ATENOLOL v PLACEBO IN MILD HYPERTENSION: RENAL, METABOLIC AND STRESS ANTIPRESSOR EFFECTS

HENDRIKA J. WAAL-MANNING & P. BOLLI*

Wellcome Medical Research Institute, Department of Medicine,
University of Otago Medical School, Dunedin, New Zealand

- 1 The effects of 8 week treatment periods of atenolol and placebo on effective renal plasma flow (ERPF), glomerular filtration rate (GFR), plasma renin activity (PRA), oral glucose, fasting lipids and Achilles tendon reflex were compared in a double-blind crossover trial in ten subjects with mild hypertension.
- 2 Atenolol reduced resting blood pressure and pulse rate but did not prevent the rise in blood pressure and pulse rate in response to three kinds of stress.
- 3 Mean glomerular filtration rate and effective renal plasma flow were below the normal range during placebo (1.31 ml/s and 7.40 ml/s respectively) but were not significantly different on atenolol (1.23 ml/s and 7.18 ml/s). Serum urea was significantly ($P < 0.01$) higher on atenolol (6.7 mmol/l) than on placebo (5.6 mmol/l) but serum creatinine did not change. PRA was lower on atenolol ($0.42 \text{ nmol l}^{-1} \text{ h}^{-1}$) than on placebo ($1.01 \text{ nmol l}^{-1} \text{ h}^{-1}$).
- 4 The mean values of fasting cholesterol, triglycerides, ankle jerk contraction time, spirometry, weight, serum potassium, sodium and chloride were similar on atenolol and placebo.
- 5 Fasting blood sugar was a little higher ($P < 0.05$) on atenolol and the 1 and 2 h post-glucose serum insulin levels were a little lower ($P < 0.01$).
- 6 The cardioselectivity of atenolol does not impair its anti-hypertensive effect and may be associated with less effect on renal function. The metabolic effects of atenolol seem to differ from those of metoprolol.

Introduction

In a previous crossover study of atenolol and three non-selective β -adrenoceptor blockers in hypertension (Waal-Manning, 1979) mean serum creatinine level on atenolol was lower than during non-selective β -adrenoceptor blockade. This might indicate that atenolol has less effect on renal function than the non-selective β -adrenoceptor blockers (propranolol, oxprenolol and pindolol) which all have been reported to cause deterioration of renal function in patients with chronic renal failure (Warren, Swainson & Wright, 1974; Snell & Wallace, 1974; Swainson & Winney, 1976).

The present study assessed the effect of atenolol on stress-induced rise in BP and pulse rate and on renal function and blood flow in comparison with levels

during placebo therapy. Glucose tolerance was also studied, as atenolol has been reported to have less effect than non-selective β -adrenoceptor blockers on insulin secretion (Harms, Gooren, Spoelstra, Hesse & Verschoor, 1978) and treatment with another cardioselective β -adrenoceptor blocker, metoprolol, was associated with an improvement in glucose tolerance in some patients with impaired glucose tolerance while taking a non-selective β -adrenoceptor blocker (Waal-Manning, 1976).

Fasting lipid estimations were done as β -adrenoceptor blockade has been reported to be associated with a rise in triglyceride levels (Waal-Manning, 1976; Waal-Manning & Simpson, 1977; Shaw, England & Hua, 1978).

The duration of the Achilles tendon response was recorded as propranolol had been found to increase it (Waal-Manning, 1969) but the effect of a cardio-selective β -adrenoceptor blocker has not been studied.

*Present address: Dr P. Bolli, Hypertonie Service, Department of Medicine, Kantonsspital Basel, 4031 Basel, Switzerland.

Methods

Patient selection and characteristics

Ten subjects (3 M, 7 F; mean age 56 years) with mild hypertension (WHO Stage I) were selected from the group of 25 patients who took part in the crossover study of atenolol and three non-selective β -adrenoceptor blockers (Waal-Manning, 1979) during which the optimum dose of atenolol had been established for each patient. The optimum mean daily dose was 100 mg, range 50–200 mg and was given as a divided twice daily regimen. Other drugs (diuretics in seven and prazosin in one patient) were kept constant. On test mornings patients took their tablets at the usual time which varied from 0.600 h–08.00 h between patients but was constant for individual patients.

