The effects of selective β -adrenoceptor antagonists and partial agonist activity on renal function during exercise in normal subjects and those with moderate renal impairment

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- 1 The effects of sustained moderate exercise in the sitting position on renal haemodynamics and glomerular filtration were measured in six normotensive patients with moderately impaired renal function and seven age-matched normal volunteers.
- 2 The changes in the effects of exercise on renal function induced by chronic cardio-selective β -adrenoceptor blockade by drugs with (epanolol) and without intrinsic sympathomimetic activity (atenolol) were examined.
- 3 Both β -adrenoceptor blockers attenuated the heart rate increase with exercise, but only atenolol lowered blood pressure significantly. In resting volunteers on atenolol, associated with the fall in blood pressure there was a significant reduction in glomerular filtration rate.
- 4 Glomerular filtration fell significantly in all groups with exercise, and renal blood flow also fell in parallel. These changes were not influenced by drug treatment.
- 5 The exercise-induced rise in PRA was suppressed by atenolol but not by epanolol.
- 6 The renal function and haemodynamic responses to moderate exercise does not appear to be mediated by the systemic renin-angiotensin system or by β_1 -adrenoceptors.

Keywords glomerular filtration rate renal haemodynamics exercise atenolol epanolol

Introduction

Oral therapy with β -adrenoceptor antagonists lowers blood pressure by reducing cardiac output, although agents with significant partial agonist activity (PAA) have less effect on cardiac output and change blood pressure little if at all (Waller, 1990).

In patients with normal renal function, renal blood flow and renal function are affected in parallel with cardiac output. Chronic oral therapy with non-selective β -adrenoceptor blockers (e.g. propranolol) reduces glomerular filtration rate (GFR) and effective renal plasma flow (ERPF) by 5–23% (Bauer, 1985). β_1 -selective adrenoceptor drugs appear to reduce GFR and ERPF less, e.g. atenolol reduces creatinine clearance less than propranolol (Wilkinson *et al.*, 1980).

Furthermore, the presence of moderate β_1 partial agonist activity in a selective β -adrenoceptor-blocker (epanolol) tends to preserve ERPF in comparison to atenolol, although it makes no difference to GFR (Mackay *et al.*, 1985). Probably the presence of PAA compensates for the loss of resting sympathetic tone during β -adrenoceptor-blockade (Epstein & Osler,

1985). Moderate sustained exercise produces decrements in GFR and ERPF that are not prevented by β -adrenoceptor-blockade with propranolol (Larson & Pederson, 1980). The effect of a β -adrenoceptor blocker with PAA on this phenomenon has not been studied, but an agent with PAA might be expected to attenuate the reduction in blood flow that occurs on exercise.

Under basal conditions selective and non-selective β -adrenoceptor blockers have different effects on renin release (Waller, 1990). Plasma renin activity (PRA) is reported to increase with exercise (Hespel *et al.*, 1988) but whether or not there is a different response during β -adrenoceptor blockade by agents with and without PAA is unclear.

In patients with moderately impaired renal function selective β -adrenoceptor antagonists are widely used and are generally regarded as having no significant adverse effect on renal function (Wilkinson, 1982). Other studies however show a decrease of 10 to 18% in GFR and ERPF (Beaufils, 1989). We report a double-blind placebo-controlled study to establish (i) whether

β_1 -adrenoceptor antagonists with and without β_1 -PAA modify the effects of exercise on renal haemodynamics and PRA in patients with normal renal function. (ii) whether β_1 -adrenoceptor antagonists with and without β_1 -PAA significantly influence renal haemodynamics and PRA at rest or on exercise in patients with impaired renal function.

Methods

The study was approved by the Royal Infirmary Ethics Committee and subjects gave informed consent in writing before participating. Seven normal volunteers (group A) and seven patients with moderately impaired renal function assessed on the basis of creatinine clearance (group B) were studied in a random order. None of those studied had taken any drug therapy in the 2 weeks prior to the study. Patients were recruited from outpatient clinics if they had a creatinine clearance of 30–70% of normal, stable renal function, absence of urinary tract obstruction and were normotensive.

Each subject was studied three times with a washout period of at least 7 days between each study. The study was double-blind and subjects were randomised to treatment with placebo, epanolol (200 mg day⁻¹) or atenolol (100 mg day⁻¹) in a random order for a 7 day period before each study day. These doses of epanolol and atenolol have been shown to be equipotent as adrenergic β_1 -adrenoceptor blocking agents in the blockade of exercise-induced tachycardia and the systolic pressor response to exercise (Pringle *et al.*, 1986).

