Br. J. clin. Pharmac. (1988), **26**, 143–154

Acute and long-term renal and metabolic effects of piretanide in congestive cardiac failure

W. R. McNABB*, F. H. NOORMOHAMED & A. F. LANT
Department of Clinical Pharmacology and Therapeutics, Charing Cross and Westminster Medical School at Westminster Hospital, London SW1P 2AP and St Stephen's Hospital, London SW10 9TH

1 The renal and metabolic effects of the sulphamoylbenzoic acid diuretic, piretanide, have been studied, under controlled dietary conditions, in 39 patients with congestive cardiac failure.

2 In acute studies, peak saluresis occurred within 4 h of oral piretanide administration; saluresis was complete within 6 h, after which a significant antidiuretic effect was observed. Addition of triamterene, 50 mg, blunted the 0–6 h kaliuretic effect of piretanide. Over 24 h, piretanide, alone, caused insignificant urinary losses of potassium when compared with control.

3 In comparative studies, the piretanide dose-response curve was found to be parallel to that of frusemide over the dose range studied. The 0–6 h saluretic responses of piretanide, 6, 12 and 18 mg, were found to be equivalent to frusemide, 40, 80 and 120 mg respectively. The collective mean ratios of all the saluretic responses to each dose of piretanide with the corresponding dose of frusemide was observed to be 0.99 ± 0.12, over 0–6 h period, and 0.86 ± 0.09 over the 24 h period. The relative potency of piretanide, when compared with frusemide was found to be 6.18 (95% confidence limits 4.87 – 8.33), over the 0–6 h period, and 4.73 (95% confidence limits 3.65 – 6.14), over 24 h period.

4 In 15 patients in severe cardiac failure, urinary recovery of piretanide, over first 6 h, at the start of treatment was 21.2 ± 2.1% while efficiency of the diuretic (mmol Na/mg drug) was 47.3 ± 4.1. Long-term piretanide therapy was continued in the same group for up to and in some cases over 3 years. No other diuretics or potassium supplements were given. Piretanide dosage ranged from 6 to 24 mg day^{-1} according to clinical need. Plasma potassium fell significantly at 12 and 24 months, though remaining within the normal range. At these same times, significant elevations in both plasma urate and total fasting cholesterol were observed. Two patients developed overt gout on high dose piretanide therapy (24 mg day^{-1}). Piretanide was well tolerated, and effective in the management of congestive cardiac failure without any other recognized metabolic or electrolyte changes.

Keywords diuretics piretanide frusemide triamterene cardiac failure

Introduction

Piretanide is a sulphamoylbenzoate diuretic with a chemical structure similar to that of bumetanide and frusemide (Figure 1), and with a weight for weight potency lying intermediate between bumetanide and frusemide (Lawrence *et al.*, 1978; Roberts *et al.*, 1978). In healthy volunteers, all three agents have been shown to have their primary renal site of action in the thick ascending

*Present address: Department of Geriatric Medicine, Guy's Hospital, St Thomas Street, London SE1 9PT
Correspondence: Professor A. F. Lant, Department of Clinical Pharmacology and Therapeutics, Westminster Hospital, Page Street, London SW1P 2AP

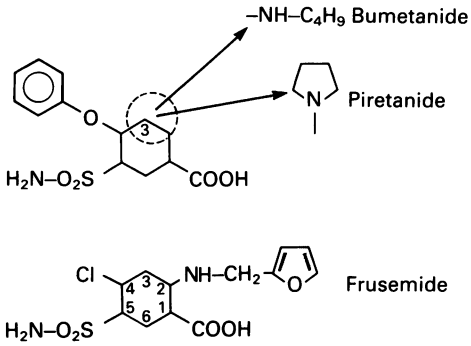

Figure 1 Comparison of structural formulae of sulphamoylbenzoate diuretics showing the 2:4 substituted side chains of frusemide and the 3:4 substituted side chains of bumetanide and piretanide.

loop of Henle (TAL), with piretanide showing additional inhibitory effects on the proximal tubular reabsorption of phosphate and urate (McNabb *et al.*, 1984a). As with other sulphamoylbenzoates, piretanide has been found to be effective in the management of congestive cardiac failure (CCF) (Sherman *et al.*, 1986); in addition, its vasodilatory activity (Brown *et al.*, 1984; Klaus *et al.*, 1984) has led to its application in the management of hypertension (Verho *et al.*, 1984). With the widespread clinical use of diuretics, on their own or in combination with other agents, attention has been focused on the possible long-term metabolic complications of therapy (Lant, 1985). Debate has largely centred on diuretic-induced hypokalaemia and hypomagnesaemia (Harrington *et al.*, 1982; Kaplan, 1983) though carbohydrate intolerance, hyperuricaemia and diuretic-induced lipid disturbances have also attracted attention (Ames & Hill, 1976; Greenberg *et al.*, 1983; Lasser *et al.*, 1984). Most of the metabolic changes described have been features of chronic benzothiadiazine therapy, and the extent to which these changes occur with 'loop' diuretics is far less clear (Losse *et al.*, 1983). The present study was carried out with the objectives of assessing, first, the relative potency of piretanide compared to frusemide in a group of patients with moderate CCF; second, in a similar group of subjects the effect of piretanide, alone and in combination with the potassium sparing diuretic, triamterene were compared; and third, the acute and long-term efficacy of piretanide alone was assessed in patients with severe CCF.

Methods

A total of 39 patients with CCF were divided into two groups according to the degree of heart failure, group A with mild to moderate CCF, and group B with more advanced CCF. All patients gave informed consent to be included in the study and protocols were approved by the Westminster Hospital Ethics Committee. The first group of patients with mild CCF took part in single dose comparative studies, whilst the group with advanced CCF received continuous piretanide therapy for 1 week as inpatients, followed by prolonged treatment for up to, and in some cases, over 3 years as out-patients.

