

RENAL EFFECTS OF ANTIHYPERTENSIVE DRUGS IN ELDERLY
HYPERTENSIVES

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Introduction:

Epidemiological evidence incriminates hypertension as a risk factor for mortality and cerebrovascular and cardiovascular disease in the elderly (1). While it is now generally accepted that high blood pressure is a potent risk factor in all these regards, considerable controversy surrounds selection of older patients for antihypertensive drug treatment and for this reason the EWPHE study was set up some time ago (2). The results of the study in relation to the possible effects of drug treatment (hydrochlorothiazide with triamterene with or without alpha methyl dopa) on mortality and hypertension-associated diseases are not yet available, but a lot of data has been published on the blood pressure lowering effects of these drugs as well as their unwanted effects in patients with hypertension over the age of 60 (3,4,5). The diuretic combination with or without a modest dose of alpha methyl dopa lowered both systolic and diastolic pressures to levels which might reasonably be expected to confer protection against complications. However, the side effects produced are not inconsiderable. Predictably, they include decreased glucose tolerance, hyperuricaemia and despite continuing the thiazide with triamterene, there was a significant fall in serum potassium of 0.3 mmol/l (see Table 1). An additional unwanted effect was a statistically

TABLE 1
 CHANGES IN SOME BIOCHEMICAL VARIABLES DURING THE EWPHE STUDY, 1982

	Serum creatinine (mg%)		Serum uric acid (mg%)		Serum potassium (mg%)		Fasting blood glucose (mg%)	
	Placebo (396)	Active (390)	Placebo	Active	Placebo	Active	Placebo	Active
During run-in period	1.02	1.02	5.5	5.3	4.22	4.16	92.0	92.7
After 5 year	0.97	1.25***	5.2	7.5***	4.35	4.05**	91.0	100.5

Significance levels between the active and placebo group : **P < .01; ***P < 0.01
 The data are for approximately 400 patients in active and placebo group

significant increase in serum creatinine. Increases in serum creatinine may be related to a reduction in renal perfusion of pressure. It seems unlikely that structural damage to the kidney occurs although triamterene may cause nephrotoxicity.

Beta adrenoceptor blocking drugs have varying effects on renal blood flow, glomerular filtration rate and renal function depending on the circumstances in which they are studied (6). Propranolol has been reported to decrease renal blood flow (7,8), while nadolol was found by Textor and colleagues (9) to leave renal blood flow unchanged in the face of a fall in cardiac output. Similarly, the cardioselective beta adrenoceptor blocking drug atenolol has been reported by Waal-Manning and Bolli (10) to have no effects on renal blood flow.

Irrespective of whether there is a significantly higher level of adverse renal effects in the elderly with beta blocking drugs, doubt has been expressed concerning their efficacy in older hypertensives (11,12).

It is against this background of doubt about antihypertensive efficacy, concern with the adverse reaction pattern seen with diuretics and apparently conflicting reports concerning the possible effects of beta adrenoceptor blocking drugs on renal function that we decided that the blood pressure lowering effects and renal action of three beta adrenoceptor blocking drugs, atenolol, nadolol and labetalol should be studied in elderly hypertensive patients. Three separate studies were carried out. Effective renal blood flow was measured using the plasma disappearance of ^{125}I hippuran and glomerular filtration rate was measured using ^{51}Cr EDTA decay from plasma. The elderly were arbitrarily defined as those over 60 years of age and all had confirmed diastolic blood pressure above 95 mmHg.

Atenolol:

This was a randomised double-blind cross-over study in which ten elderly hypertensive patients took part. Each treatment phase lasted 12 weeks and blood pressure and flow measurements were taken at the end of each of the treatment phases. On placebo the mean arterial pressure was 130 mmHg ± 2 and on atenolol 108 ± 2 . The corresponding mean (\pm SEM) renal blood flow values, ml/min/1.73m² were 513 ± 87 and 646 ± 116 (p<0.05) and GFR, 56 ± 7 and 58 ± 7 .

Nadolol:

This was a randomised single-blind study in which ten patients participated with each phase - placebo and nadolol - lasting 10 weeks. Mean arterial pressure on placebo was 559 ± 36 and 447 ml/min/1.73m² on nadolol (p<0.05). Neither glomerular filtration rate or renovascular resistance changed.

Labetalol:

In this study nine young (22-55 years) and nine elderly (65-85 years) hypertensives took part. This was a comparative study in which the effect of labetalol in these two age groups was compared. Hypertension was defined as a diastolic blood pressure greater than 95 mmHg on three successive clinic visits. After an initial dose ranging study patients entered a double-blind placebo-controlled randomized cross-over study. The blood pressure values observed at the end of each of the twelve week treatment phases are given in Table 2. Labetalol lowered blood pressure in all patients. In both groups the fall in blood pressure was similar - 17.4/12.0 mmHg in the young, compared to 21.8/14.8 mmHg in the elderly hypertensives.

TABLE 2

LABETALOL - BLOOD PRESSURE, mmHg

	<u>Young</u>	<u>Elderly</u>
Systolic		
Placebo	148.2 \pm 5.6	180.7 \pm 9.0
Labetalol	131.8 \pm 5.6	158.9 \pm 8.9
Diastolic		
Placebo	95.6 \pm 2.1	102.0 \pm 2.4
Labetalol	83.6 \pm 1.5	87.2 \pm 1.8

Mean \pm SEM

Discussion:

The aims of the present series of studies were to ascertain if 1) beta adrenoceptor blocking drugs are effective blood pressure lowering agents in elderly hypertensives, 2) Beta blocking drugs have a deleterious effect on renal function, 3) Can beta adrenoceptor blocking agents be used as first-line treatment in hypertension in the elderly. Obviously the answer to question 3 depends very much on those obtained in response to questions 1 and 2. All drugs lowered blood pressure by a clinically significant amount. In the labetalol study differences in baseline blood pressure values in the two groups make a comparison of drug efficacy difficult. However, in both groups the fall in blood pressure was similar. It would seem therefore that beta adrenoceptor blocking drugs are effective in lowering high blood pressure in the elderly though clearly properly executed comparative studies with thiazide diuretics are needed so that the relative efficacy of these two major groups of drugs can be ascertained in this population.

The pattern of effect on renal blood flow was rather unexpected. Atenolol increased renal blood flow, nadolol reduced it, while labetalol had no significant effect. In no case could a systematic difference in glomerular filtration rate be demonstrated. Also there was no clinically significant change in serum creatinine or blood urea. It is tempting to suggest that the cardioselective blocker atenolol had a beneficial effect on renal blood flow by virtue of not blocking renal β_2 -adrenoceptors. Such an effect might allow maintenance of renal blood flow in the presence of falling cardiac output but it is extremely difficult to explain an actual rise in effective renal blood flow without postulating a vasolidatory action. Our findings with nadolol are at variance with those of Textor et al (9) who examined the effects of the drug in younger hypertensives. It may be that the patient's age is an important variable in determining the pattern of response observed. In the case of labetalol, the alpha adrenoceptor blocking action of the drug had a beneficial effect in maintaining renal blood flow in the face of a probable diminution of cardiac output.

Conclusion:

Our study shows that all three beta blockers were effective in lowering blood pressure and that while these drugs had disparate effects on the renal circulation the absence of a significant effect on serum creatinine and urea and glomerular filtration rate suggest that the observed changes in effective renal blood flow are probably not clinically significant.

Thus they should be considered as alternatives to diuretics in the elderly. However, we need additional studies on large groups of patients in which the efficacy and unwanted effects of beta adrenoceptor blocking drug (s) and diuretic (s) are compared before a firm recommendation can be made.

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