Xipamide: no advantage over bendrofluazide in hypertension

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In patients with uncontrolled hypertension addition of xipamide 20 mg daily to bendrofluazide 5 mg daily produced no significant additive antihypertensive effect, and the 95% confidence limits excluded a clinically important response. Xipamide treatment worsened hypokalaemia and increased the blood urea concentration significantly.

Keywords xipamide bendrofluazide hypertension

Introduction

Xipamide is a salicylic acid derivative which has diuretic activity in laboratory animals similar in duration to that of the thiazides, but with a higher ceiling effect (Leuschner *et al.*, 1975). It has a diuretic effect additive to that of hydrochlorothiazide in rats (Leuschner *et al.*, 1975). In man an antihypertensive effect superior to that of the thiazides has been suggested (Raftery *et al.*, 1981; Bonaduce *et al.*, 1981) but the evidence is unsatisfactory (Drug and Therapeutics Bulletin, 1980). When compared directly to cyclopenthiazide, xipamide was not superior as regards blood pressure reduction but caused larger falls in serum potassium and larger rises in blood urea (MacGregor *et al.*, 1982). The aim of the present study was to determine whether xipamide has an additive antihypertensive action when added to a ceiling dose of bendrofluazide, or to disprove such a response if that is the case.

Methods

Twenty hypertensive patients with lying diastolic pressures higher than 90 mm Hg (phase 5) while taking bendrofluazide 5 mg daily alone, or with a β -adrenoceptor blocker, consented to the study which was approved by the local ethics committee. β -adrenoceptor blocker treatment was held constant throughout. The dose of bendrofluazide selected, 5 mg daily, has a maximal antihypertensive effect (Marshall *et al.*, 1977). The patients were randomly allocated to addition of bendrofluazide 5 mg daily

in a different formulation (total dose bendrofluazide 10 mg daily, $n = 10$), or addition of xipamide 20 mg daily (bendrofluazide 5 mg, plus xipamide 20 mg daily, $n = 10$), in a parallel group design. Blood pressure and body weight were measured at -2, 0, +2, +4, and +6 weeks, and biochemical variables at 0, +2, and +6 weeks, with randomisation at week 0. Blood pressure was measured by a trained nurse who was unaware of treatment in 17 patients, and by another observer (SF) in three patients. Both observers used a random-zero mercury sphygmomanometer on the right arm and measured phase 5 diastolic pressures. The results at -2 and 0 weeks (baseline), and at +2, +4 and +6 weeks (during treatment) were similar and were averaged to increase the power of the study (Freestone *et al.*, 1982). The results are expressed as the mean (and s.e.) differences between xipamide and bendrofluazide after baseline correction. The 95% confidence limits for differences between the treatments were calculated as $\pm(2.101 \times \text{s.e. mean})$, where 2.101 is the value of t with 18 degrees of freedom.

Results

The two treatment groups were well matched at randomisation apart from some imbalance in the sex distribution (Table 1). The responses to addition of xipamide, compared to increasing the dose of bendrofluazide, are shown in Table 2. Blood pressure differed very little between

Table 1 Comparability of the two treatment groups at randomisation. Mean (and s.d.) data, $n = 10$ in each group.

	<i>Bendrofluazide increased</i>	<i>Xipamide added</i>
Sex (male:female)	4:6	7:3
Age (years)	51 (8.2)	53 (12.6)
Lying BP (mm Hg)—systolic	157 (12.2)	161 (10.5)
—diastolic	100 (1.1)	101 (4.5)
Standing BP (mm Hg)—systolic	148 (17.6)	145 (13.1)
—diastolic	100 (5.7)	97 (5.5)
Number taking β -adrenoceptor blocker	6	9
Serum urea (mmol/l)	6.4 (2.3)	5.1 (1.2)
creatinine (μ mol/l)	87 (24)	102 (17)
potassium (mmol/l)	4.3 (0.6)	4.1 (0.5)

the two treatments. For lying mean arterial pressure (MAP) xipamide had an advantage of 1.3 mm Hg, and the 95% confidence limits (Table 2) indicate that any advantage is unlikely to exceed 6.0 mm Hg. For standing MAP xipamide had an advantage of 0.3 mm Hg and this is unlikely to exceed 7.9 mm Hg. Compared to the increased dose of bendrofluazide, addition of xipamide elevated the blood urea by 1.3 mmol/l ($P < 0.001$), increased serum uric acid by 31 μ mol/l ($P < 0.1$), and lowered serum potassium by 0.42 mmol/l ($P < 0.1$). The fall in serum potassium with xipamide showed a trend to progress over the 6 week period, with mean differences from bendrofluazide 10 mg of 0.26 mmol/l after 2 weeks (NS) and 0.57 mmol/l after 6 weeks ($P < 0.05$). Body weight, serum

creatinine and glucose did not differ between the treatments.