Single dose comparative studies - Group A

1) Piretanide (P) vs *frusemide (F)* Thirteen patients were included in this group with grade II CCF, according to the New York Heart Association (NYHA) classification. There were nine males and four females with a mean age of 72 ± 3 years (range 66–92). Mean creatinine clearance was 63 ± 7 ml min^{-1} (range 25–88). Seven patients had ischaemic heart disease, three had congestive cardiomyopathy and three with essential hypertension. All patients were admitted as in-patients and were stabilized on a no-added salt diet, 150 mmol day^{-1} NaCl, for a minimum of 1 week prior to inclusion into the study. Eight of the thirteen subjects were exposed to either piretanide, 6 mg/frusemide, 40 mg; four subjects to piretanide, 12 mg/frusemide, 80 mg, and five were exposed to piretanide, 18 mg/frusemide 120 mg. All doses were administered orally at 08.00 h and in a random fashion, with an interval of 2–3 days, free of any diuretic, between exposures. Urine was collected between 08.00 and 14.00 h, and between 14.00 and 08.00 h on all five days. Blood samples for plasma creatinine and electrolytes were taken each day at 08.00 h. Concurrent drug therapy remained unchanged throughout the study period and the only other drugs given consisted of digoxin (patients CR and DF), glibenclamide (patient LP) and isosorbide dinitrate (patients, SA and DF).

2) Piretanide (P) vs *piretanide plus triamterene (P + T)* Eleven patients were included in this group with grade I or II CCF (NYHA). There were seven females and four males, with a mean age of 60 ± 2 years (range 48–66). Mean creatinine clearance was 81 ± 5 ml min^{-1} (range 59–114). Nine out of eleven patients had ischaemic heart disease and two had congestive cardiomyopathy. Patients, whose diuretic therapy was discontinued, were stabilized on a metabolically controlled diet containing 150 mmol Na and 70 mmol K per day for a minimum of 3 days. Drug therapy, which was randomized, consisted of piretanide, 6 mg, alone and piretanide, 6 mg,

plus triamterene, 50 mg. All drugs were administered at 08.00 h. Urine was collected from 08.00 to 14.00 h, and from 14.00 to 08.00 h, on all control and treatment days. Blood samples were taken at 08.00, 12.00 and 16.00 h each day.

Continuous piretanide therapy – Open study – Group B

1) Short term in-patient assessment This group of 14 patients had severe CCF, nine grade III, and five grade IV (NYHA). There were 10 males and four females, with a mean age of 69 ± 3 years (range 42–78). Mean creatinine clearance was 59 ± 7 ml min^{-1} (range 20–104). Twelve patients had ischaemic heart disease, whilst two had congestive cardiomyopathy. The patients were hospitalized for a minimum of 10 days, including an initial 3 day period without any diuretic therapy. During this time, they were stabilized on a no-added salt ward diet of approximately 150 mmol Na day^{-1}. All urine passed was collected for the first week of treatment. On the control days, (3 days immediately prior to the first dose of piretanide) and days 1 and 7 of piretanide therapy, urine was collected in 0–2, 2–4, 4–6, 6–8, 8–12 and 12–24 h fractions, with 24 h collections on the intervening days 2–6 of therapy. Piretanide was continued at 6 mg daily thereafter in all but two patients. In these two patients (CS and WH), piretanide dosage was increased to 12 mg daily, on day 2 and 3 of treatment respectively, because of clinical evidence of continuing severe heart failure. All piretanide doses were given orally at 08.00 h. Concurrent therapy was not altered during the study period. The other drugs given consisted of digoxin (AE, CE, AW, LS and WH), hydralazine (AE, CS and PN), isosorbide trinitrate (AE, CE, IH, WB, PN, LS and KH), nifedipine (CE), prazosin (WH) and warfarin (CE and CS).

2) Long-term out-patient assessment – Group B Fifteen patients, with grade III or IV CCF, were followed as out-patients by the same clinician for up to, and in some cases over 3 years, with 2-monthly clinical assessment and biochemical screening. These patients included all fourteen from part (1) above, together with another patient (AD) in grade IV CCF. This patient developed severe left ventricular failure, and initially received 12 mg piretanide daily. He was therefore excluded from the short-term study in which all patients had received 6 mg piretanide daily. During the long-term study, piretanide was given in doses up to 24 mg daily, according to clinical need, and without potassium supplements or other diuretics. Patients were counselled by the same dietician and were advised to remain on a no-added salt diet throughout the follow-up period. Details of the patients are given in Table 1.

Statistical analyses

All results are expressed as mean ± s.e. of mean or mean with 95% confidence limits. The piretanide/frusemide dose-response curves were tested for linearity and parallelism by applying analysis of variance to linear regression. Appropriate use was also made of paired *t*-tests, unpaired *t*-tests and Friedman two-way analysis of variance in conjunction with Wilcoxon signed rank test. Results were considered significant at $P < 0.05$.

Analaytical methods

Urinary electrolytes were measured by atomic absorption spectrophotometry (Perkin-Elmer 603), chloride by a titratometric method (Buchler), and uric acid by a uricase method (Boehringer). Plasma and urine osmolalities were measured cryoscopically (Advanced Instruments). Urinary inorganic phosphates were measured by the method of Fiske & Subbarow, (1925), and creatinine by the alkaline picrate method (Bonsnes & Taussky, 1945). Urinary levels of piretanide were estimated only on the first day of treatment using a method published previously (Dixey *et al.*, 1987). Plasma electrolytes, creatinine and uric acid and blood glucose were measured by standard autoanalyser techniques (Technicon SMA2).

Results

Single dose comparative studies – Group A

1) Piretanide (P) vs frusemide (F) Both drugs, piretanide and frusemide, produced parallel dose-response curves (Figure 2). Over 0–6 h, the urinary excretion of sodium following piretanide, 6 mg, and frusemide, 40 mg, were of equal magnitude. Similarly sodium losses following the other two doses of piretanide, 12 and 18 mg, matched those elicited by frusemide, 80 and 120 mg, respectively. The overall ratio of the saluretic response of all doses of piretanide to all doses of frusemide, over 0–6 h assay was close to unity (0.99 ± 0.12; $n = 17$). Over 0–24 h, the saluretic response ratio was (P/F): 0.72 ± 0.09, (6/40, $n = 8$); 0.93 ± 0.04 (12/80, $n = 4$); 1.00 ± 0.25 (18/120, $n = 5$), with the resulting overall mean of 0.86 ± 0.09 ($n = 17$). The relative potency of piretanide when compared with frusemide, on a weight to weight basis, was found to be 6.18 ±

Table 1 Clinical details of 15 patients with severe congestive cardiac failure on long-term piretanide therapy. The period of study ranged from 1 week to over 3 years (186 weeks). * IHD = Ischaemic heart disease; ** BP = Hypertension; *** AF = Atrial fibrillation.

