Testosterone

Brand Name: Androgel, Testoderm, Androderm, Depo-Testosterone and Other Drugs

Drug Class:

Drug Description

Testosterone is a naturally occurring androgenic steroid hormone. [1]

HIV/AIDS-Related Uses

Testosterone (transdermal and injection) is used to treat hypogonadism, a condition that commonly occurs in HIV infected men, particularly those whose disease has progressed to AIDS. In addition to typical manifestations of hypogonadism (e.g., impaired sexual mood and functioning, loss of body hair, gynecomastia, bone loss, impaired sense of well-being), HIV infected men with hypogonadism may exhibit a disproportionate loss of lean body mass and muscle wasting. Testosterone replacement therapy is considered the treatment of choice for androgen deficiency and AIDS wasting in this population.[2] It has been investigated to assess its efficacy in reducing symptoms of increased visceral fat in HIV infected men. [3] Transdermal testosterone has also been investigated to determine its safety and efficacy in treating weight loss in HIV infected women.[4] [5]

Non-HIV/AIDS-Related Uses

Testosterone (transdermal and injection) is approved by the FDA for hormone replacement therapy in males with a congenital or acquired deficiency or absence of endogenous testosterone. Short, 6-month or less courses of injected testosterone may be given for the induction of puberty in patients with familial delayed puberty, a condition characterized by spontaneous, nonpathologic late-onset puberty, when the patient does not respond to psychological treatment.[6] Men with corticosteroid-induced hypogonadism at high risk for osteoporosis may also receive testosterone treatment. Injected testosterone is also approved for the treatment of inoperable metastatic breast cancer in women.[7]

Testosterone may also be used to treat people with congenital or acquired hypogonadotropic hypogonadism, idiopathic gonadotropin or luteinizing hormone-releasing hormone (LHRH) deficiency, or pituitary-hypothalamic injury from tumors, trauma, or radiation.[8]

Pharmacology

Testosterone is the principal endogenous androgen. Endogenous androgens are responsible for a number of physical conditions, including alterations in body musculature and fat distribution.[9] Loss of lean body mass is a common complication of HIV/AIDS, and HIV infected individuals undergoing highly active antiretroviral therapy (HAART) have a high incidence of lipodystrophy. Although the pathophysiologies of wasting and visceral obesity common to HIV infection are multifactorial, testosterone replacement appears to have a favorable impact on these syndromes.[10]

Testosterone produces retention of nitrogen, potassium, sodium, and phosphorus and increases protein anabolism.[11] Androgens are highly lipid-soluble and enter target cells by passive diffusion. Testosterone or the active metabolite 5-alpha-dihydrotestosterone (DHT) binds to an intracellular androgen receptor, which then translocates to the nucleus and attaches to specific hormone receptor elements on the chromosome. This process initiates or suppresses transcription and protein synthesis. Testosterone can produce estrogenic effects as a result of its conversion to estrogen. Endogenous plasma testosterone is maintained and regulated by gonadotropins within a normal range by a negative feedback system involving the hypothalamus and pituitary. Androgens also stimulate red blood cell production by enhancing production of erythropoietic stimulating factors.[12]

Esters of testosterone cypionate and testosterone enanthate given via intramuscular (IM) injection are absorbed slowly from the lipid tissue phase at the injection site, with peak serum concentrations reached about 72 hours after the dose is given. These esters' slow absorption results in a prolonged duration of action of 2 to 4 weeks after administration. By contrast, testosterone propionate given by IM injection has a comparatively short duration of action. Irritation at the IM injection site may cause erratic absorption of any testosterone ester.[13]

Testosterone

Pharmacology (cont.)

Transdermal testosterone is absorbed systemically through the skin. Approximately 10% of a testosterone gel dose is absorbed into systemic circulation. Increases in serum testosterone concentrations occur within 30 minutes of the application of a 100-mg dose of 1% gel. In most patients, physiologic concentrations are achieved within 4 hours, with percutaneous absorption maintained throughout the 24-hour dosing period. Serum testosterone concentrations reach steady state by the second or third day of dosing with the 1% gel.[14]

