DIURETICS, THIAZIDE (Systemic)

Category

Diuretic; antihypertensive; antidiuretic (central and nephrogenic diabetes insipidus); antiurolithic (calcium calculi).

Indications

Note: Bracketed information in the Indications section refers to uses that are not included in U.S. product labeling.

Accepted

Edema (treatment)¾Indications include edema associated with congestive heart failure, hepatic cirrhosis with ascites, corticosteroid and estrogen therapy, and some forms of renal function impairment including nephrotic syndrome, acute glomerulonephritis, and chronic renal failure. 4, 5, 6, 8 However, prompt metolazone tablets are not indicated for treatment of edema because a safe and effective diuretic dosage has not been established.

Hypertension (treatment)¾Thiazide diuretics are indicated either alone or as adjunctive therapy 4 in the treatment of hypertension. 3, 4, 5, 6, 8

[Diabetes insipidus, central or nephrogenic (treatment)] *¾Thiazide diuretics are used in the treatment of central and nephrogenic diabetes insipidus. 22

[Renal calculi, calcium (prophylaxis)] *¾Thiazide diuretics are also used for prevention of calcium-containing renal stones. 22

* Not included in Canadian product labeling.

Precautions to Consider

Cross-sensitivity and/or related problems

Patients sensitive to other sulfonamide-type medications, bumetanide, furosemide, or carbonic anhydrase inhibitors may be sensitive to this medication also.

Carcinogenicity/Mutagenicity

Bendroflumethiazide¾Studies have not been done in either animals or humans. 49, 59

Chlorothiazide¾Carcinogenicity studies have not been done in either animals or humans. Chlorothiazide was not found to be mutagenic in the Ames microbial mutation test, dominant lethal assay, or a test in Aspergillus nidulans. 8, 73

Hydrochlorothiazide¾Carcinogenicity studies have not been done in either animals or humans. Hydrochlorothiazide was not found to be mutagenic in vitro in the Ames microbial mutation test or on examination of urine from patients who received hydrochlorothiazide; however, it did induce nondisjunction in Aspergillus nidulans. 4, 65

Hydroflumethiazide¾Studies have not been done in either animals or humans. 3, 66

Methyclothiazide¾Studies have not been done in either animals or humans. 6, 67

Metolazone¾Studies in mice and rats for 11/2 to 2 years at doses of 2, 10, and 50 mg per kg of body weight (mg/kg) per day (100, 500, and 2500 times the maximum recommended human dose [MRHD]) found no evidence of carcinogenicity. 68

Trichlormethiazide¾Studies have not been done in either animals or humans. 72

Pregnancy/Reproduction

Fertility¾Hydrochlorothiazide: No adverse effects on fertility were found in rats given doses up to 2 times the maximum recommended human dose of hydrochlorothiazide. 65

Methyclothiazide: No adverse effects on fertility were found in rats given methyclothiazide in doses up to 4 mg per kg of body weight (mg/kg) per day (at least 20 times the maximum recommended human dose). 67

Metolazone: A study in which male rats were given metolazone at doses of 2, 10, and 50 mg/kg for 127 days prior to mating with untreated female rats revealed an increase in the number of resorption sites in dams mated with males given the 50 mg/kg dose. Furthermore, decreased fetal weight and reduced pregnancy rate were observed in dams mated with males from the 10 and 50 mg/kg groups. In mice, there was no evidence that metolazone alters reproductive capacity. 68

Pregnancy¾Thiazide diuretics cross the placenta and appear in cord blood. Although studies in humans have not been done, thiazide diuretics can cause fetal harm when given to pregnant women. Fetal or neonatal jaundice has been reported.

Pregnant women should be advised to contact their physician before taking this medication, since routine use of diuretics during normal pregnancy is inappropriate and exposes mother and fetus to unnecessary hazard. Thiazide diuretics do not prevent development of toxemia of pregnancy, and there is no satisfactory evidence that they are useful in the treatment of toxemia. Thiazide diuretics are indicated only in the treatment of edema due to pathologic causes or as a short course of treatment in patients with severe hypervolemia. 4, 5 Possible hazards include fetal or neonatal jaundice, thrombocytopenia, or other adverse reactions seen in adults.

Studies in animals have not shown that thiazide diuretics cause adverse effects on the fetus at several times the human dose.

Bendroflumethiazide¾

Adequate and well-controlled studies in humans and animals have not been done. 49

FDA Pregnancy Category C.

