HAEMODYNAMIC LONG-TERM EFFECTS OF PRAZOSIN PLUS TOLAMOLOL IN ESSENTIAL HYPERTENSION

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- 1 Twelve men with untreated essential hypertension in WHO stage I were studied on an outpatient basis to evaluate the haemodynamic long-term effects of a combination of prazosin and a β -adrenoceptor blocker, tolamolol.
- 2 Oxygen consumption, heart rate, cardiac output (Cardiogreen) and intra-arterial 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 the combination of prazosin (dose 3-6 mg daily) plus tolamolol (150-300 mg daily) for 7-12 months and the haemodynamic study was repeated.
- 4 The blood pressure was reduced approximately 18% at rest and during exercise. The pressure reduction was due to a combination of reduction in cardiac index and total peripheral resistance. During hard exercise the cardiac index was almost unchanged, the pressure reduction being almost entirely due to reduction in total peripheral resistance. The heart rate was reduced significantly, but less than what is seen by β -adrenoceptor-blockers alone.
- 5 One subject demonstrated the 'first dose reaction' of prazosin with syncope. During the study tolamolol was withdrawn from clinical trials due to possible side-effects in long-term high dose studies in animals. After the haemodynamic study was completed, tolamolol was replaced by timolol without changes in the blood pressure.
- 6 The combination of prazosin and a β -adrenoceptor blocking drug is very effective in most patients with mild and moderate essential hypertension. The blood pressure reduction is due to a combination of reduction in total peripheral resistance and in cardiac index, the latter being only slightly decreased during severe muscular exercise.

Introduction

Prazosin hydrochloride is a relatively new antihypertensive drug which reduces blood pressure in hypertensive animals and man by direct relaxation of vascular smooth muscle and by interference with peripheral sympathetic function at a site distal to the α -adrenergic receptor (Constantine, 1974). Short-term (Smith, Fernandez, Kim, Swartz & Onesti, 1975) and long-term (Lund-Johansen, 1974b) haemodynamic studies at rest have shown that the drop in blood pressure in hypertensive subjects is due to a reduction in total peripheral resistance and no decrease in cardiac output. Studies during muscular exercise (Lund-Johansen, 1974b) demonstrated that the cardiac output after 1 year on therapy was greater than before treatment.

As the decrease in the blood pressure by prazosin alone is sometimes modest (Amery,

Verhiest, Croonenberghs & Fagard, 1974, Lund-Johansen, 1974b), combination with other drugs might be necessary. Because of the tendency to tachycardia and the high blood flow induced by prazosin alone, combination with a β -adrenoceptor blocking drug would seem to be particularly useful.

The purpose of this work was to study the haemodynamic changes at rest and during exercise induced by 1 year of treatment with prazosin plus the β -adrenoceptor blocking drug tolamolol. This is a cardioselective β -adrenoceptor blocker without intrinsic sympathomimetic action (Miller, Vismara & Mason, 1975). Unfortunately, during the study clinical trials on tolamolol had to be stopped for safety reasons since long-term animal toxicity studies at doses 25-50 times maximum doses had shown possible danger of malignant tumors of

breast and liver (Jefferis, Pfizer Inc. 1975, personal communication). The treatment period was thus less than 1 year (7-11 months) in four subjects.

Methods

The study included twelve men, aged 36-59 years, (mean 47.7 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 mean value and $\pm$ s.d. for body weight and BSA before treatment were 74.2 ± 10.7 kg and 1.87 ± 0.13 m². At the end of the treatment period there was no significant change in body weight.

After informed consent was obtained, the subjects were studied haemodynamically at rest and during bicycling at 300, 600 and 900 kpm/min. Oxygen consumption was measured by a Douglas bag and micro Scholander technique, the arterial pressure (brachial artery) and heart rate were measured continuously and the cardiac output (Cardiograph) was measured in duplicate in each situation. The methods have been described previously in detail (Lund-Johansen, 1967).

