Androstenedione

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Uses

- Testosterone replacement therapy
- Treatment of hypogonadal men
- Age-related sarcopenia
- HIV-related muscle wasting
- Increase in bone mineral density
- Prevention of age-related frailty and falls

Perioperative Risks

- Coagulopathy
- Polycythemia

Overview

- Growing sales trend of 20–30% in USA for both medical and nonmedical use of AAS.
- AAS have been available since 1996 as an OTC nutritional supplement and were banned for sale by the Anabolic Steroid Control Act in 2004.
- Estimated 10% of AAS users are teens.
- Estimated 4.9% of male and 2.4% of female adolescents in USA have used legal androgenic/anabolic steroids.
- Current estimates indicate that there are as many as 3 million AAS users in USA.
- Surveys among community weight trainers attending gyms and health clubs indicate that AAS use is between 15% and 30%.
- AAS use is positively associated with use of alcohol, illicit drugs, and legal performance enhancing substances.
- As a major precursor to testosterone that is available without a prescription, it is purported to increase strength and athletic performance. However, significant effects on muscle strength have not been found in men after androstenedione administration, except following a large dose (1500 mg/d for 12 wk) of androstenedione given to hypogonadal men.
- AAS used to increase endogenous testosterone production to enhance athletic performance and recovery from exercise, to keep RBCs healthy, and to heighten sexual arousal and function.
- Popularity related to society's preoccupation with sustaining the male libido.

Pharmacology/Mechanism of Action/Usual Dose

- As a member of a group of compounds known as AAS, these synthetic derivatives of testosterone are thought to possibly restore sex drive and boost muscle mass.
- Testosterone enters the cell by passive diffusion and is converted by 5α-reductase to 5α-dihydrotestosterone, which binds to intracellular androgen receptors.
- Increase protein anabolism and decrease protein catabolism. Nitrogen balance is improved only when there is sufficient intake of calories and protein.
- Stimulate the production of RBCs by enhancing the production of erythropoietic stimulating factor.
- Impair preadipocyte differentiation into adipocytes and reduce subcutaneous abdominal adipose tissue in nonobese women.
- Supplementation of androstenedione in the setting of a rigorous 12-wk resistance-training program resulted in a return of baseline levels of testosterone levels and significant increases in estrone and estradiol levels. No increase in measurable lean body mass or muscular strength when compared with placebo.
- Androstenedione is produced in the gonads and adrenal glands of both males and females.
- It is synthesized from dehydroepiandrosterone and then converted to testosterone by the enzyme 17 β-hydroxysteroid dehydrogenase or to estrone by the aromatase enzyme complex.
- Usual dose:
  - Androstenedione is a direct precursor of testosterone and estrone in both males and females; it may increase testosterone levels.
  - Marketing claims include increased strength, greater fat-free mass, and improved libido; recommended doses are 100–300 mg/d or 50–100 mg twice daily taken 1 h before exercise or upon awakening. Only high doses of 1500 mg/d for 12 wk confirmed to increase muscle strength.
- Contraindications:
  - Pts with steroid-dependent carcinoma of the breast, prostate gland, and endometrium.
  - Women who are or may become pregnant.
  - Pt with serious cardiac, hepatic, or renal disease.
- Adverse effects:
  - Several AAS-induced CV concerns reported include Htn, left ventricular hypertrophy, impaired diastolic filling, arrhythmias, erythrocytosis, altered lipoprotein profile, and thrombosis.
  - AAS-induced elevations in liver enzymes (alanine- and aspartate-aminotransferases).
  - Dermatologic chances such as acne, striae, alopecia, and hirsutism are possible results induced by the action of the AAS on the skin and sebaceous glands.
  - Endocrine and/or reproductive effects include a dose-dependent depression of levels of luteinizing hormone and follicle-stimulating hormone due to the negative feedback loop of the hypothalamic-pituitary-gonadal axis.
  - Feminization (gynecomastia) in males due to the aromatization of exogenous testosterone to estrogen metabolites.
  - Male users may have their endocrine suppression lead to hypogonadotrophic hypogonadism, testicular atrophy, sperm morphology, infertility, and changes in libido.
  - Female-specific side effects of AAS incl hirsutism, increased facial hair, voice deepening, clitorial hypertrophy, oligomenorrhea, reduced breast tissue, and male-pattern baldness.
  - Restoration of hypothalamic–pituitary homeostasis, endogenous testosterone, and spermatogenesis may take between 3-12 mo after using AAS.