In absolute terms blood pressure fell after addition of bendrofluazide or xipamide to the initial dose of bendrofluazide. The mean reductions in MAP were; for addition of bendrofluazide, $4.9 \pm \text{s.d. } 4.8$ mm Hg lying ($P < 0.05$) and 6.4 ± 5.5 mm Hg standing ($P < 0.02$); and for addition of xipamide 6.2 ± 5.3 mm Hg lying ($P < 0.01$) and 6.7 ± 9.9 mm Hg standing (NS).

Discussion

We explored the possibility that xipamide might have an antihypertensive effect additive to that

Table 2 Response to adding xipamide 20 mg ($n = 10$) compared to increasing bendrofluazide to 10 mg daily ($n = 10$). Results expressed as mean (and s.e. mean) differences between treatment groups. Minus values indicate xipamide lower than bendrofluazide.

	<i>Differences between treatments</i>		<i>95% confidence limits</i>	
	<i>Mean</i>	<i>s.e. mean</i>	<i>Lower</i>	<i>Upper</i>
Lying BP (mm Hg) systolic	+0.7	4.7	-9.1	: +10.5
diastolic	-2.2	2.0	-6.5	: +2.1
MAP	-1.3	2.3	-6.0	: +3.5
Standing BP (mm Hg) systolic	-1.2	6.0	-13.8	: +11.4
diastolic	+0.2	2.8	-5.7	: +6.1
MAP	-0.3	3.6	-7.9	: +7.3
Body weight (kg)	-0.1	0.3	-0.7	: +0.6
Serum potassium (mmol/l)	-0.42	0.22	-0.89	: +0.06
urea (mmol/l)	+1.29*	0.28	+0.74	: +1.84
creatinine (μ mol/l)	-5.9	3.8	-13.9	: +2.2
glucose (mmol/l)	+0.16	0.25	-0.37	: +0.69
uric acid (μ mol/l)	+31	15	-1	: +62

* $P < 0.001$ for difference between treatments.

of a ceiling dose of bendrofluazide because it had a diuretic effect additive to that of the thiazides in rats (Leuschner *et al.*, 1975). A dose of 5 mg daily of bendrofluazide was chosen as the ceiling dose because Marshall *et al.* (1977) had shown no additional antihypertensive effect of a higher dose in a study designed specifically to examine this point. In the present study an increase in dose of bendrofluazide from 5 mg to 10 mg daily was associated with a small but significant fall in mean arterial pressure, averaging 4.8 mm Hg lying and 6.4 mm Hg standing. It is important to recognise that this *apparent* response to the increased dose of bendrofluazide does not contradict the conclusion of Marshall *et al.* (1977) that 5 mg daily is the ceiling dose. A 'response' of this magnitude would be expected with addition of placebo in this type of study (McAreevey *et al.*, 1984). The fall in blood pressure after addition of both bendrofluazide and xipamide is also irrelevant to the comparison between bendrofluazide and xipamide, the comparison for which this study was specifically designed.

We observed no additive effect of xipamide 20 mg when added to bendrofluazide, with an advantage in MAP averaging only 1.3 mm Hg lying and 0.3 mm Hg standing. It is difficult to prove 'no difference' between treatments in

clinical trials, but the 95% confidence limits indicate that the study had satisfactory power. Any advantage of xipamide over bendrofluazide is unlikely to exceed 6 mm Hg in lying MAP or 8 mm Hg in standing MAP. Thus xipamide has no important advantage when added to bendrofluazide, as was the case when it was compared directly to cyclopentiazide (MacGregor *et al.*, 1982). On the other hand it had significant disadvantages, namely larger falls in serum potassium and larger rises in blood urea concentration when compared to bendrofluazide. Similar findings were reported by MacGregor *et al.* (1982) in comparison to cyclopentiazide.

The dose of xipamide used in this study, 20 mg daily, is the dose recommended by the manufacturer for the treatment of hypertension (20–40 mg daily). At this dose xipamide offers no important advantage over the thiazides as regards blood pressure control but has more pronounced unwanted biochemical effects. Compared to the thiazides it is more expensive and less well proven as regards long-term safety, and it has no obvious place in the management of hypertension.

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