Br. J. clin. Pharmac. (1976), 3, 445-451

HAEMODYNAMIC LONG-TERM EFFECTS OF A NEW β-ADRENOCEPTOR BLOCKING DRUG, ATENOLOL (ICI 66082), IN ESSENTIAL HYPERTENSION

P. LUND-JOHANSEN

University of Bergen, School of Medicine, Medical Department A, Bergen, Norway

1 Thirteen men with untreated essential hypertension in WHO stage I were studied on an outpatient basis to evaluate the haemodynamic long-term effect of a new β-adrenoceptor blocker, atenolol.

2 Oxygen consumption, heart rate, cardiac output (Cardiogreen) and intraarterial brachial pressure were recorded at rest in a supine and sitting position and during steady state work at 300, 600 and 900 kpm/min.

3 The subjects were treated with atenolol (dose 100-200 mg/day) as the sole drug for 1 year and the haemodynamic study was repeated.

4 The blood pressure was reduced approximately 18% both at rest and during exercise, the heart rate approximately 25% and the cardiac output 16% at rest supine and 27% at rest sitting. During exercise the reductions in cardiac output were approximately 20%. The calculated total peripheral resistance was not decreased compared to pretreatment values. The mean arterial pressure-heart rate product was reduced almost 40%.

5 Apart from temporary muscular fatigue during the first weeks, no side-effects were seen.

6 Atenolol is an effective blood pressure lowering drug in mild and moderate hypertension, but the drop in blood pressure is associated with marked reduction in heart rate and cardiac output at rest as well as during exercise.

Introduction

Atenolol is a new β-adrenoceptor blocker which has been used in human hypertension with promising results with respect to blood pressure control (Hansson, Åberg, Jameson, Karlberg & Malmcrona, 1973). Acute haemodynamic studies have shown that intravenous or oral short-term administration results in marked reduction in heart rate and cardiac output with little effect upon calculated total peripheral resistance (Amery, Billiet, Joossens, Meekers, Reybrouck & Van Mieghem, 1975). No long-term haemodynamic studies have been reported.

The purpose of this work was to study the haemodynamic changes at rest and during exercise induced by 1 year of treatment with atenolol as the sole drug in subjects with mild essential hypertension.

Methods

The study included thirteen men, aged 20-48 years (mean 33.8 years) with untreated essential hypertension in WHO stage I (World Health Organization, technical report series 231). Secondary hypertension was excluded by the usual routine procedures (Lund-Johansen, 1967). All were without symptoms, the hypertension being discovered by routine control by a health officer and established by at least three visits to the outpatient clinic at medical department A, Haukeland Hospital. The mean value and ± s.d. for body weight and BSA before treatment were 75.8 ± 5.6 kg and 1.93 ± 0.13 m^2. After 1 year on therapy the body weight was not significantly changed.

The subjects were studied haemodynamically during strictly standardized conditions at rest supine and sitting and during bicycling in steady state at 300, 600 and 900 kpm/min. Oxygen consumption was measured by a Douglas bag and micro Scholander technique. The intraarterial pressure (brachial artery) and heart rate (HR) were measured continuously and the cardiac output (Cardiogreen) was measured in duplicate in each situation. The methods have been described previously in detail (Lund-Johansen, 1967, 1974a). The subjects were informed about the

nature and the purpose of the study and consent was obtained from all. All studies were made on an outpatient basis. After a treatment period of 11 to 12 months the haemodynamic study was repeated. The difference between the haemodynamic results at the first and the second study was tested by a Student's *t*-test (paired sample test). The present study does not include any untreated control group. However, it has been documented in a previous work (Lund-Johansen, 1971) that in similar subjects left untreated for 1 year the haemodynamic parameters at the restudy were not significantly different from those at the first.

Treatment

The patients received tablets of atenolol (Tenormin, ICI Ltd) 50 mg at 07.00 h and 50 mg at 17.00 hours. One patient increased the dose to 100 mg twice daily. No other drugs or any diet restrictions were given. On the day of the second haemodynamic study the patients took their morning dose at 07.00 hours. The haemodynamic study was performed between 09.00 and 12.00 hours.

