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ANTIHYPERTENSIVE AND RENAL HAEMODYNAMIC EFFECTS OF ATENOLOL AND NADOLOL IN ELDERLY HYPERTENSIVE PATIENTS

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1 As little is known of the antihypertensive efficacy or renal haemodynamic effects of β-adrenoceptor blocking drugs in the elderly we studied two such drugs, atenolol and nadolol, in elderly hypertensive patients. Ten patients took part in a placebo-controlled double-blind study of atenolol and 10 received nadolol in a single-blind placebo-controlled study. Treatment phases lasted 12 weeks for atenolol or 10 weeks for nadolol. Blood pressure, effective renal blood flow and glomerular filtration rate data obtained at the end of each treatment phase were analysed.

2 Atenolol lowered mean arterial pressure (mean ± s.e. mean) from 129.9 ± 1.5 to 108.2 ± 2.3 mm Hg ($P < 0.01$) while it increased mean effective renal blood flow from 512.5 ± 86.6 to 646.0 ± 116.1 ml min^{-1} 1.73 m^{-2} ($P < 0.05$).

3 Nadolol reduced mean arterial pressure from 133.2 ± 2.0 to 113.5 ± 3 mm Hg ($P < 0.001$) but reduced mean effective renal blood flow from 558.8 ± 32.2 to 446.0 ± 26.9 ml min^{-1} 1.73 m^{-2} ($P < 0.05$).

4 Glomerular filtration did not alter significantly with either drug.

5 We conclude that β-adrenoceptor blocking drugs are effective antihypertensive agents in the elderly but have disparate effects on effective renal blood flow perhaps because of differences in cardioselectivity.

6 These data suggest that comparative studies with thiazide diuretics and β-adrenoceptor blocking drugs are warranted in elderly hypertensives.

Keywords atenolol nadolol elderly hypertensives renal blood flow

Introduction

β-adrenoceptor blocking drugs are effective antihypertensive agents but some have been reported to cause a deterioration in renal function. Propranolol reduces renal blood flow (Schirmeister *et al.*, 1966; Nayler *et al.*, 1967; Sullivan *et al.*, 1976), and glomerular filtration rate (Ibsen & Sederberg-Olsen, 1972; Bauer & Brooks, 1979). Similar effects have been reported with oxprenolol (Bufano & Piacentini, 1969), pindolol (Heierli *et al.*, 1972) and acebutalol (Dreslinski *et al.*, 1981). In contrast, nadolol has been observed to increase renal blood flow, when administered intravenously (Hollenberg *et al.*, 1979a) and in chronic use renal blood flow is maintained in the face of diminished cardiac output (Textor *et al.*, 1982). β-adrenoceptor blockers have a direct effect on renal blood flow when administered in doses insufficient to produce systemic haemodynamic changes (Carriere, 1969; Sullivan *et al.*, 1976). However, these direct renal circulatory effects may not persist with larger doses which alter systemic haemodynamics. Therefore, when assessing renal circulatory response to β-adrenoceptors, it is important that the effects be observed when the therapeutic goal, reduction of blood pressure, is achieved.

Because there is an age related decline in renal function adverse effects on renal circulation might be greater in elderly hypertensive patients. Furthermore, doubts have been expressed concerning the efficacy of β-adrenoceptor blocking drugs in elderly hypertensives (Buhler *et al.*, 1975; Niarcos & Laragh, 1980). It was against this background of confusion about the renal haemodynamic effects of β-adrenoceptor blocking drugs in general and special concern about antihypertensive efficacy and possible renal effects in the elderly that we studied the antihypertensive and renal circulatory effects of two β-adrenoceptor

blocking drugs, atenolol, a cardioselective agent and nadolol, a non-selective drug, during chronic oral administration in elderly hypertensive patients.

