PRODUCT MONOGRAPH

[Pr]NOVAMILOR
(Amiloride Hydrochloride and Hydrochlorothiazide Tablets USP)
Each tablet contains 5 mg of Amiloride Hydrochloride
and 50 mg of Hydrochlorothiazide

DIURETIC -ANTIHYPERTENSIVE

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THERAPEUTIC CLASSIFICATION

Diuretic - Antihypertensive

ACTION AND CLINICAL PHARMACOLOGY

NOVAMILOR (amiloride hydrochloride and hydrochlorothiazide) is a diuretic-antihypertensive that combines the potent natriuretic action of hydrochlorothiazide with the potassium-conserving property of amiloride hydrochloride. Amiloride hydrochloride's diuretic and antihypertensive actions are additive with the natriuretic, diuretic and antihypertensive activities of the thiazide while potassium loss is minimized and the possibility of acid-base imbalance is decreased. The onset of the diuretic action occurs within 1 to 2 hours of administration and this action appears to be sustained for approximately 24 hours.

Amiloride Hydrochloride

Amiloride hydrochloride is an antikaliuretic drug. It has mild natriuretic, diuretic and antihypertensive activities which may be additive to the actions of thiazides or other saluretic-diuretic agents. The principal use of amiloride hydrochloride is to conserve potassium in patients who are receiving kaliuretic-diuretic agents. Amiloride hydrochloride is not an aldosterone antagonist and thus its action is not related to the level of aldosterone excretion. It acts directly on the distal portion of the nephron resulting in an increase in sodium excretion and a decrease in potassium and hydrogen ion excretion. Chloride excretion may remain unchanged; however, prolonged therapy may result in a gradual increase in chloride.

Approximately 50% of an oral dose is absorbed. The onset of drug action occurs within 2 hours of oral administration and lasts about 24 hours. The peak electrolyte effect occurs between 6 and 10 hours after administration. Plasma levels reach a peak between 3 and 4 hours and the plasma half-life varies from 6 to 9 hours. The bioavailability of amiloride hydrochloride is decreased by 25 to 42% when taken with food but is not affected by coadministration of hydrochlorothiazide.

Clinical studies have shown that amiloride hydrochloride has little effect on the glomerular filtration rate or renal blood flow. It is not metabolized by the liver. Approximately 50% of an oral dose is excreted unchanged in the urine and 38 - 40% is excreted unchanged in the stool within 72 hours.

Hydrochlorothiazide

Hydrochlorothiazide is a diuretic and antihypertensive agent that affects the renal tubular mechanism of electrolyte reabsorption. It increases excretion of both sodium and chloride in approximately equal amounts. A minimal amount of bicarbonate may also be lost. An increase in potassium excretion usually accompanies the natriuretic action.

Hydrochlorothiazide does not usually decrease normal blood pressure. The antihypertensive effect of the thiazides may be related to the redistribution and excretion of body sodium.

Approximately 55 to 60% of an oral dose is absorbed. The bioavailability decreases with fasting but remains constant when the drug is administered in combination with amiloride hydrochloride. Hydrochlorothiazide is rapidly excreted by the kidneys.

The onset of the diuretic action usually occurs within 2 hours of administration reaching peak action after approximately 4 hours. The duration of diuretic action is 6 to 12 hours.

A comparative, two-way, single-dose bioavailability study was performed on NOVAMILOR and MODURET® Tablets. The pharmacokinetic data calculated for the NOVAMILOR and MODURET® Tablet formulations are tabulated below:

Pharmacokinetic Indices for Amiloride HCl:			
	NOVAMILOR 2 x 5 mg	**MODURET® 2 x 5 mg**	**Percentage of MODURET®**
AUC_T* (ng·h/mL)	107.8 (35)	107.8 (40)	100
AUC_I* (ng·h/mL)	141.2 (35)	139.8 (41)	101
Cmax* (ng/mL)	9.12 (30)	9.12 (30)	100
Tmax+ (h)	3.92 (0.83)	4.17 (1.01)	- -
T½+ (h)	15.29 (10.70)	16.15 (16.43)	- -

*Geometric means (CV)
+Arithmetic means (SD)

