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β-Adrenoceptor Blocking Drugs and Renal Blood Flow with Special Reference to the Elderly

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Summary

Adrenergic receptors in the kidney mediate changes in renal blood flow. α-Adrenoceptor stimulation results in vasoconstriction while stimulation of β_1-adrenoceptors has a similar effect mediated through the renin-angiotensin system. On the other hand, β_2-adrenoceptors mediate direct vasodilatation. Therefore adrenoceptor blockade may be expected to alter renal blood flow.

In general, in young patients, cardioselective drugs tend to reduce renal blood flow. However, little data are available on the effects of β-blockade in elderly patients. As hypertension in this group differs in many respects from that in young patients, we observed the antihypertensive and renal effects of atenolol, nadolol and labetalol in elderly hypertensive patients.

Our data suggest that in the elderly, β-blocking drugs are effective antihypertensive agents but they have disparate effects on renal blood flow. Cardioselective agents appear to have less tendency to reduce renal blood flow than non-selective ones. However, the clinical significance of such changes in renal blood flow in the presence of unaltered glomerular filtration rate and normal biochemical indices of renal function remains to be elucidated.

1. Introduction

β-Blocking drugs have an established role in the treatment of hypertension in young and middle-aged patients (Simpson, 1974). Many adversely affect glomerular filtration and renal blood flow but the clinical significance of such changes is debatable (Wilkinson, 1982). The efficacy of β-blocking drugs in lowering blood pressure in elderly patients with hypertension has not been assessed nor indeed has their effect on renal blood flow. The elderly comprise almost half the patients undergoing treatment for hypertension in the United Kingdom (Tudor Hart, 1980). Many of these patients have reduced renal function associated with ageing. In addition they are at risk from the effects of hypertension on the kidney; thus, any deleterious effect of drugs in this group may be more important than in younger patients. In this paper we consider the role of adrenoceptors in control of renal blood flow, review existing data on the effect of β-blockade on renal function and outline our studies with atenolol, nadolol and labetalol in elderly hypertensive patients.

2. Adrenergic Receptors and Renal Blood Flow

2.1 α-Adrenoceptors

α-Adrenoceptors are present in the renal vasculature (Rector et al., 1972) and mediate renal

vasoconstriction. However, there does not appear to be a resting vasoconstrictor tone mediated through this system as renal denervation does not increase renal blood flow (Berne, 1952). Exercise is associated with α-mediated vasoconstriction with a resultant decrease in glomerular filtration rate and renal blood flow (Swainson et al., 1980). This reduction is even more pronounced when the β_2-adrenoceptors are blocked.

α-Blocking drugs such as prazosin and phenoxybenzamine have no effect on renal blood flow at rest because of the absence of α tone in renal vessels. However, these agents do prevent a fall in renal blood flow under conditions where α activity is increased, such as cardiac failure (Millard et al., 1972). Unlike some other β-blocking agents, labetalol, which has α- as well as β-blocking properties, does not reduce renal blood flow during exercise (Larsen and Pederson, 1980).

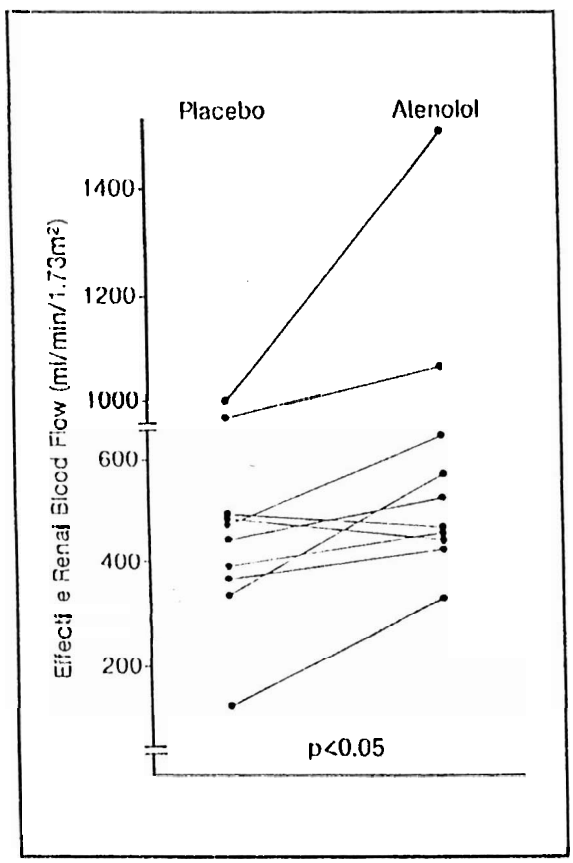

Fig. 1. Effective renal blood flow in 10 elderly hypertensive patients following 12 weeks' treatment with placebo and atenolol.

2.2 β-Adrenoceptors

β-Adrenoceptors are subdivided into β_1-β_2-receptors based on characteristic responses to sympathomimetic amines (Lands et al., 1967). The β_1-receptors mediate cardiostimulation and renin release while β_2-receptors mediate direct vasodilatation. Renin produces vasoconstriction through angiotensin II. By decreasing renin release, β_1-blockade tends to increase renal blood flow. β_2-Adrenoceptors mediate vasodilatation and have been demonstrated in the renal vasculature (Mark et al., 1969).

