Endralazine in patients with severe hypertension and renal insufficiency

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Summary

Endralazine, a new peripheral vasodilator, was given in conjunction with a beta-blocker to 21 patients with hypertension and chronic renal failure. All subjects were either poorly controlled on their previous antihypertensive regime or were experiencing unacceptable adverse effects from drugs. After 4 weeks blood pressure was reduced in all patients and symptomatic side effects were few. Two patients became anti-nuclear factor (ANF) positive in weak titre but without evidence of the lupus syndrome.

Introduction

Current management of hypertension in patients with renal impairment is often unsatisfactory and associated with unacceptable adverse effects from drugs. Endralazine is a new peripheral vasodilator chemically related to hydralazine but not dependent upon acetylation for its metabolism (Salzmann, 1973; Baldeck and Kalberer, 1978). The present study describes our experience with endralazine after one month in 21 patients with uncontrolled hypertension and chronic renal failure.

Patients and methods

Twenty-one patients who were attending the Renal Clinic at Southmead Hospital were studied. Their underlying renal disease is listed in the Table. The study had been approved by the Research and Ethical Committee of the hospital and all patients gave informed written consent. Hypertension was either uncontrolled on a maximum dose of beta-adrenergic blocking drugs (diastolic pressure ≥ 107 mmHg) or patients were experiencing unacceptable adverse effects with additional drugs. Thirteen patients were taking three or more antihypertensive

drugs. All 21 patients had stable chronic renal failure (creatinine clearance 23-86 ml/min). Five had received a cadaveric renal transplant and were receiving daily prednisolone and azathioprine (creatinine clearance 28-75 ml/min). Pregnancy, severe liver disease, renal failure requiring haemodialysis, and a positive ANF excluded entry to the study.

Before entering the study, patients were assessed clinically for evidence of cardiovascular disease. Blood pressure and heart rate were measured with the patient lying and 2 min after standing. Blood pressure was measured with a standard mercury sphygmomanometer and was calculated as the mean of two or three measurements at intervals of one minute. All measurements were made by the same investigator (ERH), the diastolic pressure being recorded as Korotkoff phase 4.

Measurements of renal function were performed weekly and consisted of blood urea, serum creatinine, creatinine clearance, 24 hr protein excretion and plasma electrolytes. In addition, blood haemoglobin, white blood cell count, plasma viscosity, blood sugar and liver function tests were recorded at the beginning and end of the study. The presence of DNA binding and ANF was also established before and at the end of the study, as was the acetylator status of each subject using the method of Price-Evans (1969). Electrocardiograms were recorded weekly and assessed for ischaemic changes.

Trial design

Antihypertensive drugs other than beta-adrenergic blockers and (in 13 patients) diuretics were discontinued on the first study day. On Day 1, following clinical assessment, patients received endralazine 2.5 mg by mouth. If there were no adverse effects in the

TABLE 1. Patient data before and after 4 weeks endralazine

Patient No/ age/sex	Renal disease	Drugs before study (excluding beta-blocker)	Plasma creatinine ($\mu\text{mol/litre}$)		ANF† After	DNA binding (units/ml)	
			Before	After		Before	After
1/55/M	Polycystic kidneys	B	201	198	neg	19	14
2/61/M	Polycystic kidneys	B, H	212	158	neg	9	18
3/61/F	Chronic pyelonephritis	H	150	169	neg	20	17
4/65/F	Chronic interstitial nephritis		152	158	neg	25	20
5/57/F	Calculus renal disease		239	240	1/100	39	20
6/59/M	Chronic pyelonephritis	B, H	177	140	neg	17	15
7/50/M	Chronic glomerulonephritis	B, H	139	141	neg	42	40
8/60/F	Hypertensive nephrosclerosis	F, MD	131	100	neg	14	56
9/35/M	Hypertensive nephrosclerosis	F, M	134	—	—	21	—
10/50/M	Chronic glomerulonephritis*	F, M	216	185	neg	10	26
11/46/M	Chronic pyelonephritis*	H, MD	136	128	neg	32	34
12/46/M	Chronic glomerulonephritis*	H	154	138	neg	23	40
13/13/M	Congenital ureteric reflux	F, M	117	92	neg	43	13
14/41/M	Polycystic kidneys	B, H	320	351	neg	48	26
15/59/M	Chronic glomerulonephritis	Mo, H	154	156	1/100	25	32
16/34/M	Diabetic nephropathy		150	132	neg	13	6
17/46/M	Polycystic kidneys	B	236	259	neg	17	6
18/55/M	Chronic glomerulonephritis	F, D	169	146	neg	12	17
19/44/M	Chronic glomerulonephritis	B, H	397	370	neg	39	72
20/17/M	Congenital ureteric reflux*	H	117	294	neg	18	—
21/30/M	Congenital ureteric reflux	B, H, MD	230	243	neg	50	30

* = Functioning renal allograft; † All negative before endralazine.

Drug code: B = bendrofluazide; H = hydralazine; MD = methyldopa; F = frusemide; M = minoxidil; Mo = Moduretic; D = diazoxide.

first 3 hr, they were continued on 2.5 mg three times daily. On Day 3, this was increased to 5 mg three times daily and subsequently on days 5, 7 and 10 by further increments of 5 mg to a total dose of 20 mg three times daily or until a satisfactory control of blood pressure was achieved (diastolic ≤ 102 mmHg).

