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EFFECTS OF PIRETANIDE, BUMETANIDE AND FRUSEMIDE ON ELECTROLYTE AND URATE EXCRETION IN NORMAL SUBJECTS

C.J.C. ROBERTS, M. HOMEIDA & FIONA ROBERTS
Departments of Medicine and Pharmacology, University of Bristol, Bristol BS8 1TD
W. BOGIE
Pharmaceutical Division, Hoechst, U.K. Ltd, Hounslow, Middlesex

1 The pharmacological actions of a new short acting loop diuretic were investigated in nine healthy male subjects and compared with those of frusemide and bumetanide. Subjects received 6 mg piretanide/day, 40 mg frusemide/day or 1 mg bumetanide/day for a period of 1 week.

2 Comparison of effects following the first dose administered showed that 6 mg piretanide is of similar potency to 40 mg frusemide in terms of diuresis, natriuresis and kaliuresis but is less potent than 1 mg bumetanide.

3 All three diuretics caused a decrease in urate excretion and a rise in serum uric acid.

4 Piretanide was well tolerated. Further investigation is required to ascertain what clinical advantage it offers over frusemide and bumetanide.

Introduction

Piretanide is a potent new loop diuretic with a chemical structure related to those of both frusemide and bumetanide, (Figure 1). In the rat it is more potent on a weight for weight basis than either frusemide or bumetanide and causes less potassium excretion (Merkel, Bormann, Mania, Muschaweck & Hropot, 1976). In the dog piretanide is less potent than bumetanide. Preliminary studies in man showed piretanide to be more potent than frusemide and less potent than bumetanide and to have a similar time course of action (W. Rupp, unpublished observations).

In this study the action of piretanide in man has been investigated in more detail and its actions compared with those of approximately equipotent doses of frusemide and bumetanide. The effects of physiological homeostatic mechanisms were also examined by comparing the water, electrolyte and urate excretions in the 6 h immediately following drug administration with those in the subsequent 18 h and by administering the drugs for 1 week.

Methods

Nine healthy male volunteers aged between 20 and 30 years consented to take part in the study which was approved by the Ethics Committee of Bristol Royal Infirmary. Alcohol was restricted during the study periods to 1 pint of beer per day but otherwise subjects ate their usual diet and pursued their usual activities.

The study consisted of three trial periods lasting 10 days each and separated by 11 days. Each trial period started with 2 control days (days 1 and 2). Then either piretanide (6 mg daily), frusemide (40 mg daily) or bumetanide (1 mg daily) was administered orally at 08 h 30 min every morning for 7 days (days 3 to 9). Each subject received each diuretic, the order being determined using a balanced design. The trial was conducted open.

On days 1, 2, 3, 4, 8 and 9 all urine passed between 08 h 30 min and 14 h 30 min (6 h) and between 14 h 30 min and 08 h 30 min the following morning (18 h)

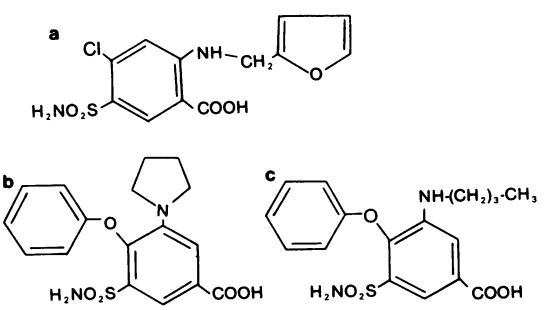

Figure 1 Chemical structure of three diuretics (a) frusemide, (b) piretanide and (c) bumetanide.

was collected separately. Volume, sodium, potassium and uric acid contents were measured in all urine collections.

Uric acid was measured in early morning plasma specimens taken on days 1, 3, 4, 8 and 10. Plasma urea and electrolytes were measured at the beginning and the end of each trial period. Haemoglobin, white cell count, platelet count, plasma viscosity and liver function tests were measured at the beginning and end of treatment with piretanide. Plasma and urine uric acid was measured by an automated phosphotungstic acid method (Musser & Ortigoza, 1966) and urine electrolytes by flame photometry.

Nonparametric statistical methods have been used throughout because non-linearity of rankit plots suggested that certain of the data were not distributed normally. The 96.4% nonparametric confidence limits for the median were obtained as follows: each group of nine observations was ranked in ascending order. The fifth observation is then the median, the second and eighth the 96.4% confidence interval. The significance of differences between paired observations was considered by examination of these limits and the binomial probability of observing so many differences in the same direction (two-tail sign test). The Wilcoxon signed ranks test and the Kruskal-Wallis one way analysis of variance were used to compare two or three independent groups of observations respectively.