Side effects

During the first 2-3 weeks three patients experienced pronounced fatigue in the thigh and leg muscles when climbing stairs, one of them also dizziness after exercise. The dose was temporarily reduced in two of them. At the end of the study these sensations had disappeared. Nobody felt that the 900 kpm/min load after 1 year was more strenuous than the first time. No patients noticed any change in physical condition or sense of well being during the study.

Results

Causal blood pressure and heart rate

The causal blood pressure (sitting) dropped in all subjects during treatment, the mean value from 163/106 mmHg before start to 135/90 mmHg at the last control shortly before the second haemodynamic study. The mean heart rate dropped from 86 to 63 beats/min.

Haemodynamic data

The haemodynamic data are shown in Tables 1 and 2 and Figure 1. The oxygen consumption (VO_2) did not change significantly either at rest or during exercise. At the 900 kpm/min load the VO_2 tended to be higher after therapy, the increase being 6%, but the change was not significant.

Cardiac index

The cardiac index decreased in all subjects both at rest and during exercise at all three work loads. The mean decrease at rest supine was 0.57 $l\,min^{-1}\,m^{-2}$ (16%) and at rest sitting 0.87 $l\,min^{-1}\,m^{-2}$ (27%). At rest sitting the reduction was greater than 12% in all subjects, and the greatest reduction 48%. Ten subjects had values below 2.5 $l\,min^{-1}\,m^{-2}$ after therapy, none before.

During exercise there were also substantial reductions in cardiac index, the mean reduction being about 1.5 $l\,min^{-1}\,m^{-2}$ or 26, 20 and 16% at the 300, 600 and 900 kpm/min loads respectively. At the 300 kpm/min load twelve patients had reductions greater than 20%. At all three work levels the post-treatment cardiac output was approximately 3 litres/min lower than before treatment.

Heart rate

The greatest changes were seen in this parameter. The heart rate was reduced in all subjects both at rest and during all three work tests. At rest supine the mean heart rate fell 17 beats/min (24%), the individual reductions ranging from 14 to 32%. Five patients had heart rates less than 48 beats/min after therapy.

Marked reductions in heart rate were also observed in patients who had low pretreatment values. Thus five patients with pretreatment heart rate ranging from 60-65 beats/min all had reductions exceeding 20%. At rest sitting the heart rate was reduced 28% or 21.8 beats/min.

During exercise the individual reductions in heart rate ranged 18 to 40%. The mean reductions in heart rate at the three work loads were 30, 40 and 44 beats/min respectively. The mean relative decrease at the three work loads was almost the same, about 27%.

Stroke index

At rest supine the stroke index showed an increase of 5.1 ml $stroke^{-1}\,m^{-2}$ or 10% (significant).

At rest sitting the changes in stroke index were small and inconsistent and the mean value practically unchanged.

During exercise the changes in stroke index differed at the three work levels. At the 300 kpm/min load the changes were inconsistent and the mean value almost unchanged. At the two highest work loads the stroke index was significantly higher than before therapy, about 8 ml $stroke^{-1}\,m^{-2}$ (13%).

Table 1 Oxygen consumption (VO_2), cardiac index (CI), stroke index (SI) and heart rate (HR) before (1) and during (2) therapy, mean difference (2-1) and *P* value of paired sample test.

	Rest				*Work (kpm/min)*					
	Supine		*Sitting*		*300*		*600*		*900*	
	1	*2*	*1*	*2*	*1*	*2*	*1*	*2*	*1*	*2*
VO_2 (ml min^{-1} m^{-2})										
Mean			150.6	154.8	542.7	556.4	778.3	804.8	1235.2	1313.5
s.d.			21.8	17.2	50.2	38.5	49.7	32.8	112.8	104.1
2-1			+4.2		+13.7		+26.5		+78.3	
P			NS		NS		NS		NS	
CI (l min^{-1} m^{-2})										
Mean	3.52	2.95	3.26	2.39	6.30	4.66	7.71	6.17	9.74	8.20
s.d.	0.67	0.39	0.89	0.32	1.09	0.53	0.98	0.67	0.99	0.83
2-1	−0.57		−0.87		−1.64		−1.54		−1.54	
P	<0.01		<0.001		<0.001		<0.001		<0.001	
SI (ml $stroke^{-1}$ m^{-2})										
Mean	50.2	55.3	41.1	42.3	56.4	57.3	57.1	64.6	58.6	67.2
s.d.	6.4	5.5	5.5	6.2	4.7	6.3	6.7	9.4	5.2	9.5
2-1	+5.1		+1.2		+0.9		+7.5		+8.6	
P	<0.01		NS		NS		<0.01		<0.01	
HR (beats/min)										
Mean	70.5	53.5	79.0	57.2	111.9	82.1	136.0	96.5	167.1	123.6
s.d.	11.9	7.5	15.7	8.1	18.2	10.9	18.8	11.0	15.3	15.5
2-1	−17.0		−21.8		−29.8		−39.5		−43.5	
P	<0.001		<0.001		<0.001		<0.001		<0.001	

