The effects of rilmenidine and atenolol on mental stress, dynamic exercise and autonomic function in mild to moderate hypertension

V. PANFILOV,¹ A. D. MORRIS,¹ R. DONNELLY,¹ M. SCEMAMA² & J. L. REID¹

¹Department of Medicine and Therapeutics, University of Glasgow, Western Infirmary, Glasgow, UK and

²IRIS (Servier International Research Institute), Courbevoie, France

- 1 The effects of 4 week treatment with rilmenidine or atenolol on tests of mental stress, dynamic exercise, autonomic function and psychometric tests were evaluated in a randomized, double-blind, placebo-controlled, cross-over study.
- 2 After a 4 week placebo run-in, 12 patients with essential hypertension (blood pressure [BP] $160/95 \pm 15/7$ mmHg) received rilmenidine $1\text{--}2$ mg day⁻¹, and atenolol $50\text{--}100$ mg day⁻¹, each for 4 weeks, with a 4 week placebo wash-out between drug treatments.
- 3 Both agents produced a comparable reduction in supine and erect BP. During the mental arithmetic test, BP and heart rate (HR) responses were similar for rilmenidine and atenolol.
- 4 During bicycle exercise, the increase in HR was significantly greater after rilmenidine ($+50$ vs 41 beats min⁻¹, $P=0.04$). During recovery, the areas under the curve for diastolic BP ($46\,450$ vs $51\,400$ mmHg s, $P=0.02$) and HR ($49\,445$ vs $63\,597$ beats min⁻¹ s, $P=0.001$) were significantly less with atenolol than rilmenidine.
- 5 Neither rilmenidine nor atenolol affected mental performance as judged by arithmetic and psychomotor tests. Physiological responses to autonomic function tests (deep breathing, facial immersion, isometric handgrip and cold pressor) were preserved with both drugs. The standing to lying ratio was higher on atenolol ($P=0.01$) and Valsalva ratio was higher on rilmenidine ($P=0.03$).
- 6 In conclusion, rilmenidine and atenolol exerted comparable antihypertensive effects both at rest and during mental and dynamic stress. Atenolol attenuated HR responses to dynamic exercise and the Valsalva manoeuvre; rilmenidine did not interfere with the physiological responses of BP and HR during autonomic function tests.

Keywords rilmenidine atenolol hypertension mental stress dynamic exercise autonomic function psychomotor tests

Introduction

Rilmenidine is an oxazoline derivative and a new antihypertensive drug with a central action that is probably more dependent on its high specificity for imidazoline receptor sites than α_2 -adrenoceptor agonist actions [1]. It has been shown to reduce blood pressure (BP) both in healthy subjects [2, 3] and hypertensive patients [4]. Double-blind comparative studies vs atenolol, hydrochlorothiazide, clonidine and methyl dopa have shown

an equivalent efficacy of rilmenidine and a satisfactory safety profile. These comparisons have revealed minimal central side effects of rilmenidine, considerably less than those of clonidine [5–7].

The antihypertensive effect of centrally active drugs, such as clonidine is related to a reduction in sympathetic outflow and enhanced parasympathetic activity. It has been shown that rilmenidine exerts similar effects in experimental animals [8, 9]. Furthermore, in normal humans under conditions of low basal sympathetic

Correspondence: Professor J. L. Reid, Department of Medicine and Therapeutics, Gardiner Institute, Western Infirmary, Glasgow G11 6NT, UK.

activity, rilmenidine enhanced parasympathetic tone as assessed by heart rate (HR) changes immediately after standing and deep breathing and blunted the reflex increase in sympathetic activity after standing for 3 min [10]. However, these effects have not been reported so far in hypertensive patients.

In the clinical assessment of antihypertensive drugs, much attention has been paid to their effects on reactivity to physical and psychological stresses. The high blood pressure peaks induced in response to naturally occurring stresses have been postulated to contribute the most to target organ damage. Therefore, there is increasing interest in drugs able to minimize the hypertensive responses to stress. At the same time, an optimal antihypertensive drug should also preserve the physiological haemodynamic responses to posture, physical and mental stresses and not impair performance.

The present study has been undertaken to further elucidate various effects of rilmenidine in a group of patients with mild to moderate hypertension in comparison with those of a well documented antihypertensive agent, the cardioselective β -adrenoceptor blocker atenolol.

Methods

Patients

Twelve male patients with mild to moderate essential hypertension (BP $160/95 \pm 15/7$ mmHg), aged 32–60 years (mean age 48.8 ± 9.6 years) participated in the study. The patients were recruited from the Cardiovascular Risk Factor Clinics at Western Infirmary, Glasgow. Ten patients were previously on antihypertensive treatment and two were newly diagnosed cases and had received no medication before the study.

