PRODUCT MONOGRAPH

METHAZOLAMIDE

Methazolamide Tablets USP

50 mg

CARBONIC ANHYDRASE INHIBITOR

Ocular Pressure Lowering Therapy

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50 mg

THERAPEUTIC CLASSIFICATION

Carbonic Anhydrase Inhibitor

Ocular Pressure Lowering Therapy

ACTIONS AND CLINICAL PHARMACOLOGY

Methazolamide is a potent inhibitor of the enzyme carbonic anhydrase. The oral administration of the drug inhibits ocular carbonic anhydrase therefore decreasing formation of aqueous humor and intraocular pressure. The time of onset of intraocular pressure fall occurs within 2 to 4 hours, with a peak effect in 6 to 8 hours. The effect lasts for 10 to 18 hours.

Methazolamide is absorbed more slowly from the gastrointestinal tract and disappears more slowly from the plasma than does acetazolamide. Methazolamide is distributed throughout the body and can be assayed in the blood plasma, the cerebrospinal fluid, the aqueous humor of the eye, the red blood cell, in the bile and the extracellular fluid.

At present, the metabolism of methazolamide is not well characterized.

Methazolamide is a sulfonamide derivative, however, it does not have any clinically significant antimicrobial properties. Although concentration in the cerebrospinal fluid is high, it is not considered an effective anticonvulsant.

Methazolamide does have a weak transient diuretic effect. The drug should not be used as a diuretic. Serum changes in sodium, potassium and chloride are minimal and return to

pretreatment levels after daily administration for 3 to 4 days. Inhibition of renal bicarbonate reabsorption produces an alkaline urine. Plasma bicarbonate decreases temporarily and a relative and transient metabolic acidosis may occur due to a disequilibrium in CO_2 transport in the red cell. This is quickly restored to balance by the initiation of compensatory mechanisms. The excretion of urinary citrate and uric acid is decreased by up to 40%. The effect on citrate excretion is less than that attributed to acetazolamide and varies according to urinary output.

Comparative Bioavailability Study ï METHAZOLAMIDE (methazolamide) vs Neptazane®

A comparative bioavailability study was performed using healthy human volunteers. The rate and extent of absorption of methazolamide was measured and compared following oral administration of a single 1 x 50 mg dose of METHAZOLAMIDE (methazolamide) or Neptazane® (methazolamide) tablets, under fasting conditions. The results from measured data are summarized the table below:

Summary Table of the Comparative Bioavailability Data Methazolamide (Dose: 1 x 50 mg under fasting conditions) From Measured Data			
	Geometric Mean Arithmetic Mean (CV%)		Ratio of Geometric Means (%)**
Parameter	METHAZOLAMIDE	Neptazane®***	
AUC_{0-72} (mcg•hr/mL)	577 584 (15)	598 602 (11)	96.5
AUC_I* (mcg•hr/mL)	-- --	-- --	--
C_{max} (mcg/mL)	11.1 11.4 (23)	11.1 11.2 (14)	100.0
T_{max} (hr)	-- 4.79 (93)	-- 4.28 (160)	--
$t_{1/2}$ (hr)*	-- --	-- --	--

* The determination of AUC_I and $t_{1/2}$ is not necessary because methazolamide is a drug with a long half-life (>24 hours).

** Based on the least squares estimate.

*** Neptazane® is manufactured by Wyeth-Ayerst Canada Inc., and was purchased in Canada.

INDICATIONS

Adjunctive treatment of 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

Severe or absolute glaucoma and chronic noncongestive angle-closure glaucoma. It is of doubtful use in glaucoma due to severe peripheral anterior synechiae or haemorrhagic glaucoma.

Methazolamide is contraindicated in patients with adrenocortical insufficiency, hepatic insufficiency, renal insufficiency, or an electrolyte imbalance state such as hyperchloremic acidosis, and sodium and potassium depletion states.