Subject	*Age (years)*	*Sex*	*Creatinine clearance (ml min^{-1})*	*Weight (kg)*	*Diagnosis*	*Maximal daily piretanide dosage (mg)*	*Weeks on therapy*	*Comments*
AE	70	M	100	93	IHD* BP**	24	52	Withdrawn – poor compliance
CE	69	M	64	93	IHD AF*** BP	12	160	
VR	75	F	38	54	IHD Hypothyroid	12	186	
IH	75	F	20	63	IHD BP diabetes mellitus	18	91	Died – myocardial infarction
WB	69	M	44	79	IHD	18	147	
CS	68	M	104	91	IHD BP	24	17	Died - myocardial infarction
AC	42	M	99	93	Myocardial infarction	6	17	Withdrawn – no need to continue diuretic
AD	59	M	68	69	IHD	24	143	
HB	78	M	42	66	IHD AF Mitral regurgitation	18	43	Died – cerebro-vascular accident
PN	63	M	68	91	IHD	24	164	Gout × 2
AW	72	M	70	50	AF Congestive cardiomyopathy	6	152	
LS	61	F	50	78	BP AF Congestive cardiomyopathy	24	160	Gout
IS	71	F	59	70	BP Myocardial infarction	6	2	Withdrawn – unwilling to continue as an outpatient
WH	78	M	54	70	IHD BP AF	12	22	Withdrawn – admitted to another hospital for hip operation
HK	77	M	69	85	IHD	6	1	Died – myocardial infarction

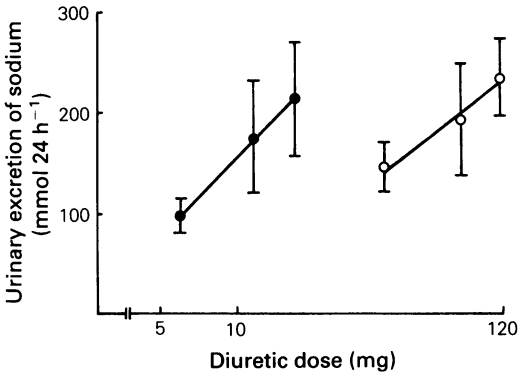

Figure 2 Comparison of saluretic responses, over a period of 24 h, of three doses of piretanide, 6, 12 and 18 mg (•), with those of frusemide, 40, 80 and 120 mg (○), in a group of patients with mild to moderate congestive cardiac failure.

0.80, over the 0–6 h period. Over the entire 24 h period the relative potency was calculated to be 4.73 ± 0.60.

2) Piretanide (P) vs piretanide plus triamterene (P + T) 0–6 h Urinary volume and excretion of sodium and chloride increased by two-fold or more in the first 6 h after treatment (Table 2). The addition of triamterene did not significantly increase the natriuretic effect of piretanide alone [$U_{Na}V$ (mmol) = 91.3 ± 13.6 (P) *vs* 100.9 ± 16.5 (P + T)]. The kaliuretic response after piretanide was blunted by the addition of triamterene (Table 2). Significantly, calciuria was observed only after piretanide plus triamterene when compared with control day (3.8 ± 0.7 *vs* 1.9 ± 0.4 mmol 6 h^{-1}; $P < 0.01$). Magnesuria was seen with both piretanide (2.4 ± 0.5 *vs* 1.1 ± 0.2 mmol 6 h^{-1}; $P < 0.01$) and piretanide plus triamterene (2.4 ± 0.5 *vs* 1.1 ± 0.3 mmol 6 h^{-1}; $P < 0.01$) respectively compared with control. No changes in urate or phosphate excretions occurred in this period. Beyond the first 6 h after piretanide, falls in both sodium and chloride excretion were observed, though these reductions did not attain significance (Table 2).

0–24 h When the responses over 24 h were compared, significant saluresis was seen with both treatments. Changes in chloride excretion paralleled those of sodium. With respect to other cations, phosphate and urate, no significant changes were noted.

Continuous therapy open study – Group B

1) Short term in-patient assessment (Days 1 and 7) 0–6 h The urinary excretion profiles (Figures 3

Table 2 Urinary response to single dose of piretanide (6 mg) (P) and piretanide (6 mg) plus triamterene (50 mg) (P + T) in eleven patients with mild to moderate congestive cardiac failure treated under metabolically controlled conditions. C = Control; D = Treatment

Urinary excretion (mmol/period)	*Time (h)* *Treatment*	*0–6* *C*	*0–6* *D*	*6–24* *C*	*6–24* *D*	*0–24* *C*	*0–24* *D*
Volume (ml/period)	P	570 ± 100	1277 ± 198**	1058 ± 120	1091 ± 120	1628 ± 134	2368 ± 306*
	P + T	564 ± 122	1193 ± 173*	1185 ± 122	978 ± 102	1750 ± 150	2171 ± 190
Sodium	P	30.1 ± 4.9	91.3 ± 13.6***	87.5 ± 17.0	65.9 ± 11.5	117.6 ± 15.8	157.2 ± 16.1*
	P + T	38.7 ± 10.5	100.9 ± 16.5*	92.0 ± 21.1	77.6 ± 10.4	130.7 ± 23.4	178.5 ± 18.0**
Potassium	P	18.8 ± 3.4	29.4 ± 4.9*	35.6 ± 4.6	32.4 ± 2.6	54.4 ± 3.9	61.8 ± 5.4
	P + T	16.9 ± 2.7	20.6 ± 3.1	34.9 ± 4.0	26.6 ± 4.3	51.8 ± 5.2	47.2 ± 5.2
Chloride	P	45.1 ± 10.2	115.2 ± 27.1*	97.0 ± 15.9	76.6 ± 13.3	143.8 ± 18.7	187.3 ± 36.5
	P + T	46.9 ± 10.5	148.4 ± 29.7**	115.2 ± 23.1	86.5 ± 15.9	164.6 ± 28.9	234.9 ± 37.1*