On the morning of study the patient had no breakfast and refrained from caffeine and alcohol. Via an antecubital vein, inulin and para-aminohippurate (PAH) were infused for the measurement of renal clearances according to a standard protocol (Taverner *et al.*, 1991). Subjects were given an oral water load of 200 ml at the start of the study and 100 ml every 0.5 h thereafter. Blood pressure and heart rate were measured at 30 min intervals, using an automated sphygmomanometer (Sentron, Bard Biomedical) the subject remained supine throughout this time except when exercising. Following a 60 min equilibration period, blood and urine samples were collected at timed intervals of 30 min throughout the study. At the start of the first sample period at rest (Period 1A), the subject took the trial medication orally. There followed two further 30 min rest periods (1B and 1C).

The subject then performed 30 min of sustained exercise in a sitting position on a bicycle ergometer at an individualised workload, previously determined to achieve a sustained tachycardia of 110 beats min⁻¹ in that subject. At the end of this period further samples were taken for clearance measurements (Period 2), the subject then rested for 1 h while two further measurements of clearance were made over 30 min period (Periods 3 and 4). PAH and inulin were measured by autoanalyser. Plasma renin activity (PRA) (Roulston *et al.*, 1983) was measured on samples taken at the end of periods 1A, 1B, 1C, 2 and 4. Urine volumes, inulin clearance (GFR) and PAH clearance (ERPF) were calculated for each of the six timed collection periods.

Results are expressed as mean $\pm$ 1s.d. Clearance data were corrected for body surface area by a standard nomogram. PRA was log-transformed to normalise the data distribution. Statistical comparisons were made by analysis of variance using a Minitab based computer programme for differences between groups at rest on periods 1A–1C, and for changes from rest to exercise on periods 1C and 2. The null hypothesis was rejected when $P < 0.05$.

Results

One patient with impaired renal function was withdrawn from the study because of deterioration in renal function, this appeared to be due to progression of the primary renal disease. No side effects occurred during the study. The data presented is on seven patients with normal renal function and six patients with impaired renal function who all completed all parts of the study. Baseline characteristics of group B subjects are given in Table 1. The mean age of the volunteers (all of whom were male) was 32 years, range 24–40, and the mean age of the patients was 28 years, range 19–39 (difference not significant). The exercise level to achieve the target heart rate in normals was 75 ± 8 watts compared with 51 ± 9 watts in patients with impaired renal function ($P < 0.001$). At rest on placebo, the resting heart rate and blood pressure were similar in groups A and B apart from a higher diastolic pressure in group B (Table 2). Atenolol lowered heart rate and blood pressure significantly in both groups at rest, while epanolol did not.

The tachycardia induced by exercise in both groups on placebo was similar, reflecting the previously individualised workloads. In group A the diastolic blood pressure rose significantly with exercise, but this response was not apparent in group B. Both β -adrenoceptor blockers significantly attenuated the heart rate response to exercise to a similar extent.

GFR on placebo at rest in group B was 64% of that of group A (Table 3). In group A, GFR at rest was significantly reduced by atenolol but not by epanolol. This difference was not apparent in group B. On exercise, GFR fell in both groups on both placebo and active medication, and the magnitude of the fall was similar on both placebo and active treatments. In both groups, ERPF was higher throughout in group A but it fell significantly in both groups and all treatments on exercise (Table 3).

Table 1 Age, plasma creatinine, GFR and resting blood pressure in patients with impaired renal function (group B)

Patient	Age (years)	Plasma creatinine (mmol l ⁻¹)	GFR (ml min ⁻¹ 1.73 m ⁻²)	BP (mm Hg)
1	22	137	65	134/80
2	35	205	68	133/84
3	23	80	63	122/84
4	26	102	48	132/74
5	29	132	59	137/74
6	39	93	70	129/77

Table 2 Heart rate and blood pressure before, during (period 2) and after exercise in normals (group A) and patients with impaired renal function (group B) treated with β -adrenoceptor blockers or placebo