Protocol

The detailed protocol was approved by the Ethics Committee of the West Glasgow Hospitals University NHS Trust and written informed consent was obtained from all patients.

Study design

All previous antihypertensive therapy was discontinued at least 2 weeks before the familiarization visit. According to a randomized, double-blind, cross-over design, a placebo run-in treatment lasting for 4 weeks was initiated. This was followed by a cross-over active drug treatment with rilmenidine or atenolol, each given for 4 weeks and separated by a 4 week placebo wash-out. After 2 weeks on active treatment, the initial dose of rilmenidine 1 mg daily, or atenolol 50 mg daily, was either maintained or doubled—rilmenidine 1 mg twice daily and atenolol 50 mg twice daily, respectively—to achieve a target diastolic BP of less than 90 mmHg. Assessments were made at the end of each respective placebo and active drug treatments.

Study days and clinical physiological tests

On each study day, patients reported to the laboratory at 08.00 h in the morning following an overnight fast and refraining from smoking and caffeine containing drinks consumption. Rilmenidine 1 mg or atenolol 50 mg or matching placebo capsule were administered and a patient was asked to rest for 2 h. Two hours later BP and HR were measured by an automated blood pressure system (Dinamap, Criticon Inc) both in the supine and erect positions and then all other tests performed. Mental stress (arithmetic) test was carried out by a patient doing serial subtractions of 7 from a number of about 400–450 during 2 min, reporting each answer to the investigator. Whatever each persons ability was, he was 'pressurized' by the investigator who placed a clock in front of the patient and encouraged him to make as many subtractions as possible. BP and HR were recorded every minute during the test and then every second minute during subsequent 10 min recovery. For dynamic exercise testing, a modification of the Balke-Ware exercise test was employed [11]. The patient cycled for 5 min at 50% maximum workload predetermined at a familiarization visit. ECG tracing and instantaneous heart rate were continuously monitored (Micromon 7141, Kontron Instruments Ltd) during 5 min exercise and subsequent 10 min recovery and BP and HR were recorded immediately after the

Table 1 Supine and erect blood pressure and heart rate during treatment with rilmenidine (R) and atenolol (A)

	<i>Rilmenidine</i>		<i>Atenolol</i>		<i>P value</i> <i>R vs A</i> <i>(active)</i>
	<i>Placebo</i>	<i>Active</i>	<i>Placebo</i>	<i>Active</i>	
<i>Supine</i>					
Systolic BP (mmHg)	156.5±13.7	143.8±12.4	152.5±21.0	137.3±15.4	0.52
Diastolic BP (mmHg)	96.5±3.8	89.4±6.8	97.3±7.5	84.5±9.4	0.13
Heart rate (beats min ⁻¹)	63.0±10.4	58.1±7.6	61.5±8.3	48.1±7.5	0.02
<i>Erect</i>					
Systolic BP (mmHg)	153.3±15.5	140.5±13.2	147.3±15.8	135.5±16.8	0.89
Diastolic BP (mmHg)	96.7±7.0	87.8±9.6	99.5±7.4	86.0±8.6	—*
Heart rate (beats min ⁻¹)	73.0±13.2	65.5±10.0	72.0±8.0	53.5±10.9	0.02

* Significant sequence effect.

Table 2 Changes (Δ) in blood pressure and heart rate and respective areas under the curve (AUC) during mental arithmetic (upper panel) and scores of psychometric tests (lower panel) during treatment with rilmenidine (R) and atenolol (A)

	Placebo			P value R vs A	Active			P value R vs A
	Rilmenidine	Atenolol	95% CI		Rilmenidine	Atenolol	95% CI	
<i>Mental arithmetic</i>								
ΔSBP (mmHg)	16.9 ± 8.5	16.3 ± 11.5	-6.2; 7.4	0.85	16.5 ± 9.3	16.8 ± 8.0	-8.5; 7.9	0.93
ΔDBP (mmHg)	7.8 ± 9.4	10.5 ± 6.7	-8.3; 3.0	0.32	6.3 ± 14.0	10.7 ± 6.1	-14.3; 5.6	0.35
ΔHR (beats min ⁻¹)	12.1 ± 7.3	9.4 ± 5.2	-0.39; 5.7	0.08	7.6 ± 7.4	7.1 ± 7.0	-4.8; 5.8	0.84
AUC-SBP (mmHg s)	73 695.0 ± 7823.8	70 105.0 ± 11 781.6	-2920.2; 10 100.2	0.25	68 775.0 ± 6298.5	66 305.0 ± 6941.4	-883.9; 5823.9	0.13
AUC-DBP (mmHg s)	44 925.0 ± 3995.6	44 000.0 ± 4410.6	-958.0; 2808.0	0.30	41 450.0 ± 3195.8	40 585.0 ± 3501.8	-1382.9; 3112.9	0.41
AUC-HR (beats min ⁻¹ s)	31 830.0 ± 4619.4	30 045.0 ± 5413.8	-372.6; 3942.6	0.10	29 060.0 ± 4747.9	24 075.0 ± 3926.0	2672.7; 7297.3	<0.001
<i>Psychometric tests</i>								
Critical flicker fusion threshold (Hz)	30.0 ± 3.2	30.0 ± 4.1		0.96	30.5 ± 3.5	31.0 ± 4.2		0.48
Choice reaction time (ms)	612.7 ± 80.7	636.5 ± 152.0		0.55	595.0 ± 67.9	600.8 ± 176.8		0.88

