Effect of Potassium Canrenoate, an Anti-aldosterone Agent, on Incidence of Ascites and Variceal Progression in Cirrhosis

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Background & Aims: Because aldosterone-dependent sodium and water retention contribute to portal hypertension, the safety and effect of an antialdosteronic drug (Kcanrenoate) have been evaluated on the occurrence of de novo appearance of ascites and the development of esophageal varices or the progression of small varices. **Methods:** Inclusion criteria were as follows: Child–Pugh A viral pre-ascitic cirrhosis, with either F1 esophageal varices or no varices, but endoscopic and/or ultrasound evidence of portal hypertension. Thirteen Italian Liver Units prospectively enrolled 120 patients randomized to receive double-blind either Kcanrenoate (100 mg/day; 66 patients) or placebo (54 patients). Endoscopy and sonography were performed at entry and at 52 weeks unless the patient developed ascites earlier, whereas laboratory examinations were performed at entry and every 3 months thereafter. An intention-to-treat analysis was performed, with each end point assessed by the Fisher exact test; the cumulative risk for the appearance of any end point was analyzed by the adjusted log-rank test (Tarone–Ware), with censoring for drop-outs. **Results:** The progression of variceal status or appearance of ascites, analyzed independently, was not significantly more frequent on placebo (24.1% and 9.2%, respectively) than on Kcanrenoate (12.1% and 1.5%, respectively), whereas the cumulative occurrence of end points was decreased on Kcanrenoate (17.6% vs 38.3% with placebo; $P < .05$, Tarone–Ware test). The incidence of adverse events was negligible and did not differ between groups. **Conclusions:** This preliminary study shows that 100 mg/day of Kcanrenoate is well tolerated and does not reduce the individual incidence of ascites and/or the appearance or progression of esophageal varices in preascitc cirrhosis, but may decrease their 1-year cumulative occurrence.

Renal sodium and water retention play a pivotal role in promoting portal hypertension in preascitic cirrhosis and hence in determining the progression to major complications, such as the development of ascites and of esophageal varices, which are among the main determinants of the negative outcome of cirrhosis.[1] In particular, fluid retention, in association with increased plasma levels of several neurohormonal vasodilators,[2,3] leads to an increase in flow in various systemic and splanchnic vascular territories, the so-called cirrhotic *hyperdynamic circulation*,[4] which contributes to maintaining increased portal pressure.[5] Fluid retention occurs before the formation of ascites[6] and is associated with activation of the renin-angiotensin-aldosterone system, with aldosterone as the final effector on the distal tubule of the kidney. In the kidney, the neurohormonal abnormalities involved in the hyperdynamic circulation do not lead to vasodilation, but rather to vasoconstriction,[5–7] which perpetuates fluid retention and ultimately induces formation of ascites.

Because of their effect on this pathogenetic mechanism, antialdosteronics, with or without loop diuretics, are the drugs of choice for the treatment of cirrhotic ascites.[8] Antialdosteronics also have been shown to decrease the pressure in the portal system and esophageal varices in humans[9–11] and experimental animals.[12] Their effect on portal pressure could be enhanced by the antifibrogenic action, for which some evidence has been accumulated at heart[13–16] and, more recently, in the liver.[17]

Although β-blockers are used commonly for prophylaxis of variceal bleeding,[18] their efficacy in delaying the growth of small varices remains to be established.[19,20] A large multicenter trial showed no significant advantage of β-blockers in comparison with placebo in preventing the de novo appearance of esophageal varices in patients with portal hypertension,[21] nor in preventing ascites.

Based on the pathophysiology of pre-ascitic cirrhosis, the aim of the present study was, therefore, to compare the efficacy and safety of Kcanrenoate (Kanrenol; Abbott, Campoverde di Latina, Italy), an antialdosteronic drug, with placebo in decreasing the incidence of de novo ascites and the appearance or progression of esophageal varices in preascitic cirrhosis.