Heart rate (beats min ⁻¹)						
	1A	1B	1C	Period 2	3	4
<i>Group A</i>						
placebo	56 $\pm$ 6	59 $\pm$ 5	59 $\pm$ 6	103 $\pm$ 5#	67 $\pm$ 5	62 $\pm$ 4
atenolol	55 $\pm$ 6	52 $\pm$ 7*	48 $\pm$ 4*	86 $\pm$ 7*#	51 $\pm$ 5	49 $\pm$ 2
epanolol	64 $\pm$ 4	57 $\pm$ 4	61 $\pm$ 7	88 $\pm$ 12*#	63 $\pm$ 3	62 $\pm$ 3
<i>Group B</i>						
placebo	61 $\pm$ 9	58 $\pm$ 9	57 $\pm$ 8	106 $\pm$ 12#	63 $\pm$ 7	66 $\pm$ 3
atenolol	59 $\pm$ 5	52 $\pm$ 10*	52 $\pm$ 9	79 $\pm$ 9*#	50 $\pm$ 8	51 $\pm$ 10
epanolol	60 $\pm$ 13	61 $\pm$ 7	56 $\pm$ 7	89 $\pm$ 10*#	62 $\pm$ 5	60 $\pm$ 5
<i>Systolic blood pressure (mm Hg)</i>						
<i>Group A</i>						
placebo	123 $\pm$ 9	121 $\pm$ 7	122 $\pm$ 8	133 $\pm$ 22	122 $\pm$ 13	120 $\pm$ 9
atenolol	116 $\pm$ 7*	110 $\pm$ 7*	110 $\pm$ 13*	113 $\pm$ 31	111 $\pm$ 2	112 $\pm$ 10
epanolol	121 $\pm$ 11	120 $\pm$ 7	121 $\pm$ 9	125 $\pm$ 15	119 $\pm$ 10	122 $\pm$ 8
<i>Group B</i>						
placebo	134 $\pm$ 9	133 $\pm$ 13	122 $\pm$ 21	132 $\pm$ 13	137 $\pm$ 13	129 $\pm$ 13
atenolol	117 $\pm$ 13*	119 $\pm$ 19*	112 $\pm$ 12*	119 $\pm$ 13*	116 $\pm$ 15	114 $\pm$ 12
epanolol	132 $\pm$ 16	134 $\pm$ 19	135 $\pm$ 17	132 $\pm$ 17	134 $\pm$ 25	136 $\pm$ 19
<i>Diastolic blood pressure (mm Hg)</i>						
<i>Group A</i>						
placebo	71 $\pm$ 6	72 $\pm$ 7	71 $\pm$ 9	86 $\pm$ 12#	71 $\pm$ 5	67 $\pm$ 8
atenolol	67 $\pm$ 7*	67 $\pm$ 9*	63 $\pm$ 8*	61 $\pm$ 10*	63 $\pm$ 6	63 $\pm$ 9
epanolol	71 $\pm$ 6	72 $\pm$ 5	71 $\pm$ 8	71 $\pm$ 10	72 $\pm$ 7	70 $\pm$ 7
<i>Group B</i>						
placebo	81 $\pm$ 15	84 $\pm$ 8	84 $\pm$ 11	74 $\pm$ 15	74 $\pm$ 15	77 $\pm$ 12
atenolol	70 $\pm$ 11*	70 $\pm$ 10*	68 $\pm$ 10*	71 $\pm$ 12	64 $\pm$ 10	64 $\pm$ 10
epanolol	81 $\pm$ 11	79 $\pm$ 17	78 $\pm$ 15	83 $\pm$ 14	77 $\pm$ 19	80 $\pm$ 16

* $P < 0.05$ c.f. placebo, # $P < 0.05$ c.f. period 1C.

Supine resting PRA was lower at rest on placebo in group B than group A, and in both groups it rose with exertion. β -adrenoceptor blockade did not alter PRA at rest. The rise in PRA with exertion was suppressed by atenolol in group A but not by epanolol (Table 3).

Discussion

Atenolol produced a marked fall in blood pressure even in normotensive volunteers. Epanolol was less hypotensive than atenolol in this study, confirming previous findings (Leonetti *et al.*, 1985). However epanolol is an effective β_1 -adrenoceptor blocker as previously reported (Pringle *et al.*, 1986), and confirmed in this study by the changes in heart rate after 30 min exercise, when epanolol and atenolol produced similar suppression of exercise-induced tachycardia.

At rest, there was no difference in ERPF between either β -adrenoceptor blocker or placebo, but GFR was significantly reduced in patients with normal renal function by atenolol compared with placebo. This change was not apparent in the group with impaired renal function, nor did it occur on epanolol. The effect of atenolol on GFR has been previously noted (Bauer,

1985). Lowered cardiac output associated with the fall in blood pressure and impaired renal autoregulation appears to be the most likely explanation in this study. With epanolol, the presence of 20% PAA may have improved GFR compared with pure β_1 -adrenoceptor-blockade by a β_1 -dependent mechanism such as intra-renal vasodilation.

GFR fell significantly with exercise in both groups on all treatment. Over the period of exercise ERPF fell significantly in the normals, a similar fall was seen in patients with impaired renal function. β_1 -adrenoceptor blockade with and without PAA did not modify the fall in ERPF with exercise, which paralleled the fall in GFR.

