

Aldactazide®

(spironolactone 50 mg/hydrochlorothiazide 50 mg)

WARNING:

Spironolactone, an ingredient of Aldactazide, has been shown to be a tumorigen in chronic toxicity studies in rats (see *Warnings*). Aldactazide should be used only in those conditions described in the *Indications* section of the complete prescribing information. Unnecessary use of this drug should be avoided. Fixed-dose combination drugs are not indicated for initial therapy of edema or hypertension. Edema or hypertension requires therapy titrated to the individual patient. If the fixed combination represents the dosage so determined, its use may be more convenient in patient management. The treatment of hypertension and edema is not static, but must be reevaluated as conditions in each patient warrant.

Contraindications: Anuria, acute renal insufficiency, significant impairment of renal function, hyperkalemia or acute or severe hepatic failure. Allergy to thiazide diuretics or to other sulfonamide-derived drugs.

Warnings: Excessive potassium intake may cause hyperkalemia. Potassium supplements should not be given with Aldactazide. Do not administer concurrently with other potassium-sparing diuretics. Sulfonamide derivatives including thiazides have been reported to exacerbate or activate systemic lupus erythematosus. Spironolactone has been shown to be a tumorigen in chronic toxicity studies in rats. In one study using 25, 75 and 250 times the usual daily human dose (2 mg/kg) there was a statistically significant dose-related increase in benign adenomas of the thyroid and testes. In female rats there was a statistically significant increase in malignant mammary tumors at the mid-dose only. In male rats there was a dose-related increase in proliferative changes in the liver. At the highest dosage level (500 mg/kg) the range of effects included hepatocytomegaly, hyperplastic nodules and hepatocellular carcinoma; the last was not statistically significant.

Precautions: 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 which may be fatal. Hypokalemia may develop as a result of profound diuresis, particularly when Aldactazide is used concomitantly with loop diuretics, glucocorticoids or ACTH. Transient elevation of BUN may occur. Reversible hyperchloremic metabolic acidosis may occur in some patients with decompensated hepatic cirrhosis. Dilutional hyponatremia or rarely low-salt syndrome may develop. Gynecomastia may develop and in rare instances some breast enlargement may persist. Thiazides may alter the metabolism of uric acid and carbohydrates with possible hyperuricemia, gout and decreased glucose tolerance. Vascular responsiveness to norepinephrine is reduced. Thiazides may also increase the responsiveness to tubocurarine. The antihypertensive effects of hydrochlorothiazide may be enhanced in sympathectomized patients. Thiazides may decrease serum PBI levels and prolonged therapy may induce hypercalcemia and hypophosphatemia. Spironolactone may and hydrochlorothiazide does cross the placental barrier. Use in pregnant women requires that the anticipated benefit be weighed against possible hazards to the fetus. Breast feeding should be discontinued when Aldactazide is being used.

Adverse Reactions: Associated with spironolactone: Gynecomastia is observed not infrequently. Gastrointestinal symptoms including cramping and diarrhea, drowsiness, lethargy, headache, maculopapular or erythematous cutaneous eruptions, urticaria, mental confusion, drug fever, ataxia, inability to achieve or maintain erection, irregular menses or amenorrhea, postmenopausal bleeding, hirsutism and deepening of the voice. Carcinoma of the breast has been reported but a cause-and-effect relationship has not been established. Associated with thiazides: Gastrointestinal symptoms (anorexia, nausea, vomiting, diarrhea, abdominal cramps), purpura, thrombocytopenia, leukopenia, agranulocytosis, dermatologic symptoms (cutaneous eruptions, pruritus, erythema multiforme), paresthesia, acute pancreatitis, jaundice, dizziness, vertigo, headache, xanthopsia, photosensitivity, necrotizing angitis, aplastic anemia, orthostatic hypotension, muscle spasm, weakness and restlessness. Adverse reactions are usually reversible upon discontinuation of Aldactazide.

SEARLE Searle & Co.
San Juan, PR 00936

Address medical inquiries to:
G. D. Searle & Co.
Medical Communications Department
Box 5110, Chicago, IL 60680

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cough. One first asks the child to breathe through the mouth as noisily as possible (throat stridor) and then asks the child to do the same as quietly as possible (panting, with relaxed throat muscles). Note how the former often precipitates coughing while the latter prevents it, even in the face of an intense tickle.

If the child fights off the first few paroxysms of coughing by voluntarily maintaining the quiet, relaxed throat position, the frequency of coughing episodes is lowered and the child soon drops quietly off to sleep.

Whole noisy families (theater coughers!) can be taught this method for shunning a thoughtless mannerism that can affect them throughout life.

S. John Ingram, MD
Palo Alto, California

Specificity and sensitivity: a significant difference

To the Editor:

Dr Steven R. Gambert and colleagues in the September 1982 issue (page 147) discussed the important topic of the interpretation of laboratory tests in the elderly. In their article, however, we noted a misuse of a statistical term which should be clarified.

In their discussion of liver function tests, the authors mention that "[results] may be normal despite the presence of significant liver pathology; therefore, more specific tests of liver function should be done" (pages 150-151). The authors referred to "specific" when "sensitive" was probably intended.

Sensitivity is the ability of a test to detect those who have disease (ie, it is the proportion of those with disease who have a positive test result).¹ The false-negative rate is the proportion of those with the disease who have a negative test result. This rate is related to sensitivity in the following way.

$$\text{Sensitivity} = 1 - \text{FN}$$

Thus, to detect those individuals with pathology or disease who have normal screening tests, more sensitive, not more specific, tests are needed.

Specificity is a test's ability to identify correctly those who do not have the disease (ie, it is the proportion of those without disease who have a negative test result). In those whose test results are positive, however, one would also like to use specific tests (those with few false-positive results) to help in confirming the diagnosis.

Gary M. Liss, MD
Mitchell Singal, MD
Cincinnati

Reference

1. Maunder JS, Bahn AK. Epidemiology: an introductory text. Philadelphia: WB Saunders, 1974

Correction

The article on day care for Alzheimer's disease (April 1983, page 245) failed to mention that the Wisconsin Regional Geriatric Center is located at Family Hospital, Milwaukee. PGM