Patients and Methods

Enrolled in the study population were patients with preascitic cirrhosis in Child–Pugh class A[22] with small esophageal varices, which flatten or disappear during insuflation, that is, F1 varices according to the Japanese classification,[23] or without esophageal varices but with clinically significant portal hypertension. Patients with larger varices should, in fact, be treated with β-blockers to prevent bleeding.[18] In patients with-

Abbreviations used in this paper: AE, adverse events; BUN, blood urea nitrogen; US, ultrasound.

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out esophageal varices, the presence of clinically significant portal hypertension was established indirectly by the simultaneous presence of at least 3 of the following signs, revealed by endoscopy and/or abdominal duplex–Doppler ultrasound (US): (1) congestive gastropathy, (2) splenomegaly (bipolar diameter of the spleen >13 cm), (3) collateral portosystemic vessels, (4) portal vein diameter greater than 13 mm, (5) reduced maximum speed of portal flow velocity (time averaged maximal velocity <24 cm/s), and (6) change in splenic or mesenteric vein caliber less than 40% between forced inspiration and expiration.

To avoid the possible bias of a different and unpredictable rate of disease progression in alcoholic patients related to their ability to true abstinence from alcohol, only patients with cirrhosis of viral (hepatitis B or C virus) origin and not treated for at least the previous 6 months and not eligible for antiviral treatment in the 12 months after enrollment, were included.

Exclusion criteria were as follows: age within 18–75 years; history of alcoholism or drug abuse (present either currently or in the 6 months before baseline examination), nephropathy or serum creatinine level greater than 1.2 mg/100 mL, human immunodeficiency virus seropositivity, primary hyperaldosteronism, heart failure, history of uncontrolled diabetes (glucose level >160 mg/100 mL or glycosuria), arterial hypertension requiring pharmacologic treatment, hepatocellular carcinoma or other neoplastic diseases, portal thrombosis, current treatment with diuretics or antihypertensive drugs, contraindication to the study drug, hyponatremia, serum potassium level greater than 5.0 mEq/L, gynecomastia or mastodynia, and hepatitis B or C antiviral treatment either at present or within the past 6 months. Treatment with diuretics, corticosteroids, nonsteroidal anti-inflammatory drugs, or any other drugs that could interfere with evaluations to be performed during the trial was not allowed during the study period and, if required, resulted in withdrawal from the study.

Enrollment of 300 patients (150 receiving Kcanrenoate, 150 receiving placebo) in 13 Italian centers was planned according to the few data available and the personal experience of the authors concerning the natural history of preascitic cirrhosis with portal hypertension and the incidence of the complications investigated. Thus, expecting a progression or onset of varices of approximately 12%–20% at 1 year[24,25] and an incidence of ascites of approximately 8%, the statistical significance could be shown for each individual and for the combined effects if the drug obtained a 75% reduction of events.

The primary end point for the evaluation of treatment efficacy was the onset of any of the following events during the 1-year period after randomization: appearance of ascites (detectable either clinically or at US), or appearance of esophageal varices in patients without esophageal varices at baseline or an increase in variceal size in patients with F1 esophageal varices at enrollment. As secondary end points, the tolerability and safety of long-term treatment with Kcanrenoate also were evaluated by monitoring the onset of adverse events, laboratory examinations (sodium, potassium, creatinine, and nitrogen levels), and modifications in systemic and renal circulatory parameters, namely arterial pressure, heart rate, and renal artery Doppler Resistance Index. Severe adverse events were those meeting any of the following criteria: (1) resulted in death, (2) involved or prolonged hospitalization, (3) involved persistent or significant disability or incapacity, (4) was life-threatening, or (5) was a medically important event or reaction. Mild adverse events were those not resulting in disability/incapacity and resolved without treatment. Moderate adverse events were those resulting in temporary and mild disability/incapacity and/or those requiring treatment.

Methods of Investigation

Patients were screened at baseline for study eligibility. US was performed to confirm the diagnosis of cirrhosis and portal hypertension and to exclude ascites. Furthermore, the renal artery Resistance Index was assessed from Doppler tracings taken from interlobular renal arteries. This index is measured over 1 cardiac cycle as follows: (systolic flow velocity − end-diastolic flow velocity) / systolic flow velocity.