Results

Urine volume, electrolyte and uric acid measurements

Control rates The control rates of water, sodium, potassium and urate excretions corresponding to the three diuretics were similar ($P > 0.2$, Kruskal-Wallis) and are summarised together in Table 1. This shows that there is little difference in the rate of urate or sodium excretion between the 6 h period and the 18 h period. There is a decrease of about 50% in the rate of potassium excretion (27 decreases out of 27; $P < 0.0001$ sign test) and an increase in urine volume of about 40% (19 increases out of 27; $P = 0.03$), in the 18 h compared with the 6 h period.

Changes in rates following the first administration of diuretic. In the first 6 h following their administration (Table 2) all three diuretics increased the volume of urine (27 out of 27; $P < 0.0001$), sodium and potassium (27 and 24 respectively out of 27; $P < 0.0001$). Urate excretion also tended to be slightly increased (20 out of 27; $P = 0.013$). The results in Table 2 show that piretanide was approximately equipotent with frusemide but less potent than bumetanide at the doses used.

In the following 18 h the effects tended to be reversed. There was a decrease in urine volume (21 out of 27; $P = 0.004$), and in excretions of sodium (24 out of 27; $P < 0.0001$), potassium (19 out of 27; $P = 0.033$) and urate (21 out of 27; $P = 0.004$). As a result of these decreases there was a slight overall decrease in urate excretion over the first 24 h (18 out of 27; $P = 0.07$) and potassium excretion was similar to that on control days (17 increased out of 27; $P = 0.12$.). Urine volume and sodium excretion were greater over the first 24 h than on the control days (25 and 24 respectively out of 27; $P < 0.0001$).

Changes in rates during continued daily administration of diuretic. Although all three diuretic continued to produce increases in urine volume, electrolyte and urate excretion during the 6 hours following their administration, these increases tended to become smaller with repeated administration (Table 3). There was a progressive rise during the 7 days' treatment in the rate of potassium excretion in the 18 h collections. Sodium and urate excretion rates during the 18 h collections remained below those on control days.

Ratio of sodium to potassium in the urine. The urinary sodium to potassium ratios on control and treatment days are shown in Table 4. Following the first administration of diuretic the ratio in the six hour collection increased (27 out of 27; $P < 0.0001$). Following repeated administration the ratio in the 6 h periods became progressively smaller (18 out of 27 decreased; $P = 0.07$) but remained greater than control values. In the 18 h period following the first administration the ratio was smaller than on control days (22 out

Table 1 Urine volume, electrolyte and uric acid excretion rates on control days. The median rates of each of the nine healthy subjects during the morning (08.30–14.30 h) and the afternoon and night (14.30–08.30 h) for days 1 and 2 of each trial period were calculated. The median and its 96.7% confidence intervals of these control rates (n = 9 x 3) are shown below: median (lower limit) (upper limit)

	Collection time (h)					
	08.30–14.30		14.30–08.30		*24*	
Volume (ml/h)	51	(45) (65)	71	(65)* (83)	71	(60) (79)
Sodium (mmol/h)	5.9	(5.0) (7.8)	6.6	(6.2) (7.1)	6.3	(6.1) (7.2)
Potassium (mmol/h)	5.0	(3.7) (5.7)	1.9	(1.8)† (2.3)	3.3	(2.9) (3.8)
Uric acid (mmol/h)	0.17	(0.16) (0.21)	0.19	(0.17) (0.20)	0.18	(0.17) (0.20)

* $P < 0.05$ compared to 6 h period
† $P < 0.001$ compared to 6 h period

of 27 decreased; $P<0.001$). The ratio in the 18 h periods decreased further following repeated administration (19 out of 27; $P=0.03$).

Serum uric acid and urate clearance

There were significant rises in serum uric acid after one week's treatment with all three diuretics. The median rises and 96% confidence limits were +0.04 (+0.01 to +0.08) mmol/l for piretanide, +0.07 (+0.04 to +0.10) mmol/l for frusemide and +0.07 (+0.03 to +0.08) mmol/l for bumetamide. These were accompanied by falls in urate clearance. The median falls and 96% confidence limits were +46 (−50 to +125) ml/h for piretanide, +167 (+13 to +242) ml/h for frusemide and +175 (+83 to +262) ml/h for bumetamide. Differences between the diuretics were not statistically significant ($P>0.2$, Kruskal-Wallis).

Toxicological screening

No plasma electrolyte abnormality occurred in any subject. There was a small rise in plasma urea after treatment with each diuretic (24 out of 27; $P<0.001$).

Piretanide was well tolerated by the subjects and no haematological abnormality or disturbance of liver function occurred in association with the treatment.