Percutaneous absorption of testosterone via transdermal systems varies considerably among individual patients; however, serum testosterone concentrations generally reach the normal physiologic range within the first day of dosing. These levels are maintained with no accumulation of testosterone during continuous dosing. Because genital skin contains high concentrations of 5-alpha-reductase, serum concentrations of the active metabolite DHT are generally in the supraphysiologic range for men following chronic scrotal application of testosterone transdermal systems. In some men, however, DHT concentrations may increase initially and then decrease to normal levels with continued therapy.[15]

In serum, testosterone is bound with high affinity to sex hormone binding globulin (SHBG) and with low affinity to albumin. The amount of SHBG in serum and the total testosterone concentration determine the distribution of pharmacologically active and nonactive forms of the androgen.[16] Approximately 40% of endogenous testosterone in plasma is bound to SHBG, 2% remains unbound, and the rest is bound to albumin and other proteins.[17]

Testosterone is in FDA Pregnancy Category X. Studies in humans have shown that androgens cause masculinization of the external genitalia of the female fetus.[18] Because the risks clearly outweigh the possible benefits in women who are pregnant or who can become pregnant, androgens are contraindicated in these patients. Women who become pregnant while receiving testosterone should be informed of the potential hazard to the fetus.[19] It is not known whether testosterone is distributed into breast milk; however, because of the potential for adverse effects in the nursing infant, androgens are not recommended for women who are breastfeeding.[20]

Protein binding of testosterone is very high (approximately 99%), with 80% binding to SHBG and 19% to albumin. The metabolite DHT has greater affinity for SHBG than does testosterone.[21]

Biotransformation of testosterone occurs primarily through the liver.[22] Both IM and transdermal administration of testosterone avoid first-pass metabolism. Testosterone esters for injection first undergo hydrolysis of the ester to the active form, free testosterone. Free testosterone is further converted into two of the major active metabolities, DHT and estradiol. The plasma half-life of testosterone is highly variable, ranging from 10 to 100 minutes. Both testosterone and its metabolites are renally excreted in urine and feces (approximately 90% and 6%, respectively, of an IM dose).[23]

Adverse Events/Toxicity

The most frequent adverse effects of testosterone include abdominal or back pain; abnormal ejaculation, or frequent or continuing penile erections; acne or local blistering of skin; anxiety; bladder irritability or urinary tract infection; breast soreness; cholestatic hepatitis, jaundice, and abnormal liver function tests; diarrhea; dizziness; edema; excessive sexual stimulation; flushing of the skin; gynecomastia; habituation; headache; hirsutism; hypercalcemia; increased serum cholesterol; insomnia; libido changes; male pattern baldness; mental depression or irritability; nausea; oligospermia; pain or irritation at injection site; priapism; prostate disorders; redness, burning, or itching at transdermal application site; retention of water, sodium, chloride, potassium, and inorganic phosphates; and seborrhea.[24] [25] [26] [27]

Frequent adverse effects among women receiving testosterone therapy include indications of virilization (amenorrhea or other menstrual irregularities; clitoral enlargement; hirsutism; and

Testosterone

Adverse Events/Toxicity (cont.)

hoarseness or deepening of the voice).[28]

Pregnant women should not receive testosterone therapy because of the potential for serious harm to the fetus. In addition, pregnant women should avoid skin contact with application sites on patients because of the possibility that transdermal testosterone can be transferred from patients to their sexual partners or others in close physical contact. Potential adverse effects to female offspring exposed to testosterone in utero include clitoral hypertrophy, labial fusion of the external genital fold, abnormal vaginal development, and persistence of a urogenital sinus.[29]

Drug and Food Interactions

Because concurrent administration of testosterone with oral coumarin- or indandione-derivative anticoagulants can cause bleeding in some patients, dosage adjustment of anticoagulants may be needed during and after coadministration of the two drugs. Concurrent administration of testosterone with hepatotoxic drugs, including but not limited to abacavir, lamivudine, nevirapine, tenofovir, and zidovudine, may increase the incidence of hepatotoxicity. Patients should be carefully monitored, especially those undergoing long-term therapy or those with a history of liver disease.[30]

Increased serum levels of oxyphenbutazone have been reported in patients receiving androgens and oxyphenbutazone concurrently. The use of testosterone by diabetic patients may result in decreased blood glucose levels and reduced insulin requirements. Increased clearance of propranolol has been reported in patients receiving the drug concurrently with testosterone cypionate.[31] [32] Concurrent administration of testosterone with corticotropin (ACTH) or corticosteroids may enhance edema formation; these drugs should be combined with caution, particularly in patients with cardiac or hepatic disease.[33]