Pharmacokinetic Indices for Hydrochlorothiazide:			
	NOVAMILOR 2 x 50 mg	**MODURET® 2 x 50 mg**	**Percentage of MODURET®**
AUC_T* (ng·h/mL)	2253 (33)	2231 (40)	101
AUC_I* (ng·h/mL)	2592 (32)	2592 (41)	100
Cmax* (ng/mL)	365 (26)	358 (30)	102
Tmax+ (h)	2.33 (0.73)	2.67 (1.01)	- -
T½+ (h)	5.95 (2.26)	6.62 (16.43)	- -

*Geometric means (CV)
+Arithmetic means (SD

INDICATIONS AND CLINICAL USE

NOVAMILOR (amiloride hydrochloride and hydrochlorothiazide) is not indicated for initial therapy. If the fixed drug combination represents the dosage determined through titration on the individual drugs, then the fixed combination may be more convenient to the patient. If it becomes necessary to adjust the dosage during maintenance treatment, the individual drugs should be used.

NOVAMILOR is indicated in the maintenance therapy of patients with edema of cardiac origin or with arterial hypertension who are hypokalemic or in whom normal potassium levels are clinically important (i.e., patients with cardiac arrhythmias, digitalized patients and those in whom adequate intake of dietary potassium is not possible).

NOVAMILOR is also indicated in the maintenance of patients with hepatic cirrhosis with ascites and edema. In these patients, satisfactory diuresis with diminished potassium loss and decreased risk of metabolic alkalosis may be attained with use of amiloride hydrochloride alone. Kaliuretic-diuretic agents may be added to the treatment regimen in resistant cases in order to obtain satisfactory diuresis and maintain a more balanced serum electrolyte pattern. As with all forms of therapy for ascites of hepatic cirrhosis, the primary objective is gradual weight loss and avoidance of electrolyte imbalance (see PRECAUTIONS).

CONTRAINDICATIONS

Hyperkalemia:
NOVAMILOR (amiloride hydrochloride and hydrochlorothiazide) is contraindicated in patients with serum potassium levels greater than 5.5 mEq/L (see WARNINGS).

Antikaliuretic Therapy or Potassium Salts:
Other antikaliuretic agents and potassium supplements are contraindicated in patients taking NOVAMILOR. This type of combination therapy may cause rapid increases in plasma potassium levels. If potassium supplements are deemed necessary, careful monitoring of serum potassium levels is required.

Impaired Renal Function:
NOVAMILOR should not be administered to patients with anuria, acute renal failure, severe or progressive renal disease or diabetic nephropathy.

Hypersensitivity:
NOVAMILOR is contraindicated in patients who are hypersensitive to either component or to other sulfonamide-derived drugs.

WARNINGS

Paresthesias, muscular weakness, fatigue, flaccid paralysis of the extremities, bradycardia, shock, and electrocardiographic (ECG) abnormalities are warning signs and symptoms of hyperkalemia.

Some patients receiving amiloride hydrochloride, with or without diuretics, may develop hyperkalemia (serum potassium levels over 5.5 mEq/litre). Elderly patients, diabetic patients, hospitalized patients with hepatic cirrhosis or cardiac edema, patients with known renal impairment, seriously ill patients, and those receiving vigorous diuretic therapy are the most susceptible to hyperkalemia. Since fatalities have occurred in such patients, they should be monitored carefully for clinical, laboratory and ECG evidence of hyperkalemia and for acidosis. Hyperkalemia is not always associated with abnormal ECG; therefore, it is also necessary to monitor serum potassium levels.

The primary characteristic of the abnormal ECG when associated with hyperkalemia is tall peaked T-waves or elevations from previous tracings. Other changes that may also occur include lowering of the R-wave and increased depth of the S-wave, widening and even the disappearance of the P-wave, progressive widening of the QRS complex, prolongation of the PR interval and ST depression.

NOVAMILOR (amiloride hydrochloride and hydrochlorothiazide) treatment should be discontinued immediately if hyperkalemia develops. Active measures, such as intravenous administration of sodium bicarbonate solution or oral parenteral glucose with a rapid acting insulin preparation should be taken to reduce serum potassium levels if they exceed 6.5 mEq/litre. A cation exchange resin, such as sodium polystyrene sulfonate, can be given orally or by enema if necessary. Dialysis may be required if hyperkalemia persists.

