

Use of piretanide, a new loop diuretic, in cirrhosis with ascites*

Relationship between the diuretic response and the plasma aldosterone level

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SUMMARY Twenty patients with cirrhosis and ascites but no renal failure were given piretanide, a new loop diuretic, in order to investigate its efficacy and to relate the diuretic response with the pre-treatment plasma aldosterone concentration. Eleven patients responded to piretanide 12 mg/day (equivalent in potency to 80 mg furosemide); there was no response in nine patients. Both groups were similar with regard to liver function, plasma urea, serum creatinine, plasma electrolytes, urine volume, and urine potassium concentration. The basal urinary sodium excretion was significantly higher in those patients who responded (23.6 ± 5.7 mmol/day vs. 4.3 ± 1.42 mmol/day; $P < 0.01$) ($M \pm SE$). Plasma renin activity (PRA) and plasma aldosterone concentration (PAC) were normal or only slightly increased in patients who responded to piretanide (PRA = 1.22 ± 0.20 ng/ml/h; PAC = 12.25 ± 2.20 ng/100 ml) and very high in patients who did not respond (PRA = 8.71 ± 1.18 ng/ml/h; PAC = 84.6 ± 16.2 ng/100 ml) ($P < 0.001$). Patients unresponsive to piretanide 12 mg/day also failed to respond when the dose was increased to 24 mg/day. However, the addition of spironolactone, 150 mg/day, to piretanide was followed in these patients by a marked increase in diuresis and natriuresis. These results strongly suggest that the pre-treatment level of aldosterone is an important factor influencing the response to loop diuretics in patients with non-azotaemic cirrhosis and ascites.

Although a variety of treatments have been suggested for ascites, the use of diuretics to inhibit sodium retention remains the most usual form of treatment. Two basic types of diuretics are used in these patients—those which act on the distal part of the nephron (spironolactone, triamterene, and amiloride) and those which inhibit chloride reabsorption in the thick ascending limb of the loop of Henle (furosemide, ethacrynic acid, and bumetanide). It is well known that the diuretics acting on the distal nephron are effective in most patients with cirrhosis and ascites in the absence of renal failure.¹⁻⁶ However, only rare reports are concerned with the efficacy of the modern loop diuretics in such patients,⁷ as in most studies these drugs are given in association with distal diuretics.⁸⁻¹⁰ Nevertheless, it is a general clinical impression that a certain number of patients with cirrhosis and ascites, without renal impairment, fail

to respond to the loop diuretics when they are given alone. In such patients the simultaneous administration of a distal diuretic causes a marked increase in urinary flow and sodium excretion, suggesting that the previous failure of treatment may be associated with the hyperaldosteronism present in these patients.

The present investigation was made to study the efficacy of a loop diuretic in patients with cirrhosis and ascites without renal failure, and to assess the relationship between the degree of activation of the renin-angiotensin-aldosterone system and the effectiveness of this type of diuretic. For this purpose we used a new diuretic, piretanide, which acts on the loop of Henle.¹¹ Previous studies in animals and in man have shown an oral dose of 6 mg piretanide to be equal in potency to 40 mg of furosemide.¹¹⁻¹³

Methods

The investigation was carried out in 20 patients with hepatic cirrhosis and ascites but without renal failure

*Supported in part by grants (12 268/76 and 12 269/76) from the Instituto Nacional de Previsión.