In addition to local actions on the renal vasculature, the overall renal haemodynamic response to β-stimulation or blockade depends on systemic effects brought about by changes in sympathetic activity, particularly cardiac output and arterial blood pressure. In the elderly, matters are further complicated as there is decreased responsiveness to both β_1- and β_2-stimulation (Dillon et al., 1980; Vestal et al., 1979), and blockade (Conway et al., 1971) compared with young adults.

In summary, the renal haemodynamic effects of any β-blocking agent are difficult to predict because of the large number of variables. Individual β-blocking drugs differ in their effect on renal blood flow because of differences in their selectivity and added properties. Furthermore, in the elderly, responsiveness is diminished.

3. Effects of β-Adrenoceptor Blocking Drugs on Renal Blood Flow in the Young

Differences have been observed between the renal haemodynamic effects of β-blocking drugs when given short term by intravenous injection and when administered orally long term. Such differences probably reflect physiological adaptation to many of the acute effects during long term therapy. As antihypertensive medication is taken long term, the effects of β-blocking drugs during long term administration are more clinically relevant.

3.1 Short Term Intravenous Administration

In young patients, the majority of β-blocking drugs, irrespective of cardioselectivity, have been shown to decrease renal blood flow following intravenous administration. This effect has been noted with atenolol and metoprolol (Swainson et al., 1980)

as well as propranolol (Sullivan et al., 1976) and pindolol (Heierli et al., 1977). The average reduction in renal blood flow is about 12%. In contrast to these findings, nadolol has been observed to increase renal blood flow in a combination of young healthy and hypertensive subjects on a low salt diet (Hollenberg et al., 1979).

3.2 Long Term Oral Administration

Long term oral therapy with propranolol reduces renal blood flow (Bauer and Brooks, 1979; O'Connor et al., 1978) while no change was observed with the non-selective drug, alprenolol, which has partial agonist activity (Pedersen, 1975). Little conclusive evidence is available regarding the effect of long term oral administration of nadolol on renal blood flow. Waal-Manning and Hobson (1980) found no change. On the other hand, Britton et al. (1980) found that renal blood flow increased following nadolol in 5 of 6 patients with normal cardiac output whereas it fell in 2 patients with initially high cardiac output. Waal-Manning and Bolli (1980) found no change in renal blood flow during long term oral therapy with atenolol.

4. *Effect of β-Adrenoceptor Blockade in Elderly Hypertensive Patients*

Hypertension in the elderly differs in many respects from hypertension in younger patients. Messerli et al. (1981) found that elderly hypertensives had a lower cardiac index and intravascular volume and higher systemic vascular resistance than matched young hypertensive patients. As β-adrenoceptor responsiveness in the elderly is altered and their renal function is reduced we observed the effect of long term oral administration of atenolol, nadolol and labetalol on blood pressure and effective renal blood flow in elderly hypertensive patients.

4.1 Atenolol

This was a randomised double-blind placebo-controlled crossover study in which 10 elderly hypertensive patients took part. Each phase lasted 12 weeks. Effective renal blood flow was measured at the end of each phase from the plasma clearance of ^{125}I-hippuran and a simultaneous haematocrit and glomerular filtration rate from the plasma clearance of ^{51}Cr EDTA. Atenolol caused a mean 25% increase in effective renal blood flow, from 512 to 646 ml/min/1.73m² ($p < 0.05$) [fig. 1]. During atenolol therapy average mean arterial pressure was reduced from 130mm Hg to 108mm Hg ($p < 0.001$). There was no significant change in glomerular filtration rate, while mean serum creatinine levels increased by an average of 9% during atenolol therapy but remained within the normal range.

4.2 Nadolol

This was a randomised, single-blind, placebo-controlled, crossover study in which 10 elderly hypertensive patients took part. Each phase lasted 10 weeks and effective renal blood flow was measured at the end of each phase. Nadolol reduced renal blood flow by an average of 20% from 55[illegible] to 447 ml/min/1.73m² ($p < 0.005$) [fig. 2]. Average mean arterial pressure was reduced from 133mm Hg to 114mm Hg ($p < 0.001$) during nadolol treatment. Glomerular filtration rate did not alter significantly, nor did serum creatinine or blood urea