Suppression of PRA at rest by β -adrenoceptor blockade was not seen in this study, although previous studies have shown that PRA may be suppressed by selective β -adrenoceptor blockade (Hespel *et al.*, 1986) and the degree of suppression is inversely correlated with the amount of PAA (Man in 't Veld & Schalekamp, 1983). The increment in PRA with exercise has been shown to be attenuated by atenolol in a previous study (Hespel *et al.*, 1986) and in the present study in normals. This is consistent with the suggestion that the adrenoceptors mediating the release of renin on moderate exertion are partly of the β_1 subtype (Hespel *et al.*, 1986).

Table 3 Glomerular filtration rate, effective renal plasma flow and plasma renin activity before, during (period 2) and after exercise in normal (group A) and patients with impaired renal function (group B) treated with β -adrenoceptor blockers or placebo

	Glomerular filtration rate (ml min ⁻¹ 1.73 m ⁻²)					
	Period					
	1A	1B	1C	2	3	4
<i>Group A</i>						
placebo	104 ± 7	112 ± 13	103 ± 14	94 ± 24#	96 ± 14	103 ± 16
atenolol	85 ± 42*	91 ± 20*	93 ± 18*	81 ± 12#	84 ± 25	98 ± 19
epanolol	119 ± 20	102 ± 15	111 ± 23	92 ± 17#	91 ± 21	103 ± 36
<i>Group B</i>						
placebo	65 ± 25	68 ± 15	63 ± 23	48 ± 15#	60 ± 28	70 ± 22
atenolol	55 ± 14	57 ± 20	59 ± 19	46 ± 21#	48 ± 23	61 ± 6
epanolol	50 ± 15	58 ± 16	61 ± 22	54 ± 16#	58 ± 21	49 ± 26
	Effective renal plasma flow (ml min ⁻¹ 1.73 m ⁻²)					
<i>Group A</i>						
placebo	670 ± 181	549 ± 108	585 ± 66	423 ± 89#	481 ± 111	592 ± 122
atenolol	584 ± 120	582 ± 103	576 ± 65	426 ± 47#	465 ± 58	675 ± 103
epanolol	683 ± 118	627 ± 159	550 ± 145	416 ± 109#	528 ± 126	613 ± 113
<i>Group B</i>						
placebo	382 ± 137	321 ± 117	321 ± 168	244 ± 87#	317 ± 233	313 ± 184
atenolol	331 ± 113	318 ± 133	341 ± 148	271 ± 132#	268 ± 148	342 ± 111
epanolol	299 ± 114	334 ± 152	307 ± 130	232 ± 86#	279 ± 113	268 ± 145
	Plasma renin activity (pmol AI h ⁻¹ ml ⁻¹)					
<i>Group A</i>						
placebo	2.4 ± 1.7	2.0 ± 1.3	1.2 ± 1.2	3.6 ± 2.4#	–	2.4 ± 1.8
atenolol	0.9 ± 0.6	1.1 ± 1.1	1.1 ± 2.0	0.9 ± 0.7*	–	0.5 ± 0.4
epanolol	1.7 ± 1.1	1.6 ± 1.3	0.9 ± 1.0	2.3 ± 1.3#	–	1.5 ± 1.4
<i>Group B</i>						
placebo	0.7 ± 0.5	0.6 ± 0.5	0.6 ± 0.4	2.0 ± 1.5#	–	0.6 ± 0.5
atenolol	0.7 ± 0.6	0.5 ± 0.5	0.5 ± 0.4	1.2 ± 1.3#	–	1.2 ± 1.1
epanolol	0.8 ± 0.7	0.6 ± 0.3	0.6 ± 0.3	1.3 ± 1.0#	–	0.5 ± 0.3

* $P < 0.05$ c.f. placebo, # $P < 0.05$ c.f. period 1C.

In group A on atenolol, the GFR fall on exercise was not associated with a rise in PRA, suggesting that this transient change in renal function is not mediated by activation of the systemic renin-angiotensin system. However the changes in GFR must be interpreted with caution since only small numbers of patients were used in the study and a difference in GFR between the two groups of up to $25 \text{ ml min}^{-1} 1.73 \text{ m}^{-2}$ would have had to occur for it to be reliably detected.

In conclusion, β_1 -adrenoceptor blockade in normals produces a significant fall in GFR at rest, but this effect is not observed when an equipotent dose of β_1 -adrenoceptor blocker possesses moderate PAA. The marked hypotensive effect of atenolol is likely to be the cause of

the observed fall in renal function. This fall in excretory function is probably of little clinical significance.

The renal haemodynamic response to sustained moderate exercise appears to be mediated neither by the systemic renin-angiotensin system nor by adrenoceptors of the β_1 -subtype.

The effect of selective β -adrenoceptor blockade on the kidney in patients with moderately impaired renal function is similar to the effect in normal man, but these small changes in renal function may be of more clinical significance in this group of patients.

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