Chlorothiazide¾

Adequate and well-controlled studies in humans have not been done.

Studies in rabbits, mice, and rats at doses up to 500 mg/kg per day (25 times the MRHD) have not shown that chlorothiazide causes adverse effects on the fetus.

FDA Pregnancy Category B. 8

Chlorthalidone¾

Adequate and well-controlled studies in humans have not been done.

Studies in rats and rabbits at doses up to 420 times the human dose have not shown that chlorthalidone causes adverse effects on the fetus.

FDA Pregnancy Category B. 5

Hydrochlorothiazide¾

Adequate and well-controlled studies in humans have not been done.

A study in rats at dosages up to 250 mg/kg per day (62.5 times the MRHD) has not shown that hydrochlorothiazide causes adverse effects on the fetus. 4

Studies in mice and rabbits with doses up to 100 mg/kg per day (50 times the maximum human dose) revealed no evidence of external abnormalities of the fetus. 65

FDA Pregnancy Category B.

Hydroflumethiazide¾

Studies have not been done in humans.

Studies have not been done in animals.

FDA Pregnancy Category C. 66

Methyclothiazide¾

Studies have not been done in humans. 67

Studies in rats and rabbits given methyclothiazide at doses up to 4 mg/kg per day have revealed no evidence of harm to the fetus. 67

FDA Pregnancy Category B.

Metolazone¾

Adequate and well-controlled studies in humans have not been done. 15

Studies in mice, rabbits, and rats at doses up to 50 mg/kg per day (333 times the MRHD) have not shown that metolazone causes adverse effects on the fetus.

FDA Pregnancy Category B.

Trichlormethiazide¾

Adequate and well-controlled studies in humans have not been done. 13

Studies in rats at doses 250 to 1250 times the recommended human daily dose have not shown that trichlormethiazide causes adverse effects on the fetus.
FDA Pregnancy Category C. 33

Breast-feeding

Thiazide diuretics are distributed into breast milk. The American Academy of Pediatrics recommends that nursing mothers avoid thiazide diuretics during the first month of lactation because of reports of suppression of lactation. 3, 4, 5, 48

Pediatrics

Although appropriate studies on the relationship of age to the effects of thiazide diuretics have not been performed in the pediatric population, 3, 4, 5 pediatrics-specific problems that would limit the usefulness of this medication in children are not expected. However, caution is required in jaundiced infants because of the risk of hyperbilirubinemia.

Geriatrics

Although appropriate studies on the relationship of age to the effects of thiazide diuretics have not been performed in the geriatric population, the elderly may be more sensitive to the hypotensive and electrolyte effects. In addition, elderly patients are more likely to have age-related renal function impairment, which may require caution in patients receiving thiazide diuretics.

Drug interactions and/or related problems

The following drug interactions and/or related problems have been selected on the basis of their potential clinical significance (possible mechanism in parentheses where appropriate)¾not necessarily inclusive (>> = major clinical significance):

Note: Combinations containing any of the following medications, depending on the amount present, may also interact with this medication.

Amantadine

(hydrochlorothiazide may reduce the renal clearance of amantadine, resulting in increased plasma concentrations and possible amantadine toxicity 27)

Amiodarone

(concurrent use of thiazide diuretics with amiodarone may lead to an increased risk of arrhythmias associated with hypokalemia 17)

Anticoagulants, coumarin- or indandione-derivative

(effects may be decreased when used concurrently with thiazide diuretics as a result of reduction of plasma volume leading to concentration of procoagulant factors in the blood; in addition, diuretic-

induced improvement of hepatic congestion may lead to improved hepatic function resulting in increased procoagulant factor synthesis; dosage adjustments may be necessary 3, 28, 29)

Antidiabetic agents, oral or 5

Insulin 3, 4, 5

(thiazide diuretics may raise blood glucose concentrations; for adult-onset diabetics, dosage adjustment of hypoglycemic medications may be necessary during and after thiazide diuretic therapy; insulin requirements may be increased, decreased, or unchanged 28)

Anti-inflammatory drugs, nonsteroidal (NSAIDs), especially indomethacin 3, 4, 28

(may antagonize the natriuresis and increase in plasma renin activity [PRA] caused by thiazide diuretics; they may also reduce the antihypertensive effect and increase in urine volume caused by thiazide diuretics, possibly by inhibiting renal prostaglandin synthesis and/or by causing sodium and fluid retention; the patient should be carefully monitored to confirm that the desired effect is being obtained 28, 47)