If amiloride hydrochloride therapy is considered essential for diabetic or suspected diabetic patients, the drug should be used with extreme caution and only after the status of renal function has been determined. Hyperkalemia is commonly associated with the use of amiloride hydrochloride in diabetic patients, particularly if they have chronic renal disease or prerenal azotemia. Such deaths have been reported in diabetic patients with prerenal azotemia being treated with amiloride hydrochloride.

Insulin requirements for diabetic patients may increase, decrease or remain unchanged due to the hydrochlorothiazide component. Latent diabetes mellitus may become manifest during administration of thiazide diuretics.

Amiloride hydrochloride should be discontinued at least 3 days before glucose tolerance testing. One patient with poorly controlled diabetes mellitus became severely hyperkalemic while on amiloride hydrochloride. This patient died following 2 repeated intravenous glucose tolerance tests.

Serum potassium levels must be carefully monitored throughout therapy.

Metabolic or Respiratory Acidosis:
Frequent monitoring of acid-base balance is necessary in patients in whom respiratory or metabolic acidosis may occur, such as those patients with cardiopulmonary disease or diabetes. Antikaliuretic therapy should be instituted with caution in these patients. Changes in the acid-base balance disrupts the ratio of extracellular/intracellular potassium, and acidosis may develop in association with rapid increases in serum potassium levels.

Impaired Renal Function:
Renal impairment may accentuate the potassium retention associated with the use of NOVAMILOR which may result in the rapid development of hyperkalemia. Those patients with impaired renal function other than those listed under CONTRAINDICATIONS and who have BUN levels over 30 mg/100 mL, serum creatinine levels over 1.5 mg/l00 mL or blood urea levels over 60 mg/l00 mL should not receive NOVAMILOR unless frequent, careful monitoring of serum electrolytes, creatinine and BUN levels is maintained. Renal impairment may also prolong the excretion of amiloride hydrochloride.

PRECAUTIONS

Electrolyte Imbalance and BUN Increases:
Use of NOVAMILOR (amiloride hydrochloride and hydrochlorothiazide) can result in the development of hyponatremia, hypochloremia, and hypokalemia (to a lesser degree than with thiazides alone). In seriously ill patients, such as those with hepatic cirrhosis with ascites and metabolic alkalosis or those with resistant edema, increases in BUN levels are usually accompanied by vigorous fluid elimination. Chloride deficiencies are usually mild and may be prevented by near normal salt intake and corrected with ammonium chloride treatment in patients not suffering from hepatic disease. When using NOVAMILOR, careful monitoring of serum electrolytes and BUN levels is important.

Hydrochlorothiazide treatment may precipitate or increase azotemia in patients with impaired renal function. It is therefore necessary to monitor these patients carefully. NOVAMILOR should be discontinued if increasing azotemia and oliguria occur during treatment.

Effects Related to Diuresis in Cirrhotic patients:
Acute shifts in electrolyte balance cannot be tolerated by patients with hepatic cirrhosis and ascites. Pre-existing hypokalemia may also be present in these patients as a result of secondary hyperaldosteronism. Therefore, it is necessary to ensure that diuresis is gradual and that these patients are carefully monitored for shifts in electrolyte imbalances.

Hepatic encephalopathy which is manifested by tremors, confusion and coma has been reported in association with amiloride hydrochloride treatment.

When treated with amiloride hydrochloride alone, some cirrhotic patients have experienced a deepening of the jaundice associated with the underlying disease process; however, the relationship between this and the drug is not known.

Other precautions:
Thiazides may decrease serum PBI levels without signs of thyroid disturbance.

Hydrochlorothiazide causes a decrease in urinary calcium excretion and an increase in urinary magnesium excretion.

In a few patients on prolonged thiazide therapy, pathological changes in the parathyroid glands with hypercalcemia and hypophosphatemia have been observed. However, complications

commonly associated with hyperparathyroidism such as renal lithiasis, bone resorption and peptic ulceration have not been observed. It is advisable to discontinue thiazide treatment before performing parathyroid function tests.