test and then at 2 min intervals during the recovery period.

Autonomic nervous function (parasympathetic) was investigated with the following tests. Heart rate variation with deep breathing (in the supine position) was assessed by calculating the ratio between the longest and shortest R-R interval [12]. For calculating the standing to lying ratio [13], the mean of 10 R-R intervals immediately before lying down was divided by the shortest R-R interval during the first 30 s supine. For the Valsalva manoeuvre [14, 15], the patient was asked to maintain the forced expiration to hold a column of mercury at 50 mm for 15 s, the Valsalva ratio (VR) was defined as the longest R-R interval during phase IV (bradycardic) divided by the shortest R-R interval during the strain. Facial immersion in cool water, also known as diving test [16, 17], was done for the assessment of the maximum reduction in HR by calculating the difference between the longest R-R interval during the immersion and the mean of five R-R intervals preceding the immersion. For all the above tests, R-R intervals were derived from continuously recorded ECG. Sympathetic function was studied by measuring BP and HR responses to forearm isometric exercise (handgrip) at 30% of patients' maximum force for 2 min [18] and to cold pressor test, i.e. immersion of hand up to mid-forearm in melting ice for 2 min [19].

For psychomotor testing, critical flicker fusion threshold and choice reaction time scores were measured with the Leeds Psychomotor Tester [20].

Statistical analysis

Changes in BP, HR and other parameters during stress and physiological reflex testing were subjected to analysis of variance (ANOVA) for repeated measures. Prior to assessment of any treatment effect, homogeneity before treatment was verified with regard to all parameters used. Interpretation of the treatment effect was carried-out if no significant carry-over, sequence effect or treatment $\times$ period interaction were found. Delta values, i.e. maximum difference from baseline during the period of stress at the end of chronic treatment, were used. In addition, to assess modifications of BP and HR during recovery periods after mental stress and dynamic exercise, the area under the curve (AUC) was calculated based on the trapezoidal rule. Results throughout are expressed as mean $\pm$ s.d.

Results

Baseline homogeneity analysis

For various functional tests employed in this study, baseline homogeneity analysis by the ANOVA did not show any significant difference between pre-treatment values on placebo (before rilmenidine and atenolol), apart from the maximal change in systolic BP during isometric exercise ($P=0.02$), and the maximal change in

diastolic BP during cold pressor test ($P=0.05$). Post-treatment values of these parameters were not analysed.

Blood pressure and heart rate at rest

By the end of each active drug treatment period lasting for 4 weeks, both rilmenidine and atenolol produced comparable reductions in BP both in the supine and erect positions. Decreases in supine and erect HR were significantly greater with atenolol as compared with rilmenidine (Table 1).

Mental and dynamic stress tests

After 4 weeks of active treatment with rilmenidine and atenolol, BP and HR responses to mental arithmetic were similar for both drugs (Table 2, Figure 1). The AUC for HR was significantly smaller after the atenolol treatment ($P<0.001$). The average numbers of subtractions done after rilmenidine, atenolol and placebo treatment were 40.8, 41.2 and 41.3, respectively.

During bicycle exercise, BP and HR followed similar patterns on placebo as well as on rilmenidine and atenolol (Figure 1). However, the increase in HR was

slightly but significantly greater on rilmenidine ($P=0.04$, Table 3) than on atenolol. During the recovery period, the AUC for diastolic BP ($P=0.02$) and that for HR ($P=0.001$) was smaller on atenolol than on rilmenidine.

Psychometric tests showed no significant treatment effects (Table 2).