Received for publication 19 February 1980

Table 1 Clinical and biochemical data of 20 patients studied

Case no.	Sex	Age (yr)	Aetiology of cirrhosis	Ascites	Previous ascites episodes (no.)	Time elapsed since first episode of ascites (months)	Diuretic medication before admission (mg/day)	Total bilirubin* (μmol/l)	Plasma albumin* (g/l)	Prothrombin time (s. prolonged)
Patients who responded to piretanide										
1	M	40	Alcoholic	Moderate	0	1	Furosemide 40	92	22.2	1.6
2	M	53	Alcoholic	Severe	1	6	None	11	35.1	0.5
3	M	51	Alcoholic	Mild	1	18	Bumetanide 1	39	28.0	3.3
4	F	54	Alcoholic	Severe	0	1	None	328	38.9	5.0*
5	M	70	Idiopathic	Severe	0	1	Furosemide 40 + Spironolactone 50	28	31.6	1.0
6	F	40	Alcoholic	Severe	0	1	None	88	35.9	2.8
7	M	63	Idiopathic	Severe	0	2	None	35	31.2	1.0
8	F	62	Idiopathic	Mild	1	14	Furosemide 80	70	25.8	2.6
9	M	43	Alcoholic	Mild	0	1	None	7	31.2	1.0
10	M	49	Alcoholic	Mild	0	2	None	35	23.8	2.0
11	M	55	Alcoholic	Mild	3	24	Furosemide 80	10	24.9	1.2
Patients who did not respond to piretanide										
12	M	47	Alcoholic	Mild	0	1	None	95	24.1	3.1
13	M	49	Alcoholic	Severe	0	2	Furosemide 80	43	32.4	1.0
14	F	40	Alcoholic	Moderate	0	4	None	151	31.6	2.4
15	F	62	Idiopathic	Severe	4	44	Furosemide 80	105	23.9	2.3
16	M	71	Idiopathic	Mild	3	48	Furosemide 80 + Spironolactone 100	30	30.7	1.0
17	F	50	Alcoholic	Severe	1	4	Furosemide 40 + Spironolactone 100	283	25.5	4.5
18	M	48	Idiopathic	Moderate	1	7	None	74	24.5	2.0
19	F	32	Alcoholic	Mild	2	12	Bumetanide 1	47	31.5	0.7
20	F	49	Alcoholic	Severe	0	1	None	154	30.4	7.6

*Normal values for serum bilirubin 5–20 μmol/l, and for plasma albumin 35–53 g/l.

(plasma urea <7 mmol/l, serum creatinine <120 μmol/l). The diagnosis of cirrhosis was based on clinical features and biochemical investigations and in 17 patients it was confirmed by histology. In Table 1 clinical and laboratory data of the patients are presented. There was no evidence of cardiovascular or renal disease in any of the patients, nor had any patient suffered gastrointestinal haemorrhage or hepatic encephalopathy during the three months preceding the investigation. All patients gave informed consent to taking part in the investigation.

The patients were given a diet containing less than 50 mmol sodium daily and no diuretics for one week. Water intake was not restricted. On the eighth day, while the patients were fasting and after they had been lying down for at least two hours, blood samples were taken for measurement of the plasma renin activity (PRA) and the plasma aldosterone concentration (PAC). The samples were collected under ice in potassium EDTA tubes, they were centrifuged at 4°C and the plasma was frozen down to -30°C until assayed. Directly after this, treatment with piretanide was started. The starting dose was 12 mg (two tablets of 6 mg) daily in a single dose. If after five days there was no definite response, the amount was increased to 24 mg daily in two doses of 12 mg separated by an eight hour interval. Those patients who did not respond to this treatment after

five days were also given spironolactone 150 mg daily. For the purpose of this investigation a patient was considered to have responded to treatment if his body weight fell by more than 200 g each day after the drug was started.

The patients' urine volume and body weight were measured daily throughout the investigation. The plasma urea, serum creatinine and plasma, and urine sodium and potassium were measured using conventional laboratory techniques every two days. Liver function was assessed by measuring the total plasma bilirubin, the plasma albumin concentration, and the prothrombin time.

PRA and PAC were measured by radioimmunoassay using methods previously described.¹⁴ Normal values for PRA and PAC in our laboratory for subjects at rest on a diet containing less than 50 mmol sodium per day are 1.13±0.18 ng/ml/h and 10.5±1.18 ng/100 ml (M±SE) respectively.

The results given for urine volume and urine sodium and potassium excretion are the means of the various measurements performed during each part of the investigation. The results given for plasma potassium and for body weight are those found on the last day of each part of the investigation.

Statistical analysis of the results was carried out on a CompuCorp 445 Statistician using Student's *t* test for dependent and independent variables. Results are presented as mean±SE.

