

Concomitant use of prostaglandin synthase inhibiting drugs, e.g., indomethacin, may decrease the hypotensive effects of beta-blockers.

Lithium generally should not be given with diuretics because they reduce its renal clearance and add a high risk of lithium toxicity. Read prescribing information for lithium preparations before use of such preparations with atenolol and chlorthalidone.

Beta-blockers may exacerbate the rebound hypertension which can follow the withdrawal of clonidine. If the two drugs are coadministered, the beta-blocker should be withdrawn several days before the gradual withdrawal of clonidine. If replacing clonidine by beta-blocker therapy, the introduction of beta-blockers should be delayed for several days after clonidine administration has stopped.

While taking beta-blockers, patients with a history of anaphylactic reaction to a variety of allergens may have a more severe reaction on repeated challenge, either accidental, diagnostic or therapeutic. Such patients may be unresponsive to the usual doses of epinephrine used to treat the allergic reaction.

Both digitalis glycosides and beta-blockers slow atrioventricular conduction and decrease heart rate. Concomitant use can increase the risk of bradycardia.

Other Precautions

In patients receiving thiazides, sensitivity reactions may occur with or without a history of allergy or bronchial asthma. The possible exacerbation or activation of systemic lupus erythematosus has been reported. The antihypertensive effects of thiazides may be enhanced in the postsympathectomy patient.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Two long-term (maximum dosing duration of 18 or 24 months) rat studies and one long-term (maximum dosing duration of 18 months) mouse study, each employing dose levels as high as 300 mg/kg/day or 150 times the maximum recommended human antihypertensive dose*, did not indicate a carcinogenic potential of atenolol. A third (24 month) rat study, employing doses of 500 mg/kg/day and 1,500 mg/kg/day (250 and 750 times the maximum recommended human antihypertensive dose*) resulted in increased incidences of benign adrenal medullary tumors in males and females, mammary fibroadenomas in females, and anterior pituitary adenomas and thyroid parafollicular cell carcinomas in males. No evidence of a mutagenic potential of atenolol was uncovered in the dominant lethal test (mouse), *in vivo* cytogenetics test (Chinese hamster) or Ames test (*S typhimurium*).

Fertility of male or female rats (evaluated at dose levels as high as 200 mg/kg/day or 100 times the maximum recommended human dose*) was unaffected by atenolol administration.

*Based on the maximum dose of 100 mg/day in a 50 kg patient.

Animal Toxicology

Six month oral administration studies were conducted in rats and dogs using atenolol and chlorthalidone doses up to 12.5 mg/kg/day (atenolol/chlorthalidone 10/2.5 mg/kg/day -- approximately five times the maximum recommended human antihypertensive dose*). There were no functional or morphological abnormalities resulting from dosing either compound alone or together other than minor changes in heart rate, blood pressure and urine chemistry which were attributed to the known pharmacologic properties of atenolol and/or chlorthalidone.

Chronic studies of atenolol performed in animals have revealed the occurrence of vacuolation of epithelial cells of Brunner's glands in the duodenum of both male and female dogs at all tested dose levels (starting at 15 mg/kg/day or 7.5 times the maximum recommended human antihypertensive dose*) and increased incidence of atrial degeneration of hearts of male rats at 300 mg atenolol/kg/day but not 150 mg atenolol/kg/day (150 and 75 times the maximum recommended human antihypertensive dose,* respectively).

*Based on the maximum dose of 100 mg/day in a 50 kg patient

Use in Pregnancy

See WARNINGS - Pregnancy and Fetal Injury.

Nursing Mothers

Atenolol is excreted in human breast milk at a ratio of 1.5 to 6.8 when compared to the concentration in plasma. Caution should be exercised when atenolol is administered to a nursing woman. Clinically significant bradycardia has been reported in breastfed infants. Premature infants, or infants with impaired renal function, may be more likely to develop adverse effects.

Neonates born to mothers who are receiving atenolol at parturition or breastfeeding may be at risk for hypoglycemia and bradycardia. Caution should be exercised when atenolol and chlorthalidone is administered during pregnancy or to a woman who is breastfeeding. (See WARNINGS, Pregnancy and Fetal Injury.)

Pediatric Use

Safety and effectiveness in pediatric patients have not been established.

Geriatric Use

Clinical studies of atenolol and chlorthalidone did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and concomitant disease or other drug therapy.

ADVERSE REACTIONS

Atenolol and chlorthalidone is usually well tolerated in properly selected patients. Most adverse effects have been mild and transient. The adverse effects observed for atenolol and chlorthalidone are essentially the same as those seen with the individual components.