* $P < 0.05$; ** $P < 0.01$; *** $P < 0.001$

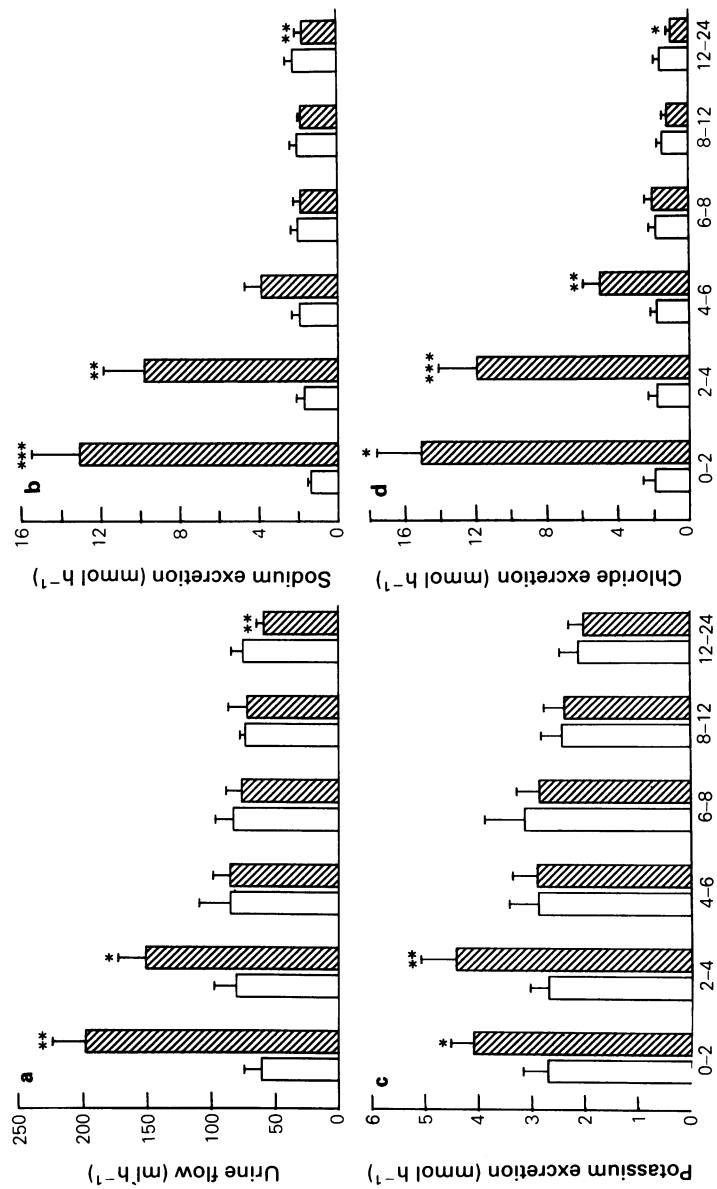

Figure 3 Mean urinary excretions of water (a), sodium (b), potassium (c) and chloride (d), followed sequentially for the 24 h, on control day (□), and after a single oral dose of piretanide (6 mg; ▨), in 14 patients with severe congestive cardiac failure. $*P < 0.05$; $**P < 0.01$; $***P < 0.001$.

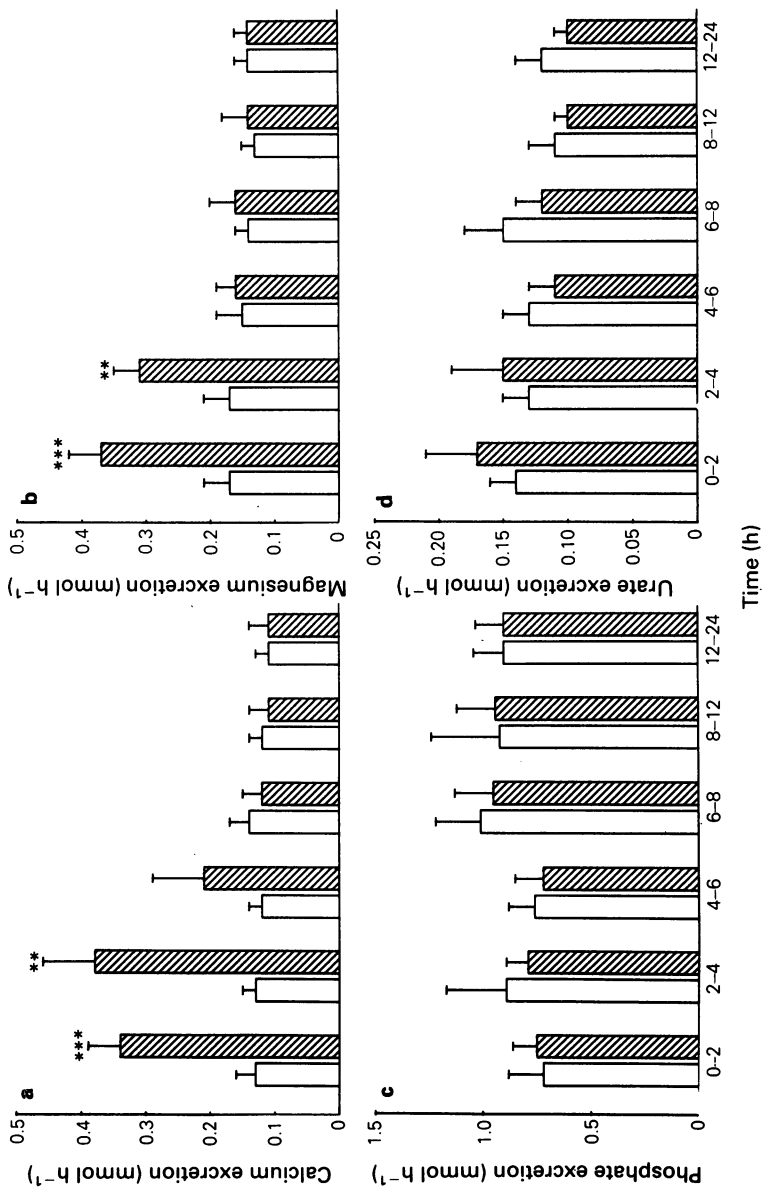

Figure 4 Mean urinary excretions of calcium (a), magnesium (b), phosphate (c) and urate (d), followed sequentially for the 24 h on control day (□) and after a single oral dose of piretanide (6 mg; ▨), in 14 patients with severe congestive cardiac failure. $*P < 0.05$; $**P < 0.01$; $***P < 0.001$.