Assessment Points

System	Effect	Assessment by Hx	Test
CV	Decreased HDL, atherosclerosis	Angina	ECG, cholesterol
GI	Cholestasis, hepatocellular tumors, hepatitis, nausea		Liver enzymes, bilirubin
HEME	Polycythemia, chronic usage, suppression of clotting factors, sodium and water retention	Easy bruising	PT, PTT Lytes
CNS	Depression, anxiety, behavioral changes, headache		

Key References: Broeder CE, Quindry J, Brittingham K, et al.: The Andro Project: physiological and hormonal influences of androstenedione supplementation in men 35 to 65 years old participating in a high-intensity resistance training program, *Arch Intern Med* 160(20):3093–3104, 2000; Dodge T, Hoagland MF: The use of anabolic androgenic steroids and polypharmacy: a review of the literature, *Drug Alcohol Depend* 114(2–3):100–109, 2011.

Perioperative Implications

- Retention of sodium, chloride, potassium, calcium, inorganic phosphate, and water.
- N/V, rarely hepatocellular neoplasms and hepatitis.
- Suppression of clotting factors II, V, VII and X; bleeding in pts on concomitant anticoagulant therapy.
- Polycythemia.
- Increased serum cholesterol, decreased HDL.
- Pts with osteolytic lesions or who are semi-ambulatory may develop nephrocalcinosis.
- In geriatric pts, high risk of prostate hypertrophy and prostate carcinoma.

Possible Drug Interactions

- Metabolic effects of androgens may decrease blood glucose level and insulin requirements.
- Androgens decreased levels of thyroxin-binding globulin, resulting in decreased total T_4 serum levels and decreased resin uptake of T_3 and T_4.
- May interfere with androgenic or estrogenic drug therapy.

β-Sitosterol

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Uses

- CHD and hypercholesterolemia.
- BPH and prostatitis.
- Gallstones.
- Enhances sexual activity.
- Prevents colon cancer.
- Boosts immune system.
- Topically for treating wounds and burns.
- Migraine headache, chronic fatigue syndrome, and symptoms of menopause.
- Asthma, allergies, bronchitis, SLE, and alopecia.
- Areas of potential application currently under investigation include the prevention of breast, ovarian, and lung cancers.

Overview

- β-sitosterol is one of the major plant sterols found in humans. Its chemical structure is similar to that of cholesterol with an ethyl group added at position 24.
- β-sitosterol is available in many nonprescription supplements and with dietary plant consumption.
- With a low absorption rate, it inhibits intestinal absorption of cholesterol by competing for limited space with cholesterol in mixed micelles and also accelerates the esterification rate of the lecithin cholesterol acyltransferase enzyme.
- In benign prostatic hyperplasia, it binds to prostatic tissue, inhibits prostaglandin synthesis in the prostate, and has anti-inflammatory activity.
- Enhances proliferative responses of T cells in vitro.
- Inhibits colon cancer growth in vitro.
- Alternative for pts seeking modest reductions in LDL-C (<15%): Higher doses (4 g/d) can lead to reductions in LDL-C up to 19.8%, equivalent to doubling the dose of statin in dyslipidemic pts.
- Reductions in triglycerides (6–9%) seen as well with 2 g/d doses of sterol.
- May alter CNS disease progression, especially disorders that are correlated with an altered cholesterol metabolism, such as AD, MS, and ALS-PDC.
- Some studies have shown anti-diabetic properties of β-sitosterol.

Pharmacology/Usual Dose

- The reduction of dietary cholesterol available to the body may be due to inhibition of absorption in the intestine.
- Large amounts of dietary β-sitosterol may displace cholesterol during absorption and increase fecal excretion.
- Inhibition of 5-alpha reductase prevents the conversion of testosterone to dihydrotestosterone. This reduction of androgens may reduce prostatic hyperplasia in the same manner that finasteride (Proscar) does.
- For hypercholesterolemia, usual dosage is 800 mg–6 g before meals; for severe cases, can be up to 15 g.
- For benign prostatic hyperplasia and prostatitis, implement 60–130 mg tid.
- About 175–200 mg is consumed daily in typical diet.
- Contraindications include sitosterolemia, which is an inherited lipid storage disease with increased absorption of cholesterol and β-sitosterol from diet. Elevated liver β-sitosterol competitively inhibits cholesterol catabolism, which will lead to hypercholesterolemia.