Methods

Patients

Twenty elderly patients (12 male, eight female, age range 63–80 years, mean age 70.5 years) with systolic blood pressure > 160 mm Hg and/or diastolic blood pressure > 95 mm Hg, were studied. None had secondary hypertension or was receiving antihypertensive therapy prior to the study. Patients in whom treatment with β-adrenoceptor blocking drugs was contraindicated were excluded as were patients with serum creatinine greater than 120 μmol/l. Ten patients (mean age ± s.e. mean, 71 ± 1.8 years) were given atenolol and ten patients (mean age 70 ± 1.8 years) received nadolol. The study protocols were approved by the Hospital Ethics Committee and informed consent was obtained in each case.

Study design

(a) Atenolol: This was a randomised, double-blind, placebo-controlled, cross-over study. Each treatment phase lasted 12 weeks. The initial daily dose of atenolol was 100 mg. Patients were seen at two weekly intervals when dosage was increased in increments of 50 mg to a maximum of 200 mg if blood pressure had not fallen below 160/90 mm Hg.

(b) Nadolol: This was a randomised, single-blind, placebo-controlled cross-over study. Each treatment phase lasted 10 weeks. The initial daily dose of nadolol was 80 mg daily. Patients were seen at two weekly intervals when dosage was increased in increments of 80 mg to a maximum of 240 mg if blood pressure had not fallen below 160/90 mm Hg.

Methodology

Blood pressure was measured indirectly with a standard mercury sphygmomanometer at each visit. Recordings were made from the right arm while the patient was seated having rested for 3 min. Korotkoff phase V (disappearance of sounds) was accepted as the diastolic level. Mean arterial pressure is defined as the diastolic pressure plus one third of the pulse pressure, expressed in mm Hg.

Glomerular filtration rate and effective renal blood flow were measured at the end of each treatment phase, by the single intravenous isotope injection technique using an open two compartmental model for plasma clearance (Harries *et al.*, 1972; Pearson, 1979). Glomerular filtration rate was measured using ^{51}Cr-EDTA clearance after an intravenous dose of 30 μCi. Effective renal plasma flow was measured using [^{125}I]-hippuran clearance after an intravenous dose of 30 μCi and effective renal blood flow was then calculated by correction for the simultaneously determined haematocrit. All values were corrected for a body surface area of 1.73 m^2. During the procedure patients were seated and after the single intravenous injection of the isotopes, blood samples were withdrawn through a venous cannula in the opposite arm at 0, 5, 10, 15, 20, 30, 40, 50, 60, 80, 100, 120, 140, 160 and 180 min. Samples were assayed in a standard well counter along with a blank tube and standards from the stock solutions from which the administered doses were drawn. Renovascular resistance was calculated as mean arterial pressure divided by effective renal blood flow and is expressed in arbitrary units. Values were compared between placebo and active drug phase in each study using Student's *t*-test for paired data. A probability value less than 5% was taken to be significant.

Results

The mean (± s.e. mean) data for systolic and diastolic pressure as well as heart rate for placebo and active treatment are given in Table 1. Mean differences are also given.

Atenolol

Eight patients received a maximum daily dose of 100 mg, one received 150 mg and one received 200 mg. Atenolol significantly reduced mean arterial pressure from 129.9 ± 1.5 to 108.2 ± 2.3 mm Hg ($P < 0.001$). This represents a mean fall in systolic pressure of 31.8 ± 3.2 mm Hg and 16.6 ± 1.5 mm Hg in diastolic pressure with atenolol. Heart rate fell from 85.2 ± 2.4 to 63.8 ± 1.9 beats/min ($P < 0.001$). Glomerular filtration rate did not change significantly, 56.4 ± 6.7 as against 58.4 ± 7.0 ml min^{-1} 1.73^{-2}. Effective renal blood flow increased from 512.5 ± 86.6 to 646.0 ± 116.1 ml min^{-1} 1.73 m^{-2} ($P < 0.05$) (Figure 1). Renovascular resistance fell from 0.33 ± 0.06 to 0.20 ± 0.02 units ($P < 0.05$).