Hyperuricemia may occur or gout may be precipitated in certain patients receiving thiazide therapy.

Patients should be monitored for signs of liver dysfunction, idiosyncratic reactions or blood dyscrasias.

Patients with or without a history of allergy or bronchial asthma may experience sensitivity reactions to thiazides.

Systemic lupus erythematosus may be exacerbated or activated by thiazide therapy.

Pregnancy:
NOVAMILOR is not recommended for use during pregnancy due to limited clinical experience.

No evidence of impaired fertility has been demonstrated in reproduction studies in rats. Teratologic studies with rabbits and mice have failed to produce evidence that amiloride hydrochloride harms the fetus. Some toxicity was seen in adult rats and rabbits and a decrease in rat pup survival and growth was observed when the animals were given a dose of 8 mg/kg/day. A trace amount of the drug has been shown to cross the placental barrier in rats.

Thiazides cross the placental barrier and occur in cord blood.

Use of NOVAMILOR during pregnancy or suspected pregnancy requires that the benefits be weighed against the potential hazards to the fetus. Some potential hazards include fetal or neonatal jaundice, thrombocytopenia and the possibility of other side effects that have occurred in adults.

Nursing Mothers:
Amiloride hydrochloride is excreted in rat's milk, but it is not known if it is present in human breast milk. Thiazides are known to be excreted in human milk. If use of NOVAMILOR is deemed essential, the patient should stop nursing due to the potential for serious adverse reactions in nursing infants.

Pediatric Use:
NOVAMILOR is not recommended for pediatric patients since the safety of amiloride hydrochloride alone or in combination with hydrochlorothiazide has not been determined for this age group.

Drug Interactions:
The actions of other antihypertensive drugs are potentiated by hydrochlorothiazide. It may therefore be necessary to reduce the dosage of other antihypertensive agents, especially ganglion blockers when NOVAMILOR is added to the regimen.

Diuretic drugs increase the risk of lithium toxicity; therefore, patients receiving diuretics generally should not receive lithium.

Responsiveness to tubocurarine may be increased by thiazide drugs. Post-sympathectomy enhances the drug's antihypertensive effect.

Arterial responsiveness to norepinephrine may be decreased by hydrochlorothiazide; however, this decrease is not sufficient to preclude the effectiveness of the pressor agent for therapeutic use.

Orthostatic hypotension may occur and may be potentiated by alcohol, barbiturates or narcotics.

ADVERSE REACTIONS

Although rare, the most severe adverse effect associated with the use of NOVAMILOR (amiloride hydrochloride and hydrochlorothiazide) is symptomatic hyperkalemia. Other metabolic changes that occur are asymptomatic hyperkalemia, hypokalemia and hypochloremia.

The following adverse reactions with the approximate incidences were reported:

Gastrointestinal: Adverse reactions were reported in 6% of the patients. Nausea/anorexia (4%), diarrhea (2%), gastrointestinal pain (2%), abdominal pain (1-3%), constipation, GI bleeding, GI disturbance, appetite changes (1-3%), abdominal fullness, hiccups, thirst (≤1%), vomiting (0.5%), flatulence and bad taste (≤1%).

Nervous System: Adverse reactions were reported in 4% of the patients. Headaches (8%). dizziness (3%), weakness (3%), paresthesia/numbness (0.5%), stupor, vertigo, insomnia, nervousness, depression, sleepiness (0.5%), mental confusion and visual disturbance (≤l%).

Dermatologic: Adverse reactions were reported in 5% of the patients. Rashes (3%), pruritus (2%) and flushing.

Cardiovascular: Adverse reactions were reported in 4% of the patients. Arrhythmia (2%), tachycardia, digitalis toxicity, orthostatic hypotension (≤1%) and angina pectoris (≤1%).

Musculoskeletal: Leg aches, muscle cramps/spasm (1-3%), joint pain, chest pain and back pain.

Respiratory: Adverse reactions were reported in 2% of the patients. Dyspnea (2%) and nasal congestion.

Urogenital: Adverse reactions were reported in 3% of the patients. Impotence, nocturla (0.5%), dysuria (0.5%), and incontinence (0.5%).