Assessment Points

System	Effect	Assessment by Hx	PE	Test
CV	CAD	Angina MI		ECG
RESP	Asthma	Wheezing	Wheezing	

Key References: Wong NC: The beneficial effects of plant sterols on serum cholesterol, *Can J Cardiol* 17(6):715–721, 2001; Vanmierlo T, Bogie JF, Mailleux J, et al.: Plant sterols: friend or foe in CNS disorders? *Prog Lipid Res* 58:26–39, 2015.

Perioperative Implications

- Obtain adequate Hx to determine indication since there may be significant comorbidity.
- No known periop implications.

Anticipated Problems/Concerns

Side Effects

- May cause N/V, indigestion, gas, diarrhea, or constipation.
- Interactions: Ezetimibe (Zetia) may reduce absorption of β-sitosterol.
- Antihyperlipidemic drugs such as atorvastatin (Lipitor), cholestyramine, and gemfibrozil have additive effects in lowering cholesterol level.
- Pravastatin (Pravachol) can lower the blood level of β-sitosterol.
- Increased risk of deficiency of fat soluble vitamins. β-sitosterol may reduce absorption and blood level of α- and β-carotene and vitamin E.
- Erectile dysfunction and loss of libido have been reported in pts on β-sitosterol.

Blue Cohosh *(Caulophyllum thalictroides)*

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Uses

- Commonly used by midwives as a uterine stimulant and for induction of labor. Major uses, therefore, include (1) inducing labor; (2) as an emmenagogue; (3) as an antispasmodic; and (4) as an abortifacient.
- Properties also include anti-inflammatory, antipyretic, diuretic, expectorant, vasoconstrictor, and smooth muscle relaxants.
- According to a national survey, 64% of midwives still use blue cohosh to induce labor and 7–45% of women use herbal medications during pregnancy.

Risk

- Ingestion of the leaf or seeds can lead to severe toxicity.
- Case reports document seizures, renal failure, and resp distress after use.
- Avoidance is advised in diabetic pts due to concern for hyperglycemia and potential inhibition of antiglycemic medications.
- Reports of perinatal stroke, aplastic anemia, chest pain (angina), hypertension, acute MI, CHF, shock, and multi-organ hypoxia in infants following maternal use from the first trimester to right before delivery.
- Should not be used by women with estrogen-sensitive conditions or cancers, and in pts with diarrhea.
- Also causes mucous membrane irritation, diarrhea, and cramping, and constricts coronary arteries.
- Possesses several components that can be teratogens, cytotoxic, or lethal to embryos and/or can cause birth defects and congenital malformations.

Perioperative Risks

- Coronary artery vasoconstriction that can lead to myocardial ischemia
- Alteration in antiglycemic and antihypertensive drug levels
- Interaction with medications dependent on cytochrome P-450 enzymes

Worry About

- Differentiate from black or white cohosh, which have other physiologic effects.
- Product safety and efficacy profiles differ among manufacturers.
- Usage in pregnancy due to concern of uterine stimulation, teratogenicity, and neonatal multisystemic complications.
- Usage in pts with diabetes, hypertension, or acute history of tobacco/nicotine use.

Overview/Pharmacology

- Several alkaloids and saponins are considered responsible for the pharmacologic effects.
- Anagyrine, *N*-methylcytosine, and taspine are constituents identified likely to be teratogenic.
- *N*-methylcytosine acts similarly to nicotine, which can cause elevated BP, tachycardia, diaphoresis, abdominal pain, vomiting, fasciculations, and produce hyperglycemia in the developing fetus.
- Alkaloid components found to be cytochrome P-450 inhibitor based on in vitro studies, and thus may pose a risk of drug-drug interactions when taken with other medications dependent on CYP450 enzymes.
- Blue cohosh preliminarily appears to have estrogenic effects with enhancement of estradiol binding to estrogen receptors.

Etiology

- Berberidaceae or Leonticaceae family.
- Listed in the US Pharmacopoeia 1882–1905 as a labor inducer.
- Typically the dried rhizome/root parts are used.