

SPIRONE

Tablets

Composition

Each tablet contains Spironolactone 100 mg.

Action

Spironolactone is a specific pharmacologic antagonist of aldosterone, acting primarily through competitive binding of receptors at the aldosterone dependent sodium-potassium exchange site in the distal convoluted renal tubule. Spironolactone causes increased amounts of sodium and water to be excreted, while potassium and magnesium is retained.

Spironolactone acts both as a diuretic and as an antihypertensive agent. It may be given alone or with other diuretic agents, which act more proximally in the renal tubule. Increased levels of the mineralocorticoid, aldosterone, are present in primary and secondary hyperaldosteronism, Oedematous states in which secondary aldosteronism is usually involved include congestive cardiac failure, hepatic cirrhosis, and the nephrotic syndrome. By competing with aldosterone for receptor sites, spironolactone provides effective therapy for the oedema and ascites in those conditions.

Spironolactone is effective in lowering the systolic and diastolic blood pressure in patients with primary hyperaldosteronism. It is also effective in most cases of essential hypertension despite the fact that aldosterone secretion may be within normal limits in benign essential hypertension. Through its action in antagonizing the effect of aldosterone, spironolactone inhibits the exchange of sodium for potassium in the distal renal tubule and helps to prevent potassium loss.

Spironolactone has not been demonstrated to elevate serum uric acid, to precipitate gout or to alter carbohydrate metabolism.

Spironolactone has moderate anti-androgenic activity in humans by inhibition of the interaction between dihydrotestosterone and the intracellular androgen receptor. It also inhibits several steps in ovarian steroidogenesis resulting in lowered plasma levels of testosterone and some other weak androgenic steroids. Through this activity, spironolactone is effective in the treatment of female hirsutism.

Pharmacokinetics

In the human, the bioavailability of spironolactone from orally administered spironolactone tablets exceeds 90 percent when compared with an optimally absorbed solution (spironolactone in polyethylene glycol 400). Food increases the bioavailability of spironolactone by increasing the absorption and possibly decreasing the first-pass metabolism of spironolactone.

Spironolactone is rapidly and extensively metabolised. Approximately 24% to 30% of the dose administered is converted to canrenone. The sulphur-containing products, canrenone and 7-alpha-(thiomethyl) spironolactone, are the predominant metabolites and are thought to be primarily responsible for the therapeutic effects of the drug. Canrenone attains peak serum levels at two to four hours following single oral administration. Canrenone plasma concentrations decline in two distinct phases, being rapid in the first 12 hours and slower from 12 to 96 hours. The log-linear phase half-life of canrenone, following multiple doses of spironolactone, is between 13 and 24 hours. Unchanged spironolactone appears in serum, with a half-life of 1 hour and T_{max} of 1.3 hours after single dosing. Both spironolactone and canrenone are more than 90-percent bound to plasma proteins. The activity of canrenone is reported to be 10-33% that of spironolactone. The metabolites of spironolactone are excreted primarily in urine, but also in bile.

Spironolactone has a gradual onset of diuretic action with a maximum effect being reached on the third day of therapy. Diuresis continues for two or three days after discontinuation.

Following the administration of 100 mg of spironolactone daily for 15 days in non-fasted healthy volunteers, time to peak plasma concentration (t_{max}), peak plasma concentration (C_{max}), and

elimination half-life ($t_{1/2}$) for spironolactone is 2.6 hours, 80 ng/mL, and approximately 1.4 hours, respectively. For the 7- α -(thiomethyl) spironolactone and canrenone metabolites, t_{max} was 3.2 hours and 4.3 hours, C_{max} was 391 ng/mL and 181 ng/mL, and $t_{1/2}$ was 13.8 hours and 16.5 hours, respectively.

Indications

Congestive Heart Failure

For the management of edema and sodium retention when the patient is only partially responsive to, or intolerant of, other therapeutic measures. Spirone is also indicated for patients with congestive heart failure taking digitalis, when other therapies are considered inappropriate.

Hepatic Cirrhosis with Ascites and Oedema

Cirrhosis of the liver accompanied by Edema and / or Ascites Aldosterone levels may be exceptionally high in this condition, Spironolactone is indicated for maintenance therapy, together with bed rest and the restriction of fluid and sodium.