Methodology for the assessment of all abdominal US parameters was agreed on, following published guidelines,[7,26] by all the US operators from the various centers during a specific meeting held in Bologna before the start of the study. Likewise all endoscopists met before the study to define the criteria to be used to report esophageal varices and gastropathy.[18] Endoscopic and sonographic parameters were assessed directly by these trained operators at the time of each procedure.

Study Design

Patients eligible for this phase III study were randomized to double-blind administration of oral Kcanrenoate (100 mg/day) or placebo, using a random scheme prepared by a biometric agency for each center. The randomization scheme and associated sealed envelopes (code breaks) were produced by computer software that incorporated a standard procedure for generating random numbers. Patients were allocated to randomized treatment in balanced blocks of 10. Investigators retained any unused drug and recorded the study drug dispensed and returned at each visit. Compliance was evaluated on the basis of tablets returned by the patient. If compliance repeatedly was less than 90%, the patient was withdrawn from the study. Seals were opened by biostatisticians only after closure of the study.

Because patients had to be in a pre-ascitic condition, no specific sodium restriction was recommended after enrollment and all patients were allowed to consume their ongoing free diet.

Clinical and laboratory examinations then were assessed in all patients, again at 4 weeks (visit 2), 17 weeks (visit 3), 34 weeks (visit 4), and 52 weeks (visit 5). At each visit, laboratory tests, including serum sodium level, potassium level, creatinine level, nitrogen level, alanine and aspartate aminotransferase levels, total bilirubin level, glucose level, whole blood cell count, and electrocardiogram were performed. Each study center performed all laboratory investigations on their own patients.

Duplex–Doppler US was repeated at visits 4 and 5 to check for ascites and to measure the renal Resistance Index or, at any time earlier, to confirm the development of ascites. Endoscopy was repeated at visit 5. Each patient was always assessed by the same US or endoscopic operator throughout the study.

Code breaks were opened prematurely, after having informed the sponsor, only in 2 cases, as a result of the development of adverse events requiring hospitalization and treatment. Otherwise the seals were broken only by centralized statisticians after completion of the study.

The study was conducted in accordance with the Declaration of Helsinki. The study protocol was approved by the Ethics

Committees of all centers taking part in the trial, after approval of the Ethics Committee of the coordinating center (Florence, July 20, 1998). Each patient was asked to provide written consent before beginning protocol-specified procedures.

Patients

The study began in September 1999 and was closed in September 2002 before reaching the calculated sample size. A total of 120 patients from 13 centers were randomized to treatment. Participating centers belonged either to secondary or tertiary referral centers at university or general hospitals. A total of 54 patients received placebo and 66 received Kcanrenoate (cumulative age range, 36–74 y).

Statistical Method

The intention-to-treat approach was used as in other trials that test drugs to prevent complications of cirrhosis.[21] The occurrence of primary end points was assessed individually using the Fisher exact test. The occurrence of primary end points also was cumulatively evaluated according to survival analysis using the product limit method. Comparisons between treatment groups was effected using the adjusted log-rank test (Tarone–Ware), which includes all enrolled patients. Patients who withdrew or dropped out before study completion were considered as not having reached the end-points, in accordance with the intention-to-treat approach.

Adverse events were analyzed using the Fisher exact test as an evaluation of the incidence of each individual case. Laboratory examinations were evaluated in the 2 groups comparing baseline results according to the analysis of variance (ANOVA) with repeated measures and multiple comparisons. For ANOVA, as an intention-to-treat analysis, missing data were replaced according to the last observation carried forward method.

Renal duplex–Doppler Resistance Index, heart rate, and arterial blood pressure were analyzed according to ANOVA with repeated measures (visits) and 1 grouping factor (treatment). Multiple comparisons within groups are reported according to the least significant difference Student *t* test and related 95% confidence interval, with the lower and upper limits.

Results

A total of 66 patients were randomized to Kcanrenoate and 54 to placebo. No significant difference was found between the 2 groups at entry in any of the variables examined (Table 1). At entry, duplex–Doppler parameters were comparable in the 2 groups: the portal vein diameter was 1.23 ± .16 cm in the placebo and 1.19 ± .17 cm in the Kcanrenoate group (P = NS), and the time-averaged maximal portal vein blood flow velocity was 24.8 ± 8.9 cm/s and 27.3 ± 14.0 cm/s (P = NS), respectively.