The study had been approved by the Hospital Ethical Committee. The trial plan and procedures were explained to the patients and their consent obtained.

Atenolol and placebo were each given for 8 weeks. Treatment order was assigned by envelope randomization. The first treatment was atenolol in six patients and placebo in four. During the eighth week patients attended for a morning test of resting blood pressure and pulse rate during which four lying and standing readings were recorded by trained technicians using an electronic version of the London School of Hygiene and Tropical Medicine blind manometer and phase IV of the Korotkoff sounds. At the completion of the blood pressure test at 11.30 h a blood sample for plasma renin activity was taken, the duration of the right ankle jerk was recorded (Waal-Manning, 1969) and spirometry was performed. Patients took their morning dose of tablets as usual on the day of this test and on another day during the eighth week when they fasted and attended for a 2 h oral glucose tolerance test (50 g of glucose). Half-hourly blood samples were taken for glucose and insulin estimations for 2 h. Fasting lipids were also estimated on that day.

Stress tests

In the same week but on a separate occasion, patients attended during the late morning (about 4 h after the morning dose of tablets) for a recording of blood pressure and pulse during three kinds of stress. The first was an exercise test on an electrically braked bicycle on which patients had had a training session on a prior occasion when a work load producing a moderate rise in blood pressure and pulse rate had been determined. Recordings strictly timed were made as follows: 5 min baseline recordings while seated on the exercycle (three readings at 1, 2.5 and

4 min); during 5 min period of warming up exercise (exercise I, Figure 1) with a load of 0–200 kpm/min (two readings at 1.5 and 3 min and one immediately after exercise); a 5 min rest period (three readings at 1.5, 3 and 4 min), a second period of exercise (exercise II, Figure 1) at the previously determined moderate work load which was fixed for each patient and varied between patients from 100 to 500 kpm/min (readings as for exercise I); 10 min rest period (six readings, after the third reading patients dismounted from the exercycle and seated themselves at a table); mental arithmetic (the continual subtraction of 17 from a five digit figure) for 5 min (three readings); 5 min rest period (three readings), handgrip, one-third their maximum grip, an easily reproducible form of isometric exercise (Lind, Taylor, Humphreys, Kennelly & Donald, 1964) for 5 min (three readings) followed by a further 5 min rest period (three readings).

Baseline values for exercycle stress were calculated by averaging the readings immediately before exercise I and II and the third reading after exercise II. Baseline values for mental arithmetic and handgrip were calculated by averaging the readings immediately before the mental and handgrip stress and the third reading after the handgrip stress (see Figure 1).

Renal function tests

Glomerular filtration rate (GFR) was determined by ^{51}Cr -EDTA clearance (Bailey, Rogers & Tait, 1970) and effective renal plasma flow (ERPF) by the ^{125}I -hippurate clearance (Blaufox & Merrill, 1966) in eight patients using a double-isotope single shot technique and sampling at 7, 10 and 17 min for ERPF and at 2, 4, 6 h for GFR. All values were corrected to the standard surface area of 1.73 m².

Plasma renin activity

Plasma renin activity was measured at the Endocrine Laboratory, Princess Margaret Hospital, Christchurch by a radioimmunoassay of angiotensin I generated *in vitro* (Espiner, Donald & Miles, 1978).

Achilles tendon reflex

Achilles tendon reflex duration was measured as 'CR time' a readily identifiable and reproducible time interval between the time of maximum rate of contraction (C) and the time of maximum rate of relaxation (R) of the Achilles tendon reflex (Waal-Manning, 1969).

Spirometry

Spirometry was performed with a Godart water spirometer at the Dunedin Respiratory Laboratory before and after isoprenaline.

Biochemical estimations

The following methods were used for the biochemical estimations: sodium and potassium-flame photometry II 143 with automatic dilutor; urea-diacetyl monoxime autoanalyzer Mk II clinical method 01; glucose-cupric neocuproine autoanalyzer Mk II technicon method No. SEZ-002PM3; creatinine-Jaffe reaction autoanalyzer I method N116; cholesterol-ion salts with extraction autoanalyzer I N24a; triglycerides-colorimetric (Demacker, Van Oppenraay, Baadenhuysen & Jansen, 1975). Insulin was estimated by radioimmunoassay.