Nadolol

Five patients received a maximum daily dose of 80 mg, two received 160 mg and three received 240 mg. Nadolol significantly reduced mean arterial pressure from 133.2 ± 2.0 to 113.5 ± 2.0 mm Hg ($P < 0.001$), systolic pressure falling by 33.4 ± 2.6 mm Hg and diastolic pressure by 12.0 ± 0.9 mm Hg. Heart rate fell from 84.2 ± 2.0 to 68.0 ± 1.2 beats/min ($P < 0.001$). Glomerular filtration rate did not change significantly, 49.9 ± 3.5 as against 52.5 ± 2.7 ml min^{-1} 1.73

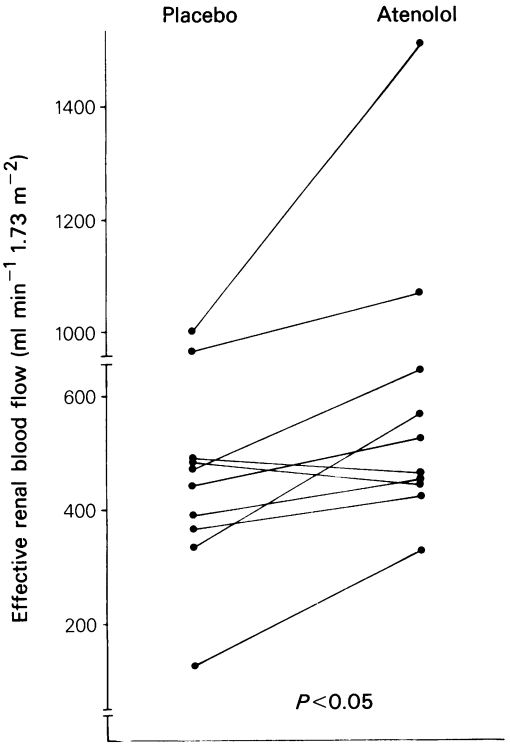

Figure 1 Effective renal blood flow following 12 weeks of placebo and atenolol.

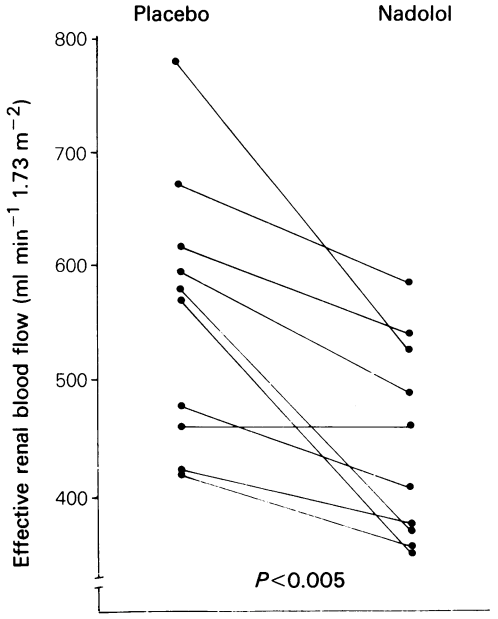

Figure 2 Effective renal blood flow following 10 weeks of placebo and nadolol.

m^{-2}. Effective renal blood flow decreased significantly from 558.8 ± 36.2 to 447.0 ± 26.9 ml min^{-1} 1.73 m^{-2} ($P < 0.005$) (Figure 2). Renovascular resistance did not change, 0.25 ± 0.02 as against 0.27 ± 0.02 units.

Discussion

Both atenolol and nadolol reduced blood pressure and by roughly similar amounts, atenolol by an average 31.8/16.4 and nadolol by 33.4/12.1 mm Hg but they had disparate effects on effective renal blood flow. The decrease in effective renal blood flow with nadolol contrasts with the increase observed by Hollenberg and colleagues (1979a). However, there are important differences between the studies. They observed the acute effects of intravenous nadolol in young patients not all of whom were hypertensive and in whom a fall in arterial pressure was not reported. Our study was in elderly hypertensive patients in whom chronic oral nadolol reduced arterial blood pressure. Furthermore, Hollenberg's method of measuring renal blood flow, by ^{133}Xe washout from the kidney, was different from that of our study. More pertinent perhaps is the recent study of Textor and colleagues (1982) who demonstrated unchanged renal blood flow despite a fall in