All studies were made on an outpatient basis. After a treatment period of 7-12 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).

Treatment

The patients were given tolamolol and prazosin as tablets at 07.00 h, 12.00 h and 17.00 h. The starting dose of prazosin was 0.5 mg three times a day and of tolamolol 50 mg three times a day aiming at a sitting casual blood pressure $\leq$ 140/90 mm Hg. If necessary the dose was increased up to a total daily dose of prazosin (6 mg) and tolamolol (300 mg) (in one subject even higher - see later). The mean daily doses were: prazosin (4 mg) and tolamolol (200 mg).

One subject did not respond to tolamolol (600 mg) plus prazosin (12 mg) and was excluded.

The following values concern the eleven subjects who were treated only by prazosin plus tolamolol - without any other drugs or diet restrictions.

When tolamolol had to be withdrawn (after the second haemodynamic study), this drug was replaced by timolol (without any difficulties or blood pressure changes).

Side-effects

One subject experienced a syncope 1 hour after the first dose. No other side-effects were seen.

Results

Casual blood pressure and heart rate

The casual blood pressure (sitting) dropped in all subjects during treatment, the mean value from 170/115 mm Hg before starting to 129/89 mm Hg at the last control shortly before the second haemodynamic study. The mean heart rate dropped from 79.6 to 64.0 beats/min.

Haemodynamic data

The haemodynamic data are shown in Tables 1 and 2 and Figure 1. The oxygen consumption (VO₂) did not change significantly either at rest or during exercise.

Cardiac index

At rest and during light exercise the cardiac index showed a small, but almost significant, reduction. At rest supine and sitting the decreases were 9% and 15%, respectively. At the two highest work levels the decrease in cardiac index was insignificant and at the highest work level the mean values before and after therapy were almost the same.

Heart rate

The heart rate decreased in all subjects in all situations, all changes being highly significant. The mean reduction was 15% at rest supine and 17% at rest sitting. During exercise the mean reduction was about 20%. The lowest heart rate at rest supine was 52, at rest sitting 54 beats/min.

Stroke index

At rest there were no consistent or significant changes in the stroke index, either supine or sitting. During exercise, however, the post-treatment stroke index was increased, the increase being significant at all work levels. At the two highest work levels the increase in stroke volume was about 20%, thus compensating for the reduction in the heart rate.

Arterial pressure

The blood pressure was reduced in all subjects both at rest and during all work loads. At rest the

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

	<i>Rest</i>		<i>Work (kpm/min)</i>		
	<i>Supine</i>	<i>Sitting</i>	<i>300</i>	<i>600</i>	<i>900</i>
VO_2 ($\text{ml min}^{-1} \text{m}^{-2}$)					
Mean		164.2	638.3	905.7	1362.3
s.d.		26.2	107.4	107.1	143.2
Δ		-14.8	-24.7	-12.0	-98.8
<i>P</i>		NS	NS	NS	NS
CI ($\text{l min}^{-1} \text{m}^{-2}$)					
Mean	3.34	2.90	5.87	7.10	8.49
s.d.	0.39	0.39	0.87	0.69	1.17
Δ	-0.31	-0.44	-0.61	-0.38	-0.15
<i>P</i>	< 0.05	< 0.05	< 0.05	NS	NS
SI ($\text{ml stroke}^{-1} \text{m}^{-2}$)					
Mean	48.6	39.2	53.1	53.8	53.1
s.d.	5.3	5.3	5.1	5.1	8.2
Δ	+3.4	+1.2	+5.5	+10.1	+11.3
<i>P</i>	NS	NS	< 0.05	< 0.001	< 0.001
HR (beats min^{-1})					
Mean	68.7	74.1	110.2	132.6	161.1
s.d.	5.4	4.1	9.3	14.4	17.4
Δ	-10.3	-12.9	-20.1	-27.2	-31.3
<i>P</i>	< 0.001	< 0.001	< 0.001	< 0.001	< 0.001