Nephrotic syndrome

For nephrotic patients when treatment of the underlying disease, restriction of fluid and sodium intake, and the use of other diuretics fail to provide an adequate response.

Essential hypertension

Usually in combination with other drugs, Spirone is indicated for patients who cannot be treated adequately with other agents, or for whom other agents are considered inappropriate.

Primary Hyperaldosteronism

Establishing the diagnosis of primary hyperaldosteronism by therapeutic trial.

Short-term preoperative treatment of patients with primary hyperaldosteronism.

Long-term maintenance therapy for patients with discrete aldosterone-producing adrenal adenomas who are judged to be poor operative risks, or who decline surgery.

Long-term maintenance therapy for patients with bilateral micro- or macronodular adrenal hyperplasia (idiopathic hyperaldosteronism).

Hypokalemia

For the treatment of patients with hypokalemia, when other measures are considered in appropriate or inadequate.

Spirone is also indicated for the prophylaxis of hypokalemia in patients taking digitalis, when other measures are considered inadequate or in appropriate.

Hirsutism in Females

Spironolactone is effective in the treatment of females with hirsutism, an androgen-related increase in facial and body hair. A reduction in hair growth, hair shaft diameter and hair pigmentation is seen.

Contraindications

Spironolactone is contraindicated for patients with anuria, acute renal insufficiency, significant impairment of renal excretory function, or hyperkalemia.

Warnings

Potassium supplementation, either in the form of medication or as a diet rich in potassium, should not ordinarily be given in association with Spironolactone therapy. Excessive potassium intake may cause hyperkalemia in patients receiving Spironolactone. Spironolactone should not be administered concurrently with other potassium-sparing diuretics.

Spironolactone, when used with angiotensin converting Enzyme (ACE) inhibitors, even in the presence of a diuretic, has been associated with severe hyperkalemia. Extreme caution should be exercised when Spironolactone is given concomitantly with ACE inhibitors.

Spironolactone has been shown to be tumorigenic in chronic toxicity studies performed on rats.

Pregnancy

Category C

Spironolactone or its metabolites may cross the placental barrier. Therefore, the use of Spironolactone in pregnant women requires that the anticipated benefit be weighed against the possible hazard to the fetus.

Nursing Mothers

Canrenone, a metabolite of Spironolactone, appears in breast milk. If use of the drug is deemed essential, an alternative method of infant feeding should be instituted.

Adverse Reactions

Gynecomastia may develop in association with the use of Spironolactone, and physicians should be alert to its possible onset. A few cases of agranulocytosis have been reported in patients taking Spironolactone.

Other adverse reactions that have been reported in association with Spironolactone are gastrointestinal symptoms including cramps and diarrhea, drowsiness, lethargy, headache and mental confusion, drug fever, ataxia, maculopapular or erythematous cutaneous eruptions, urticaria, inability to achieve or maintain erection, irregular menses or amenorrhea, postmenopausal bleeding, hirsutism and deepening of the voice, gastric bleeding, ulceration, gastritis and vomiting.

Adverse Reactions are usually reversible upon discontinuation of the drug.

Precautions

Because of the diuretic action of Spironolactone, patients should be carefully evaluated for possible disturbances of fluid and electrolyte balance. Hyperkalemia may occur in patients with impaired renal function or excessive potassium intake, and can cause cardiac irregularities that may be fatal. Consequently, no potassium supplement should ordinarily be given with Spironolactone. Hyperkalemia can be treated promptly by the rapid intravenous administration of glucose (20-50 %) and regular insulin, using 0.25-0.5 units of insulin per gram of glucose. This is a temporary measure, to be repeated as required. Spironolactone should be discontinued and potassium intake (including dietary potassium) restricted.

Reversible hyperchloremic metabolic acidosis, usually in association with hyperkalemia, has been reported in some patients with decompensated hepatic cirrhosis, even in the presence of normal renal function.