Contraindications

Testosterone products should not be used in patients with known hypersensitivity to any ingredients in the preparation. Testosterone is contraindicated in men with carcinoma of the breast or known or suspected carcinoma of the prostate.[34] [35] It is also contraindicated in pregnant or lactating women and patients with serious cardiac, hepatic, or renal disease.[36]

Risk-benefit should be considered in patients with cardiac failure, cardiac function impairment, cardiorenal disease, or edema; hepatic function impairment, nephritis, nephrosis, or renal function impairment; coronary heart disease or myocardial infarction; hepatic function impairment; hypercalcemia due to metastatic breast cancer; or benign prostatic hyperplasia with urethral obstructive symptoms.[37]

Clinical Trials

For information on clinical trials that involve Testosterone, visit the ClinicalTrials.gov web site at http://www.clinicaltrials.gov. In the Search box, enter: Testosterone AND HIV Infections.

Dosing Information

Mode of Delivery: Topical for transdermal absorption.[38]

Parenteral for intramuscular injection.[39]

Dosage Form: IInjectable suspension containing testosterone 25, 50, or 100 mg/ml.[40]

Testosterone cypionate or testosterone enanthate injection containing testosterone 100 or 200 mg/ml.[41]

Testosterone propionate injection containing testosterone 100 mg/ml.[42]

Testosterone gel containing 5, 7.5, or 10 g delivering testosterone 50, 75, or 100 mg, respectively, per day.[43]

Matrix-type transdermal system delivering testosterone 4 or 6 mg per system, per day.[44]

Reservoir-type transdermal system delivering testosterone 2.5 or 5 mg per system, per day.[45]

Storage: Store testosterone gel at controlled room

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Dosing Information (cont.)

temperature, between 20 C to 25 C (68 F to 77 F).[46]

Store testosterone matrix-type transdermal systems between 15 C and 30 C (59 F and 86 F).[47]

Store testosterone injection below 40 C (104 F), preferably between 15 C and 30 C (59 F and 86 F), unless otherwise specified by the manufacturer. Protect from freezing.[48]

Chemistry

CAS Name: Androst-4-en-3-one, 17-hydroxy-, (17beta)-[49]

CAS Number: 58-22-0[50]

Molecular formula: C19-H28-O2[51]

C79.12%, H9.78%, O11.09%[52]

Molecular weight: 288.42[53]

Melting point: 155 C[54]

Physical Description: White to practically white crystalline powder [55] or white to slightly creamy white odorless crystals.[56] Testosterone needles will crystallize from diluted acetone.[57]

Stability: Crystals may form at low temperatures; warming and shaking the vial of testosterone will redissolve any crystals. Use of a wet needle or syringe may cause solution to become cloudy; however, potency of the medication will not be affected.[58]

Solubility: Practically insoluble in water, freely soluble in dehydrated alcohol [59] , alcohol, ether, and other organic solvents [60] ; soluble in vegetable oils.[61]

Other Names

Sustanon[62]

Testosterona[63]

Further Reading

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Manufacturer Information

Depo-Testosterone
Pharmacia Corporation
100 Route 206 North
Peapack, NJ 07977
(888) 768-5501

Depo-Testosterone
Pfizer Inc
235 East 42nd Street
New York, NY 10017-5755
(800) 438-1985

Testoderm
ALZA Corporation
1900 Charleston Road / PO Box 7210
Mountain View, CA 94039-7210
(800) 227-9953

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Manufacturer Information (cont.)

Androderm
Watson Laboratories Inc
311 Bonnie Circle
Corona, CA 92880-2882
(800) 272-5525

Testosterone
Watson Laboratories Inc
311 Bonnie Circle
Corona, CA 92880-2882
(800) 272-5525

Androgel
Unimed Pharmaceuticals Inc
4 Parkway North 2nd floor
Deerfield, IL 60015
(847) 282-5400

For More Information

Contact your doctor or an AIDSinfo Health Information Specialist:

• Via Phone: 1-800-448-0440 Monday - Friday, 12:00 p.m. (Noon) - 5:00 p.m. ET

• Via Live Help: http://aidsinfo.nih.gov/live_help Monday - Friday, 12:00 p.m. (Noon) - 4:00 p.m. ET

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