Table 1. General Characteristics of Study Population at Enrollment

	Placebo	Kcanrenoate
Total patients	54	66
Age, *y*, mean ± SD	61.0 ± 8.3	60.4 ± 9.5
M/F	40/14	43/23
No varices/F1 varices	26/28	33/33
Congestive gastropathy (absent/present)	29/25	34/32
Body weight, *kg*, mean ± SD	73.9 ± 11.6	71.6 ± 11.3
Height, *cm*, mean ± SD	167.8 ± 6.7	168.2 ± 7.9

NOTE. No statistically significant difference was found in any parameter between the 2 groups.

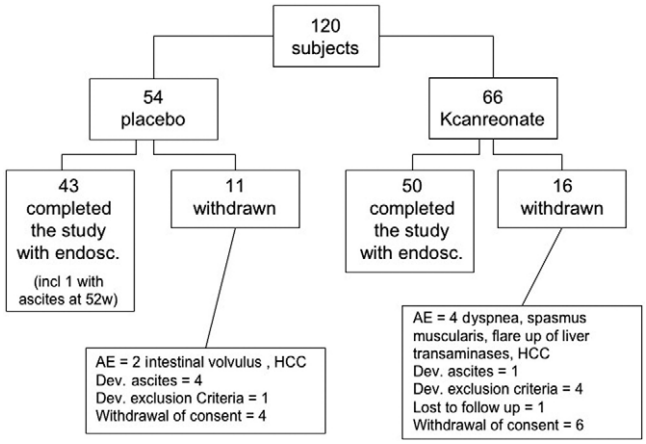

Figure 1. Patient flow after randomization. HCC, hepatocellular carcinoma; Dev., development of.

The patient disposition is shown in Figure 1. A total of 22 patients (7 in the placebo group and 15 in the Kcanrenoate group) had to withdraw from the study before completion on account of adverse events (4 in the Kcanrenoate group: dyspnea, cramps, flare of liver transaminase levels, development of hepatocellular carcinoma; and 2 in the placebo group: intestinal volvulus and development of hepatocellular carcinoma), development of exclusion criteria (5 in the Kcanrenoate group: 2 diabetes decompensation, 2 mastodynia with gynecomastia, 1 serum potassium level >5 mEq/L; and 1 in the placebo group because of hypertension), loss to follow-up evaluation (1 in the Kcanrenoate group), withdrawal of consent (6 in the Kcanrenoate and 4 in the placebo group) related primarily to lack of consent to repeat endoscopy or the wish to commence antiviral treatment. Five patients (4 in the placebo group and 1 in the Kcanrenoate group) did not attend visit 5 because they developed ascites before this time point and started diuretic treatment. Another patient on placebo was found to have ascites at visit 5 and also underwent endoscopy. Therefore, the study was considered complete (either with all the parameters at visit 5 or having reached the end point of ascites) in 98 patients (51 in the Kcanrenoate group and 47 in the placebo group).

The time of exposure to treatment was not significantly different between the 2 groups (mean ± SD: 328 ± 97 days in the placebo group and 325 ± 99 days in the Kcanrenoate group, P = NS), whereas compliance to treatment was significantly lower in the Kcanrenoate group at visit 5 (96.5% vs 99.1%, $P < .05$), but not at visits 2, 3, and 4.

Analyzing the different end points separately, a nonsignificant trend toward a reduction in the incidence of ascites was observed (9.0% in the placebo group and 1.5% in the Kcanrenoate group, $P = .089$, Table 2). A similar pattern was observed for worsening of endoscopic status (24.1% in the placebo group and 12.1% in the Kcanrenoate group, $P = .097$, Table 3). No patient presented with variceal bleeding during the study period.