Endocrine: Gout and dehydration (1%).

Other: Fatigue/tiredness (3%), malaise (0.5%).

Other reactions that have been reported with the individual components include:

Cardiovascular: Necrotizing angiitis (vasculitis, cutaneous vasculitis).

Gastrointestinal: Abnormal liver function, activation of pre-existing peptic ulcer, cramping, gastric irritation, jaundice (intrahepatic cholestatic jaundice), pancreatitis, dry mouth and sialadenitis.

Endocrine: Glycosuria, hyperglycemia, hyperuricemia.

Hypersensitivity*:* Urticaria and anaphylactic reactions.

Respiratory: Respiratory distress including pneumonitis.

Special Senses: Photosensitivity, transient blurred vision and xanthopsia.

Hematologic: Agranulocytosis, aplastic anemia, hemolytic anemia, leukopenia, purpura, thrombocytopenia and neutropenia.

Others: Restlessness and fever.

SYMPTOMS AND TREATMENT OF OVFRDOSAGE

There is no data available concerning overdosage with the combination of amiloride hydrochloride and hydrochlorothiazide or with amiloride hydrochloride alone in humans.

Electrolyte imbalance and dehydration are the most common signs and symptoms to be expected from overdosage with NOVAMILOR (amiloride hydrochloride and hydrochlorothiazide). It is therefore necessary to monitor serum electrolyte levels carefully. Special attention should be given to potassium levels.

Digitalized patients are particularly prone to cardiac arrhythmias which can be caused by abnormal potassium levels.

No specific antidote is available for NOVAMILOR. Treatment is symptomatic and supportive, and the induction of emesis and/or gastric lavage is suggested. If overdosage occurs, NOVAMILOR therapy should be discontinued immediately and the patient should be observed closely.

It is not known whether the drug is dialyzable.

DOSAGE AND ADMINISTRATION

Patients should be titrated with the individual drugs in order to establish optimum dosage.

Maintenance doses may be lower than those required to initiate diuresis; therefore, reduction in the daily dosage should be attempted when the patient's weight is stabilized. In cirrhotic patients, gradual weight reduction is especially desirable to reduce the likelihood of untoward reactions associated with diuretic therapy.

Hepatic Cirrhosis with Ascites and Edema:
The usual maintenance dose of NOVAMILOR (amiloride hydrochloride and hydrochlorothiazide) is 1 tablet given once a day. The dosage should not exceed 4 tablets a day in single or divided doses.

Edema of Cardiac 0rigin:
The usual maintenance dose of NOVAMILOR is 1 or 2 tablets given once a day or in divided doses. The dosage should not exceed 4 tablets a day. Therapy may be on an intermittent basis.

Hypertension:
The usual maintenance dosage is 1 or 2 tablets given once a day or in divided doses. The dosage should not exceed 4 tablets a day.

PHARMACEUTICAL INFORMATION

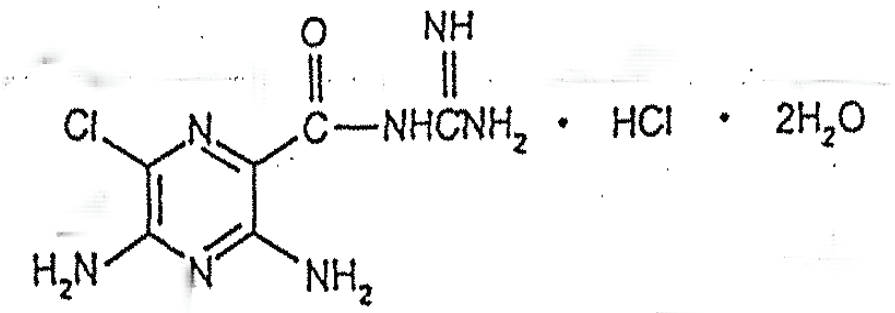
DRUG SUBSTANCE:

Proper Name: Amiloride Hydrochloride and Hydrochlorothiazide

Amiloride Hydrochloride

Chemical Name: Pyrazinecarboxamide 3,5-diamino-N-(aminoiminomethyl)-6-chloro-monohydrochloride dihydrate.