and 4) demonstrates that the diuretic and saluretic effect of piretanide were complete within 6 h. Over 0–6 h, Na and Cl losses were four-fold over control, increasing from 11.7 ± 3.6 to 52.8 ± 7.5 mmol ($P < 0.001$), and from 11.3 ± 3.0 to 65.4 ± 8.9 mmol ($P < 0.001$), respectively. Potassium excretion increased significantly in the first 6 h from 16.8 ± 2.3 to 22.6 ± 2.6 mmol ($P < 0.01$), whilst urinary calcium and magnesium excretion doubled in the first 6 h, from 0.7 ± 0.1 to 1.6 ± 0.2 mmol ($P < 0.01$), and from 1.0 ± 0.2 to 1.8 ± 0.2 mmol ($P < 0.01$), respectively. During the same period urinary phosphate excretion was less than during the equivalent control period [5.1 ± 0.9 (control) *vs* 3.8 ± 0.6 mmol (day 1; $P < 0.05$)], whilst urate excretion did not change (Figure 4). Urinary recovery of piretanide over this period was found to be 21.2 ± 2.1% of the dose administered. Efficiency of piretanide, when administered orally, in this group of patients ($n = 14$) was found to be 47.3 ± 4.1 (mmol Na/mg piretanide). The responses noted over 0–6 h on day 7 of continuous piretanide therapy paralleled in all respects, the urinary responses on day 1 though the absolute magnitude of saluresis was less (mmol $6\ h^{-1}$) [$U_{Na}V$ = 52.8 ± 7.5 (day 1) *vs* 39.5 ± 5.0 (day 7); $P < 0.05$, and $U_{Cl}V$ = 65.4 ± 8.9 (day 1) *vs* 48.9 ± 5.6 (day 7); $P < 0.05$].

6–24 h When compared with control values, a significant reduction in sodium and chloride excretion was observed on day 1 (mmol): $U_{Na}V$ = 42.4 ± 7.2 (control) *vs* 33.8 ± 6.0 (day 1, $P < 0.05$); and $U_{Cl}V$ = 33.6 ± 6.8 (control) *vs* 23.9 ± 4.5 (day 1), ($P < 0.05$). This rebound fall in sodium and chloride excretion was even more marked on day 7, when values (mmol) were 28.2 ± 4.6 and 15.1 ± 3.3, respectively ($P < 0.05$). Very little additional drug was excreted over 6–24 h period (5.0 ± 0.8% of administered dose).

0–24 h Over 24 h, urinary volume did not change, but there were significant increases in urinary sodium and chloride excretions of 55.6 ± 17.9% (Na) and 82.1 ± 17.1% (Cl) over their respective control values. These increases were not maintained by day 7 when values did not differ significantly from control (Table 3). During the first week of piretanide, 6 mg daily, plasma potassium concentration (mmol l^{-1}) was significantly lower at the end of day 1, 4.27 ± 0.09, and day 7, 4.20 ± 0.09, when compared with the mean control values of 4.40 ± 0.09 ($P < 0.05$). Plasma magnesium concentration fell during the first day of treatment from 0.86 ± 0.02 to 0.83 ± 0.02 ($P < 0.05$). By the end of the first week plasma bicarbonate concentration had increased from 24.1 ± 0.8 to 26.0 ± 8.0 mmol l^{-1} ($P < 0.01$), whilst chloride concentration had fallen from 99.1 ± 1.0 to 97.5 ± 0.9 mmol l^{-1} ($P < 0.05$). No changes in plasma creatinine, sodium, calcium, uric acid, fasting glucose, cholesterol or triglycerides were observed over the first week of piretanide therapy (Table 4).

Long term out-patient assessment

Clinical details Data concerning the 15 patients treated with piretanide long-term are given in Table 1. The majority of patients required daily piretanide in doses greater than 6 mg. The highest daily dose received was 24 mg. In general, symptoms and signs of heart failure were well controlled following appropriate adjustments in dosage. Two patients (PN and LS) developed gout within 3 days of increasing piretanide from 18 to 24 mg daily. One of these patients (PN) had a further

Table 3 Comparison of 24 h urinary excretion profiles between the first and seventh day of continuous piretanide treatment (6 mg day^{-1}) in 14 patients with severe congestive cardiac failure. C = control

Urinary excretion (mmol/period)	*C*	*Day 1*	*Day 7*
Volume (ml/period)	1844 ± 260	1893 ± 198	1999 ± 261
Sodium	59.6 ± 6.9	88.6 ± 11.8**	67.7 ± 8.6
Potassium	55.1 ± 6.5	60.7 ± 7.6	60.7 ± 8.3
Chloride	49.0 ± 4.2	89.3 ± 12.2***	64.0 ± 8.0
Calcium	2.7 ± 0.5	3.4 ± 0.6	3.6 ± 0.7
Magnesium	3.1 ± 0.4	4.1 ± 0.6*	3.9 ± 0.7
Phosphate	20.4 ± 2.6	19.7 ± 2.8	20.0 ± 2.9
Urate	2.71 ± 0.21	2.59 ± 0.32	2.70 ± 0.24

* $P < 0.05$; ** $P < 0.01$; *** $P < 0.001$

Table 4 Plasma biochemical profile in patients with severe congestive cardiac failure treated continuously with oral piretanide therapy (6–24 mg day^{-1}) for up to 24 months