Table 2. Incidence of Ascites

	Placebo		Kcanrenoate	
Onset of ascites	N	%	N	%
No	49	90.8	65	98.5
Yes	5	9.2	1	1.5
Total	54	100	66	100

NOTE. $P = .0891$, Fisher exact test.
Fisher exact test refers to significance in incidence of de novo ascites in the placebo group vs the Kcanrenoate group analyzed according to intention-to-treat (patients who withdrew before completing the study were considered not to have reached the end point of ascites: 7 in the placebo group and 15 in the Kcanrenoate group). If only patients who completed the study were analyzed (47 in the placebo group and 51 in the Kcanrenoate group) the statistical significance would remain nonsignificant ($P = .101$).

The cumulative incidence of primary end points (de novo appearance of ascites or appearance or progression of varices) was significantly higher in patients given placebo than in those on Kcanrenoate at the Tarone–Ware analysis (18 events in 47 patients on placebo completing the study vs 9 events in 51 patients on Kcanrenoate, $P = .048$, Figure 2).

Secondary End Points

Adverse events. Both Kcanrenoate and placebo were well tolerated by most patients. The incidence of adverse events did not differ between the 2 groups (rate of affected patients was 36.4% receiving Kcanrenoate and 30.0% receiving placebo, P = NS).

A total of 34 adverse events in 24 patients occurred in the Kcanrenoate group. The most frequent adverse events were as follows: asthenia, cramps (3 cases each), all being evaluated as moderate and generally considered either possibly or probably related to the study drug; dizziness, hyperglycemia, and gynecomastia (2 cases each) generally were evaluated as mild or moderate and either possibly or probably related to the study drug. Only in 1 patient was the observed event (gynecomastia, mastodynia) considered severe by the attending physician and the relationship with the study drug probable. In fact, another 2 cases of adverse events of severe intensity observed during the study (increase in serum transaminase levels and liver tumor) were considered not to be study related.

A total of 25 adverse events occurred in 18 patients in the placebo group, 4 of which were judged as severe (1 liver tumor, 1 chest pain, 1 intestinal volvulus, and 1 reticular lymphangitis).

No deaths occurred either during the study or in the 30 days after the end of the study period.

Both cases of hepatocellular carcinoma, 1 in each group, were detected at visit 5 (1 year). Given the expected time of these neoplasms to reach a size detectable at ultrasonography, and the expected incidence rate of such malignancies in cirrhosis (≈4% at 1 year),[27] the tumors were considered not to be study-drug related.

Laboratory and circulatory parameters. A slight increase in serum potassium level (.22 mmol/L at visit 5, $P < .05$) and a decrease in sodium level (−2.2 mmol/L, $P < .05$) occurred in patients treated with Kcanrenoate (Table 4). Renal function remained substantially stable (Table 4). Systolic and diastolic blood pressure showed a slight decrease in patients treated with Kcanrenoate (Table 5), whereas heart rate and intrarenal arterial resistance, assessed by the interlobular Doppler Resistance Index, remained substantially stable with no difference observed between the 2 groups (Table 5).

As far as liver parameters are concerned, the total bilirubin level showed a significant and comparable increase in both groups; the prothrombin time index remained stable and α-fetoprotein levels did not increase significantly (Table 4).

The incidence of the disappearance or onset of congestive gastropathy did not differ between the 2 groups. Indeed, disappearance occurred in 8 (18%) and 13 (24%) patients on placebo and Kcanrenoate, respectively. An onset of congestive gastropathy occurred in 7 (15%) and 6 (12%) patients on placebo and Kcanrenoate, respectively. In most patients, the status of gastropathy (present or absent) remained as at baseline (unchanged in 32 of 47 [67%] placebo patients who underwent final endoscopy and in 35 of 54 [64%] patients on Kcanrenoate).

Discussion

This double-blind, randomized, controlled trial showed that 1-year oral treatment with Kcanrenoate at a dose of 100 mg/day does not decrease the individual incidence of de novo appearance of ascites and the appearance or progression of esophageal varices in Child–Pugh A preascitic cirrhotic patients, but may decrease their cumulative occurrence.