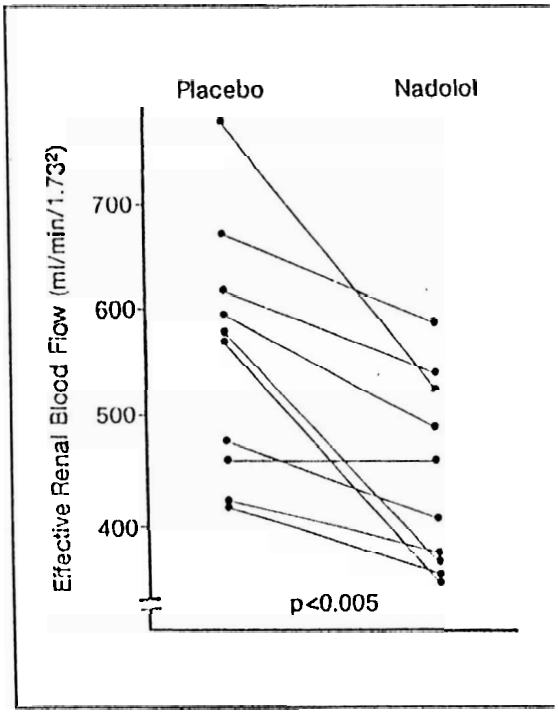

Fig. 2. Effective renal blood flow in 10 elderly hypertensiv patients following 10 weeks' treatment with placebo and nadolol.

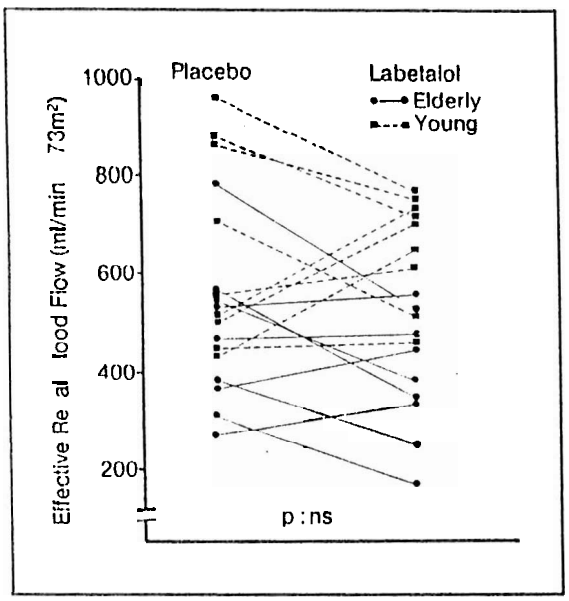

Fig. 3. Effective renal blood flow in 9 elderly and 9 young hypertensive patients following 12 weeks' treatment with placebo and labetalol.

4.3 Labetalol

Labetalol has α- and β-blocking properties. We compared its effect on effective renal blood flow during long term oral therapy in 9 elderly and 9 young hypertensive patients. It was a randomised single-blind placebo-controlled crossover study in which each phase lasted 12 weeks. There was no significant alteration in effective renal blood flow in either age group (fig. 3), while mean arterial pressure was reduced by 17mm Hg ($p < 0.005$) in the elderly group and 13mm Hg ($p < 0.001$) in the young group. Glomerular filtration rate did not change, nor did serum creatinine or blood urea.

5. Discussion

Our findings reveal an improvement in renal blood flow with atenolol, a reduction with nadolol and no change with labetalol, during long term oral therapy in elderly hypertensive patients. Glomerular filtration rate was maintained despite a reduction in arterial pressure. The difference between the drugs in their effect on renal blood flow may be explained at least in part by their selectivity. Atenolol blocks β_1-adrenoceptors but not β_2-receptors, thus a combination of reduced β_1-mediated vasoconstriction and unimpaired β_2-mediated vasodilatation might result in an overall increase in renal blood flow. Nadolol, on the other hand, blocks β_2-receptors, thus inhibiting renal vasodilatation and reducing renal blood flow. Labetalol, even though a non-selective blocking drug, does not alter renal blood flow, as the tendency to do so is offset by its α-blockade. The maintenance of glomerular filtration rate with all drugs suggests that autoregulation is less readily altered by β-blocking agents.

Our data suggest that selective β-blocking drugs increase effective renal blood flow in elderly patients while non-selective agents may decrease it. However, as changes in glomerular filtration rate, creatinine and blood urea were not clinically significant, the clinical importance of alterations in effective renal blood flow in the present studies remains to be elucidated.

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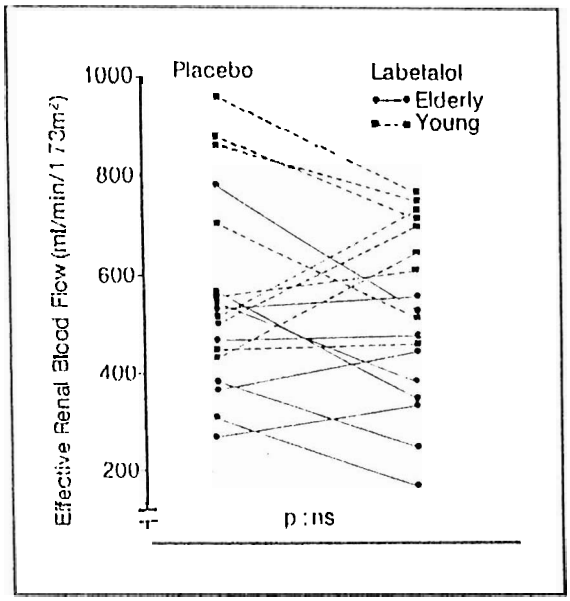

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