Statistical analysis

The data were analysed as described by Cochrane & Cox (1966) for a crossover design. Where the analysis of variance indicated a significant effect due to treatment a paired *t*-test was done. The test of the difference between the stress induced rise in BP and pulse on placebo and those on atenolol was performed by a *t*-test on the contrast extracted from the analysis of variance model.

Results

Blood pressure and pulse rate response

Lying systolic and diastolic pressure and pulse rate and standing diastolic pressure and pulse rate were all significantly lower on atenolol (Table 1). Stress baseline values-baseline I while seated on the bicycle ergometer and baseline II while seated at a table were also all significantly lower on atenolol. Baseline II BP values significantly lower than baseline I BP values during placebo and also during atenolol treatment.

The changes in mean systolic and diastolic pressure and pulse rate due to physical and mental activity are illustrated in Figure 1. The baseline and maximum values during stress are listed in Table 2. On

placebo treatment, systolic pressure rose significantly in response to each of the three forms of stress, whereas diastolic pressure rose significantly only during handgrip stress. During atenolol treatment the rises in systolic pressure in response to stress were somewhat less but not significantly less than those during the placebo phase, the rises in diastolic pressure were very similar. Because of the significantly lower baseline values on atenolol, the mean peak pressure reached during atenolol was always significantly less than during placebo treatment. Baseline pulse rate was lower during atenolol but the increase in pulse rate during bicycle exercise was much the same on atenolol and placebo. There was no rise in pulse rate during mental arithmetic and handgrip stress in either treatment period.

Renal function tests

GFR and ERPF values were corrected to the standard body surface of 1.73 m². Mean GFR and ERPF during placebo treatment were below the normal range (Table 3) and there was no significant change on atenolol (Table 3). Serum creatinine was also similar on placebo and atenolol (Table 3). Serum urea was significantly higher on atenolol than on placebo. PRA (Table 3) was reduced by 60% on atenolol.

Lipids and glucose tolerance

Glucose and insulin levels during the glucose tolerance tests are shown in Table 4. Fasting glucose was a little higher and 1 h and 2 h post-glucose serum insulin levels were a little lower on atenolol. Fasting cholesterol and triglyceride (Table 5) levels were similar on placebo and atenolol.

Other parameters

The results of these are listed in Table 5.

There was no statistically significant difference between values on placebo and atenolol for the

Table 1 Resting BP (mmHg) and pulse (beats/min) at 8 weeks (mean $\pm$ s.e. mean); *n* = 10

	On placebo P	On atenolol A	Difference A-P
Lying			
systolic BP	170 $\pm$ 4.7	153 $\pm$ 5.7	-17*
diastolic BP	95 $\pm$ 2.5	84 $\pm$ 3.7	-11**
pulse rate	76 $\pm$ 3.8	59 $\pm$ 2.5	-17***
Standing			
systolic BP	150 $\pm$ 4.8	146 $\pm$ 5.5	-4
diastolic BP	96 $\pm$ 2.5	83 $\pm$ 3.2	-13**
pulse rate	83 $\pm$ 4.2	62 $\pm$ 3.3	-21***

by analysis of variance **P* < 0.05; ***P* < 0.01; ****P* < 0.001

Figure 1 Effect of different forms of stress (exercise I and exercise II bicycle ergometry; mental arithmetic; handgrip) on blood pressure and pulse rate. See stress-test in section on **Methods** for description of procedure and calculation of baseline I and II. $\circ$ values on placebo, $\bullet$ values on atenolol. Asterisks indicate that the level of statistical significance (*t*-test) between mean baseline value and stress induced change on placebo is at most $P < 0.01$. On atenolol baseline and stress values for most parameters were statistically significantly lower (by analysis of variance) than those on placebo. The exception was systolic pressure rise during mental arithmetic. $\triangle$ indicate that the level of statistical significance between mean baseline value and stress induced change on atenolol is at most $P < 0.01$.

following parameters (Table 5): duration of Achilles tendon reflex ('CR time'); weight, serum sodium, potassium and chloride. There was also no difference between values on placebo and atenolol for VC, FEV₁ and FVC before and after isoprenaline. One patient, however, who had smoked heavily in the past and who had a tendency to bronchitis had a response to isoprenaline in FEV₁ and FVC on placebo but not on atenolol 200 mg/day. This patient developed florid asthma some months later, while still taking atenolol during an exacerbation of his bronchitis.