Table 1 Blood pressure and heart rate response to atenolol and nadolol

	Placebo	*Atenolol*	*Difference*	*Placebo*	*Nadolol*	*Difference*
Blood pressure (mm Hg)						
Systolic	181.6	149.8	31.8	188.6	155.2	33.4
	±3.8	±4.2	±3.2	±3.5	±4.7	±2.6
Diastolic	104.0	87.4	16.6	105.6	92.6	12.0
	±1.1	±1.6	±1.5	±1.8	±2.3	±0.9
Mean	129.9	108.2	21.7	133.2	113.5	19.7
	±1.5	±2.3	±1.9	±2.0	±2.0	±1.4
Heart rate (beats/min)	85.2	63.8	21.4	84.2	68.0	16.2
	±2.4	±1.9	±2.9	±2.0	±1.2	±1.9

Mean ± s.e. mean; $n = 10$. All differences between placebo and active drugs were significant at $P < 0.001$ level (paired t-test).

cardiac output with chronic nadolol treatment in young hypertensive patients. In the present study renovascular hypertension did not change so there appears to be a failure of autoregulation with this drug in our population. We speculate that the difference in results may in part be related to patient age—the elderly patient's autoregulatory responses being different in some way.

Because of lack of detail it is difficult to compare our results with other published reports some of which are only in symposia proceedings (Britton *et al.*, 1980; Danesh & Brunton, 1980). The remaining study of Waal-Manning & Hobson (1980) included patients receiving various other drugs in addition to nadolol so interpretation is very difficult.

Neither atenolol nor nadolol has a consistent effect on glomerular filtration rate, possibly because of redistribution of renal blood flow. It would perhaps have been surprising if atenolol increased glomerular filtration rate because, with the exception of teprotide (Hollenberg *et al.*, 1979b), no antihypertensive drug systematically increases it.

As the baseline data (age, blood pressure, heart rate, glomerular filtration rate and renal blood flow) were similar for both groups, it would seem reasonable to compare the results for both drugs. The difference between atenolol and nadolol with regard to renal blood flow change is noteworthy. Atenolol increased renal blood flow by 25% whereas nadolol reduced flow by 20%. Changes in renovascular resistance suggest that renovascular autoregulation was not only maintained with atenolol but a vasodilatory effect must be postulated.

These drugs differ primarily in their cardioselectivity. Atenolol blocks β_1-adrenoceptors only while nadolol blocks both β_1- and β_2-adrenoceptors. As all β-adrenoceptor blocking drugs, irrespective of selectivity, reduce renin secretion (Aberg, 1974; Wilcox, 1977; Zech *et al.*, 1971) the different effects cannot be explained by disparate actions on the renin-angiotensin system. The renal vasculature contains β-adrenoceptors (McNay & Goldberg, 1966). If β_2-adrenoceptors mediate renal vasodilatation in man, their blockade by nadolol but not atenolol would explain the reduction in effective renal blood flow with the former and the maintenance of renal autoregulation with the latter. However, this hypothesis does not explain the increased renal blood flow observed with atenolol.

The treatment of hypertension in the elderly (O'Malley & O'Brien, 1980), is a controversial subject. The efficacy and unwanted effects of most antihypertensive drugs have not been assessed in elderly patients. Because of a preponderance of low renin hypertension in the elderly it has been suggested that β-adrenoceptor blocking drugs would be ineffective (Niarchos & Laragh, 1980). This study indicates that both atenolol and nadolol are effective blood pressure lowering drugs in elderly hypertensive patients but in the case of nadolol it must be borne in mind that the observer was not 'blinded' so that observer bias was possible. On the present evidence atenolol would appear preferable to nadolol but comparative studies employing the same patients would be required to give definitive information. As thiazide diuretics are not without significant side effects in the elderly (O'Malley & O'Brien, 1980) the relative efficacy and propensity to cause side effects of these two groups of drugs should be studied so that an informed decision can be made as to which is the drug of first choice in elderly hypertensives.

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