Structural Formula:



Molecular Formula: $C_6H_8ClN_7O \cdot HCl \cdot 2H_2O$

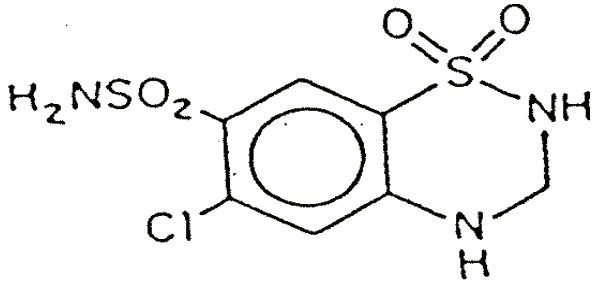
Molecular Weight: 302.12

Description:
Amiloride hydrochloride is a yellow to greenish yellow, odourless or practically odourless powder. Slightly soluble in water; insoluble in ether, in ethyl acetate, in acetone, and in chloroform; freely soluble in dimethylsulfoxide; sparingly soluble in methanol.

Hydrochlorothiazlde

Chemical Name: 6-chloro-3,4-dihydro-2-H-1,2,4-benzothiadiazine-7-sulfonamide-1 ,1-dioxide.

Structural Formula:



Molecular Formula: $C_7H_8ClN_3O_4S_2$

Molecular Weight: 297.73

Description:
Hydrochlorothiazide is a white or practically white, practically odourless crystalline powder. Slightly soluble in water, freely soluble in sodium hydroxide solution, in n-butylamine, and in dimethylformamide; sparingly soluble in methanol; insoluble in ether, in chloroform, and in dilute mineral acids.

STABILITY AND STORAGE RECOMMENDATIONS:

Store between 15 and 30°C. Unit dose strips should be stored between 15°C and 25°C and protected from high humidity.

AVAILABILITY OF DOSAGE FORMS

NOVAMILOR (amiloride hydrochloride and hydrochlorothiazide) is available as peach coloured, diamond-shaped, compressed tablets engraved '5/50' on one side and 'novo' on the other side. Each tablet contains 5 mg amiloride hydrochloride and 50 mg hydrochlorothiazide.

NOVAMILOR is available in bottles of 100, 500, and 1000 tablets and in boxes of 100 as unit dose strips.

PHARMACOLOGY

Amiloride Hydrochloride

Amiloride hydrochloride is a salt of a moderately strong base (pka 8.7). It is not chemically related to any other antikaliuretic or diuretic agent.

At an oral dose of 0.1 mg/kg or less, amiloride hydrochloride increases the excretion of sodium and, to a lesser extent, chloride in dogs and rats. Potassium excretion was not increased at this dose.

Amiloride hydrochloride administration has resulted in potassium retention in experimental animals. This effect is most evident when potassium excretion is high such as, upon loading with potassium chloride, following acetazolamide or thiazide pretreatment, or in adrenalectomized rats that are treated with deoxycorticosterone. The decrease in hydrogen ion excretion which accompanies the natriuresis causes an increase in urinary pH.

Amiloride hydrochloride administered orally in dogs causes an increase in the sodium excretion rate. This effect is not as pronounced as that seen with more potent agents but is of increased duration. The effect on sodium excretion lasts more than 6 hours. Increasing the oral dose from 0.25 to 4.0 mg/kg results in only moderate increases in natriuresls.

When amiloride hydrochloride is given in conjunction with chlorothiazide, hydrochlorothiazide or acetazolamide in rats, sodium excretion is increased.

The kaliuretic effect of the other diuretics is antagonized by amiloride hydrochloride. Amiloride hydrochloride (0.1 to 0.5 mg/kg oral) administered in conjunction with ethacrynic acid (1.0 mg/kg oral) or hydrochlorothiazide (0.5 mg/kg oral) to dogs resulted in an increased sodium excretion and a decrease in potassium excretion.

The Na+/K+ excretion ratio is increased in adrenalectomized rats given amiloride hydrochloride. Amiloride hydrochloride reverses the sodium retention induced by steroids in adrenalectomized rats treated with aldosterone, deoxycorticosterone or hydrocortisone. It also increases the Na+/K+ excretion ratio to above that of untreated adrenalectomized rats.