Discussion

Blood pressure and pulse rate response

The small extent of the BP reduction at rest is a reflection of the mildness of the hypertension in these patients which is an ethical requirement in a trial of this nature. Baseline I values while sitting on the bicycle ergometer were statistically significantly higher than baseline II while sitting at the table for both treatment periods. This may have been due to reflex elevation of BP in response to gripping the handle bar (Freyschuss, 1970).

Atenolol did not prevent stress-induced blood pressure rise though systolic pressure and pulse rate rise in response to bicycle ergometry were a little attenuated. Absolute levels of pressure and pulse on atenolol were lower because atenolol had lowered the baseline levels. Thus the main effect of atenolol was to lower the blood pressure level around which variations occurred. Clement, Bogaert & Pannier (1977) came to a similar conclusion.

The circulatory responses to the three types of stress used in this study are mediated by several mechanisms leading to vagal withdrawal and sympathetic activation with varying effects on heart rate, cardiac output and peripheral resistance. The stimuli for the responses are thought to include baroreceptor activation, pain, psychological factors (Irving, Britton, Wood, Podgham & Carruthers, 1974) and reflexes originating in contracting skeletal muscle (Donald, Lind, McNichol, Humphreys, Taylor & Stounton, 1967; Freyschuss, 1970).

Renal function and renin

Glomerular filtration rate is reversibly lowered by about 13% by long-term propranolol therapy (Ibsen & Sederberg-Olsen, 1973). β -blockers do differ in their effect on renal blood flow. Thus Duchin, Antonaccio & Steinbacher (1978) showed that whereas propranolol reduced renal blood flow in dogs, nadolol, another non-selective β -adrenoceptor blocker, caused a significant increase in renal blood flow. There was no change in serum creatinine, GFR or ERPF on atenolol in the present study nor in creatinine clearance on atenolol in a study by Wilkinson (1979).

Serum urea on atenolol in our study did rise a little ($P < 0.01$). As renal blood flow was not significantly reduced this rise may have been due to the blood pressure lowering effect of atenolol affecting tubular reabsorption (Reubi, 1978). Two other studies of atenolol in patients with adequate renal function showed no change in blood urea (Gostick, Mayhew, Million, Sagar, Suxena, Ingram & Barker, 1977) and a 10% increase (Zech, Labeuw, Pozet, Hadj-Aissa,

Table 2 Baseline and maximum values for blood pressure (mm Hg) and pulse rate (beats/min) during stress (mean $\pm$ s.e. mean)

	Baseline I sitting on exercycle a	Maximum values		Baseline II sitting at a table d	Maximum values	
		Exercise I b	Exercise II c		Mental arithmetic e	Handgrip f
<i>Placebo</i>						
1 Systolic BP	173 $\pm$ 3.5	205 $\pm$ 6.2	214 $\pm$ 10.8	157 $\pm$ 2.7	175 $\pm$ 6.6	191 $\pm$ 9.2
2 Diastolic BP	109 $\pm$ 2.1	111 $\pm$ 4.4	112 $\pm$ 3.4	99 $\pm$ 2.3	103 $\pm$ 4.0	116 $\pm$ 3.4
3 Pulse rate	84 $\pm$ 3.7	111 $\pm$ 7.5	126 $\pm$ 10.0	79 $\pm$ 2.9	86 $\pm$ 5.3	85 $\pm$ 4.9
<i>Atenolol</i>						
4 Systolic BP	158 $\pm$ 3.4	178 $\pm$ 6.6	190 $\pm$ 5.8	140 $\pm$ 2.5	162 $\pm$ 5.7	177 $\pm$ 8.3
5 Diastolic BP	96 $\pm$ 2.4	98 $\pm$ 4.9	104 $\pm$ 4.0	84 $\pm$ 2.6	91 $\pm$ 4.0	103 $\pm$ 3.8
6 Pulse rate	66 $\pm$ 2.8	86 $\pm$ 5.4	99 $\pm$ 7.4	63 $\pm$ 2.5	68 $\pm$ 4.6	65 $\pm$ 4.8