WARNINGS

Pregnancy

Studies in rats have demonstrated teratogenic effects (skeletal anomalies) at high doses. There is no evidence of these effects in human beings and no fetal defects have been reported. However, methazolamide should not be used in women of childbearing potential or in pregnancy, especially in the first trimester, unless the benefits to be gained in the control of glaucoma outweigh potential adverse effects.

PRECAUTIONS

Potassium excretion is increased initially, upon administration of methazolamide, and in patients with cirrhosis or hepatic insufficiency could precipitate a hepatic coma. It should be used with caution in patients on steroid therapy because of the potentiality of a hypokalemic state.

Adequate and balanced electrolyte intake is essential in all patients whose concomitant clinical condition may bring about electrolyte imbalance.

The potential for drug accumulation and toxic manifestations exists in patients with renal insufficiency.

In patients with pulmonary obstruction or emphysema where alveolar ventilation may be impaired, methazolamide, which may precipitate or aggravate acidosis, should be used with caution.

Since systemically administered carbonic anhydrase inhibitors may cause hyperglycemia and glycosuria in patients with diabetes mellitus, the drug should be used with caution in these patients.

ADVERSE EFFECTS

Most adverse reactions to methazolamide have been relatively mild in character and disappear upon withdrawal of the drug or adjustment of dosage. They are as follows: anorexia, nausea, vomiting, malaise, fatigue or drowsiness, headache, vertigo, mental confusion, depression. Paresthesias of fingers, toes, hands or feet and, occasionally, at the mucocutaneous junction of the lips, mouth and anus can be experienced. Dose reduction may be required in patients who experience paresthesia following the use of methazolamide. Rarely photosensitivity has been reported.

Adverse reactions common to all sulfonamide derivatives may occur: anaphylaxis, fever, rash (including erythema multiforme, Stevens-Johnson syndrome, toxic necrolysis), crystalluria, renal calculus.

Bone marrow depression, thrombocytopenic purpura, hemolytic anemia, leukopenia, pancytopenia, and agranulocytosis can occur. Baseline and periodic hematological determinations thereafter should be performed for early detection of blood dyscrasias. If significant changes are detected in laboratory parameters, the drug should be discontinued and appropriate therapy instituted.

DOSAGE

The dosage of methazolamide must be adjusted to the patient's requirements and response. The effective therapeutic dose administered in tablet form varies from 50 to 100 mg 2 to 3 times daily. The drug may be used concomitantly with miotic and osmotic agents.

PHARMACEUTICAL INFORMATION

Drug Substance

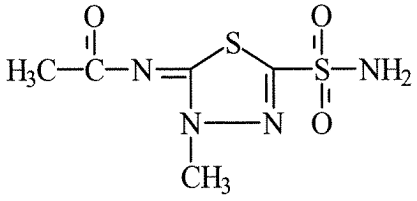
Proper/Common Name: METHAZOLAMIDE

Chemical Names: 1) *N*-[5-(Aminosulfonyl)-3-methyl-1,3,4-thiadiazol-2(3*H*)-ylidene] acetamide.

2). *N*-(4-Methyl-2-sulfamoyl-æ^2-1,3,4-thiadiazolin-5-ylidene) acetamide.

3). 5-Acetylamino-4-methyl-æ^2-1,3,4-thiadiazolin-2-sulfonamide.

Structural Formula:



Molecular Formula: $C_5H_8N_4O_3S_2$

Molecular Weight: 236.28

Description: Methazolamide is a white to slightly yellow crystalline powder, that is non-hygroscopic, has a slight odour, is non-porous and has extremely low surface area. Methazolamide has been shown to have a melting point between 205 to 206°C, and a single exothermic peak temperature at approximately 213°C. The pH of a 1% methazolamide water solution is 4.71, and the pKa is 7.30. Methazolamide is soluble in dimethylformamide, slightly soluble in acetone, and very slightly soluble in water (0.999 g/L) and ethanol.

