DIAMOX

Acetazolamide

250mg tablet

PRESENTATION

Acetazolamide tablets, 250mg: round, convex, white, cross scored, marked Lederle on reverse, diameter 11mm.

DESCRIPTION

DIAMOX (acetazolamide) is a carbonic anhydrase inhibitor. It is N-[5-(aminosulphonyl)-1,3,4-thiadiazole-2-yl] acetamide and its structural formula is:

![Structural formula of acetazolamide](image)

It is a white to yellowish-white crystalline substance, sparingly soluble in cold water with a mp of 258-259°C, a weak acid, a pKa of 7.2 and a molecular weight of 222.25 (C₄H₆N₄O₃S₂).

ACTION

DIAMOX is a carbonic anhydrase inhibitor, effective in the control of fluid secretion (e.g. some types of glaucoma), in the treatment of certain convulsive disorders (e.g. epilepsy) and in the promotion of diuresis in instances of abnormal fluid retention (e.g. cardiac oedema).

DIAMOX is not a mercurial diuretic. Rather it is a nonbacteriostatic sulfonamide possessing a chemical structure and pharmacological activity distinctly different from the bacteriostatic sulfonamides.

DIAMOX is an enzyme inhibitor that acts specifically on carbonic anhydrase, the enzyme that catalyzes the reversible reaction involving the hydration of carbon dioxide and the dehydration of carbonic acid. In the eye this inhibitory
action of acetazolamide decreases the secretion of aqueous humour and results in a drop in intraocular pressure, a reaction considered desirable in cases of glaucoma and even in certain nonglaucomatous conditions. Evidence seems to indicate that DIAMOX has utility as an adjuvant in the treatment of certain dysfunctions of the central nervous system (e.g. epilepsy). Inhibition of carbonic anhydrase in this area appears to retard abnormal, paroxysmal, excessive discharge from central nervous system neurons. The diuretic effect of DIAMOX is due to its action in the kidney on the reversible reaction involving hydration of carbon dioxide and dehydration of carbonic acid. The result is renal loss of \( \text{HCO}_3^- \) ions, that carry out sodium, water and potassium. Alkalinization of the urine and promotion of diuresis are thus effected.

**INDICATIONS**

For adjunctive treatment of: oedema due to congestive heart failure; drug-induced oedema; centrencephalic epilepsies (petit mal, unlocalized seizures); chronic simple (open-angle) glaucoma, secondary glaucoma and preoperatively in acute angle-closure glaucoma where delay of surgery is desired in order to lower intraocular pressure.

**CONTRAINDICATIONS**

Situations in which sodium and/or potassium blood serum levels are depressed, in cases of marked kidney and liver disease or dysfunction, suprarenal gland failure, hyperchloremic acidosis and hypersensitivity to acetazolamide, sulfonamides, or sulfonamide derivatives, or any excipients in the formulation. Cross sensitivity between acetazolamide, sulfonamides and other sulfonamide derivatives is possible.

Acetazolamide is contraindicated in patients with marked liver disease or impairment of liver function, including cirrhosis because of the risk of development of hepatic encephalopathy. Acetazolamide decreases ammonia clearance.

Long-term administration in patients with chronic noncongestive angle-closure glaucoma since it may permit organic closure of the angle to occur while the worsening glaucoma is masked by lowered intraocular pressure.

**WARNINGS**

Pharmacokinetic studies in four volunteers showed that the plasma protein binding and renal clearance of acetazolamide were significantly reduced during chronic salicylate dosing. Salicylate appears to competitively inhibit plasma protein binding of acetazolamide and simultaneously to inhibit acetazolamide renal secretion that may produce serious metabolic acidosis.
When acetazolamide and phenytoin are given together, accelerated development of osteomalacia has been reported. The concurrent use of these two agents should be avoided or else monitoring to detect osteomalacia should be instituted.

**PRECAUTIONS**

Increasing the dose does not increase the diuresis and may increase the incidence of drowsiness and/or paraesthesia. Increasing the dose often results in a decrease in diuresis. Under certain circumstances however, very large doses have been given in conjunction with other diuretics in order to secure diuresis in complete refractory failure.