(in addition, concurrent use of NSAIDs with a diuretic may increase the risk of renal failure secondary to a decrease in renal blood flow caused by inhibition of renal prostaglandin synthesis)

Calcium-containing medications

(concurrent use of thiazide diuretics with large doses of calcium may result in hypercalcemia because of reduced calcium excretion 53, 54, 55)

>> Cholestyramine or 13, 28, 46

>> Colestipol 28

(may inhibit gastrointestinal absorption of the thiazide diuretics; administration of thiazide diuretics 1 hour before or 4 hours after cholestyramine or colestipol is recommended 3)

Diazoxide 59, 63, 64

(concurrent use with thiazide diuretics may enhance hyperglycemic effects; monitoring of blood glucose levels and/or dosage adjustment of one or both agents may be necessary 59, 63, 64)

(in addition, concurrent use with thiazide diuretics may enhance hyperuricemic and antihypertensive effects 59)

Diflunisal

(concurrent use of hydrochlorothiazide with diflunisal produces significantly increased plasma concentrations of hydrochlorothiazide; in addition, the hyperuricemic effect of hydrochlorothiazide is decreased 18)

>> Digitalis glycosides

(concurrent use with thiazide diuretics may enhance the possibility of digitalis toxicity associated with hypokalemia or hypomagnesemia 3, 4, 5, 6, 8, 29, 30, 31)

Dopamine

(concurrent use may increase the diuretic effect of either thiazide diuretics or dopamine, as a result of dopamine's direct effect on dopaminergic receptors to produce vasodilation of renal vasculature and increase renal blood flow; dopamine also has a direct natriuretic effect 57, 58)

Hypokalemia-causing medications, other (see Appendix II)

(risk of severe hypokalemia due to other hypokalemia-causing medications may be increased; monitoring of serum potassium concentrations and cardiac function and potassium supplementation may be necessary 3, 4, 5, 32)

Hypotension-producing medications, other (see Appendix II)

(antihypertensive and/or diuretic effects may be potentiated when these medications are used concurrently with thiazide diuretics; although some antihypertensive and/or diuretic combinations are frequently used for therapeutic advantage, when used concurrently dosage adjustments may be necessary 15)

>> Lithium

(concurrent use with thiazide diuretics is not recommended, as they may provoke lithium toxicity because of reduced renal clearance; in addition, lithium has nephrotoxic effects 3, 4, 5, 6, 8, 28)

Neuromuscular blocking agents, nondepolarizing

(thiazide diuretics may induce hypokalemia, which may enhance the blockade of nondepolarizing neuromuscular blocking agents; serum potassium determinations may be necessary prior to administration of nondepolarizing neuromuscular blocking agents; careful postoperative monitoring of the patient may be necessary following concurrent or sequential use, especially if there is a possibility of incomplete reversal of neuromuscular blockade 4, 6, 13, 28)

Sympathomimetics

(may antagonize the antihypertensive effect of the thiazide diuretics; the patient should be carefully monitored to confirm that the desired effect is being obtained 3, 4, 13)

Medical considerations/Contraindications

The medical considerations/contraindications included have been selected on the basis of their potential clinical significance (reasons given in parentheses where appropriate)¾ not necessarily inclusive (>> = major clinical significance).

Risk-benefit should be considered when the following medical problems exist

>> Anuria or severe renal function impairment

(ineffective; may precipitate azotemia; may produce cumulative effects 3, 4, 5)

Diabetes mellitus

(hypoglycemic medication requirements may be altered 3, 4)

Gout, history of or 3, 4, 5

Hyperuricemia 3, 4, 5

(serum uric acid concentrations may be elevated)

Hepatic function impairment

(risk of dehydration which may precipitate hepatic coma and death; plasma half-life is unaltered 4, 5)

Hypercalcemia or 4

Hypercholesterolemia or 34, 35, 36

Hypertriglyceridemia or 34, 35, 36

Hyponatremia 3

(conditions may be exacerbated; onset of hyponatremia can be sudden and life-threatening 43, 44)

Lupus erythematosus, history of

(exacerbation or activation by thiazide diuretics has been reported 4)

Pancreatitis

Sensitivity to thiazide diuretics or other sulfonamide-derived medications 59

Sympathectomy

(antihypertensive effects may be enhanced 3, 4, 5)

>> Caution is required also in jaundiced infants because of the risk of hyperbilirubinemia.