Atenolol

The frequency estimates in the following table were derived from controlled studies in which adverse reactions were either volunteered by the patient (US studies) or elicited, e.g., by checklist (foreign studies). The reported frequency of elicited adverse effects was higher for both atenolol and placebo-treated patients than when these reactions were volunteered. Where frequency of adverse effects for atenolol and placebo is similar, causal relationship to atenolol is uncertain.

	Volunteered (US Studies)		Total-Volunteered and Elicited (Foreign + US studies)	
	Atenolol (n = 164) %	Placebo (n = 206) %	Atenolol (n = 399) %	Placebo (n = 407) %
CARDIOVASCULAR				
Bradycardia	3	0	3	0
Cold Extremities	0	0.5	12	5
Postural Hypotension	2	1	4	5
Leg Pain	0	0.5	3	1
CENTRAL NERVOUS SYSTEM/NEUROMUSCULAR				
Dizziness	4	1	13	6
Vertigo	2	0.5	2	0.2
Light-Headedness	1	0	3	0.7
Tiredness	0.6	0.5	26	13
Fatigue	3	1	6	5
Lethargy	1	0	3	0.7
Drowsiness	0.6	0	2	0.5
Depression	0.6	0.5	12	9
Dreaming	0	0	3	1
GASTROINTESTINAL				
Diarrhea	2	0	3	2
Nausea	4	1	3	1
RESPIRATORY (see WARNINGS)				
Wheeziness	0	0	3	3
Dyspnea	0.6	1	6	4

During postmarketing experience, the following have been reported in temporal relationship to the use of the drug: elevated liver enzymes and/or bilirubin, hallucinations, headache, impotence, Peyronie's disease, postural hypotension which may be associated with syncope, psoriasisform rash or exacerbation of psoriasis, psychoses, purpura, reversible alopecia, thrombocytopenia, visual disturbance, sick sinus syndrome, and dry mouth. Atenolol and chlorthalidone, like other beta-blockers, has been associated with the development of antinuclear antibodies (ANA), lupus syndrome, and Raynaud's phenomenon.

Chlorthalidone

Cardiovascular: orthostatic hypotension; Gastrointestinal: anorexia, gastric irritation, vomiting, cramping, constipation, jaundice (intrahepatic cholestatic jaundice), pancreatitis; CNS: vertigo, paresthesia, xanthopsia; Hematologic: leukopenia, agranulocytosis, thrombocytopenia, aplastic anemia; Hypersensitivity: purpura, photosensitivity, rash, urticaria, necrotizing angitis (vasculitis) (cutaneous vasculitis), Lyell's syndrome (toxic epidermal necrolysis); Miscellaneous: hyperglycemia, glycosuria, hyperuricemia, muscle spasm, weakness, restlessness. Clinical trials of atenolol and chlorthalidone conducted in the United States (89 patients treated with atenolol and chlorthalidone) revealed no new or unexpected adverse effects.

POTENTIAL ADVERSE EFFECTS

In addition, a variety of adverse effects not observed in clinical trials with atenolol but reported with other beta-adrenergic blocking agents should be considered potential adverse effects of atenolol. Nervous System: Reversible mental depression progressing to catatonia; an acute reversible syndrome characterized by disorientation for time and place, short-term memory loss, emotional lability, slightly clouded sensorium, decreased performance on neuropsychometrics; Cardiovascular: Intensification of AV block (see CONTRAINDICATIONS); Gastrointestinal: Mesenteric arterial thrombosis, ischemic colitis; Hematologic: Agranulocytosis; Allergic: Erythematous rash, fever combined with aching and sore throat, laryngospasm and respiratory distress.

Miscellaneous

There have been reports of skin rashes and/or dry eyes associated with the use of beta-adrenergic blocking drugs. The reported incidence is small, and, in most cases, the symptoms have cleared when treatment was withdrawn. Discontinuance of the drug should be considered if any such reaction is not otherwise explicable. Patients should be closely monitored following cessation of therapy. (See DOSAGE AND ADMINISTRATION.)

The oculomucocutaneous syndrome associated with the beta-blocker practolol has not been reported with atenolol. Furthermore, a number of patients who had previously demonstrated established practolol reactions were transferred to atenolol therapy with subsequent resolution or quiescence of the reaction.

To report SUSPECTED ADVERSE REACTIONS, contact Novitium Pharma, LLC, at 1-855-204-1431 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch for voluntary reporting of adverse reactions.