Results

EFFECTIVENESS OF TREATMENT WITH PIRETANIDE

Eleven patients out of the 20 responded to treatment with 12 mg piretanide/day (cases 1 to 11) and nine patients showed no response. The daily weight loss in the patients who responded was 655 ± 115 g/day, ranging between 250 g/day and 1457 g/day. In the patients who did not respond the weight loss was only 14 ± 54 g/day, ranging between a loss of 180 g/day and a gain of 300 g/day. In those patients who responded, the urinary sodium excretion rose from 23.6 ± 5.7 mmol/day to 103.2 ± 13.6 mmol/day and the urine volume from 622.2 ± 23.6 ml/day to 1705 ± 104 ml/day. In those patients who did not respond the urinary sodium excretion rose only from 4.3 ± 1.4 mmol/day to 22.2 ± 4.9 mmol/day and the urine volume from 683.3 ± 72.1 ml/day to 1033 ± 102 ml/day.

The dose was increased to 24 mg daily in eight of the nine patients who did not respond to 12 mg piretanide/day. This was not done for one patient (case 12) because he developed hepatic encephalopathy. None of the eight patients responded to this increase in the dose of piretanide. Their body weights remained virtually unchanged (65.1 ± 6.1 kg before and 64.8 ± 6.1 after therapy with 24 mg piretanide/day), the urinary sodium excretion rose only from 20.5 ± 5.2 mmol/day to 29.8 ± 4.6 mmol/day, and the urine volume from 1012 ± 101 ml/day to 1143 ± 111 ml/day.

EFFECTIVENESS OF COMBINATION OF PIRETANIDE (24 MG/DAY) AND SPIRONOLACTONE (150 MG/DAY)

One hundred and fifty milligrams of spironolactone/day was added to the regime of seven of the eight patients who did not respond to 24 mg piretanide/day. This was not done for one patient (case 13) because he developed a gastrointestinal haemorrhage. All the patients responded to the combination of piretanide and spironolactone. The urinary excretion of sodium increased from 31.0 ± 5.1 mmol/day to 100.8 ± 14.1 mmol/day and the urine volume from 1152 ± 120 ml/day to 1971 ± 205 ml/day. Weight loss on this regime was 500 ± 32.7 g/day, ranging between 369 g/day and 575 g/day.

OVERALL EFFECTIVENESS OF TREATMENT USED IN THIS INVESTIGATION

With the treatment used in this investigation ascites disappeared in 18 of the 20 patients. Ascites was successfully treated in 11 patients with 12 mg piretanide/day, but seven patients needed 24 mg piretanide/day together with 150 mg spironolactone/

day to achieve this result. The duration of the treatment was 12.6 ± 1.55 days in the first group of patients and 22.1 ± 1.05 days in the second. The diuretic treatment was interrupted in two patients because they developed a gastrointestinal haemorrhage and hepatic encephalopathy respectively.

EFFECT OF PIRETANIDE ON POTASSIUM METABOLISM

Administration of 12 mg piretanide/day caused a fall in the plasma potassium levels in 19 of the 20 patients treated. The baseline plasma potassium level was 4.22 ± 0.11 mmol/l and it fell to 3.31 ± 0.14 mmol/l ($P < 0.001$). It fell regardless of whether the patients responded to the diuretic or not. In those patients who responded it fell from 4.18 ± 0.08 mmol/l to 3.16 ± 0.13 mmol/l ($P < 0.001$). The period of treatment lasted 12.6 ± 1.55 days and two patients needed potassium supplements during the last days of treatment. There was a smaller fall from 4.27 ± 0.23 mmol/l to 3.50 ± 0.27 mmol/l ($P < 0.01$) in the patients who did not respond, but the period of treatment was shorter (five days).

Administration of 24 mg piretanide/day to eight of the nine patients not responding to 12 mg daily did not result in further decrease of their plasma potassium levels (3.53 ± 0.30 mmol/l before and 3.35 ± 0.31 mmol/l after therapy with 24 mg piretanide/day). However, three of the patients were given 60 mmol of potassium daily by mouth from the start of treatment.