The study was terminated before reaching the complete planned study population of 300. A forecast of unsatisfactory further recruitment, mainly because candidates eligible to enter the study also had become eligible for antiviral treatments, as pegylated interferons, which might be recommended also in well-compensated cirrhotic patients,[28] and lamivudine, had become available on the market soon after the present study had

Table 3. Worsening of Variceal Status

	Placebo		Kcanrenoate	
Worsened	N	%	N	%
No	41	75.9	58	87.9
Yes	13[a]	24.1	8[b]	12.1
Total	54	100	66	100

NOTE. $P = .0970$, Fisher exact test.
Worsening of variceal status was considered as either appearance of varices in patients not presenting with varices at baseline or an increase in variceal size in patients with F1 varices at baseline, analyzed according to intention-to-treat approach (total 54 placebo patients: 43 concluded the study with the second endoscopy, whereas 11 were censored before the second endoscopy; the Kcanrenoate group comprised a total of 66 patients, with 16 censored before study completion; patients who did not undergo a second endoscopy were considered as not reaching the end point of variceal status worsening).
[a]The 13 patients receiving placebo with worsening of variceal status included 7 patients with newly developed varices and 6 patients with varices progressing from F1 to F2.
[b]The 8 patients on Kcanrenoate included 6 patients with newly developed varices and 2 patients with varices progressing from F1 to F2. If only patients who concluded the study (1 year of treatment and second endoscopy) were considered, the statistical significance likewise would remain nonsignificant ($P = .1365$).

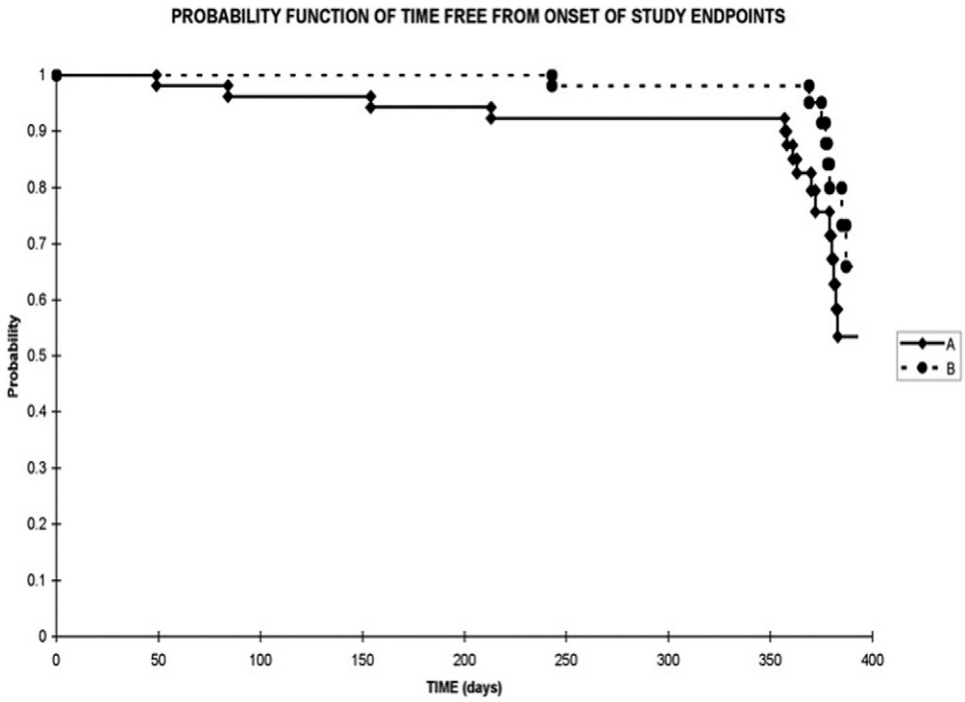

Figure 2. Probability of remaining free from any end point (onset of ascites, development of esophageal varices, or progression of F1 varices) in patients receiving placebo (◆, group A, n = 51) or Kcanrenoate (●, group B, n = 47). The difference between the groups is statistically significant ($P = .048$).

started. Given the early cessation of the study, type II errors cannot be concluded.

