DRUGS OF TODAY Vol. 20, Suppl. 1, 1984, pp. 27-31

THE EFFICACY OF INDAPAMIDE IN HYPERTENSIVE PATIENTS FAILING TO RESPOND TO A β-BLOCKER ALONE

C.P. O'Boyle, D. Fitzgerald, J.G. Kelly, K. O'Malley and E.T. O'Brien

The Blood Pressure Clinic, The Charitable Infirmary, Jervis Street, Dublin 1, Ireland, and Department of Clinical Pharmacology, Royal College of Surgeons in Ireland, St. Stephen's Green, Dublin 2, Ireland

Summary: *A double blind, placebo controlled, cross over study was carried out to evaluate the efficacy and safety of 2.5 mg indapamide in 24 hypertensive patients failing to respond to oxprenolol alone. An additional 6 patients were assessed by ambulatory blood pressure recordings over a 15 hour period with a Remler M2,000 semi automatic sphygmomanometer. On average, indapamide reduced supine blood pressure by 18.5/10 mm Hg and standing blood pressure by 19.6/8.9 mm Hg. The ambulatory recordings carried out in 6 patients detected a fall in diastolic pressure not observed using clinic readings in these 6 patients, suggesting that this is a more sensitive method of detecting antihypertensive effect.*

These responses were not associated with significant changes in heart rate or body weight and there was no significant postural fall in blood pressure. No serious side effects were reported. Changes in serum potassium, chloride and urate similar to those seen with diuretics were observed. These results suggest that indapamide is a useful and safe adjunct to β adrenoceptor blocking therapy for uncontrolled hypertension.

Key words: Indapamide - oxprenolol - Remler ambulatory blood pressure recording - hypertension

Introduction

Indapamide has an antihypertensive effect in animals (1, 2) and man (3-5), the precise mechanism of which is not known. Although it has diuretic effects (6-8), a reduction in vascular reactivity compatible with direct vasodilation due to calcium antagonism has also been shown (2, 9, 10). Clinically the drug is not associated with the side-effects generally seen with vasodilator monotherapy.

Indapamide has been shown to be more effective than chlorothiazide (11) or frusemide (12) when used on its own, and as effective as a combination of amiloride and hydrochlorothiazide *(Moduretic®)* when used in combination with a variety of other antihypertensive agents (3).

This study is a double-blind placebo-controlled study of the efficacy of indapamide when added to oxprenolol monotherapy in patients not controlled on this drug alone.

Patients and Methods

Twenty four patients with benign essential hypertension, whose blood pressure was uncontrolled (diastolic blood pressure > 95 mm Hg) despite treatment with oxprenolol *(Slow-Trasicor®)* for at least 4 weeks were studied. Informed consent was obtained from patients and the protocol was approved by the Hospital Ethics Committee. Patients were randomly allocated to placebo or indapamide and crossed-over to alternate treatment after 8 weeks. A fixed dose of 2.5 mg indapamide was used for the duration of the study and patients continued on their initial oxprenolol dose which ranged from 160 to 480 mg/day. Assessments were made at baseline (at least 4 weeks of treatment with oxprenolol) and at 4 and 8 weeks of each treatment phase. We report here the data obtained at the end of each 8-week phase.

On each visit body weight, supine and standing systolic and diastolic blood pressure (5th phase) and heart rate were recorded. Single readings of blood pressure were obtained after 10 minutes' rest in the supine position and after two minutes standing. All blood pressure readings were made using a Hawksley random-zero sphygmomanometer. Unwanted effects were recorded at each visit. Blood urea, serum creatinine, sodium, chloride, potassium, calcium and urate were estimated at baseline and at the end of each treatment phase.

The mean age of the patients was 51.9 years

(range 36-67) and their mean ± SEM baseline weight was 70.5 ± 21.0 kg. Data were analysed using Student's 't' test for paired data.

An additional 6 patients were further studied by indirect ambulatory blood pressure recordings before and during each treatment phase with the Remler M2,000 semi-automatic recorder (13, 14). This device records blood pressure during waking hours only. Mean ambulatory recordings and clinic recordings for each period were compared by linear regression analysis. The hourly recordings for active drug and placebo periods were compared by Student's 't' test.