Fatalities have occurred, due to severe reactions to sulfonamides and sulphonamide derivatives, including acetazolamide. Adverse reactions common to all sulfonamide derivatives may occur: fever, rash (including erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis), fulminant hepatic necrosis, crystalluria, renal calculus, bone-marrow depression, thrombocytopenic purpura, haemolytic anaemia, leucopenia, pancytopenia, agranulocytosis, aplastic anaemia and other blood dyscrasias, anaphylaxis, renal and ureteral colic and renal lesions.

There have been reports of increased muscular weakness, occasionally severe, in patients with hyperkalaemic periodic paralysis who have taken acetazolamide.

Serious and occasionally fatal hypersensitivity (anaphylactic/anaphylactoid [including shock]) reactions have been reported in patients receiving acetazolamide. Hypersensitivity reactions may recur if a sulfonamide or sulfonamide derivative is re-administered, irrespective of the route of administration. The drug should be discontinued and appropriate therapy instituted if such reactions are detected. To monitor for haematological reactions common to all sulfonamides, it is recommended that a baseline CBC, platelet count and electrolyte levels be obtained on patients prior to initiating DIAMOX therapy and at regular intervals during therapy. If significant changes or toxic skin manifestations occur, early discontinuation and institution of appropriate therapy are important. Fatalities have occurred due to severe adverse reactions to sulfonamides.

**Other concomitant conditions:** Both increases and decreases in blood glucose levels have been described in patients treated with acetazolamide. This should be taken into consideration in patients with impaired glucose tolerance or diabetes mellitus.

**Acid/base and electrolyte balance**

Acetazolamide treatment may cause electrolyte imbalances, including hyponatraemia and hypokalaemia, as well as metabolic acidosis. Therefore, periodic monitoring of serum electrolytes is recommended. Particular caution
is recommended in patients with conditions that are associated with, or predisposed to, electrolyte and acid/base imbalance, such as patients with impaired renal function (including elderly patients, patients with diabetes mellitus, and patients with impaired alveolar ventilation). (such as patients with pulmonary obstruction or emphysema). In patients with moderate to severe renal impairment, the dose should be reduced by half or the dosage interval should be increased to every 12 hours.

**Interactions with other drugs**

*Amphetamines:* By increasing the pH of renal tubular urine, acetazolamide reduces the urinary excretion of amphetamine and so may enhance the magnitude and duration of the effect of amphetamines.

*Carbonic Anhydrase Inhibitors:* Because of possible additive effects with other carbonic anhydrase inhibitors, concomitant use is not advisable.

*Cyclosporine:* When given concomitantly, acetazolamide may elevate cyclosporine blood levels. Caution is advised when administering acetazolamide in patients receiving cyclosporine.

*Folic Acid Antagonists:* Acetazolamide may potentiate the effects of other folic acid antagonists.

*Hypoglycaemics Agents:* Both increases and decreases in blood glucose levels have been described in patients treated with acetazolamide. This should be taken into consideration in patients with impaired glucose tolerance or diabetes mellitus treated with antidiabetic agents.

*Lithium:* Acetazolamide increases lithium excretion due to impaired reabsorption of lithium in the proximal tubule. The effect of lithium carbonate may be decreased.

*Methenamine compounds:* By increasing the pH of urine, acetazolamide may prevent the urinary antiseptic effect of methenamine compounds.

*Phenytoin:* When given concomitantly, acetazolamide modifies the metabolism of phenytoin, leading to increased serum levels of phenytoin. Acetazolamide may increase the occurrence, or accelerate the manifestation of osteomalacia in some patients receiving chronic phenytoin therapy. Caution is advised in patients receiving chronic concomitant therapy.

*Primidone:* By decreasing the gastrointestinal absorption of primidone, acetazolamide may decrease serum concentrations of primidone and its metabolites, with a consequent possible decrease in anticonvulsant effect. Caution is advised when beginning, discontinuing, or changing the dose of acetazolamide in patients receiving primidone.