Clinical Laboratory Test Findings

Clinically important changes in standard laboratory parameters were rarely associated with the administration of atenolol and chlorthalidone. The changes in laboratory parameters were not progressive and usually were not associated with clinical manifestations. The most common changes were increases in uric acid and decreases in serum potassium.

OVERDOSAGE

No specific information is available with regard to overdosage and atenolol and chlorthalidone in humans. Treatment should be symptomatic and supportive and directed to the removal of any unabsorbed drug by induced emesis, or administration of activated charcoal. Atenolol can be removed from the general circulation by hemodialysis. Further consideration should be given to dehydration, electrolyte imbalance and hypotension by established procedures.

Atenolol

Overdosage with atenolol has been reported with patients surviving acute doses as high as 5 g. One death was reported in a man who may have taken as much as 10 g acutely.

The predominant symptoms reported following atenolol overdose are lethargy, disorder of respiratory drive, wheezing, sinus pause, and bradycardia. Additionally, common effects associated with overdosage of any beta-adrenergic blocking agent are congestive heart failure, hypotension, bronchospasm, and/or hypoglycemia. Other treatment modalities should be employed at the physician's discretion and may include:

BRADYCARDIA: Atropine 1 mg to 2 mg intravenously. If there is no response to vagal blockade, give isoproterenol cautiously. In refractory cases, a transvenous cardiac pacemaker may be indicated. Glucagon in a 10 mg intravenous bolus has been reported to be useful. If required, this may be repeated or followed by an intravenous infusion of glucagon 1 mg/h to 10 mg/h depending on response.

HEART BLOCK (SECOND OR THIRD DEGREE): Isoproterenol or transvenous pacemaker.

CONGESTIVE HEART FAILURE: Digitalize the patient and administer a diuretic. Glucagon has been reported to be useful.

HYPOTENSION: Vasopressors such as dopamine or norepinephrine (levarterenol). Monitor blood pressure continuously.

BRONCHOSPASM: A beta₂-stimulant such as isoproterenol or terbutaline and/or aminophylline.

HYPOGLYCEMIA: Intravenous glucose.

ELECTROLYTE DISTURBANCE: Monitor electrolyte levels and renal function. Institute measures to maintain hydration and electrolytes.

Based on the severity of symptoms, management may require intensive support care and facilities for applying cardiac and respiratory support.

Chlorthalidone

Symptoms of chlorthalidone overdose include nausea, weakness, dizziness and disturbances of electrolyte balance.

DOSAGE AND ADMINISTRATION

DOSAGE MUST BE INDIVIDUALIZED. (See INDICATIONS AND USAGE.)

Chlorthalidone is usually given at a dose of 25 mg daily; the usual initial dose of atenolol is 50 mg daily. Therefore, the initial dose should be one Atenolol and Chlorthalidone tablet, USP 50 mg/25 mg given once a day. If an optimal response is not achieved, the dosage should be increased to one Atenolol and Chlorthalidone tablet, USP 100 mg/25 mg given once a day.

When necessary, another antihypertensive agent may be added gradually beginning with 50 percent of the usual recommended starting dose to avoid an excessive fall in blood pressure.

Since atenolol is excreted via the kidneys, dosage should be adjusted in cases of severe impairment of renal function. No significant accumulation of atenolol occurs until creatinine clearance falls below 35 mL/min/1.73m² (normal range is 100 mL/min/1.73m² to 150 mL/min/1.73m²); therefore, the following maximum dosages are recommended for patients with renal impairment.

Creatinine Clearance (mL/min/1.73m ²)	Atenolol Elimination Half-Life (hrs)	Maximum Dosage
15-35	16-27	50 mg daily
<15	>27	50 mg every other day

HOW SUPPLIED

Atenolol and Chlorthalidone Tablets, USP 50 mg/25 mg (atenolol, USP 50 mg and chlorthalidone, USP 25 mg) are white to off-white, round, biconvex, uncoated tablets, bisected on one side and debossed with "N 390" on the other side, supplied in bottles of 100 tablets (NDC 70954-390-10).

Atenolol and Chlorthalidone Tablets, USP 100 mg/25 mg (atenolol, USP 100 mg and chlorthalidone, USP 25 mg), are white to off-white, round, biconvex, uncoated tablets, debossed with "N" on one side and "391" on other side, supplied in bottles of 100 tablets (NDC 70954-391-10).

Store at controlled room temperature, 20° to 25°C (68° to 77°F) [see USP]. Dispense in well-closed, light-resistant containers.

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