Table 2 Systolic (SAP), diastolic (DAP) and mean arterial pressures (MAP) and the total peripheral resistance index (TPRI) before (1) and during (2) therapy, mean difference (2-1) and *P* value of paired sample test.

	Rest				*Work (kpm/min)*					
	Supine		*Sitting*		*300*		*600*		*900*	
	1	*2*	*1*	*2*	*1*	*2*	*1*	*2*	*1*	*2*
SAP (mmHg)										
Mean	144.8	127.0	157.8	134.4	180.1	149.9	189.2	156.0	205.4	176.2
s.d.	10.2	10.5	11.8	12.6	17.1	10.6	13.2	12.6	10.0	12.6
2-1	−17.8		−23.4		−30.2		−33.2		−29.2	
P	<0.001		<0.001		<0.001		<0.001		<0.001	
DAP (mmHg)										
Mean	89.1	73.3	100.0	81.9	102.1	84.5	103.7	83.8	110.6	92.5
s.d.	6.8	5.0	6.0	5.6	9.3	6.1	9.8	6.7	6.8	7.0
2-1	−15.8		−18.1		−17.6		−19.9		−18.1	
P	<0.001		<0.001		<0.001		<0.001		<0.001	
MAP (mmHg)										
Mean	110.5	91.5	121.9	101.3	135.3	111.4	138.2	112.2	147.2	126.3
s.d.	6.7	7.0	6.6	7.4	12.5	6.9	14.1	9.0	8.5	8.4
2-1	−19.0		−20.6		−23.9		−26.0		−20.9	
P	<0.001		<0.001		<0.001		<0.001		<0.001	
TPRI (dyn s^{-1} cm^{-5} m^2)										
Mean	2 591	2 519	3 150	3 435	1 759	1 930	1 459	1 475	1 218	1 246
s.d.	485	375	707	456	300	225	260	235	149	187
2-1	−72		+285		+171		+16		+28	
P	NS		NS		<0.05		NS		NS	