Discussion

Piretanide has been shown to be a potent diuretic when administered orally to normal subjects. In common with many other diuretics it causes an increased excretion of potassium and a decrease in urate clearance with elevation of plasma uric acid. This study has also examined the effect of physiological homeostatic mechanisms on the actions of loop diuretics and has provided data suggesting that urate retention may be directly related to these mechanisms.

Comparison of urine volume and sodium excretion after the initial administration of the three diuretics allows an interpretation of relative potencies at the doses used. Bumetanide 1 mg produced the greatest diuresis with respect to urine volume, sodium and potassium excretion. The natriuresis and kaliuresis produced by

Table 2 Urine volume, electrolyte and uric acid excretion rates following first administration of diuretic at 08.30 h. The median rates for each of nine healthy subjects during days 1 and 2 were subtracted from the rate of that subject during day 3. The median and 96.4% confidence intervals of each group of nine differences are shown below.

	Diuretic	*08.30–14.30 h*		*14.30–08.30 h*		*24 h*	
Volume (ml/h)	Piretanide 6 mg	+197	(158)*** (223)	−6	(−44)** (+15)	+42	(18)*** (53)
	Frusemide 40 mg	+152	(126) (252)	−2	(−59) (0)	+19	(4) (42)
	Bumetanide 1 mg	+247	(201) (258)	−17	(−41) (+14)	+36	(25) (72)
Sodium (mmol/h)	Piretanide 6 mg	+13.3	(10.0)*** (17.8)	−2.8	(−4.9)*** (+0.1)	+1.6	(0.4)*** (3.3)
	Frusemide 40 mg	+14.2	(7.2) (18.3)	−1.9	(−4.2) (−0.2)	+1.5	(0.8) (3.5)
	Bumetanide 1 mg	+20.5	(12.3) (26.8)	−2.7	(−5.5) (−2.0)	+3.2	(1.1) (5.1)
Potassium (mmol/h)	Piretanide 6 mg	+2.00	(0)*** (2.33)	+0.06	(−0.33)* (+0.89)	+0.33	(−0.58) (+0.88)
	Frusemide 40 mg	+1.17	(0) (5.83)	−0.78	(−2.28) (+0.72)	−0.21	(1.71) (0.67)
	Bumetanide 1 mg	+3.50	(0) (4.00)	−1.00	(−1.39) (+0.72)	+0.75	(−0.04) (+0.79)
Urate (mmol/h)	Piretanide 6 mg	+0.022	(−0.003)* (+0.085)	−0.011	(−0.053)** (+0.028)	+0.007	(−0.028) (+0.031)
	Frusemide 40 mg	+0.055	(−0.055) (+0.087)	−0.051	(−0.140) (−0.001)	−0.040	(−0.091) (−0.009)
	Bumetanide 1 mg	+0.065	(−0.100) (+0.100)	−0.022	(−0.042) (+0.016)	−0.006	(−0.017) (+0.060)

*** $P<0.0001$; ** $P<0.01$; * $P<0.05$

piretanide 6 mg was similar to that of frusemide 40 mg suggesting equipotency at these doses. The findings are consistent with a potency ratio between frusemide and bumetanide in excess of forty to one (Branch, Read, Levine, Vander Elst, Sheldon, Rupp & Ramsay 1976; Davies, Lant, Millard, Smith, Ward & Wilson, 1974). However, with repeated daily administration the differences between the diuretics became less obvious.

Physiological homeostatic mechanisms are known to be stimulated in response to diuresis (Lant, Baba & Wilson, 1966). These mechanisms comprise increased tubular reabsorption of sodium ions in the proximal tubule of the nephron (Brenner & Berliner, 1969; De Wardener, 1969) and increased aldosterone secretion (Nicholls, Espiner, Donald & Hughes, 1974). They account for the altered relationship

Table 3 Change in urine volume, electrolyte and uric acid excretion rates during continued daily administration of diuretic. The median rate for each of nine healthy subjects during days 1 and 2 were subtracted from the median for that subject during days 3, 4, 8, 9, the diuretic being administered at the beginning of each morning collection on days 3 to 9. The median and 96.4% confidence intervals of each group are shown below.