Results

Twenty three patients completed the study — 1 patient was withdrawn as she required an emergency hysterectomy. Baseline values and results of treatment with indapamide are compared with placebo in Table I. On indapamide, supine blood pressure (systolic/diastolic) was 18.5 ± 5.3/10.0 ± 2.3 mm Hg lower than on placebo. Standing blood pressure was 19.6 ± 5.6/8.9 ± 2.7 mm Hg lower on the active treatment. Magnitude of response varied considerably and in 5 patients there was a change in diastolic pressure of less than 5 mm Hg.

There were differences in response depending on whether patients started on placebo or indapamide (Table II). Although the level of supine blood pressure was similar following 8 weeks on indapamide, the baseline level was lower in those starting treatment with indapamide and the values for systolic blood pressure did not return to baseline following the placebo phase.

Ambulatory recording

The pattern of hourly blood pressure readings is shown in Fig. 1. There was a positive correlation between Remler ambulatory recordings and clinic

Table I: Mean blood pressure response to indapamide and oxprenolol at 8 weeks. Values are means ± SEM; n = 23; p values are indapamide against placebo

		Baseline phase (oxprenolol alone)	Placebo phase (oxprenolol + placebo)	Treatment phase (oxprenolol + indapamide)	P
Supine	SBP	186.5 ± 6.4	183.6 ± 5.4	165.1 ± 6.4	<0.01
	DBP	108.3 ± 1.3	108.9 ± 1.6	98.9 ± 2.3	<0.001
	HR	67.7 ± 1.2	72.1 ± 1.6	70.7 ± 1.9	n.s.
Standing	SBP	180.7 ± 5.8	175.5 ± 6.8	155.9 ± 7.0	<0.005
	DBP	113.0 ± 1.6	111.3 ± 1.8	102.4 ± 2.6	<0.005
	HR	73.5 ± 1.6	76.4 ± 2.1	76.3 ± 1.9	n.s.

Table II: Comparison of supine baseline data and blood pressure response in group 1 who received placebo first and group 2 who received indapamide first. Values are mean ± SEM

Group 1, n = 11	Baseline phase (oxprenolol alone)	Placebo phase (oxprenolol + placebo)	Treatment phase (oxprenolol + indapamide)
SBP	188.4 ± 8.2	193.5 ± 7.3	165.6 ± 7.3
DBP	110.4 ± 1.8	112.2 ± 2.7	99.1 ± 3.2
Group 2, n = 12	**Baseline phase (oxprenolol alone)**	**Placebo phase (oxprenolol + placebo)**	**Treatment phase (oxprenolol + indapamide)**
SBP	184.8 ± 10.0	174.7 ± 7.1	164.7 ± 10.6
DBP	106.3 ± 1.9	105.8 ± 2.6	98.7 ± 3.6

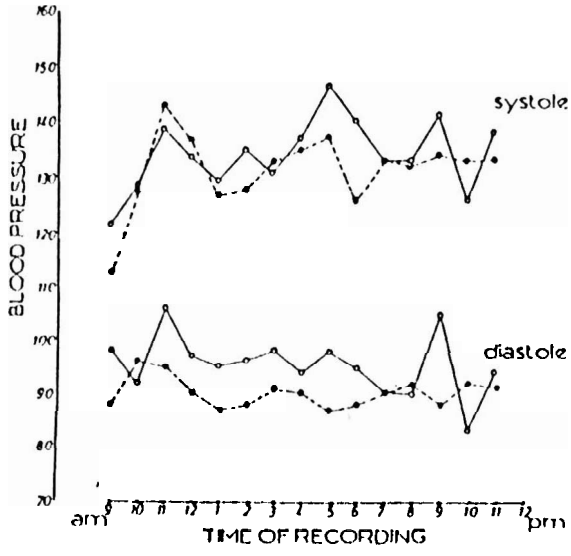

Fig. 1. Ambulatory hourly response in systolic and diastolic blood pressure on indapamide (•- - -•) compared to placebo (o——o). (Values are means for the number of patients who made recordings at any particular hour).

recordings both for systolic ($r = 0.63$) and diastolic ($r = 0.43$) blood pressure. Remler recordings at baseline were lower than clinic recordings by an average of 26 mm Hg for systolic blood pressure and 4 mm Hg for diastolic blood pressure (Table III). Although there was no significant change in clinic blood pressures in these 6 patients, univariate analysis of the mean hourly recordings for the group during ambulatory recording showed a significant fall in diastolic blood pressure ($P < 0.01$) but not for systolic blood pressure ($0.1 > P > 0.05$).

