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ONCE DAILY TREATMENT OF MILD TO MODERATE HYPERTENSION WITH XIPAMID: A CONTROLLED STUDY

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1 A double-blind, placebo controlled, crossover trial of 20 and 40 mg of xipamid once daily in the treatment of mild to moderate hypertension is reported and some of the difficulties and pitfalls of multicentre trials of this type are described.

2 Both doses were significantly more effective in reducing the blood pressure than the placebo and neither was superior to the other. Both produced some potassium loss. Xipamid acted for at least 22 h and was effective in up to 83% of the patients.

3 Further trials are suggested to investigate the activity of a lower dose than 20 mg.

Introduction

Xipamid (4-chloro-5-sulphamylsalicylic acid 2',6'-dimethylanilide) a non-thiazide diuretic is new to the United Kingdom, though several controlled clinical trials have been carried out in this country (Harding, Kalos, Weber & Dixon, 1974; Kalos, Dixon & Weber, 1974; Davies & Prichard, 1975; Piyasena, Havard & Weber, 1975). Its structure and pharmacology have been described by Harding *et al.* (1974) and by Davies & Prichard (1975) and its diuretic activity appears to be roughly equivalent to that of frusemide (Piyasena *et al.*, 1975). Its onset is, however slower and its effect more gradual, lasting for 12 h or more. This latter property suggested its use in hypertension in which successful results have been reported (Davies & Prichard, 1975; Harding *et al.*, 1974; Heimsoth, Bock & Debusmann, 1968).

Methods

Single daily doses of 20 mg and 40 mg of xipamid were compared with each other and with a negative control (placebo) in a randomized double-blind, double-crossover trial. Four hospital centres took part in the trial and at three the patients took the diuretic at 08.00 hours. In the remaining centre it was taken at 12.00 h in order to obtain information on its duration of action.

There were 28 men and 20 women of mean age 50.3 years (s.d. 6.4). They were suffering mainly from primary hypertension with a standing diastolic pressure between 95 and 120 mmHg. Secondary (e.g. renal) hypertension was not specifically excluded where treatment which might interfere with assessment of response was not required. Patients over the age of 65 years were excluded from the study as were pregnant women, those requiring cardiac glycosides, diabetics and any with a history of gout.

Trial design

The trial was designed to include a run-in period of at least 4 weeks at the commencement of which untreated patients whose informed consent to inclusion had been obtained were given a placebo tablet, known to the physician but not to the patient (single-blind phase). This tablet was substituted for the patient's usual treatment where necessary and was considered ethically justifiable as the hypertension was not severe (see above). At the end of this phase, if the standing diastolic pressure was still within the prescribed limits of 95 and 120 mmHg the patient was randomly allocated to either 20 or 40 mg of xipamid once daily or to the placebo in the double-blind phase of the trial. This point was designated Day 0.

If the standing diastolic pressure was very close to the prescribed limits and appeared to be still rising, or falling, a further period of observation was undertaken. After 4 weeks, sequential allocation of the drug supplies to the patients resulted in changing the treat-

ment, and again after a further 4 weeks. Each patient had four weeks' treatment with placebo, the 20 mg and the 40 mg tablet of xipamid according to a completely replicated six-line block design.

Patients were seen fortnightly and the following observations made:

1. A record of any symptoms since the last visit.
2. Blood-pressure measurements, taken by an independent observer, who did not know the previous readings or the results of biochemical tests, using either a Hawksley random zero apparatus or, in one centre, the London School of Hygiene sphygmomanometer. The measurements taken were:
   (a) Supine. The patient was allowed to rest for 5 min and the pressure taken 1 min after assuming decubitus (apart from a 20° backrest) and again at 3 minutes. The latter observation was used for the record.
   (b) Standing.
   (c) Immediately after exercise (IPE) (with the patient standing).
   (d) One min after exercise, with the patient standing (1 mPE). The exercise consisted of 24 steps in 1 min on and off an 8″ high platform.
3. Record of the patient's body weight.