Composition

In addition to the active ingredient, methazolamide, each METHAZOLAMIDE 50 mg tablet contains the following non-medicinal ingredients: methylcellulose, colloidal silicon dioxide and magnesium stearate.

Stability and Storage Recommendations

Store at room temperature (15 to 30°C), in well closed containers.

AVAILABILITY OF DOSAGE FORMS

METHAZOLAMIDE 50 mg Tablets: Each white, round, biconvex, straight edge tablet, scored and engraved ñMZòover ñ50òon one side, contains 50 mg of methazolamide. Available in bottles of 100 and 500 tablets.

PHARMACOLOGY

PHARMACODYNAMICS

Methazolamide is a potent inhibitor of the enzyme carbonic anhydrase. In general, carbonic anhydrase inhibitors reduce the formation of hydrogen and bicarbonate ions from carbon dioxide and water by noncompetitive, reversible inhibition of the enzyme carbonic anhydrase, thereby reducing the availability of these ions for active transport into secretions. It has been postulated that methazolamide reduces the transport of those ions from the secretory cells of the ciliary body into the nascent aqueous humour, and decreases aqueous secretion through a local osmotic effect.

After oral administration of the drug, the onset of fall in intraocular pressure occurs within 2 to 4 hours, with a peak effect in 6 to 8 hours. The effect lasts for 10 to 18 hours.

Methazolamide has a weak and transient diuretic effect. Since the effect is transient and of low degree, the drug is not used as a diuretic. Inhibition of carbonic anhydrase and the subsequent reduction in hydrogen ion concentration in the renal tubules results in increased excretion of bicarbonate and to a lesser extent sodium, potassium and chloride. Inhibition of renal bicarbonate reabsorption produces an alkaline urine. Plasma bicarbonate decreases temporarily, and a relative and transient metabolic acidosis may occur due to a disequilibrium in CO_2 transport in the red cell. This is quickly restored to balance by the initiation of compensatory mechanisms. Serum changes in sodium, potassium and chloride are minimal and return to pretreatment levels after daily administration for 3 to 4 days. Reabsorption of water is decreased, and urine volume is increased. Urinary excretion of ammonia and titrable acidity are decreased. Urinary citrate excretion is decreased by 40% on doses of 100 mg every 8 hours with variations in urinary volume output. Uric acid output was decreased 36% in the first 24 hour period and varied

thereafter. Calcium excretion may also be increased, slightly decreased or unchanged. Excretion of citrate and uric acid is decreased and excretion of lithium is increased. The carbonic anhydrase inhibitors have little effect on excretion of magnesium or phosphate.

Methazolamide is distributed throughout the body. Although its concentration in the cerebrospinal fluid is high, and methazolamide has been demonstrated to be more potent than acetazolamide in protecting rats and mice against electroshock seizures, it is not considered an effective anticonvulsant in humans.

Systemically administered carbonic anhydrase inhibitors depress iodine uptake by the thyroid gland in patients with hyperthyroidism or normal thyroid function, and not in patients with hypothyroidism, but the drugs are not useful as antithyroid agents.

Methazolamide is a sulfonamide derivative, however it does not have any clinically significant antimicrobial properties. The drug is considered non-bactericidal.

PHARMACOKINETICS

More than 95% of methazolamide in blood is strongly but reversibly bound to carbonic anhydrase in the red blood cells. Following oral administration, methazolamide rapidly penetrates erythrocytes and undergoes extensive red blood cell sequestration. Erythrocyte methazolamide concentrations greatly exceeded those measured in plasma. Methazolamide displays dose-proportionality in whole blood concentrations over a dose range of 25 to 150 mg, and in plasma concentrations over a dose range of 100 to 150 mg. Plasma drug concentrations at doses below 100 mg are too low to provide a reliable measure. At lower doses (25 and 50 mg), methazolamide binds quantitatively to high affinity CA-II isoenzyme of carbonic anhydrase, with

little drug being available in plasma. At the 100 mg dose, all binding sites of CA-II become saturated, and the drug begins to bind to the CA-I isoenzyme. Because of the low affinity of CA-I for methazolamide, a portion of the drug becomes available to the plasma volume and concentrations in plasma rise accordingly. At the 300 mg dose, all CA-II and CA-I binding sites are possibly occupied, and more methazolamide distributes to the plasma, causing a marked increase in plasma drug concentrations.