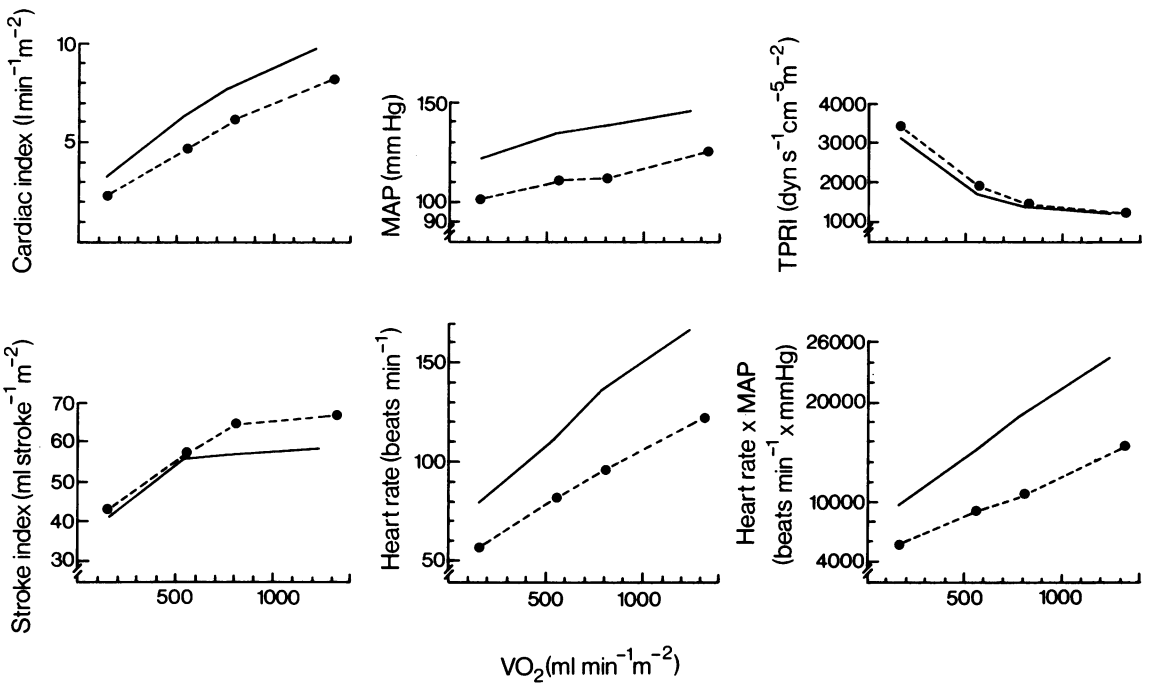

Figure 1 Mean (n = 13) haemodynamic changes at rest sitting and during exercise before (——) and during (- - - -) treatment with atenolol. MAP mean arterial pressure; TPRI total peripheral resistance index.

Arterial pressure

The blood pressure was reduced in all subjects both at rest and during all work loads. At rest sitting the mean arterial pressure was reduced 10% or more in all but one subject. The reductions in the mean values of systolic arterial pressure, diastolic arterial pressure and mean arterial pressure were about 15 to 18% both at rest and during exercise.

Although the WHO definitions of hypertension and normotension are based on arbitrary dividing lines, it is of some interest that before treatment at rest sitting all subjects fell in the 'hypertensive' group. And after therapy nine subjects had a systolic arterial pressure of less than 140 mmHg at rest sitting and eleven subjects a diastolic arterial pressure of less than 90 mmHg, (the remaining two gave values of 93 and 95 mmHg). Thus nine of the thirteen had become 'normotensive'.

Total peripheral resistance

At rest supine the changes were inconsistent and the mean value almost unchanged. At rest sitting the total peripheral resistance index (TPRI) rose in eleven subjects, the mean rise being 9%, but not significant.

During exercise the TPRI rose in most subjects compared with pretreatment values. The mean increase at 300, 600 and 900 kpm/min loads being 10% (significant), 1% and 2% respectively. A 10% decrease in TPRI at rest sitting and during two work loads was seen in only one subject.

Discussion

From a clinical point of view this new β-adrenoceptor blocker resulted in satisfactory blood pressure control in almost all subjects. All but one had a reduction in resting blood pressure of 10% or more, and nine of thirteen became 'normotensive' based on intraarterially recorded pressure at rest sitting. The dose regime was simple and apart from muscular fatigue in three subjects for a few weeks, side-effects were not seen.

The drug induced very consistent changes in central haemodynamics both at rest and during exercise, the main changes being marked reduction in heart rate and cardiac index. The calculated total peripheral resistance index was higher than before therapy in most situations.

The results at rest supine resemble those reported by Amery *et al.* (1975) in a short-term study in eleven patients. The relative decreases in

heart rate and cardiac output in their study were more pronounced, 33% and 22% respectively.

The changes in the stroke volume need some comments. Studies in animals have shown that atenolol has no negative ionotropic effect (Harry, Knapp & Linden, 1974). No decrease in stroke volume was found in this study. At rest supine the stroke volume was higher after therapy than before. This could reflect a better filling of the heart due to slower heart rate and undisturbed venous return. However, another mechanism might also be of importance. In untreated essential hypertension the stroke index during exercise is subnormal compared to what is found in normotensive age matched controls (Lund-Johansen, 1967). This subnormal stroke index, seen also in early essential hypertension in WHO stage I, could reflect an incipient cardiac insufficiency due to the high work load on the myocardium and an inappropriate blood supply. After therapy with atenolol the pressure-heart rate product was decreased almost 40%. This should result in a great reduction in the work load on the heart and in myocardial oxygen consumption. It could be possible that the higher stroke volume after therapy could reflect better cardiac haemodynamics. The long-term results of such a change could possibly have a favourable affect on the myocardium with respect to later development of regional hypoxia.