Side-effects and laboratory investigations

There were few unwanted symptoms and the antihypertensive effect was not associated with any change in body weight. One patient complained of an altered sleep pattern with early morning wakening which persisted for the active period and resolved on placebo therapy. A second patient on active treatment complained of an interrupted sleep pattern with unusual dreams, lasting for 5 days.

There were statistically significant falls in serum potassium and chloride levels and a significant rise in serum uric acid on indapamide (Table IV), but the mean levels remained within normal limits. Four patients who had normal baseline potassium levels had levels below 3.6 mmol/l at the end of the indapamide phase and 1 of these had a level of 2.9 mmol/l.

Table IV: Mean values for biochemical parameters on placebo and indapamide

Parameter	Placebo (8 weeks) (mmol/l)	Indapamide (mmol/l)	P
Potassium	4.2 ± 0.12	3.8 ± 0.11	< 0.02
Chloride	104.0 ± 0.48	99.9 ± 0.61	< 0.001
Urate	0.37 ± 0.02	0.42 ± 0.02	< 0.005

Discussion

The results of this study show that indapamide is an effective antihypertensive agent when given to patients who are inadequately controlled on a β-adrenoceptor blocking agent alone. The fall in supine systolic blood pressure and diastolic blood pressure due to indapamide of approximately 10 % from baseline is similar to the percentage falls in blood pressure seen when indapamide is used as the sole agent in either short- (15-17) or long-term studies (18-20). Although more effective than diuretics (11, 12, 21), its antihypertensive effect in combination with a β-adrenoceptor blocking agent is not as great as that seen with existing vasodilators (22-24).

Table III: Comparison of mean clinic recordings with mean of ambulatory recordings in 6 patients

	Baseline (oxprenolol)	Placebo	Indapamide	P
SYSTOLIC				
Clinic	173 ± 25.9	158 ± 19.9	153 ± 23.4	> 0.05
Remler	147 ± 32.0	139 ± 15.2	135 ± 15.6	> 0.05
DIASTOLIC				
Clinic	106 ± 10.5	100 ± 5.0	93 ± 4.6	> 0.05
Remler	102 ± 20.0	98 ± 13.4	91 ± 8.6	< 0.01

The difference in response between those starting on placebo and those starting on indapamide, although partially due to a difference in baseline values, was also due to a 'hang-over' of drug effect throughout the placebo phase in group 2. This effect has been documented with other drugs, including indapamide (25, 26).

The time course of response to indapamide is interesting in that the drug has a long half-life (27) and a duration of actioh in excess of 24 hours in animals. Although a 24-hour profile of blood pressure control has not been studied, ambulatory recordings (Fig. 1) confirm a prolonged action. In addition the 'hang-over' effect suggests an action which cannot be explained by the long half-life alone.

The Remler detected drug-induced changes in diastolic pressure that were not apparent with clinical measurement. The lack of effect on ambulatory systolic blood pressure is probably due to the comparatively low levels of systolic pressure in the ambulatory recordings.

Side-effects were uncommon. Sleep disturbances previously described (16) occurred in 2 patients and suggest a central effect. The statistically significant rise in serum urate and fall in serum potassium and chloride are similar to changes with thiazide diuretics. Although the fall in potassium did not pose problems clinically, it was greater in some individuals than that previously documented by Demanet et al. (18).

We conclude that low-dose indapamide is an effective and safe antihypertensive agent when combined with a β-adrenoceptor blocking drug.

Acknowledgements

The authors wish to thank Servier Laboratories for supplying indapamide and matching placebos.

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