Biochemical tests

Urine tests for glucose, protein and blood (by dipstick) were done at each attendance and plasma potassium was estimated. Plasma urate, blood urea and plasma bicarbonate and chloride were estimated at Day 0 and at the end of Weeks 4, 8 and 12. SGOT and alkaline phosphatase were estimated at Day 0 and Week 12.

Adverse reactions

Information on these was elicited as a response to a standard non-leading question.

Potassium supplements

Potassium supplements were commenced whenever the plasma potassium fell to below 3.0 mmol/l.

Results

Forty-eight patients were available for some of the analyses but two were withdrawn late in the trial where the exigencies of completing the trial in a reasonable time made it impracticable to replace them. One was a man from Centre 4 who failed to attend during the last few weeks of the trial, and the other a woman from Centre 1 whose early pregnancy was unknown at the commencement.

The overall comparisons between the placebo and the two doses of xipamid in terms of the average blood pressures reached after 4 weeks treatment were determined by two-way variance analyses and are set out in Table 1.

It will be seen that there was, for practically every measurement a significant or highly significant difference between the levels reached on placebo and those on xipamid, but no significant difference between the two doses of xipamid. The average diastolic pressures (standing and supine) for the placebo were, it will be noted, towards the lower end of the acceptance range for the trial. The results for the placebo (in terms of standing diastolic pressure) were therefore grouped according to their position in the treatment sequence. Thus, Placebo– was designated Position 1, –Placebo–, Position 2 and –Placebo, Position 3. The normality of the distribution

Table 1 Average blood pressures after four weeks treatment (mmHg to nearest whole number) and significance values (*P*)

	Average blood pressure (mmHg)			
Regimen	*Supine*	*Standing*	*IPE*	*1 mPE*
Placebo	159/97	153/99	166/102	159/100
Xipamid (20 mg)	148/94	144/93	156/94	149/94
Xipamid (40 mg)	145/90	142/93	154/92	147/96
Comparisons:				
Placebo with 20 mg	<0.001/NS	<0.05/<0.01	<0.05/<0.01	<0.01/<0.01
Placebo with 40 mg	<0.001/<0.01	<0.01/<0.01	<0.01/<0.01	<0.001/<0.01
20 mg with 40 mg	NS/NS	NS/–	NS/NS	NS/NS

IPE immediately post-exercise; 1 mPE 1 min after exercise.

of these three sets of figures was first confirmed by variance ratio test when F was found to be <1. The percentage changes in blood pressure from the respective Day 0 values for the three positions were calculated and the results collated in Table 2. The difference at Position 1 was not significant but was so at Positions 2 and 3. Moreover the difference between Positions 1 and 3 was itself significant ($P<0.05$).

Because of these observations, the two doses of xipamid were also examined in a similar way. The 20 mg dose showed a mean fall of 19% in Position 1 and 14.6% in Position 3, ($P=0.3$), and the 40 mg dose 12.5% in Position 1 and 19% in Position 3 ($P>0.1$). Thus the effects were in an opposite direction for the two doses, but the differences could easily have occurred by chance. It therefore seemed possible that the results due to the placebo were being influenced by carry-over effects from the preceding eight weeks treatment with the diuretic.

Finally, to complete this analysis the possibility that effects due to 20 mg of xipamid were being influenced by immediate proximity to 4 weeks treatment with 40 mg was investigated. The percentage fall from Day 0 when 20 mg immediately preceded 40 mg was 15.6%, and 13.5% when it followed it. This difference, again in an opposite direction from what might have been expected, was not significant ($P>0.6$).

Because in this series of patients there was no demonstrable difference in the effects of xipamid throughout the trial, and the effects of 20 and 40 mg were comparable, it was thought reasonable to examine the overall effect of the 20 mg dose on the standing diastolic blood pressure on a within-patient basis with reference to Day 0. The fall in standing diastolic pressure was 15% with a s.e. mean of 1.98%. The 95% confidence limits were therefore about 11–19%.