Autonomic function tests

Tests of sympathetic function, isometric forearm exercise and cold pressor test, showed that BP control on rilmenidine and atenolol was similar to that on placebo although BP levels at given time points tended to be lower with study drugs (Figure 2). There were no statistically significant differences between the two drugs. Furthermore, a significant period effect was shown for the maximal difference in diastolic BP ($P=0.03$) during isometric exercise.

Responses to parasympathetic function tests in terms of changes in R-R intervals were qualitatively similar after placebo and active treatment with both drugs (Figure 3). However, calculation of quantitative indices of these tests (Table 4) showed that the standing to

Figure 1 Blood pressure and heart rate (mean values $\pm$ s.d.) during and after tests of a) mental arithmetic and b) dynamic bicycle exercise after different treatments (—○— rilmenidine, —●— atenolol, —△— placebo). The start (↓) and end (↑) of the respective tests.

Table 3 Changes (Δ) in blood pressure and heart during bicycle exercise test and respective areas under the curve (AUC) during the test and recovery period during treatment with rilmenidine (A) and atenolol (A)

	Placebo			Active			P value R vs A
	Rilmenidine	Atenolol		Rilmenidine	Atenolol		
Δ SBP (mmHg)	23.2 $\pm$ 14.2	26.0 $\pm$ 17.0		24.8 $\pm$ 9.4	20.7 $\pm$ 14.8		0.41
Δ DBP (mmHg)	0.3 $\pm$ 9.6	-0.3 $\pm$ 8.5		5.2 $\pm$ 12.0	-3.7 $\pm$ 12.7		0.12
Δ HR (beats min ⁻¹)	58.8 $\pm$ 17.0	57.9 $\pm$ 14.2		50.0 $\pm$ 9.5	41.3 $\pm$ 10.4		0.04
AUC-SBP (mmHg s)	88 490.0 $\pm$ 7764.9	87 380.0 $\pm$ 10 709.3		83 520.0 $\pm$ 8417.8	80 390.0 $\pm$ 8942.0		0.10
AUC-DBP (mmHg s)	54 550.0 $\pm$ 3913.8	54 495.0 $\pm$ 4948.7		51 400.0 $\pm$ 4066.0	46 450.0 $\pm$ 6046.2		0.02
AUC-HR (beats min ⁻¹ s)	73 150.0 $\pm$ 9731.8	72 837.5 $\pm$ 11 033.2		63 597.5 $\pm$ 11 165.9	49 445.0 $\pm$ 6359.8		0.001
						95% CI	
						-6.4; 14.6	
						-2.7; 20.4	
						0.36; 17.1	
						-778.6; 7038.6	
						838.1; 9061.9	
						7089.6; 21 215.5

Figure 2 Blood pressure and heart rate (mean values $\pm$ s.d.) during a) isometric forearm exercise and b) cold pressor test after different treatments (-○- rilmenidine, -●- atenolol, -△- placebo). **Figure 3** R-R interval (mean values) during tests for parasympathetic function after different treatments (-○- rilmenidine, -●- atenolol, -△- placebo).

lying ratio was higher on atenolol ($P=0.01$) and Valsalva ratio was higher on rilmenidine ($P=0.03$).

Tolerability

Both rilmenidine and atenolol were well tolerated. Several patients experienced minor adverse events such as dizziness, headache and fatigue. The episodes were of mild severity and their number were essentially the same on rilmenidine and atenolol. One patient complained of dry mouth while on 2 mg day⁻¹ rilmenidine. Another patient reported a transient episode of diplopia while on atenolol but that was not substantiated by detailed ophthalmological examination. Furthermore, while on placebo four patients reported episodes of pruritus, dizziness and dyspepsia. Those events did not prevent the patients from completing the study and there were no drop-outs.

Discussion

In the present study, the focus was on a comparison of the effects of atenolol and rilmenidine on cardiovascular

Table 4 Indices of tests for parasympathetic function during treatment with rilmenidine (R) and atenolol (A)

	<i>Rilmenidine</i>		<i>Atenolol</i>		<i>P value</i> <i>R vs A</i> (<i>active</i>)
	<i>Placebo</i>	<i>Active</i>	<i>Placebo</i>	<i>Active</i>	
Standing to lying ratio (normal > 1.07)	1.18 ± 0.09	1.17 ± 0.07	1.18 ± 0.10	1.24 ± 0.11	0.01
Valsalva ratio (normal > 1.20)	1.78 ± 0.41	1.60 ± 0.42	1.72 ± 0.34	1.36 ± 0.22	0.03
Diving test (difference in R–R, ms)	370.9 ± 213.9	505.5 ± 500.4	439.2 ± 325.9	576.0 ± 675.6	0.76
Deep breathing (difference in R–R, ms)	371.7 ± 203.5	315.8 ± 200.5	323.3 ± 155.6	353.5 ± 240.5	0.32

reactivity to various stress tests under standardized laboratory conditions. Although autonomic function tests with indices based on R–R interval ratios have been found highly reproducible [21], physiological responses to stress in terms of blood pressure changes are generally characterized by large inter-individual variability [22]. That is why a wide battery of tests was utilized and a cross-over study design with a second placebo wash-out period between the active drugs was chosen. Despite these precautions, variability in responses to stress remained high.