Administration of the combination of 150 mg spironolactone/day and 24 mg piretanide/day to seven of the eight patients not responding to 24 mg piretanide/day caused the plasma potassium to rise in all the patients from 3.25 ± 0.25 mmol/l to 4.52 ± 0.12 mmol/l ($P < 0.001$). None of the patients received potassium supplements during this part of the study which lasted 11.1 ± 1.05 days.

Administration of 12 mg piretanide/day brought about a significant rise in urinary potassium excretion from the baseline of 27.2 ± 3.8 mmol/day to 55.2 ± 4.8 mmol/day. Excretion of potassium in urine increased in all the patients whether they responded to the diuretic or not. In those patients who did respond, the urinary excretion increased from 23.2 ± 3.7 to 60.9 ± 6.6 mmol/day ($P < 0.01$) but there was a smaller increase from 32.7 ± 7.0 to 49.5 ± 6.7 mmol/day ($P < 0.05$) in the patients who did not respond. Increasing the dose to 24 mg daily did not significantly increase the urinary potassium excretion in those patients who did not respond to 12 mg daily (46.9 ± 7.0 mmol/day before and 56.1 ± 10.1 mmol/day after therapy with 24 mg piretanide/day). Administration of spironolactone in addition to 24 mg piretanide/day did not cause a significant

fall in urinary potassium excretion (urinary potassium excretion was 53.7 ± 11.4 mmol/day with 24 mg/piretanide/day and 51.1 ± 8.2 mmol/day when 150 mg spironolactone/day was added to piretanide).

FACTORS INFLUENCING DIURETIC RESPONSE TO PIRETANIDE (Tables 1 and 2)

There were no significant differences in clinical data and in liver function between patients who responded to piretanide and those who did not. Both groups also had similar plasma urea and serum creatinine levels, which suggests that they had a similar glomerular filtration rate. The plasma sodium and potassium levels, the urine volume, and the urinary potassium concentration were also the same in both groups. The basal urinary sodium excretion was significantly higher ($P < 0.01$) in those patients who responded to treatment with piretanide than in those who did not respond.

There was a marked difference in PRA and PAC between the two groups (Figure). In the patients who responded to piretanide the PRA and PAC levels were normal or slightly increased. On the other hand, plasma renin and aldosterone levels were very high in the patients who did not respond.

Discussion

The present study shows that the plasma aldosterone level is an important factor influencing the response to loop diuretics of patients with cirrhosis and ascites. Eleven of the 20 patients in this investigation responded to administration of piretanide. In nine patients the diuretic brought about only a slight increase of urinary sodium excretion. The clinical data and the hepatic and renal function were similar in both groups but there were marked differences in the degree of activation of the renin-angiotensin-aldosterone system. The pre-treatment plasma renin activity and plasma aldosterone levels were normal or only slightly raised in the patients who responded to the diuretic, but they were markedly increased in

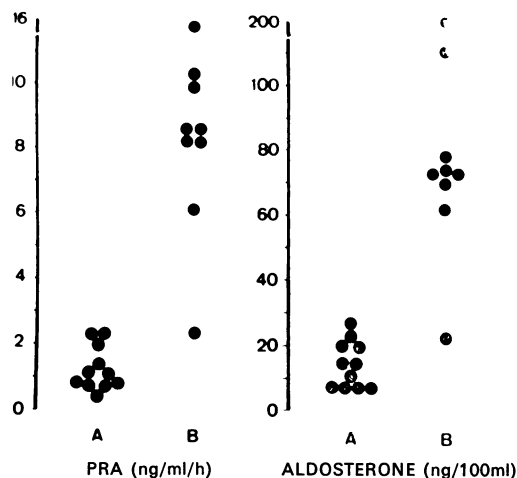


Figure Plasma renin activity (PRA) and plasma aldosterone concentration in patients who showed (A) and who did not show (B) a diuretic response to piretanide.

all but one of the patients who failed to respond. The different baseline urinary sodium excretion shown by the two groups was possibly related to the different degrees of hyperaldosteronism.