Hyponatremia, manifested by dryness of the mouth, thirst, lethargy and drowsiness, and confirmed by a low serum sodium level, may be caused or aggravated, especially when Spironolactone is administered in combination with other diuretics. Spironolactone therapy may cause a transient elevation of blood urea nitrogen (BUN), especially in patients with Preexisting renal impairment. May cause mild acidosis.

Drug Interactions

Spironolactone\Antihypertensives

Antihypertensive effects may be potentiated when used concurrently.

Spironolactone\Potassium-containing Preparations

Concurrent administration tends to promote serum potassium accumulation with possible resultant hyperkalemia, especially in patients with renal insufficiency.

This effect is because of the potassium-sparing nature of Spironolactone.

Spironolactone\Lithium Salts

Concurrent use is not recommended, as it may provoke lithium toxicity because of reduced renal clearance.

Spironolactone\Noradrenaline

Spironolactone decreases vascular responsiveness to noradrenaline. Caution is recommended if local or general anesthesia is required in patients receiving this drug.

Spironolactone\ACE Inhibitors\Indomethacin

Concomitant administration of potassium-sparing diuretics with ACE inhibitors or indomethacin has been associated with severe hyperkalemia.

Spironolactone\Digoxin

Spironolactone has been shown to increase the half-life of digoxin. This may result in increased serum digoxin levels and subsequent digitalis toxicity. It may be necessary to reduce the maintenance and digitalization doses when Spironolactone is administered, and patients should be carefully monitored to avoid over digitalization or under-digitalization.

Dosage and Administration

Congestive heart Failure, Hepatic Cirrhosis and nephritic Syndrome

Adults

An initial daily dosage of 100 mg, in either single or divided doses, is recommended. The daily dosage may range from 25-200 mg.

When given as the sole agent for diuresis, Spirone should be continued for at least 5 days at the initial dosage level, after which it may be adjusted to the optimal therapeutic or maintenance level.

If, after 5 days, an adequate diuretic response to Spironolactone has not occurred, a second diuretic, which acts more proximally in the renal tubule, may be added to the regimen. Because of the additive effect of Spirone when administered concurrently with such diuretics, enhanced diuresis usually begins on the first day of combined treatment. Combined therapy is indicated when more rapid diuresis is desired. The dosage of Spirone should remain unchanged when other diuretic therapy is added.

Children

The recommended daily dosage is 3-mg/kg body weight, in either single or divided doses.

Essential Hypertension

For adults, an initial daily dosage of 50-100 mg, in divided doses, is recommended. Treatment should be continued for at least 2 weeks, since the maximum response may not occur before this time. Subsequently, dosage should be adjusted according to the response of the patient.

Primary Hyperaldosteronism

Spirone may be employed as an initial diagnostic measure to provide presumptive evidence of primary hyperaldosteronism while patients are on normal diets.

Long Test: Spironolactone is administered at a daily dosage of 400 mg for three to four weeks. Correction of hypokalemia and hypertension provides presumptive evidence for the diagnosis of primary hyperaldosteronism.

Short Test: Spironolactone is administered at a daily dosage of 400 mg for four days. If serum potassium increases during spironolactone administration but drops when spironolactone is discontinued, a presumptive diagnosis of primary hyperaldosteronism should be considered.

After the diagnosis of hyperaldosteronism has been established by more definitive testing procedures, Spirone may be administered in daily doses of 100-400 mg, in preparation for surgery. For patients who are considered unsuitable for surgery, Spirone may be employed for long-term maintenance therapy at the lowest effective dosage determined for the individual patient.

Hypokalemia

Spirone in a dosage ranging from 25 –100 mg daily is useful in treating diuretic induced hyperkalemia when oral potassium supplement or other potassium sparing regimens are considered inappropriate.

Female Hirsutism

100 mg to 200 mg daily in divided doses is usual however; 50 mg daily has also been shown to be effective.

Note: This medicine may cause you to have an unusual feeling of tiredness when you begin to take it you may also notice an increase in the amount in the urine or in your frequency of urination. After you have taken the medicine for a while, these effects should lessen. In general, to keep the increase in urine from affecting your sleep: If you are to take a single dose a day. Take it in the morning after breakfast. If you are to take more than one dose no later than 6.p.m, unless otherwise directed by your doctor.

Presentation

Box of 20 tablets