*Quinidine:* By increasing the pH of renal tubular urine, acetazolamide reduces the urinary excretion of quinidine and so may enhance the effect of quinidine.
**Salicylates**: Caution is advised for patients receiving concomitant aspirin and acetazolamide, as severe toxicity has been reported. Severe metabolic acidosis has been reported in patients with normal renal function during treatment with acetazolamide and salicylates. Pharmacokinetic studies showed that the plasma protein binding and renal clearance of acetazolamide were significantly reduced during chronic salicylate therapy. Systemic acidosis produced by acetazolamide may increase salicylate toxicity by enhancing salicylate tissue penetration.

Precaution is advised for patients receiving concomitant high-dose aspirin and DIAMOX as anorexia, tachypnoea, lethargy and coma have been reported due to a possible drug interaction. (See WARNINGS).

Concomitant administration with high-dose aspirin may potentiate the adverse reactions of DIAMOX.

**Sodium Bicarbonate**: The use of concurrent sodium bicarbonate therapy enhances the risk of renal calculus formation in patients taking acetazolamide.

**Cardiovascular Agents**: Potentiation of the effects of oral anticoagulants is possible when administered with DIAMOX, and may warrant a reduction in the dose of the anticoagulant. Adjustment of dose may be required when DIAMOX is given with cardiac glycosides or antihypertensive agents.

**Use in Pregnancy**

Pregnancy Category B3.

Acetazolamide, administered orally or parenterally, has been shown to be teratogenic (defects of the limbs) in mice, rats, hamsters and rabbits, at oral or parenteral doses in excess of ten times those recommended in human beings. As there are no adequate and well-controlled studies in pregnant women, DIAMOX should not be used in pregnancy, especially during the first trimester.

**Use During Lactation**

DIAMOX has been detected in low levels in the milk of lactating women who have taken DIAMOX. Therefore the potential exists for adverse reactions in the infant. Extreme caution should be utilized when DIAMOX is administered to lactating women.

**Use in Paediatrics**

The safety and effectiveness of acetazolamide in paediatric patients have not been established. Growth retardation has been reported in children receiving long-term therapy, believed secondary to chronic acidosis. (See DOSAGE & ADMINISTRATION)

**Use in the Elderly**
Metabolic acidosis, which can be severe, may occur in the elderly with reduced renal function.

**Patient Monitoring**

Monitoring serum electrolyte levels (particularly potassium) and blood pH levels should be considered if overdose with acetazolamide is suspected. In the case of overdosage when complicated by the presence of renal failure, dialysis may be beneficial since acetazolamide is dialyzable.

**Interference with Laboratory Tests**

Sulfonamides may give false negative or decreased values for urinary phenolsulfonphthalein and phenol red elimination values for urinary protein, serum non-protein and for serum uric acid. Acetazolamide may produce an increased level of crystals in the urine.

Acetazolamide interferes with the HPLC method of assay for theophylline. Interference with the theophylline assay by acetazolamide depends on the solvent used in the extraction; acetazolamide may not interfere with other assay methods for theophylline.

**Effects on Cognitive and Motor Performance**

Some adverse reactions to acetazolamide, such as drowsiness, fatigue and myopia, may impair the ability to drive and operate machinery.

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**ADVERSE REACTIONS**

Adverse reactions during short-term therapy are minimal. Those effects that have been noted include: paraesthesias, particularly a tingling feeling in the extremities and face, some loss of appetite, polyuria, polydipsia, flushing, thirst, headaches, dizziness, fatigue, irritability and occasional instances of drowsiness and confusion. Rarely, photosensitivity has been reported.

General reactions such as malaise, pain at injection site, fever, growth retardation in children and anaphylactic/anaphylactoid reactions, including shock and fatalities have been reported.

Gastrointestinal reactions such as abnormal liver function including cholestatic jaundice, gastrointestinal disturbances such as nausea, vomiting and diarrhoea have been reported.

Haematological and lymphatic reactions reported include blood dyscrasias such as aplastic anaemia, agranulocytosis, leucopenia, thrombocytopenia, and thrombocytopenic purpura.