Proportion of patients responding

The clinical response of the patients was classified arbitrarily into three grades: Satisfactory, if after 4 weeks treatment their standing blood pressures were at or below 160/100 mmHg, and their post-exercise pressures showed no marked tendency to rise or fall; Partly satisfactory if the standing diastolic pressure was only a few mm above 100 mmHg and the patient would in normal practice have been given a small additional dose of an antihypertensive agent, and Unsatisfactory if these criteria were not met.

The results on 47 patients are shown in Table 3.

The differences between the proportion of patients responding completely satisfactorily whilst taking the placebo and the 20 and 40 mg doses respectively were significant ($\chi^2=6.229$, $P<0.02$ and $\chi^2=9.939$, $P<0.01$).

The high placebo response of around 43% is noteworthy. Four patients out of 47 responded to neither xipamid nor the placebo, and the capricious nature of patient-response to antihypertensive agents is illustrated by the fact that, on the criteria used, three patients appeared to respond to the placebo but not to xipamid.

Success in relation to previous treatment

There was no particular relationship between the previous treatment of the patients and their response to xipamid. Of the seven patients who failed to respond satisfactorily three had had no previous treatment, two had been treated with methyldopa, and two with a β-adrenergic receptor blocker. Of the 35 whose results were completely satisfactory, seven had previously had treatment with a thiazide diuretic, one with guanethidine, three with methyldopa and two

Table 2 Mean % changes in standing diastolic pressure (from Day 0) in placebo-treated patients related to their position in the treatment sequence

Observation	*Position 1*	*Position 2*	*Position 3*
Mean % change	−3.9	−6.97	−11.5
s.e. mean	2.98	2.22	2.22
n	15	16	16
P	<0.2	<0.01	<0.001

Table 3 Number of patients responding to treatment

Response	*Placebo*	*%*	*Xipamid (20 mg)*	*%*	*Xipamid (40 mg)*	*%*
Satisfactory	20	42.6	33	70.2	36	76.6
Partly satisfactory	0	—	6	12.8	2	4.3
Unsatisfactory	27	57.4	8	17.0	9	19.1

with β-adrenergic receptor blockers. The patient on guanethidine and one of those on methyldopa had also been treated with a thiazide diuretic simultaneously.

Effect of posture and exercise

Table 1 shows that there was no evidence, as regards the average values, of postural or post-exercise hypotension with either dose of xipamid. None of the individual patients exhibited these tendencies under the conditions of this trial.

Comparison of results between the treatment centres

Table 4 compares the actual mean standing diastolic pressures after four weeks treatment with the placebo and the two doses of xipamid respectively at each of the four treatment centres.

Centre 4 obtained consistently lower values than the other three centres and it will be noted that, for the placebo, the between-centre variation was statistically significant. The differences were not significant, however, for either of the two doses of xipamid.

Duration of action of xipamid

The patients at Centre 3 were instructed to take their dose of xipamid at mid-day rather than at breakfast time as at the other centres. This was done to see if xipamid had a long duration of action. Patients were seen in the morning about 22 h, therefore, after the last dose of xipamid. As has been seen (Table 4) the blood pressures achieved were not significantly different from those obtained at the other centres.

Clinical biochemistry

There was a tendency to dose-related changes in plasma electrolytes, blood urea and plasma urate. These results are set out in Table 5. The increase in blood urea between the 20 and 40 mg doses was itself significant ($P < 0.01$).

Although the changes described are well outside the limits of chance distribution they do not represent differences of clinical significance. They indicate a trend, however, which is clearly drug-related and is compatible with the pharmacology of xipamid and most other diuretics.