Our study groups showed a similar increase in the level of total bilirubin, whether treated or not with Kcanrenoate (10.2% and 17.8%, respectively, during the 12-month study period). This finding suggests a slight but similar progression of liver failure in the 2 groups during this time frame, consistent with our intention to study homogeneous populations with progressive disease. For this reason, alcoholic patients were not enrolled in the present study because disease progression is related to drinking habits. Given the relatively short observation period of 1 year, we chose to study patients with clinically significant portal hypertension, as shown by the presence of small (F1) esophageal varices or by typical findings at abdominal Doppler US. This choice was aimed at studying a population more prone to developing complications of cirrhosis related to the primary end points of the study. Even if the sonographic and Doppler signs used in the present study to establish a diagnosis of portal hypertension in patients without varices already had been shown to be reliable expressions of the presence of portal hypertension in cirrhotic patients,[29–34] we nonetheless chose to include only patients with at least 3 concurrent signs to make the diagnosis even more reliable. We also chose to assess the appearance of ascites by US, not only by clinical physical examination, to maximize the rate of study events in 1 year, and to avoid any possible variability among the different centers. In-

Table 4. Renal Function and Serum Electrolyte Levels

	Placebo	Kcanrenoate	Placebo	Kcanrenoate
	Serum creatinine level, *mg/dL*		BUN level, *nmol/L*	
N	53	63	53	63
Visit 1	.962 ± .146	.884 ± .134	30.5 ± 10.7	30.8 ± 10.7
Visit 5	.870 ± .146	.912 ± .149	31.0 ± 10.7	34.5 ± 12.3[a]
	Creatinine clearance, mL/min		Diuresis, mL/day	
N	23	23	31	37
Visit 1	98.5 ± 36.0	117.3 ± 77.7	1748 ± 497	1653 ± 507
Visit 5	94.8 ± 30.7	95.4 ± 60.0	1585 ± 442	1618 ± 427
	Serum sodium level, mmol/L		Serum potassium level, mmol/L	
N	52	63	52	63
Visit 1	141.6 ± 2.8	140.5 ± 2.9	4.16 ± .35	4.22 ± .36[a]
Visit 5	140.8 ± 2.6	138.3 ± 5.3[a]	4.17 ± .34[b]	4.44 ± .49[a,b]

NOTE. Modifications in renal function and serum electrolyte levels during the 12-month study period in the 2 groups are shown. Mean ± SD are shown for visits. N = number of patients. Visit 1 = baseline, visit 5 = end of study at 52 weeks. Serum creatinine, sodium, kalium, and blood urea nitrogen (BUN) remained within normal laboratory values in all patients.

[a] $P < .05$ vs visit 1 (baseline).

[b] $P < .05$ for comparison between treatments.

Table 5. Hemodynamic Changes

	Placebo	Kcanrenoate	Placebo	Kcanrenoate
	Systolic blood pressure, mm/Hg		Heart rate, beats per minute	
N	50	63	53	63
Visit 1	136.1 ± 14.3	133.1 ± 15.0	69.3 ± 10.8	71.4 ± 8.8
Visit 5	134.4 ± 15.9	125.9 ± 15.5[a,b]	68.4 ± 9.4	72.0 ± 8.9
	Diastolic blood pressure, mm/Hg		Renal artery Resistance Index	
N	50	63	41	46
Visit 1	81.1 ± 7.8	80.4 ± 7.4[a]	.64 ± .09	.67 ± .14
Visit 5	80.9 ± 7.6[b]	78.1 ± 7.1[a,b]	.66 ± .08	.66 ± .09

NOTE. Modifications in systemic hemodynamics and interlobular Renal Artery Resistance Index (mean) during the study period in the 2 treatment groups are shown. Mean ± SD shown for visits. N = number of patients. Visit 1 = baseline, visit 5 = end of study at 52 weeks.
[a]$P < .05$ in comparison with visit 1 (baseline).
[b]$P < .05$ for comparison between treatments.

deed, the sonographically observed incidence in the placebo group (10% at 1 year) is consistent with that reported in the literature (nearly 7% of onset of clinical ascites in compensated patients with portal hypertension at 1 year)[35]; this finding strengthens the reliability of our control group.