Metabolic/Nutritional adverse reactions have included electrolyte imbalance, hyponatraemia, osteomalacia with long-term therapy, taste alteration and
hyper/hypoglycaemia. During long-term therapy, metabolic acidosis and hypokalaemia may occur. This can usually be corrected by the administration of bicarbonate and/or potassium.

Adverse reactions in the nervous system include reports of, depression, excitement, ataxia and confusion.

Skin reactions reported with the use of acetazolamide include allergic skin reactions, Stevens-Johnson syndrome and toxic epidermal necrolysis.

Hearing disturbances and tinnitus have been reported. Transient myopia is rare and invariably subsides upon diminution or discontinuation of the medication.

Adverse reactions in the urogenital system include crystalluria, increased risk of nephrolithiasis with long-term therapy and renal failure.

Other occasional adverse reactions include urticaria, melaena, haematuria, glycosuria, hepatic insufficiency, flaccid paralysis and convulsions.

DOSAGE & ADMINISTRATION

Glaucoma

DIAMOX should be used as an adjunct to the usual therapy. The dosage employed in the treatment of chronic simple (open-angle) glaucoma ranges from 250 mg to 1 g of DIAMOX per 24 hours, usually in divided doses for amounts over 250 mg. It has usually been found that a dosage in excess of 2 g per 24 hours does not produce an increased effect. In all cases, the dosage should be adjusted with careful individual attention both to symptomatology and ocular tension. Continuous supervision by a physician is advisable.

In treatment of secondary glaucoma and in the preoperative treatment of some cases of acute congestive (closed-angle) glaucoma, the preferred dosage is 250 mg every 4 hours, although some cases have responded to 250 mg twice daily on short-term therapy. In some acute cases, it may be more satisfactory to administer an initial dose of 500 mg followed by 125 or 250 mg every 4 hours depending on the individual case. Intravenous therapy may be used for rapid relief of ocular tension in acute cases. A complementary effect has been noted when DIAMOX has been used in conjunction with miotics or mydriatics as the case demanded.

Epilepsy

It is not clearly known whether the beneficial effects observed in epilepsy are due to direct inhibition of carbonic anhydrase in the central nervous system or whether they are due to the slight degree of acidosis produced by the divided dosage. The best results to date have been seen in petit mal in children. Good results, however, have been seen in both adult and paediatric patients,
in other types of seizures such as grand mal, mixed seizure patterns, myoclonic jerk pattern etc. The recommended dose in paediatric patients is 8-30 mg/kg daily in divided doses not to exceed 750 mg/day. In adults the recommended dose is 250-1000 mg daily in divided doses.

When DIAMOX is given in combination with any other anticonvulsant, it is suggested that the starting dose should be 250 mg once daily in addition to the existing medication. This can be increased to the levels indicated above.

The change from other medication to DIAMOX should be gradual in accordance with usual practice in epilepsy therapy.

CONGESTIVE HEART FAILURE

For diuresis in congestive heart failure, the starting dose is usually 250 to 375 mg once daily in the morning (5 mg/kg). If after an initial response, the patient fails to continue to lose oedema fluid, do not increase the dose but allow for kidney recovery by omitting medication for a day.

DIAMOX yields best diuretic results when given on alternate days, or for 2 days alternating with a day of rest.

Failures in therapy may be due to overdosage or too frequent dosage. The use of DIAMOX does not eliminate the need for other therapy such as digitalis, bed rest and salt restriction.

DRUG-INDUCED OEDEMA

Recommended dosage is 250 to 375 mg once daily for 1 to 2 days, alternating with a day of rest.

Note: The dosage recommendations for glaucoma and epilepsy differ considerably from those for congestive heart failure, since the first two conditions are not dependent upon carbonic anhydrase inhibition in the kidney which requires intermittent dosage if it is to recover from the inhibitory effect of the therapeutic agent.

OVERDOSAGE & TREATMENT

No specific antidote. Supportive measures with correction of electrolyte and fluid balance. Force fluids.

PHARMACEUTICAL PRECAUTIONS

Store below 30°C
MEDICINE CLASSIFICATION

Prescription medicine

PACKAGE QUANTITIES

Tablets, 250 mg 100s

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