Plasma potassium

This has already been referred to in Table 5. A further investigation was made to determine if there was an increased frequency of hypokalaemia (as already defined) at the 40 mg dose. At the end of the first four weeks of the study estimations of plasma potassium were made on each of the 16 patients taking the 20 mg dose, and similarly for the 16 taking 40 mg. Four estimations gave values of less than 3.0 mmol/l for the first group, and three for the second. It was necessary to exclude these patients from subsequent consideration as they received treatment thereafter with potassium supplements in accordance with the trial protocol. The number of estimations considered during Weeks 5–8 was therefore $16-4=12$ for the 20 mg dose, and $16-3=13$ for the 40 mg dose. There were no further hypokalaemic values for patients taking the 20 mg dose but 4/13 (during Weeks 5–8) and 1/9 (during Weeks 9–12) for the 40 mg dose.

Table 4 Comparison of mean standing blood pressure (mmHg) between the four treatment centres (after 4 weeks treatment with placebo, 20 or 40 mg of xipamid)

	Centre 1	*Centre 2*	*Centre 3*	*Centre 4*	*F*	P
Number of patients	7	12	6	12		
Placebo	104.1	100.0	108.0	89.2	4.340	<0.01
Xipamid (20 mg)	95.1	94.6	95.8	85.8	1.624	NS
Xipamid (40 mg)	95.8	95.8	90.5	85.4	1.054	NS

Table 5 Plasma electrolytes, urate and blood urea levels during the trial

	Regimen			*Significance (P) of differences from placebo*		
		Xipamid			*Xipamid*	
Measurement	*Placebo*	*(20 mg)*	*(40 mg)*	*Normal range*	*(20 mg)*	*(40 mg)*
Blood urea (mmol/l)	5.4	6.4	7.1	1.4–8.2	<0.001	<0.001
Plasma Cl^- (mmol/l)	102	97	98	95–105	<0.001	<0.001
Plasma Na^+(mmol/l)	139	138	137	135–143	NS	<0.05
Plasma K^+ (mmol/l)	4.1	3.5	3.4	3.5–4.5	<0.001	<0.001
Plasma HCO_3^- (mmol/l)	26.1	28.7	28.8	23–33	<0.01	<0.001
Plasma urate (μmol/l)	335	406	414	100–400	<0.001	<0.001

The frequency of values of plasma K less than 3.0 mmol/l was therefore 4/40 (10%) for 20 mg of xipamid daily and 8/37 (21%) for 40 mg ($P > 0.3$).

The values given in Table 5 were calculated without regard to potassium supplementation. If the necessary adjustments are made, the mean value of 3.5 mmol/l for the 20 mg dose remains unchanged. The value of 3.4 mmol/l for the 40 mg dose falls to 3.3. The difference, however, is not significant ($P > 0.1$).

In this study, therefore, it was not possible to demonstrate that the extent of hypokalaemia was dose-related. There remains some reason for believing that the frequency of hypokalaemia may be greater with the higher dose, though this again is unsupported statistically.

Toxicology biochemistry

The alanine aminotransferase and plasma alkaline phosphatase values showed no suggestion of any drug-related change during the trial.

Side-effects

Symptoms elicited by the standard non-leading question, and clearly unrelated to some other obvious clinical cause were as set out in Table 6.

Of the symptoms elicited, headache seemed to be more common when the patients were taking the placebo, and dizziness and tiredness when they were taking either of the two doses of xipamid. The numbers are too small, however, to reflect any statistically significant differences although there remains a possibility that dizziness and tiredness were drug-related.

Body weight

The mean body weight of the patients whilst taking the placebo was 73.96 kg. After four weeks treatment with 20 mg of xipamid it was 73.00 kg ($P < 0.001$) and after 40 mg 73.24 kg ($P < 0.01$) representing the diuretic effect of the drug.

Returned tablet count

Patients were asked to return their tablet containers at each visit with any unused tablets. Provision had been made for two extra tablets per two week period, so that the total return for the six fortnightly visits should have been 12. Two patients were completely uncooperative in this respect and returned no tablets at any time. Nevertheless, their blood pressure responses suggested that they may have been taking treatment. One other patient defaulted late in the trial, and another was removed from the trial as she had become pregnant. The mean number of tablets returned was 13 (s.d. 5.6). Patient cooperation is always problematical in out-patient trials, and returned tablet counts are open to several interpretations.