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

	<i>Rest</i>		<i>Work (kpm/min)</i>		
	<i>Supine</i>	<i>Sitting</i>	<i>300</i>	<i>600</i>	<i>900</i>
SAP (mm Hg)					
Mean	152	168.0	194.1	199.0	214.6
s.d.	23.4	21.6	20.5	24.0	20.9
Δ	-19.7	-29.4	-33.9	-34.6	-28.0
<i>P</i>	< 0.01	< 0.001	< 0.001	< 0.001	< 0.001
DAP (mm Hg)					
Mean	91.9	104.9	108.6	109.0	114.8
s.d.	12.9	10.0	9.6	11.0	10.1
Δ	-14.5	-19.6	-21.5	-21.2	-17.8
<i>P</i>	< 0.001	< 0.001	< 0.001	< 0.001	< 0.001
MAP (mm Hg)					
Mean	116.4	128.9	144.6	145.1	155.1
s.d.	17.3	13.9	14.3	17.0	16.6
Δ	-18.9	-24.3	-25.4	-25.3	-21.1
<i>P</i>	< 0.001	< 0.001	< 0.001	< 0.001	< 0.001
TPRI ($\text{dyn s}^{-1} \text{cm}^{-5} \text{m}^2$)					
Mean	2820	3597	2000	1649	1494
s.d.	476	489	317	251	336
Δ	-179	-113	-169	-203	-180
<i>P</i>	NS	NS	< 0.05	< 0.001	< 0.05

Figure 1 Mean ($n = 11$) haemodynamic changes at rest sitting and during exercise before (—) and during (---) treatment with prazosin plus tolamolol. MAP mean arterial pressure; TPRI total peripheral resistance index.

reductions in mean arterial pressure was 16% supine and 20% sitting. During exercise the reductions in mean arterial pressures were about 17%.

Before therapy started, all but one subject had a diastolic blood pressure of 100 mm Hg or more at rest sitting. At the restudy all but one subject had values below 95 mm Hg.

Total peripheral resistance

At rest the changes in total peripheral resistance index (TPRI) were inconsistent and insignificant. During exercise, however, the TPRI decreased in all but one or two subjects on each work level. The changes were statistically significant. At the two highest work levels the TPRI was reduced 12%.

Discussion

From a clinical point of view combined therapy with prazosin plus tolamolol was very effective in eleven of twelve patients with mild to moderate essential hypertension in WHO stage I. No explanation can be found for the lack of effect in the single subject who did not respond to this combination, but reacted with a very marked blood

pressure drop when a thiazide diuretic was added.

The mechanism behind the pressure reduction differs from what has been observed by β -adrenoceptor blockers alone (Lund-Johansen, 1974a; Lund-Johansen, 1976a, b) or by prazosin alone (Lund-Johansen, 1974b) in similar patients. In a group of patients treated with prazosin alone in doses up to 7.5 mg daily, the reductions in mean arterial pressure at rest supine and sitting were 9% and 13%, and during exercise about 11%. With combined therapy the pressure reductions were greater at rest as well as during exercise. The pressure reduction induced by prazosin alone was entirely due to reduction in total peripheral resistance as the cardiac output after therapy was increased, significantly so during muscular exercise. The increase in the cardiac index after therapy was mainly due to increase in stroke volume. The combination of a β -adrenoceptor blocker and prazosin resulted in a significant reduction in heart rate. This reduction in heart rate was less than what has been observed by the use of β -adrenoceptor blockers alone. The post-treatment stroke index during moderate and maximal exercise was increased and almost completely compensated for the reduction in heart rate. At rest supine and sitting the increase in

stroke index was small and not significant and did not compensate for the reduction in the heart rate. The net effect was a relatively small, but statistically significant reduction in cardiac index at rest and during light exercise, but with the ability to achieve a high cardiac output during severe exercise intact. The haemodynamic changes differs from those induced by β -adrenoceptor blockers alone when the heart rate during exercise is so much reduced that in spite of some compensatory increase in the stroke volume, the cardiac output during exercise might be reduced 20% or even more (Lund-Johansen, 1976a, b).