For calculation of Baseline I and II see stress tests in **Methods**

Statistical significance: All values on atenolol are significantly lower than on placebo (at most $P < 0.01$). Maximum increase over baseline on atenolol is not different from that on placebo for each stress maximum observation.

a-b	NS for 2, 5 $P < 0.01$ for 3, 4, 6 $P < 0.001$ for 1	a-d	NS for 3, 6 $P < 0.01$ for 1, 2 $P < 0.001$ for 4, 5	d-e	NS for 2, 3, 5, 6 $P < 0.01$ for 1, 4
a-c	NS for 2, 5 $P < 0.001$ for 1, 3, 4, 6			d-f	NS for 3, 6 $P < 0.01$ for 2, 5 $P < 0.001$ for 1, 4

Table 3 Renal function tests and 11.30 h plasma renin activity ($n=8$) at 8 weeks; mean $\pm$ s.e. mean

	On placebo P	On atenolol A	Difference A-P
GFR ($^{51}\text{Cr-EDTA}$) (ml/s)† normal > 1.5 ml/s	1.31 $\pm$ 0.127	1.23 $\pm$ 0.092	-0.08
ERPF ($^{125}\text{I-iodo-hippurate}$)† clearance (ml/s) normal 8.83-13.97 ml/s	7.40 $\pm$ 0.856	7.18 $\pm$ 0.044	-0.22
Serum (mmol/l)			
creatinine	0.087 $\pm$ 0.004	0.089 $\pm$ 0.004	+0.002
urea	5.6 $\pm$ 0.37	6.7 $\pm$ 0.44	+1.1**
Plasma renin activity (nmol angiotensin I l $^{-1}$ h $^{-1}$)	1.01 $\pm$ 0.345	0.42 $\pm$ 0.232	-0.59*

By analysis of variance * $P < 0.05$; ** $P < 0.01$

†corrected to the standard body surface of 1.73 m 2

Sassard & McAinsh, 1977) respectively. In a study of atenolol in patients with impaired renal function the slight increase in blood urea that was observed was not statistically significant (Zech *et al.*, 1977), nor was there a significant change in serum creatinine.

Thus chronic treatment with atenolol appears to have less intrinsic harmful effect on renal function than propranolol, oxprenolol, pindolol and metoprolol (Warren *et al.*, 1974; Snell & Wallace, 1974; Swainson & Winney, 1976; Waal-Manning, 1979), but within patient comparisons of these drugs are needed to confirm this impression.

A significant reduction in plasma renin levels by atenolol (60% reduction in our study) has been reported also by Wilcox (1977) and Sassard, Pozet, McAinsh, Legheand & Zech (1977) who found a reduction of 50–70% in PRA on atenolol 50 to 200 mg/day. This inhibition of renin secretion by atenolol is maintained even in hypertension of renal origin (Zech *et al.*, 1977).

Fasting lipids and glucose tolerance

The lack of effect of atenolol on fasting triglycerides (Table 5) is contrary to the findings of others (Shaw *et al.*, 1978; Day, Simpson, Metcalfe & Page, 1979) who found a rise in triglycerides on not only the cardioselective β -adrenoceptor blockers atenolol and metoprolol but also on non-selective β -adrenoceptor blockers such as pindolol and propranolol.

Reports of the effect of metoprolol on fasting triglycerides have also been conflicting, several workers finding an increase (Waal-Manning & Simpson, 1977; Shaw *et al.*, 1978; Day *et al.*, 1979; Wright, Barber, Kendall & Poole, 1979) but others (Nilsson, Hansson & Hökfelt, 1978) no change. To explain these discrepancies further studies are needed with due attention to other factors known to affect triglyceride concentrations such as alterations in diet, alcohol intake (Castelli, Gordon, Hjortland, Kagan, Doyle, Hames, Hulley & Zukel, 1977), weight,

Table 4 Glucose and insulin levels before and after 50 g glucose ($n=8$) at 8 weeks; mean $\pm$ s.e. mean