Plasma measurement (*mmol l^{-1}*)	*Control* *n = 15*	*Months on therapy*						
		Day 1 *n = 15*	*Day 7* *n = 15*	*4* *n = 12*	*8* *n = 9*	*12* *n = 9*	*18* *n = 8*	*24* *n = 7*
Na^+	137.9 ± 0.8	137.6 ± 0.7	138.3 ± 0.7	139.7 ± 0.5*	141.1 ± 0.7*	140.2 ± 0.7	140.1 ± 1.7	142.1 ± 1.2
Cl^-	99.1 ± 1.0	98.4 ± 0.9	97.5 ± 0.9*	100.2 ± 0.9	99.8 ± 0.6	98.2 ± 0.8	98.6 ± 1.2	98.9 ± 0.8
K^+	4.40 ± 0.09	4.27 ± 0.09*	4.20 ± 0.09*	4.05 ± 0.10**	4.15 ± 0.06**	4.03 ± 0.08**	3.88 ± 0.13**	4.16 ± 0.16*
Ca^{2+}	2.36 ± 0.02	2.35 ± 0.03	2.37 ± 0.03	2.37 ± 0.03	2.43 ± 0.05	2.39 ± 0.03	2.39 ± 0.02	2.34 ± 0.04
Mg^{2+}	0.86 ± 0.02	0.83 ± 0.02*	0.84 ± 0.02	0.83 ± 0.04	0.88 ± 0.03	0.83 ± 0.03	0.83 ± 0.04	0.81 ± 0.04
PO_4^{3-}	1.11 ± 0.05	1.18 ± 0.05	1.16 ± 0.05	1.14 ± 0.03	1.00 ± 0.05	1.03 ± 0.05	1.14 ± 0.10	1.03 ± 0.08
Urate	0.43 ± 0.02	0.44 ± 0.02	0.45 ± 0.03	0.45 ± 0.03	0.45 ± 0.02	0.48 ± 0.02**	0.45 ± 0.03	0.47 ± 0.05**
Creatinine	0.11 ± 0.01	0.12 ± 0.01	0.11 ± 0.01	0.13 ± 0.01	0.13 ± 0.02	0.13 ± 0.02	0.13 ± 0.02	0.12 ± 0.02
HCO_3^-	24.1 ± 0.8	25.1 ± 0.8	26.0 ± 0.8**	24.3 ± 0.8	24.6 ± 1.0	25.7 ± 0.9	25.4 ± 0.8	27.1 ± 1.4**
Glucose	5.7 ± 0.4	5.9 ± 0.4	6.1 ± 0.4	6.4 ± 0.9	5.5 ± 0.7	6.0 ± 0.7	6.3 ± 0.7	5.6 ± 0.3
Cholesterol	5.6 ± 0.3	5.4 ± 0.03	5.8 ± 0.3	6.6 ± 0.3*	7.0 ± 0.4*	6.6 ± 0.3*	6.4 ± 0.5	6.3 ± 0.05*
Triglyceride	1.86 ± 0.30	1.76 ± 0.50	1.64 ± 0.40	2.36 ± 0.51	1.55 ± 0.55	1.72 ± 0.27	1.75 ± 0.27	1.41 ± 0.17

* $P < 0.05$; ** $P < 0.01$

episode of gout, 2 days after commencing benzylpenicillin therapy for coincidental pneumonia. In both patients, hyperuricaemia was controlled with allopurinol. Piretanide was otherwise well tolerated in all patients with no adverse effects. Piretanide was discontinued in four patients AE, AC, IS and WH, for reasons detailed in Table 1.

Metabolic profile The most consistent changes in biochemical measurements, over the first 2 years of long-term piretanide therapy, were a gradual decrease in plasma potassium concentration and an increase in fasting cholesterol (Table 4). Although the lowest individual plasma potassium observed was 3.40 mmol l^{-1}, on one occasion in one patient, mean potassium concentrations were within the normal range for our laboratory (95% confidence limits: 3.50 – 5.50 mmol l^{-1}). Mean plasma potassium concentrations at 1 year and 2 years were (mmol l^{-1}) 4.03 ± 0.08 ($P < 0.01$) and 4.16 ± 0.16 ($P < 0.05$), respectively. Elevations in plasma uric acid, sodium and bicarbonate concentrations were significant on occasions, but less consistently so in comparison with changes in plasma potassium. Overall there were no changes in plasma chloride, calcium, magnesium, phosphate, creatinine, fasting blood sugar and triglyceride concentrations on long-term piretanide therapy. No further changes in plasma parameters were seen in seven subjects studied in excess of 33 months (33–43 months). Plasma potassium concentration at the end of their treatment was 4.14 ± 0.14 (mmol l^{-1}) ($P < 0.05$) while plasma bicarbonate was 26.1 ± 0.1 (mmol l^{-1}) ($P < 0.05$).

Safety profile Regular urinalyses were undertaken to check for proteinuria and haematuria. No changes attributable to drug therapy were found. Neither were any significant changes noted in plasma alkaline phosphatase, bilirubin, alanine and asparate aminotransferases, haemoglobin, total and differential white blood count and platelet count.

Discussion

The patients who participated in this study varied in the extent of severity of their cardiac failure and as such were categorized into groups A and B. Using established comparative assay technique previously validated (Lant *et al.*, 1969), we have compared the potency of piretanide with respect to frusemide at three different dose levels. In the 6 h assay piretanide, 6, 12 and 18 mg, yielded an overall response ratio of 0.99 ± 0.12 with respect to the corresponding doses of fruse-

mide, 40, 80 and 120 mg. Over the whole 24 h, the saluretic response ratio averaged 0.86 ± 0.09, reflecting longer duration of action of frusemide in patients with CCF (Vasko *et al.*, 1985). These findings of an overall potency ratio P/F of approximately 6:40, on a weight to weight basis, is in agreement with other reports of relative potency ratios for comparative short-term studies (Clissold & Brogden, 1985). In previous reports from this laboratory the bioavailability of piretanide in patients with severe CCF was found to be 68 ± 7% (n = 3) compared with 79 ± 6% (n = 4) in normal subjects (McNabb *et al.*, 1984b). While there was no change in t_{max} (time for maximal plasma concentration), the C_{max} (maximum plasma concentration) tended to be lower in the cardiac failure group, the mean values were, however, not significantly different from those obtained in normals [t_{max} (min) 60 ± 12 (n = 4) *vs* 58 ± 6 (n = 13) and C_{max} (ng ml^{-1}) 189 ± 36 (n = 4) *vs* 273 ± 38 (n = 13) respectively (unpublished observations)]. A recent report has shown that oral bioavailability of bumetanide, a closely related sulphamoylbenzoate diuretic, is not diminished in grossly oedematous patients (Bailie *et al.*, 1987).

The efficiency of orally administered piretanide [sodium excretion (mmol)/piretanide excretion (mg)], over 0–6 h, in the present group of CCF patients was observed to be 47.3 ± 4.5 mmol mg^{-1} (n = 14), a value significantly different from those seen in healthy volunteers (84.0 ± 9.9 mmol mg^{-1}; n = 13; $P < 0.01$, unpublished observations). Such difference in the efficiency is consistent with the view that sodium conserving mechanisms are activated in cardiac failure (Skorecki & Brenner, 1982). The extent of sodium retention can be shown to parallel the degree of cardiac failure. The urinary excretion of sodium, after 3 days free from any diuretic, was 104.3 ± 14.2 mmol 24 h^{-1} in group A patients (n = 17) and only 59.5 ± 6.9 mmol 24 h^{-1} in group B patients (n = 14; $P < 0.01$). It is possible that sodium retention observed in the more severe cases of failure (group B) is directly related to excessive depletion of body electrolyte stores following previous diuretic therapy. This is unlikely, as in the patients studied, daily sodium output on 3 days, free from any diuretic therapy prior to piretanide exposure was: 64.2 ± 11.3; 59.4 ± 7.9 and 53.9 ± 9.5 mmol 24 h^{-1} (n = 14), a clear indication of steady state conditions.