An ideal prophylactic treatment should be easy to perform, noninvasive, safe, and inexpensive. The family of antialdosteronic drugs share all these characteristics. One side effect is gynecomastia, possibly with mastodynia, and potassium retention. Gynecomastia is, indeed, frequent in cirrhotic patients, who may show hyperestrogenism and hyperprolactinemia, but it is not dangerous. A second dreaded drawback of diuretic treatment is deterioration of renal function and serum electrolytes. The lack of an increase in Doppler renal indices in patients on Kcanrenoate in the present study should be regarded as a favorable finding because these indices have been shown to express renal vascular resistance in experimental models[36] and in the clinical setting,[36,37] and an increase could predict the onset of hepatorenal syndrome.[38] Nonetheless slight increases in serum creatinine and nitrogen levels were observed in patients receiving Kcanrenoate, and further long-term studies are warranted. Moreover, in keeping with the antialdosteronic mechanism, an increase in serum potassium and a decrease in sodium levels were observed in our study group. The extent of the increase was, however, on average, very mild (.22 mmol/L). Only 1 of 66 patients (1.5%) was withdrawn from the study because serum potassium levels exceeded the established threshold value of 5 mmol/L. The value reached was 5.4 mmol/L, which did not require any additional or specific action to be taken. The low rates of these 2 common side effects also could be explained by the strict inclusion criteria used.

The present data confirm the need for strict monitoring of serum creatinine, sodium, and potassium levels in all patients receiving chronic treatment with Kcanrenoate.

The rationale for the use of Kcanrenoate stemmed from experimental evidence showing that antagonists of aldosterone, such as spironolactone and canrenone, reduce portal hypertension in cirrhotic patients.[9–12] Soon after the start of the present study it was shown that Kcanrenoate, when added to nadolol, reduces complications related to portal hypertension.[39] This effect probably is not mediated merely by the diuretic activity of the drugs and, therefore, by hypovolemia. Indeed, both end points studied in the present investigation (ie, onset of ascites and progression of varices) may emerge, at least in part, from a common factor corresponding to renal fluid retention. However, whether the results observed in the present investigation were associated pathophysiologically with a reduction in portal pressure still remains a likely hypothesis, but was beyond the scope of this study. A long-term effect of these antialdosteronic compounds also could depend on their ability to slow the rate of liver fibrogenesis. Spironolactone has been shown to favorably affect cardiac remodeling in patients with heart failure,[40,41] and canrenone was found to reduce the activation of liver stellate cells in vitro.[17]

In the current routine clincial practice, no treatment is recommended to prevent ascites formation and/or the appearance of esophageal varices in cirrhosis and there is no general agreement on the effect of β-blockers in preventing variceal progression.[20] Therefore, in the light of the safety and relatively low cost of antialdosteronics, the present findings, despite Kcanrenoate showing only a trend in the reduction of portal hypertension–related complications, nonetheless may be of relevance and trigger further investigation on the use of this drug in preascitic Child–Pugh A cirrhotic patients. Indeed, the need has emerged not only for new prospective trials testing antialdosteronics alone on a larger number of patients recruited in more and possibly international centers, but also the need to test the combination of β-blockers and antialdosteronics with the aim to further improve the effect of β-blockers[20] on the progression of small varices. Last, but not least, the association of an antialdosteronic drug with antiviral treatment based on pegylated interferons, which was one of the main exclusion criteria limiting the number of patients recruited in this study, could become an attractive potential treatment to be investigated prospectively.

A further point in the rationale for using Kcanrenoate is that intestinal absorption is almost complete and it is converted promptly in the body to canrenone, an active metabolite of spironolactone; it therefore would have a prolonged biological activity of more than 16 hours.

It still remains to be established whether lower doses of Kcanrenoate (eg, 25 or 50 mg/day) would be as effective and possibly associated with an even lower incidence of side effects.

In conclusion, the present study shows that oral administration of 100 mg/day of Kcanrenoate is well tolerated in compensated viral cirrhosis, but does not significantly reduce the individual incidence of ascites and/or the appearance or progression of esophageal varices in pre-ascitic cirrhosis, although it may decrease the 1-year cumulative occurrence of these end-

points. Given the preliminary nature of this study which was terminated early, these data require confirmation and a type II error cannot be excluded.

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