Parameter	Mean values	
	On placebo	On atenolol
Glucose (mmol/l)		
fasting	5.7 $\pm$ 0.40	5.9 $\pm$ 0.44*
30 min	8.4 $\pm$ 0.82	8.3 $\pm$ 0.96
60 min	7.1 $\pm$ 1.20	7.5 $\pm$ 1.30
90 min	6.0 $\pm$ 1.10	6.0 $\pm$ 0.91
120 min	5.5 $\pm$ 0.80	5.0 $\pm$ 0.80
Insulin (pmol/l)		
fasting	133 $\pm$ 19	165 $\pm$ 44
30 min	764 $\pm$ 147	695 $\pm$ 149
60 min	639 $\pm$ 85	569 $\pm$ 70**
90 min	417 $\pm$ 38	388 $\pm$ 41
120 min	381 $\pm$ 27	307 $\pm$ 40**

By analysis of variance * $P < 0.05$; ** $P < 0.01$

Table 5 Achilles tendon reflex, weight, electrolytes and fasting lipids at 8 weeks; mean $\pm$ s.e. mean

Parameter	n	Mean values	
		On placebo	On atenolol
Achilles tendon reflex, 'CR time' (ms)	6	219 $\pm$ 9	232 $\pm$ 17
Weight (kg)	10	74.8 $\pm$ 4.7	75.4 $\pm$ 4.6
Serum sodium (mmol/l)	8	142 $\pm$ 0.68	142 $\pm$ 0.78
Serum potassium (mmol/l)	8	4.1 $\pm$ 0.25	4.0 $\pm$ 0.17
Serum chloride (mmol/l)	8	101 $\pm$ 0.98	100 $\pm$ 0.57
Fasting cholesterol (mmol/l)	9	5.6 $\pm$ 0.23	5.8 $\pm$ 0.34
Fasting triglycerides (mmol/l)	9	1.6 $\pm$ 0.20	1.5 $\pm$ 0.22

By analysis of variance all differences $P < 0.05$

posture, season, exertion (Björntorp, de Jonge, Sjöström & Sullivan, 1970), recent myocardial infarction (Day *et al.*, 1979) or cerebro-vascular accident (Tanaka, Sakaguchi, Oshige, Niimura & Kanehisa, 1976), the potential for difference in response in normal, hyper-lipidaemic, diabetic and hypertensive subjects, and lastly dosage and duration of β -adrenoceptor blocker therapy.

The overall effect of atenolol on glucose and insulin levels before and after a 50 g glucose load was slight (Table 4) but there was a tendency for fasting glucose levels to be higher ($P < 0.05$) and insulin levels to be lower (NS) on atenolol in eight patients including three that had impaired glucose tolerance.

These results differ from those of Day *et al.* (1979) who found no significant change in glucose tolerance on atenolol and though they found serum insulin levels to be a little lower on atenolol the change was not statistically significant.

Glucose-insulin homeostasis is a complex interplay of many factors and the net effect of administering a β -adrenoceptor blocker probably depends on various factors including patient characteristics such as diabetic status (Wright *et al.*, 1979; Day *et al.*, 1979).

Ankle jerk

The readily identifiable and reproducible time interval between the maximum rate of contraction (C) and the maximum rate of relaxation (R) of the Achilles tendon reflex, the 'CR time', has been found to increase in most subjects on propranolol (Waal-Manning, 1969), the mean increase being 25 ms. (+)-Propranolol does not prolong the Achilles reflex

hence the prolongation caused by d (+) 1-propranolol is probably related to β -adrenoceptor blockade. The receptors involved in this prolongation resemble those mediating relaxation of smooth muscle (Bohmer & Raper, 1975), i.e. they are β_2 type. The lack of prolongation of the Achilles reflex by atenolol in this study is consistent with this hypothesis.

Spirometry

As expected in these non-asthmatic subjects there was no mean change on atenolol in the various spirometric parameters studied. However, the occurrence of asthma in one of the patients at a later date indicates that like practolol (Waal-Manning & Simpson, 1971) atenolol should be used with extreme caution in patients who have chronic bronchitis. The cardioselectivity of atenolol does not impair its antihypertensive effects. Atenolol may be specially indicated in renal hypertension because it has little effect on renal function and lowers renin levels. The metabolic effects of atenolol especially those on glucose, insulin and lipid levels and renal function may differ from those of metoprolol; however, this will need to be investigated by a direct comparison between the two drugs.

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