An important sequel to effective saliuresis is the secondary wastage of urinary potassium that follows it. Whether this plays a role in the induction of potassium depletion in patients with CCF treated with diuretics is still a matter of some controversy. One view is that, after an initial but transient drop in plasma concentration, potassium status remains stable and any changes in total body potassium can be attributed to muscle wasting (Morgan *et al.*, 1978). Other studies however, present evidence to the contrary. Total body potassium is shown to be reduced in CCF patients as a result of activation of renin-angiotensin-aldosterone system and in absence of any changes in muscle mass (Cleland *et al.*, 1987). We have previously demonstrated an acute kaliuretic effect of piretanide in healthy volunteers undergoing sustained water-diuresis (McNabb *et al.*, 1984a). As with volunteers, a kaliuretic effect was also seen acutely with piretanide in cardiac failure and this was abolished by the addition of triamterene. The overall 24 h losses of potassium did not differ significantly from control. The rapid re-establishment of potassium status in presence of continued piretanide therapy was clearly shown in the third group of patients. The kaliuretic response remained stable over seven days of treatment and did not differ significantly from control. This is further reflected in the long-term follow up where, despite a gradual but significant fall in plasma potassium over a three year period with piretanide doses ranging from 6 to 24 mg, mean plasma potassium concentrations were within our normal laboratory range (3.50 to 5.50 mmol l^{-1}). A similar lack of effect on plasma potassium has also been reported in hypertensives treated for 12 weeks with piretanide (Verho *et al.*, 1984) and over a shorter period in a group of CCF patients (Sherman *et al.*, 1986). Over the long term, magnesium status in our patients was virtually unaltered.

Chronic use of diuretics in the treatment of hypertension and CCF is associated with increase in plasma urate levels (Buckert *et al.*, 1984; Kostis *et al.*, 1982). The mechanisms involved in the rise of plasma urate is still a matter of some debate but it is generally accepted to be a post-saluretic phenomenon related to diuretic induced shrinkage of extracellular volume (Steele, 1969). Further support for this view comes from our findings of significantly elevated plasma urate concentration in states of experimental sodium depletion (McNabb *et al.*, 1986). With the exception of predisposition to gout, asymptomatic elevation of plasma urate concentration is not considered harmful (Langford *et al.*, 1987). In the present study, significant hyperuricaemia was observed during long term therapy though not consistently, as shown in Table 4. Acute clinical gout occurred in two of the patients on 24 mg piretanide/day therapy.

Concern has been expressed on possible long

term metabolic consequences of diuretic therapy. There is considerable debate as to the significance of metabolic changes observed after chronic therapy with benzothiadiazines and to the extent to which such changes occur with 'loop' diuretics (Anderson *et al.*, 1971; Gabriel & Baylor, 1981; Losse *et al.*, 1983; Lant, 1985). The concern has largely centred on impaired glucose tolerance and changes in lipid metabolism. The increase in total cholesterol that was found in our study was not further characterized as lipid subfractionation was not performed. Other workers have reported an increase in low density lipoproteins after chronic piretanide therapy (Glück *et al.*, 1978; Välimäki *et al.*, 1983).

On the basis of the present study we conclude that piretanide emerges as approximately five to six times more potent, on a weight to weight basis, when compared with frusemide. The time course of action of piretanide is not significantly altered by cardiac failure. In its long term use, piretanide emerged as a potent diuretic with a profile of action similar to frusemide. Piretanide was well tolerated and clinically effective in the continued control of cardiac failure, causing minimal metabolic changes.

We wish to acknowledge our grateful thanks to the Special Trustees of Westminster and Roehampton Hospitals for financial support; Dr B. A. Brooks and Dr. D. J. R. Morgan for advice and help in the planning of this study; Dr S. L. Dombey, formerly of Hoechst UK, for supplies of piretanide; Mr A. J. Hewett for statistical advice; Sister M. Clift and the nursing staff on Ellen Terry Ward, St Stephen's Hospital; Mrs M. Phillips for the preparation of metabolically controlled diets; Messrs N. Brammer, M. Johnson and Miss E. Jennings for technical assistance.

References

Ames, R. & Hill, P. (1976). Elevation of serum lipids during diuretic therapy of hypertension. *Am. J. Med.*, **61**, 748–757.

Anderson, J., Godfrey, B. E., Hill, D. M., Munro-Faure, A. D. & Sheldon, J. (1971). A comparison of the effects of hydrochlorothiazide and of frusemide in the treatment of hypertensive patients. *Quart. J. Med.*, **160**, 541–560.

Bailie, G. R., Grennan, A. & Waldek, S. (1987). Bioavailability of bumetanide in grossly oedematous patients. *Clin. Pharmacokin.*, **12**, 440–443.

Bonsnes, R. W. & Taussky, H. H. (1945). Colorimetric determination of creatinine by the Jaffe reaction. *J. biol. Chem.*, **158**, 581–591.

Brown, N. L., Maura, A. M. & Worcel, M. (1984). Extrarenal effects of diuretics on vascular smooth muscle. In *Diuretics – Chemistry, pharmacology and clinical applications*, eds Puschett, J. B. & Greenberg, A. pp. 450–452. New York: Elsevier.

Buckert, C., Mülhäusler, W., Fratzer, U. & Verho, M. (1984). A double-blind multicentre study of piretanide and hydrochlorothiazide in patients with essential hypertension. *J. int. med. Res.*, **12**, 81–86.

Cleland, J. G., Dargie, H. J., Robertson, I., Robertson, J. I. S. & East, B. W. (1987). Total body electrolyte composition in patients in heart failure: a comparison with normal subjects and patients with untreated hypertension. *Br. Heart J.*, **58**, 230–238.

Clissold, S. P. & Brogden, R. N. (1985). Piretanide: a preliminary review of its pharmacodynamic and pharmacokinetic properties and therapeutic efficacy. *Drugs*, **29**, 489–530.