Our observations are consistent with previously reported antihypertensive efficacy of both rilmenidine and atenolol in mild to moderate hypertension as well as good acceptability of the drugs [5]. Neither drug affected mental performance as judged by arithmetic and psychomotor tests.

Significant differences between treatments were only shown for the change in HR during dynamic exercise, the Valsalva manoeuvre and standing to lying test. In addition, a significant difference between treatments was seen in the AUC for diastolic BP during the recovery period after exercise. These differences essentially reflect the β -adrenoceptor blocking activity of atenolol, in particular, its pronounced bradycardic effect. During the mental and physical stress tests the changes in BP were similar on rilmenidine and atenolol. However, lesser decrease in diastolic BP in the recovery period after the dynamic exercise may suggest that BP adaptation is more preserved with rilmenidine. This is in agreement with a previous report on the effect of the latter drug on BP during effort [23]. The differences between rilmenidine and atenolol may be explained by the mechanisms of action of the drugs: rilmenidine acts essentially on the central command of the sympathetic response which initiates parasympathetic withdrawal and tachycardia at the onset of exercise and remains predominant at work loads up to 30% of the maximum [24]. In the present study, the exercise were limited to 50% of the maximum load and it is conceivable that atenolol with its effect mainly on peripheral β -adrenoceptors might have a more pronounced inhibitory effects on HR and BP during and after the exercise.

Both rilmenidine and atenolol tended to attenuate BP and HR responses to isometric forearm exercise (handgrip) and cold pressor test. As stated previously

by other investigators [22], these tests show rather large variability. Furthermore, appropriate statistical evaluation of the handgrip test was hindered by showing a significant treatment-period interaction for changes in the systolic BP ($P=0.02$) before, and period effect for the diastolic BP ($P=0.03$) after active treatments. Similarly, the cold pressor test exhibited a period effect for changes in the diastolic BP ($P=0.05$) before active treatments.

All tests for parasympathetic function demonstrated that HR responses on active treatment were qualitatively similar to those on placebo but with lower HR (i.e. longer R–R intervals). It may reflect the fact that both drugs preserved normal physiological responses but augmented parasympathetic tone. However, it does not necessarily imply that atenolol produces more parasympathetic stimulation than rilmenidine but rather that it causes more sympathetic inhibition. Only those of tests which possessed a sympathetic component—standing to lying test and the Valsalva manoeuvre—allowed discrimination between the two study drugs. The first of these tests allows the assessment of the degree of vagal withdrawal in the immediate part (the first 3 beats) of the HR response to lying down [13]. The standing to lying ratio following rilmenidine treatment was not different from that on placebo, and was actually in the normal range [13]. After atenolol, this ratio was significantly increased. It is difficult to differentiate whether this reflects a further increase in vagal tone and less vagal withdrawal immediately on lying down or simply a more pronounced increase in resting R–R interval. Similarly, analysis of the Valsalva manoeuvre was also hampered by the bradycardic effect of atenolol. Normally, during phase II of the test (straining) there is heart rate acceleration and a bradycardic response during phase IV [25]. The Valsalva ratio is regarded as an index of parasympathetic tone and normally is higher than 1.20 [15]. In the present study, the Valsalva ratio was normal in baseline conditions and tended to decrease, but still within normal range, with both drugs, especially with atenolol. The calculated ratio was essentially related to the bradycardic effect of the drug with higher mean R–R intervals both at phase II and IV. Again, the scope for further bradycardic response might be limited under β -adrenoceptor blockade produced by atenolol. The other two tests, HR variation

with deep breathing and the diving test, can be considered 'pure' parasympathetic and did not show any significant differences between the two drugs.

Overall, our findings in hypertensive patients support the view that both rilmenidine and atenolol attenuate sympathetic and enhance cardiac parasympathetic tone as previously shown in normotensive volunteers [10, 26].

In conclusion, rilmenidine and atenolol exerted comparable antihypertensive effects both at rest and during mental and dynamic stress. Atenolol attenuated HR responses to dynamic exercise and the Valsalva manoeuvre. Rilmenidine did not interfere with the physiological responses of BP or HR during tests of autonomic function undertaken.

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