Reduction of intraocular pressure can be seen with methazolamide plasma concentrations in the range of 8-16 :M. Such concentrations can be achieved with a dosage of 50 to 100 mg every 12 hours.

Peak plasma concentrations are observed in 1 to 2 hours after dosing. In a multi-dose pharmacokinetic study, administration of 25, 50 and 100 mg BID demonstrated a linear relationship between plasma methazolamide and methazolamide dose (*i.e.* C_{max}'s were 2.5, 5.1 and 10.7 mcg/mL, and the AUC's were 1130, 2571 and 5418 mcg.min/mL, respectively). In a study involving 5 healthy fasting volunteers (weight range 50 - 80 kg), average plasma C_{max} and T_{max} values following a 1.5 mg/kg dose (using a commercially available tablet) were 4.00 ± 1.45 mcg/mL and 3.0 ± 0.63 hours, respectively. $AUC_{0-Þ}$ was estimated to be 97.2 ± 30.6 mcg/mL•h.

Methazolamide is not a chiral substance, and there are no reports stating that genetic polymorphism affects its pharmacokinetics.

Absorption

Methazolamide is absorbed more slowly from the gastrointestinal tract and disappears more slowly from the plasma than does acetazolamide, which may account for the delay in onset and duration of its activity.

The drug crosses the placenta in unknown quantities. In addition, it is not known if methazolamide is distributed into the milk of nursing women.

Metabolism

At present, the metabolism of methazolamide is not well characterised. Urinary excretion of unchanged drug is reported to be 25% (based on the plasma clearance and 3-4 h urine collection) and has been reported 60% based on the blood concentrations.

Elimination

The elimination half-life of methazolamide was estimated to be 126 ± 61 hours in whole blood but only 21.1 ± 8.6 hours in plasma. For this reason estimates of $T_{1/2}$ from plasma concentration are poor indicators of methazolamide disposition *in vivo*.

Renal clearance accounts for 20 to 25% of the total clearance of drug.

TOXICOLOGY

Extensive work with the strong carbonic anhydrase inhibiting sulfonamides as teratogens in the chick embryo, showed that using acetazolamide, dichlorphenamide and methazolamide with doses of 0.5 to 2.0 mg given at 96 hours incubation, they produced short upper beaks and

syndactylism in embryonic chicks. Methazolamide can also cause skeletal defects in embryonic rats, an effect also seen with acetazolamide.

No abnormalities were observed among the embryos of pregnant rabbits treated with 20 times the human therapeutic dose of methazolamide prior to implantation. Data on methazolamide are not sufficient for conclusions about possible reproductive risks in humans, however, the literature on acetazolamide suggests that the anomalies shown in chicks and rodents are not produced in primates, including humans.

The quality and quantity of data on which teratogen risk estimate is based is very limited. There is no conclusive evidence that sulphonamides, like methazolamide, are teratogenic in man. The magnitude of teratogenic risk to a child born after exposure or during gestation is undetermined. A small risk cannot be excluded, but a high risk of congenital anomalies in the children of women treated with methazolamide during pregnancy is unlikely.

In a follow up of 1,400 pregnancies exposed to methazolamide during the first four months, no increase in number of defects have been reported. Also, at four years, no IQ differences were found among children.

Summary table of methazolamide acute toxicity data		
Species	**Route of Administration**	**LD_{50} / LC_{50}**
Mouse	Intraperitoneal	2420 mg/kg
Mouse	Intravenous	> 1 g/kg

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