Past experience has shown that more than 80% of patients with non-azotaemic cirrhosis with ascites respond to the administration of diuretics acting on the distal tubule.¹⁻⁶ In the present study the percentage of patients with a positive response to piretanide was lower, suggesting that distal diuretics should be preferred to loop diuretics in the initial treatment of these patients. This is also supported by the effect of loop diuretics on potassium metabolism. In our patients, piretanide caused the plasma potassium to fall in all but one patient. This hypokalaemia was associated with increased urinary loss of potassium. Hypokalaemia is a well-recognised complication in patients suffering from cirrhosis and ascites treated with diuretics which act on the ascending limb of the loop of Henle.^{8, 10} It has been suggested

Table 2 Renal and liver function, PRA, and plasma aldosterone in patients who did and did not respond to piretanide

	Plasma urea (mmol/l)	Serum creatinine (μ mol/l)	Urine volume (ml/day)	Urinary sodium excretion (mmol/day)	Urinary potassium excretion (mmol/day)	Plasma sodium (mmol/l)	Plasma potassium (mmol/l)	Total bilirubin (μ mol/l)	Prothrombin time (s. prolonged)	Plasma albumin (g/l)	PRA (ng/ml/h)	Aldosterone (ng/100 ml)
Patients with positive response												
Mean	4.09	79.20	622.2	23.6	23.2	137.3	4.18	70.4	2.00	29.9	1.22	12.25
\pm SE	0.43	6.16	23.6	5.7	3.7	0.5	0.08	30.3	0.40	1.6	0.20	2.20
Patients with negative response												
Mean	4.34	87.00	683.3	4.3	32.7	135.4	4.27	109.1	2.73	28.3	8.71	84.60
\pm SE	0.54	9.66	72.1	1.4	7.0	1.5	0.23	26.3	0.72	1.2	1.18	16.27
	NS*	NS	NS	$P < 0.01$	NS	NS	NS	NS	NS	NS	$P < 0.001$	$P < 0.001$

*NS = Not significant.

that this is attributable to increased uptake of sodium in the distal tubules after inhibition of reabsorption of this ion in the more proximal parts of the nephron.¹⁵ Reabsorption of sodium in the distal tubules would increase potassium excretion and its elimination in urine. In this investigation urinary excretion of potassium increased regardless of whether or not the patients responded to piretanide, which suggests that this diuretic acted in both groups of patients by inhibiting sodium reabsorption in the ascending limb of the loop of Henle. However, in those patients who have marked hyperaldosteronism, piretanide was unable to bring about a significant increase in sodium excretion, probably because most of the sodium which was not reabsorbed in the loop of Henle was subsequently taken up along the distal tubules. In those patients who had normal or only slightly raised plasma aldosterone levels, reabsorption of sodium in the distal tubules was probably not as great, and piretanide was able to increase urinary sodium excretion.

The combination of spironolactone with piretanide in those patients who did not respond to piretanide alone brought about an increase in urine flow and in urinary sodium excretion. These results strongly support the contention that hyperaldosteronism is a very important factor influencing the response to loop diuretics in patients with cirrhosis of the liver. When these patients were given spironolactone the plasma potassium returned to normal. This increase in potassium is difficult to explain, as the administration of spironolactone did not significantly lower the urinary excretion of potassium. This finding has been demonstrated in other investigations when patients with cirrhosis were treated with diuretics acting on the distal tubule. The use of spironolactone, triamterene, or amiloride alone raises the plasma potassium without lowering its excretion in urine.¹⁶⁻¹⁸

In the conclusion, the results of the present study indicate that loop diuretics should not be used as the initial therapy in non-azotaemic cirrhotics with ascites, as these drugs fail to increase the urinary sodium excretion in patients with hyperaldosteronism, but increase the urinary potassium excretion and may lead to hypokalaemia. A rational form of therapy in these patients is to start with a distal diuretic and add a loop diuretic if the natriuretic response is inadequate.

We wish to express our thanks to Drs. A. Valdés, A. Parés, R. Planas and M. Bruguera and to Mrs. E. Calvo for their participation in the study. Piretanide was supplied by Hoechst AG. The manuscript was prepared by Miss V. Llagostera.

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Gut 1980 21: 855-859

doi: 10.1136/gut.21.10.855

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