Comparison of the mean returned tablet counts from the four centres gives:

1. 12.1; 2. 13.6; 3. 16.0; 4. 12.1.

The differences between the centres, by one-way variance analysis are not statistically significant. One patient from Centre No. 3 (No. 44) responded well to both doses, having taken only 79% of his quota of 20 mg tablets and 93% of his 40 mg tablets. Another (No. 45), responded satisfactorily to 68% of her 40 mg tablets, but slightly better to 86% of her 20 mg tablets. Patient No. 43, from the same centre, did not do so well on the 20 mg dose, but his returned tablet count was quite unreliable, and it is not clear how many tablets he actually took. The apparently successful outcome of four weeks treatment with doses of the order of 70% of that recommended leads one to wonder whether a lower dose than 20 mg or, because of carry-over effects demonstrable four weeks after discontinuing eight weeks treatment, dosage at less frequent intervals might be equally efficacious.

Discussion

This clinical trial was planned principally to compare the hypotensive effects of the 20 and 40 mg doses of

Table 6 Symptoms elicited in response to standard non-leading question

		Xipamid		
Symptom	*Placebo*	*(20 mg)*	*(40 mg)*	*Total*
Dizziness	4	9	9	22
Tiredness	4	9	9	22
Headache	10	5	6	21
Constipation	4	6	3	13
Weakness	4	1	4	9
Diarrhoea	3	2	2	7
Nausea	2	1	2	5
Frequency or polyuria	2	0	2	4
Total	33	33	37	103

xipamid with each other and with a placebo. Both doses of xipamid produced falls in blood pressure which were statistically significant when compared with the placebo and there was no significant difference between the effects of the two doses. The latter finding confirms the conclusions of Davies & Prichard (1975) in a longer study in a smaller number of patients using xipamid in combination with anti-hypertensive agents. Both doses lowered the plasma potassium, and it seems likely that potassium supplements will sometimes be necessary in the long term treatment of hypertension with xipamid.

The changes in the other plasma electrolytes, blood urea and plasma urate were not unexpected as they occur with other diuretics, e.g. thiazides. No serious side effects were seen.

No evidence of postural or post-exercise hypotension was obtained but it seems possible that mild dizziness may have been a drug-related side effect.

The sensitiveness of patients' blood pressures to placebo effects and to the attitude of the clinician is well known. Observer error, digit-bias and unmasking of the identity of the prescribed drug were some sources of error it was hoped would be eradicated by the design of this trial. A multicentre trial is clearly not the best method of investigating a hypotensive agent since it can only increase the potential number of variables. However, such considerations sometimes have to give precedence to the need to collect an adequate number of patients in a reasonable time, and this applies particularly when the patients are those who are usually managed outside hospital practice. The variability of the placebo effect between the centres and also in relation to its position in the treatment sequence illustrates some of the difficulties encountered.

The fall in standing diastolic pressure after four weeks treatment was compared with the Day 0 values on a within-patient basis in an attempt to obtain an approximate idea of the therapeutic potential of xipamid. The mean fall of 15% however, must be interpreted with due caution since the Day 0 values may not have been strictly basal, and the trial was not designed to investigate this aspect. The absence of sequence related changes in standing diastolic pressure for the two doses of xipamid as occurred whilst the patients were taking the placebo, and of between-centre variation in the Day 0 standing diastolic pressure values suggests that they were reasonably stable.

Up to 83% of the patients made a complete or partial therapeutic response whilst taking xipamid. 42.6% apparently responded completely when taking the placebo, and this large proportion again illustrates the high placebo response rate in these patients with mild or moderate hypertension.

A returned tablet count was used to attempt to quantify the patients' cooperation. Whilst its limitations are recognized and reference to the high placebo response has already been made, it seemed possible that some patients were obtaining a satisfactory response on fewer tablets than prescribed. Further trials are therefore recommended to determine if a lower dose than 20 mg daily is effective.

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