Dixey, J. J., Noormohamed, F. H., Lant, A. F. & Brewerton, D. A. (1987). The effects of naproxen and sulindac on renal function and their interaction with hydrochlorothiazide and piretanide in man. *Br. J. clin. Pharmac.*, **23**, 55–63.

Fiske, C. H. & Subbarow, Y. (1925). The colorimetric determination of phosphorus. *J. biol. Chem.*, **66**, 375–400.

Gabriel, R. & Baylor, P. (1981). Comparison of the chronic effects of bendrofluazide, bumetanide and frusemide on plasma biochemical variables. *Postgrad. med. J.*, **57**, 71–74.

Glück, Z., Baumgartner, G., Weidmann, P., Peheim, E., Bachmann, C., Mordasini, R., Flammer, J. & Keusch, G. (1978). Increased ratio between serum β- and α-lipoproteins during diuretic therapy: an adverse effect? *Clin. Sci.*, **55**, 325S–328S.

Greenberg, G., Brennan, P. J. & Miall, W. E. (1984). Effects of diuretic and beta-blocker therapy in Medical Research Council Trial. *Am. J. Med.*, **76** (2A), 45–51.

Harrington, J. T., Isner, J. M. & Kassirer, J. P. (1982). Our national obsession with potassium. *Am. J. Med.*, **73**; 155–159.

Kaplan, N. M. (1983). The clinical use of diuretics in the treatment of hypertension. *Clin. exp. Hyperten.*, **A5(2)**, 309–320.

Klaus, E., Alpermann, H. G., Caspirtz, G., Hropot, M., Linz, W. & Scholkens, B. (1984). Extrarenal and vascular effects of piretanide in several animal models. In *Diuretics – Chemistry, pharmacology and clinical applications*, eds Puschett, J. B. & Greenberg, A. pp. 85–93. New York: Elsevier.

Kostis, J. B., Cosgrove, N., Krieger, S., Moreyra, A. E., Baumgardner, S. & Weinstein, J. (1982). Comparison of piretanide and hydrochlorothiazide in congestive cardiac failure. *Clin. Res.*, **30**. 198 A.

Langford, H. G., Blaufox, M. D., Borhani, N. O., Curb, J. D., Molteni, A., Schneider, K. A. & Pressel, S. (1987). Is thiazide produced uric elevation harmful? *Arch. intern. Med.*, **147**, 645–649.

Lant, A. F. (1985). Diuretics – Clinical pharmacology and clinical use. *Drugs*, **29**, Part I 57–87; part II 162–188.

Lant, A. F., Smith, A. J. & Wilson, G. M. (1969). Clinical evaluation of amiloride, a potassium sparing diuretic. *Clin. Pharmac. Ther.*,**10**, 50–63.

Lasser, N. L., Grandits, G., Caggiula, A. W., Cutler, J. A., Grimm, R. H., Kuller, L. H., Sherwin, R. W. & Stamler, J. (1984). Effects of antihypertensive therapy on plasma lipids and lipoproteins in the multiple risk factor intervention trial. *Am. J. Med.*, **76(2A)**, 52–66.

Lawrence, J. R., Ansari, A. F., Elliott, H. J., Sumner, D. J., Brunton, G. F., Whiting, B. & Whitesmith, R. (1978). Kinetic and dynamic comparison of piretanide and furosemide. *Clin. Pharmac. Ther.*, **2**, 558–565.

Losse, L., Zumkley, H. & Quante, T. (1983). Side effects of diuretics. *Clin. exp. Hyperten.*, **A5(2)**, 309–320.

McNabb, W. R., Noormohamed, F. H. Brooks, B. A. & Lant, A. F. (1984a). Renal actions of piretanide and three other 'loop' diuretics. *Clin. Pharmac. Ther.*, **35**, 328–337.

McNabb, W. R., Noormohamed, F. H. & Lant, A. F. (1984b). Acute and chronic effects of piretanide in congestive cardiac failure. In *Diuretics – Chemistry, pharmacology and clinical applications*, eds Puschett, J. B. & Greenberg, A. pp. 355–357. New York: Elsevier.

McNabb, W. R., Noormohamed, F. H. & Lant, A. F. (1986). The effects of enalapril on blood pressure and the kidney in normotensive subjects under altered sodium balance. *J. Hyperten.*, **4**, 39–47.

Morgan, D. B., Burkinshaw, L. & Davidson, C. (1978). Potassium depletion in heart failure and its relation to long-term treatment with diuretics: a review of the literature. *Postgrad. med. J.*, **54**, 72–79.

Roberts, C. J. C., Homeida, M., Roberts, F. & Bogie, W. (1978). Effects of piretanide, bumetanide and frusemide on electrolyte and urate excretion in normal subjects. *Br. J. clin. Pharmac.*, **6**, 129–133.

Sherman, L. G., Liang, C., Baumgardner, S., Charuzi, Y., Chardo, F. & Kim, C. S. (1986). Piretanide, a potent diuretic with potassium sparing properties, for the treatment of congestive heart failure. *Clin. Pharmac. Ther.*, **40**, 587–594.

Skorecki, K. L. & Brenner, B. M. (1982). Body fluid homeostasis in congestive heart failure and cirrhosis with ascites. *Am. J. Med.*, **72**, 323–350.

Steele, T. H. (1969). Evidence of altered renal urate reabsorption during changes in volume of extracellular fluid. *J. lab. clin. Med.*, **74**, 288–299.

Välimäki, M., Harno, K. & Nikkilä, E. A. (1983). Serum lipoproteins and indices of glucose tolerance during diuretic therapy: a comparison between hydrochlorothiazide and piretanide. *J. cardiovasc. Pharmac.*, **5**, 525–530.

Vasko, M. R., Brown-Cartwright, D., Knochel, J. P., Nixon, J. V. & Brater, D. C. (1985). Furosemide absorption altered in decompensated congestive cardiac failure. *Ann. intern. Med.*, **102**, 314–318.

Verho, M., Rangoonwala, B., Dols, W., Fratzer, U., Kaczynski, J. & Mülhäusler, W. (1984). Piretanide, a potassium stable diuretic, in the treatment of essential hypertension. *Eur. J. clin. Pharmac.*, **27**, 407–414.

(Received 24 December 1987, accepted 8 April 1988)