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## SPIRONOLACTONE AND CANRENOATE: DIFFERENT ANTIALDOSTERONIC DIURETIC AGENTS

Andriulli A, Arrigoni A, Gindro T, Karbowski I, Buzzetti G, Armanini D. Canrenone and androgen receptor-active materials in plasma of cirrhotic patients during long-term K-canrenoate or spironolactone therapy. *Digestion* 1989;44:155-162.

### ABSTRACT

Plasma levels of canrenone and androgen receptor-active materials (ARM) were determined during long-term oral K-canrenoate or spironolactone therapy in cirrhotics with chronic recurrent ascites. Mean plasma canrenone level was approximately 3 times higher under K-canrenoate than under spironolactone treatment; moreover, the levels were not dose related. Either type of treatment did not affect plasma aldosterone and testosterone concentrations. Plasma ARM during K-canrenoate treatment did not change, whereas in the spironolactone group a 3-fold increase of ARM occurred ( $p < 0.05$ ). No dose-related effect was evident with the latter treatment. The lower incidence of gynecomastia in the K-canrenoate group was not correlated with values of plasma canrenone or ARM ( $p > 0.05$ ).

Our study questions the traditional view that the mode of action of spironolactone is via its metabolite canrenone. The two antialdosterone drugs, although equally effective in clearing ascites from cirrhotics, appear to act through partially different metabolites. The lower incidence of antiandrogenic or estrogen-like side effects during K-canrenoate seems to be related to metabolites other than canrenone itself.

### COMMENTS

The concept of "sequential therapy" for the treatment of sodium and water retention in cirrhotic patients with ascites is widely accepted (1). Although loop diuretics are in general quantitatively more potent than antialdosteronic agents, the latter are much more effective in inducing natriuresis in cirrhotic patients with ascites and are, therefore, considered to be the treatment of choice (2). Moreover, their potassium-sparing effect is particularly useful in this clinical setting, which is characterized by potassium depletion. Antialdosteronic agents directly and specifically counteract the distal tubular effects of secondary hyperaldosteronism. However, they are also effective in cirrhotic patients with normal renin and aldosterone levels (3), as shown in the paper by Andriulli et al. In such patients, an increased sensitivity to aldosterone in the distal and collecting tubules has been hypothesized. It is pos-

sible, however, that antialdosteronic substances act by different mechanisms. It has been shown that K-canrenoate can stimulate renal prostaglandin and kinin synthesis in hypertensive patients (4). It is therefore also conceivable that in cirrhotic patients the natriuretic action of this drug is associated with increased intrarenal production of vasodilating autacoids that play a "protective" role against activated vasoconstrictive and sodium-retaining factors such as catecholamines, angiotensin II and thromboxane A<sub>2</sub> (5).

The paper by Andriulli et al. deals with another effect of antialdosteronic agents, their antiandrogenic activity. This action is responsible for most of the common side effects that occur after prolonged administration, particularly the development of gynecomastia. In this study, the antiandrogenic effect of spironolactone and K-canrenoate was documented by the demonstration of gynecomastia and the determination of circulating androgen receptor-active material (ARM) using a previously described radioreceptor assay (6). In addition, plasma levels of canrenone, testosterone and aldosterone were determined every 3 mo during prolonged administration of minimal doses of spironolactone or K-canrenoate (100 mg daily or on alternate days for 1 yr) in cirrhotic patients with ascites. Cirrhotic patients treated with K-canrenoate showed significantly higher levels of plasma canrenone, confirming that this compound is not likely to be the main metabolite of spironolactone (7). Indeed, metabolism of spironolactone leads to the formation of several sulfur-containing moieties, especially 7- $\alpha$ -thiomethylspironolactone. All these metabolites have antimineralocorticoid and antiandrogenic activity. On the other hand, canrenone and canrenoic acid, which are the main metabolic products of K-canrenoate metabolism, are not sulfur-containing metabolites, a feature that could explain the low antiandrogenic activity of K-canrenoate. In addition, circulating levels of ARM increase in patients treated for 3 mo with spironolactone, whereas they remain unchanged after K-canrenoate. This latter therapy is characterized by a lower incidence of gynecomastia, although a clear correlation with plasma canrenone and ARM levels was not seen. Furthermore, in contrast to other reports (8), antialdosteronic therapy, probably because of the low doses used, does not affect plasma testosterone levels. Studies of animals (9) and of hypertensive patients (8) have suggested that the antiandrogenic activity of spironolactone may be caused by a decreased testosterone biosynthesis. The authors do not provide information about the degree of hepatic and renal function impairment. Also, it would have been desirable to have evaluated the effects of higher doses of spironolactone and K-canrenoate used in clinical practice.

In conclusion, the paper by Andriulli et al. provides some pharmacological evidence for the preferential use of K-canrenoate in the management of avid sodium and water retention in cirrhotic patients with ascites. In addition, the results of this study are in agreement with a previous report by Francavilla et al. (10) that showed

a drastic reduction of liver androgen-receptor activity in rats treated for a prolonged period with spironolactone but not in those treated with K-canrenoate.

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#### CONGESTIVE GASTROPATHY IN CIRRHOSIS—HOW BAD IS RED?

D'Amico G, Montalbano L, Traina M, Pisa R, Menozzi M, Spano C, Pagliaro L, et al. Natural history of congestive gastropathy in cirrhosis. *Gastroenterology* 1990;99:1558-1564.

#### ABSTRACT

**In a prospective study of the natural history of congestive gastropathy, 212 consecutive cirrhotic patients (75 treated with sclerotherapy) were included. Mean follow-up was 46 months. Mild gastropathy (mosaiclike pattern) was found in 110 patients and severe gastropathy (granular mucosa with cherry spots) was found in 20. Prevalence of *Helicobacter pylori*, formerly *Campylobacter pylori*, was 50% in patients without, 43% in those with mild, and 28% in those with severe gastropathy. Congestive gastropathy was significantly more frequent in patients treated with sclerotherapy (83% vs. 50%,  $P < 10^{-5}$ ). Sixty-month actuarial propor-**