Renal clearance studies show that intravenous administration of 1.0 mg/kg does not affect the glomerular filtration rate, renal plasma flow or reabsorption of glucose in dogs. Amiloride hydrochloride acts directly on the distal portion of the nephron inhibiting tubular secretion of potassium and reabsorption of sodium. It is not known whether the affect of amiloride hydrochloride on the nephron is enzymatically based. Amiloride hydrochloride does not inhibit the actions of carbonic anhydrase, glutaminase, histidine decarboxylase, adenyl cyclase, or membrane ATP-ase, even when administered at high doses.

A profound reduction in blood pressure and changes in the electrocardiogram are seen in anesthetized dogs when amiloride hydrochloride is administered parenterally (2.5 to 5.0 mg/kg). If amiloride hydrochloride is injected slowly or is given at lower doses, the effects that are coincident with histamine release into the plasma are not seen. Oral doses of 0.5 to 2.0 mg/kg produce a slight increase in gastric secretion and intestinal motility in dogs. The response of dogs to ouabain is not altered by several days of oral pretreatment with amiloride hydrochloride (5.0 mg/kg/day).

Hydrochlorothiazide
Hydrochlorothiazide has diuretic and antihypertensive properties which increase the excretion of sodium and chloride in approximately equal amounts and cause a simultaneous usually minimal loss of bicarbonate. Ammonia excretion is decreased slightly which may result in an increase in blood ammonia levels. Hydrochlorothiazide also causes an increase in potassium and magnesium excretion and a decrease in calcium excretion.

Hydrochlorothiazide is eliminated rapidly by the kidneys. The coadministration of probenecid decreases the rate of elimination without reducing diuresis.

TOXICOLOGY

Route	Animal	Acute Toxicity Oral LD_{50} (mg/kg) Amiloride Hydrochloride	Hydrochlorothiazide	Amiloride Hydrochloride/ Hydrochlorothiazide 5/50
Oral	Mice	56	>10,000	189
	Rats	36 - 85	>10,000	422 (females) 377 (males)

Acute oral toxicity studies in mice and rats showed that the toxicity of an amiloride plus hydrochlorothiazide (5/25 and 5/50 mg/kg) combination depends upon the amiloride content. The LD_{50} values of the mixtures were not significantly different from the LD_{50} values of amiloride.

Chronic Toxicity:

Amiloride Hydrochloride and Hydrochlorothiazide

Rats tolerated the oral combination of amiloride/hydrochlorothiazide at 5/100 mg/kg 5 days per week for 25 weeks but experienced high mortality rates at 10/500 mg/kg amiloride/hydrochlorothiazide. Dogs tolerated oral combinations of 1/5 mg/kg amiloride/hydrochlorothiazide and 4/40 mg/kg amiloride/hydrochlorothiazide 5 to 7 days per week for 25 weeks but did not tolerate 5/50 mg/kg amiloride/hydrochlorothiazide 7 days per week for 13 weeks.

The toxic effects of the amiloride/hydrochlorothiazide combination in rats and dogs (adrenal zona glomerulosa hyperplasia, electrolyte imbalance, elevated BUN, ECG disturbances and focal tubular fatty changes of kidney) may be attributed to exaggerated pharmacological effects of the drugs since similar effects are caused by other diuretics.

Amiloride Hydrochloride

MODERATE TO MARKED HYPERKALEMIA DEVELOPED AT DOSES GREATER THAN 8.0 mg/kg/day. ELECTROCARDIOGRAPHIC CHANGES WERE OBSERVED. SERUM SODIUM AND CHLORIDE DECREASED.

Rats tolerated amiloride at oral daily doses of 2.5 and 5 mg/kg for up to 18 months. Higher dosage levels (10-15 mg/kg/day) caused a high incidence of deaths probably due to severe electrolyte imbalance. Drug-induced changes considered to be related to the diuretic and antikaliuretic activity of amiloride included alterations in urinary and serum electrolytes, reversible hyperplasia of the adrenal zona glomerulosa (all dosage levels) and renal tubular dilation (10 mg/kg).

