthritis, 200 mg 3 times PO or 400 mg IV.
- For alcoholic liver disease, cirrhosis, or intrahepatic cholestasis, 1200–1600 mg/d PO or 800 mg/d IV.
- For AIDS myelopathy, 800 mg/d IV for 14 d.
- For fibromyalgia, 800 mg/d PO.

Assessment Points

System	Effect	Assessment by Hx	PE
GI	N/V, diarrhea	GI complaints	KUB
MS	Osteoarthritis	Stiff joints	ROM

Key References: Guo T, Chang L, Xiao Y, et al.: S-adenosyl-L-methionine for the treatment of chronic liver disease: a systematic review and meta-analysis, *PLoS ONE* 10(3):e0122124, 2015; Su ZR, Cui ZL, Ma JL, et al.: Beneficial effects of S-adenosyl-L-methionine on post-hepatectomy residual liver function: a prospective, randomized, controlled clinical trial, *Hepatogastroenterology* 60(125):1136–1141, 2015.