A reduction in total peripheral resistance by antihypertensive therapy is considered to be an advantage since this should correct the cardinal haemodynamic disorder in essential hypertension. Long-term use of β -adrenoceptor blockers alone have little effect upon calculated total peripheral resistance at rest as well as during exercise (Lund-Johansen, 1974a, 1976a, b). With a combined therapy the total peripheral resistance index remains decreased as on prazosin alone, but the decrease was significant only during muscular

exercise. The results obtained by a combination of prazosin and tolamolol resemble those obtained by Sannerstedt, Stenberg, Johnsson & Werkø, 1971, in a study on the combination of alprenolol and dihydralazine.

In summary the combined therapy seems to induce favourable changes in the central haemodynamics in subjects with mild to moderate essential hypertension. The blood pressure is reduced significantly and there is a modest reduction in the heart rate at rest and during exercise. The post-treatment stroke volume is increased particularly during exercise and the heart is then able to deliver almost the same cardiac output after therapy as before. The drop in blood pressure, particularly during exercise, is mainly due to reduction in the total peripheral resistance. It might be expected that this combination would be particularly useful in patients who will not tolerate any great reduction in blood flow.

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References

- AMERY, A., VERHIEST, W., CROONENBERGHS, J. & FAGARD, R. (1974). Double blind cross-over study with a new vasodilator - prazosin - in the treatment of mild hypertension. In *Prazosin - Evaluation of a new anti-hypertensive agent*, ed. Cotton, D.W.K., pp. 100-110. Amsterdam: Excerpta Medica.
- CONSTANTINE, J.W. (1974). Analysis of the hypotensive action of prazosin. In *Prazosin - Evaluation of a new anti-hypertensive agent*, ed. Cotton, D.W.K., pp. 16-36. Amsterdam: Excerpta Medica.
- LUND-JOHANSEN, P. (1967). Haemodynamics in early essential hypertension. *Acta med. scand.*, Suppl., **482**, 1-101.
- LUND-JOHANSEN, P. (1974a). Haemodynamic changes at rest and during exercise in long-term beta-blocker therapy of essential hypertension. *Acta med. scand.*, **195**, 117-121.
- LUND-JOHANSEN, P. (1974b). Haemodynamic 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. Amsterdam: Excerpta Medica.
- LUND-JOHANSEN, P. (1976a). Haemodynamic changes at rest and during exercise in long-term timolol therapy of essential hypertension. *Acta med. scand.*, **199**, 263-267.
- LUND-JOHANSEN, P. (1976b). Haemodynamic long-term effects of a new β -adrenoceptor blocking drug, atenolol (ICI 66082), in essential hypertension. *Br. J. clin. Pharmac.*, **3**, 445-451.
- MILLER, R.R., VISMARA, L.A. & MASON, D.T. (1975). Comparative effects of tolamolol and propranolol on cardiac and peripheral circulatory function in patients with coronary artery disease. *Clin. Pharmac. Ther.*, **17**, 713-721.
- SANNERSTEDT, R., STENBERG, J., JOHNSSON, G. & WERKØ, L. (1971). Haemodynamic interference of alprenolol with dihydralazine in normal and hypertensive man. *Am. J. Cardiol.*, **8**, 316-320.
- SMITH, I.S., FERNANDES, M., KIM, K.E., SWARTZ, C. & ONESTI, G. (1975). A three-phase clinical evaluation of prazosin. In *Prazosin - Clinical Symposium Proceedings*, ed. McGraw-Hill, pp. 53-60. Postgraduate Medicine.
- WORLD HEALTH ORGANIZATION (1962). Arterial hypertension and ischaemic heart disease. Preventive aspects. *Technical Report Series No. 231*.

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