	Diuretic	*08.30–14.30 h*	*14.30–08.30 h*	*24 h*
Volume (ml/h)	Piretanide 6 mg	+157 (121)*** (223)	−19 (−37)** (+16)	+31 (+15)*** (+35)
	Frusemide 40 mg	+150 (99) (184)	−22 (−60) (−6)	+21 (−4) (+32)
	Bumetanide 1 mg	+153 (139) (219)	−26 (−45) (−2)	+14 (+1) (+46)
Sodium (mmol/h)	Piretanide 6 mg	+12.7 (6.3)*** (14.5)	−2.4 (−7.1)*** (−0.9)	+1.3 (−0.7) (+2.8)
	Frusemide 40 mg	+9.8 (6.0) (17.3)	−2.2 (−4.3) (−0.1)	+0.8 (−1.4) (+3.0)
	Bumetanide 1 mg	+12.3 (9.8) (20.5)	−4.1 (−5.2) (−2.6)	+0.04 (−1.5) (+2.5)
Potassium (mmol/h)	Piretanide 6 mg	+3.00 (+0.67)** (+4.00)	+0.06 (−0.78) (+0.38)	+0.54 (−0.42)* (+1.25)
	Frusemide 40 mg	+0.83 (−0.83) (+3.50)	+0.33 (−1.94) (+0.72)	+0.08 (−1.25) (+0.83)
	Bumetanide 1 mg	+1.67 (−0.67) (+3.17)	−0.39 (−1.0) (0.00)	+0.21 (+0.04) (+0.54)
Uric acid (mmol/h)	Piretanide 6 mg	+0.035 (−0.038) (+0.082)	−0.003 (−0.005)** (0.000)	−0.005 (−0.028)* (+0.005)
	Frusemide 40 mg	+0.018 (−0.055) (+0.080)	−0.029 (−.112) (−0.008)	−0.020 (−0.079) (−0.014)
	Bumetanide 1 mg	+0.025 (−0.052) (+0.050)	−0.033 (−0.063) (+0.008)	−0.023 (−0.036) (−0.007)

*** $P<0.0001$; ** $P<0.001$; * $P<0.05$

Table 4 Ratio of urinary sodium to potassium on control days and following the first administration of diuretic and over continued daily administration. The median ratios for each subject during days 1 and 2, and days 3,4,8,9 were obtained. The median and 96.7% confidence intervals for each group of 27 values are shown.

	08.30–14.30 h	*14.30–08.30 h*	*24h*
Control days 1 and 2	1.54 (1.18) (1.76)	2.56 (2.27) (2.91)	2.36 (1.76) (2.65)
Following first administration, day 3	3.38 (2.64)*** (3.71)	1.55 (1.24)** (2.12)	2.47 (2.06) (3.04)
Over continued administration, days 3,4,8,9	2.91 (2.63) (3.26)	1.31 (1.15)* (1.50)	2.05 (1.79) (2.35)

*** $P<0.0001$ compared to control; ** $P<0.001$ compared to control; * $P<0.05$ compared to day 3.

between plasma frusemide and sodium excretion rate seen in subjects when sodium depleted (Branch, Roberts, Homeida & Levine, 1977). In this study the decrease in both sodium and potassium excretion found following the first diuresis suggests increased proximal tubular reabsorption. However the subsequent increase in potassium excretion found in the 18 h collections accompanied by the fall in Na/K ratio suggests increasing aldosterone secretion (Adamson & Jamieson, 1972). Thus a combination of early increased proximal tubular reabsorption of sodium followed by increased aldosterone secretion explains the decreased natriuresis found after repeated doses of the diuretics and the return of the 24 h sodium excretion to baseline at the end of treatment periods. The diminished differences between diuretics in 24 h electrolyte excretion compared to 6 h excretion are also explained by the modifying effect of these homeostatic mechanisms.

All three diuretics caused urate retention as judged by a rise in serum uric acid and a fall in urate clearance. Whilst these effects were least with piretanide, differences between the drugs were not statistically significant. It was noted that urate excretion tended to be increased during the 6 h periods following diuretic administration when the drugs' activity and excretion were at a maximum (Branch *et al*, 1977; Davies *et al*, 1974) and decreased during the subsequent periods of sodium retention. These observations are in keeping with the suggestion that diuretic induced urate retention is fundamentally related to diminished extracellular fluid volume (Steele, 1971; Suki, Hull, Rector & Seldin, 1967) rather than competition between drug and urate for a common tubular secretory pathway (Bryant, Yu, Berger, Schvartz, Torosdag, Fletcher, Fertig, Schwartz & Quan, 1962; Olesen, Sigurd, Steiness & Leth, 1973). The similarity between the patterns of urate and sodium excretion observed in this study are consistent with the previously reported relationship between their excretions and the suggestion that mechanisms which adjust tubular sodium reabsorption may also alter urate excretion (Cannon, Svahn, & Demartini, 1970).

This study carried out in man has shown piretanide to be a potent diuretic with actions comparable to those of frusemide and bumetanide. It is well tolerated and no immediate toxic effects are apparent. Clinical studies should be undertaken to determine whether it offers major advantages over other agents. Physiological homeostatic mechanisms stimulated by diuresis and extracellular fluid volume depletion modify the effect of subsequent diuretic administration and may be responsible for the development of hyperuricaemia.

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