Atenolol reduced cardiac output approximately 3 litres/min during exercise. As the VO_2 was unchanged or tended to be increased this implies that the arteriovenous oxygen difference had to be increased. It is likely that during the first days and weeks of treatment the fall in the cardiac output might have been even greater. Three patients complained of marked fatigue in leg and thigh muscles during stair climbing. After a few weeks this symptom had disappeared. It is likely that the symptom is due to insufficient muscle blood flow during severe exercise possibly resulting in accumulation of lactic acid. After some weeks local adjustments probably take place in the muscles, perhaps similar to what happens during physical training.

It should be stressed that the patient group included several patients who enjoyed vigorous physical exercise like running in the mountains and cross-country skiing. No subjects experienced any change in physical condition or sense of well being after several months of treatment.

In this type of patients no clear reduction in calculated total peripheral resistance was achieved after 1 year on long-term treatment in spite of a significant reduction in arterial pressure. Thus from a pathophysiological point of view atenolol has less favourable effects on the total peripheral vascular resistance than thiazide diuretics (Lund-Johansen, 1971) and prazosin (Lund-Johansen, 1974c).

The changes induced by long-term therapy of atenolol resemble those obtained by 400 to 800 mg of alprenolol given to a similar group of patients in a previous study (Lund-Johansen, 1974b). The effects on heart rate, cardiac output and blood pressure were more marked than those obtained in the alprenolol study.

It is concluded that atenolol is a very efficient β-adrenoceptor blocking drug resulting in good blood pressure control in subjects with mild and moderate essential hypertension in WHO stage I. The drug induces favourable changes in the pressure-heart rate product, but still after 1 year on treatment there is no clear decrease in calculated total peripheral vascular resistance compared with the pretreatment values.

Reprint requests should be addressed to P. L-J, Medical Department A, 5016 Haukeland Hospital, Bergen, Norway.

References

AMERY, A., BILLIET, L., JOOSSENS, J.V., MEEKERS, J., REYBROUCK, T. & VAN MIEGHEM, W. (1975). Preliminary report on the haemodynamic response of hypertensive patients treated with a beta blocker (ICI 66082). *Acta clin Belgica*, **28**, 358-363.

HANSSON, L., ÅBERG, H., JAMESON, S., KARLBERG, B. & MALMCRONA, R. (1973). Initial clinical experience with ICI 66082, a new beta-adrenergic blocking agent, in hypertension. *Acta med. scand.*, **194**, 549-550.

HARRY, J.D., KNAPP, M.F. & LINDEN, R.J. (1974). The actions of a new beta-adrenergic blocking drug, ICI 66082, on the rabbit papillary muscle and on the dog heart. *Br. J. Pharmac.*, **51**, 169-177.

LUND-JOHANSEN, P. (1967). Hemodynamics in early essential hypertension. *Acta med. scand.*, Suppl. **482**, 1-101.

LUND-JOHANSEN, P. (1971). Hemodynamic changes in long-term diuretic therapy of essential hypertension. *Acta med. scand.* **187**, 509-518.

LUND-JOHANSEN, P. (1974a). Hemodynamic changes at rest and during exercise in long-term clonidine therapy of essential hypertension. *Acta med. scand.*, **195**, 111-115.

LUND-JOHANSEN, P. (1974b). Hemodynamic changes at rest and during exercise in long-term beta-blocker therapy of essential hypertension. *Acta med. scand.*, **195**, 117-121.,

LUND-JOHANSEN, P. (1974c). Hemodynamic changes at rest and during exercise in long-term prazosin therapy of essential hypertension. In *Prazosin—Evaluation of a new anti-hypertensive agent*, ed. Cotton, D.W.K., pp. 43-53. Excerpta Medica.

WORLD HEALTH ORGANISATION (1962). Arterial hypertension and ischaemic heart disease. Preventive aspects. *Technical report series No. 231.*,

(Received August 11, 1975)