Results

One patient (no. 9) was withdrawn after 2 weeks for failing to comply with the drug regime and this precipitated hypertensive heart failure. His results have not been included in the study.

Renal function was not affected significantly, although there was a tendency for serum creatinine to fall over the course of the study (Table 1).

The Figure shows the mean systolic and diastolic blood pressure and heart rate before and after the addition of endralazine in 20 patients. Nineteen patients had a reduction in lying and standing blood pressure. Final daily dose of endralazine was 7.5 or 15 mg (12 patients) and 30 or 45 mg (7 patients). Only one patient received 60 mg daily. Three patients failed to achieve acceptable blood pressure control at the end of the study. Patient 10 had a functional renal allograft and hypertension resistant to minoxidil. Subsequently he had a bilateral host nephrectomy but is now taking labetalol 600 mg a day with a blood pressure of 180/110 mmHg lying and standing. He is reluctant to start minoxidil because of previous fluid retention. Patient 14, who had already suffered a

cerebrovascular accident in association with hypertension had a blood pressure of 175/132 mmHg while taking hydralazine, oxprenolol and bendrofluazide. After one month blood pressure control was not improved by the substitution of endralazine 45 mg daily. Subsequently he was successfully treated with minoxidil but at the expense of hypertrichosis and a 6 kg fluid weight gain. In patient 18, diastolic pressure was not reduced below 105 mmHg by endralazine. However, he was able to discontinue the oral hypoglycaemic agent and most of the frusemide necessitated by his previous regime which included diazoxide.

Two patients became ANF positive by the end of the study, but with no clinical evidence of the lupus syndrome, and no significant rise in DNA binding (Table 1); both were taking 15 mg of endralazine daily. They have continued to be followed up, and at 6 months there has been no change in their titre of ANF and no adverse clinical effects have been seen. Neither patient was on any other drug known to produce a positive ANF. Patient 5 was a slow, and patient 15 a fast acetylator, acetylating less than and greater than 30% of an oral dose of sulphadimidine respectively.

The side effects which were mild and self-limiting consisted in four patients of tiredness, in three of facial flushing and headache (lasting approximately one week) and in one of unexplained vomiting during the first week of taking endralazine. Patient 12 had transient leucopenia during the study due to

cytomegalovirus infection in association with renal transplantation. This improved with reduction of his azathioprine. There was no evidence of hepatic or renal toxicity or any other laboratory or clinical abnormality. Mean body weight was unaffected by endralazine and no patient became clinically oedematous.

Discussion

Hypertension is a common problem in patients with renal impairment, which if inadequately controlled can lead to a more rapid decline in the patient's renal function (Moyer *et al.*, 1956). Treatment in these patients can be difficult because of the severity of the hypertension and the side effects of current drug regimes. The vasodilator hydralazine is in common use in the treatment of hypertension resistant to diuretics and beta-blockers. However, hydralazine often causes unpleasant haemodynamic symptoms such as headache and postural hypotension. Treatment with hydralazine is associated with seroconversion of antinuclear factor and, more rarely, development of a lupus-like syndrome (Perry, 1973). This effect is related to exposure to free drug and the major excretion of hydralazine is as the acetylated metabolite. Patients who acetylate the drug slowly are therefore those most at risk of developing this adverse effect (Perry *et al.*, 1970; Bing *et al.*, 1980). The present study has examined a new vasodilator, endralazine which is chemically related to hydralazine but for which acetylation is not a major route of metabolism (Baldeck and Kalberer, 1978).

Twenty-one patients entered the study and one was withdrawn after 2 weeks for failing to comply with regular drug taking. At the end of one month all but one patient had a reduction in lying and standing systolic and diastolic blood pressure while taking endralazine 7.5 mg to 60 mg daily in conjunction with beta-adrenergic blocker. Before the study nine patients were taking hydralazine, three minoxidil, one diazoxide and three methyl dopa. None of these patients has had to return to their previous drugs while receiving endralazine. There was no postural hypotension and no change in pulse rate after endralazine. Those patients previously treated with methyl dopa or minoxidil felt better than on their previous drug regime. Patient 14 failed to respond adequately to endralazine and is now controlled with minoxidil. Fluid weight gain is however only partially controlled with frusemide and he feels less well.

The dose of endralazine required to produce adequate blood pressure control was not dependent on the initial level of blood pressure nor the overall renal function.

Though two patients became ANF positive at a

FIG. 1. Mean ($\pm$ s.e.m.) blood pressure and pulse rate/minute before and after endralazine.

* $P < 0.005$

** $P < 0.001$ before vs after paired Student's *t*-test

titre of 1/100 during the study, there were no clinical signs of development of lupus syndrome and their DNA binding did not rise significantly. There was no correlation in the two patients with acetylator status, patient 5 being a slow and patient 15 a fast acetylator. At 6 months follow up of three patients none has developed any evidence of a lupus syndrome and the titre of ANF has remained low. The significance of these observations thus remains uncertain.

Though endralazine is a potent vasodilator, oedema and weight gain were not seen in this study. Severe symptomatic side effects did not develop during the 4 weeks of the study and have not been apparent in those patients who have continued therapy for up to 6 months. Fourteen patients in the study who had had troublesome side effects with their previous regime felt so well while taking endralazine that they have asked to be continued on the drug. We conclude that endralazine is a potent antihypertensive drug when used in conjunction with beta-adrenergic blockage. Further long-term studies are in progress.

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