Other than the expected changes in body weight, water intake, and serum electrolytes, dogs tolerated oral doses of amiloride ranging from 2 to 8 mg/kg/day 5 days/week for 58 weeks. Histologically, hyperplasia of the adrenal zona glomerulosa was seen in all amiloride treated dogs.

Amiloride administered orally to dogs 7 days/week at 2 and 4 mg/kg/day in an 11-week electrolyte balance study did not alter tissue electrolytes in the atrium, skeletal muscle or ileum.

In a 6-week study, GI ulcerations were observed in 1 of 4 dogs at 2.5 mg/kg and 2 of 4 dogs at 10 mg/kg. This ulceration may be related to the histamine releasing action of amiloride in the dog. No GI ulcerations were observed in the 58-week dog study at comparable doses although positive fecal occult blood tests were noted.

Monkeys tolerated amiloride well at oral doses up to 9 mg/kg/day, 5 days/week for 49 weeks. Excitability, irritability and apparent electrolyte imbalance occurred at a higher dose (12 mg/kg). In contrast to the rat and dog, no adrenal hyperplasia occurred although adrenal weights were increased.

Special Toxicity Studies Belated to Adrenal Zona Glomerular Hyperplasia and Diabetes:

Subacute studies (3 months of dosing) in rats showed that the adrenal zona glomerulosa hyperplasia disappeared in 19 to 30 days after cessation of treatment and that adrenals were completely normal 30 and 58 days after withdrawal of treatment. The hyperplasia can also be reduced by substitution of physiologic saline for drinking water. Hyperplasia of the adrenal zona glomerulosa occurred in maternal mice but not in the offspring in a teratogenicity study. The hyperplasla is considered physiological and reversible, the result of altered serum electrolytes and/or inhibition of aldosterone activity.

Toxicity of amiloride and triamterene is the same in obese-diabetic Zucker rats and normal-thin rats showing that amiloride has no effect on carbohydrate metabolism in this model of diabetes. Furthermore, amiloride has no adverse effects on glucose tolerance in acute experiments in rats or in a chronic study in dogs.

Hydrochlorothiazide
Reported results of a 6 month chronic oral toxicity study in the rat using doses of up to 2 g/kg/day (5 days/week) showed no signs of toxicity.

In dogs, oral doses up to 500 mg/kg/day were given 7 days/week for as long as 45 weeks. Slight depression of plasma potassium and small amounts of yellow crystalline precipitate in the bladder in two of 12 dogs were found on gross examination. Histomorphologic examination showed no drug related changes.

Carcinogenicity:
Amiloride was not carcinogenic when administered at maximally tolerated oral doses of 10 mg/kg/day for 92 weeks to mice or 104 weeks to rats at 6 mg/kg/day.

Mutagenicity:
Amiloride was devoid of mutagenic activity in several strains of Salmonella typhimurium (Arnes test) at concentrations up to 2000 µg/plate in the presence or absence of an *in vitro* mammalian metabolic activation system.

Reproductive Studies:
Amiloride had no effect on fertility or general reproductive performance in male or female rats given oral doses of 2, 4 or 8 mg/kg/day. No teratogenic effects on fetuses were noted when

amiloride was given orally during the period of organogenesis to rabbits at doses up to 8 mg/kg/day or mice up to 10 mg/kg/day. Signs of maternal toxicity (body weight loss, anorexia) and deaths were evident in both species at these dosage levels. Amiloride was without effect on various peri-and postnatal parameters when given to rats during late gestation through weaning at doses of 2 or 4 mg/kg/day. Pup survival and growth were reduced at 8 mg/kg/day.

Teratogenicity studies showed that the drug combination had no adverse effect on fetal development at oral dosage levels up to 2/20 mg/kg amiloride/hydrochlorothiazide in the rabbit and 5/50 mg/kg amiloride/hydrochlorothiazide in the mouse. Male and female fertility in the rat was unimpaired at doses up to 5/50 mg/kg amiloride/hydrochlorothiazide. Other than a reduced maternal and alive pup body weight gain at 5/25 mg/kg amiloride/hydrochlorothiazide, perinatal and postnatal parameters in rats were unaffected by drug administration during late gestation and weaning.

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