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W. Reiterer, M.D.

*I. Medical Department,
Poliklinik, Vienna, Austria*



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Summary

Fifteen patients suffering from mild to moderate essential hypertension were treated with a beta-blocker/diuretic combination (tablets containing 10 mg pindolol and 5 mg clopamide). An individually adjusted dose was given daily over a period of 12 months (mean dose: 1.23 tablet; median: 1 tablet). Rectangular-triangular bicycle ergometry was carried out at the end of the placebo period and again after 2 and 12 months of treatment. Testing was performed twice, first at the end of a 24-hour therapy-free period and again 90 minutes after 1 tablet of the combination product. The stress tests were always terminated in each patient at the same work load (approximately 60% of the individual maximal load). The acute effects of the beta-blocker combination on exercise heart rate (-17.3%) and on systolic blood pressure (-20.2%) were not intensified by long-term treatment, except for a continued reduction in the diastolic blood pressure. After withdrawal of therapy for 24 hours, no abnormal increase in the exercise blood pressure data was seen during long-term treatment. From the analysis of the ergospirometric data it may be concluded that the reduction in the exercise heart rate by the beta-blocker combination did not affect the adaptation (aerobic power) to increasing work rates similar to those in which the patients are engaged during daily life. The anaerobic energy release was increased by a delayed increase in oxygen uptake, but this can be ignored as signs of increased metabolic acidosis were not seen. After beta-blockade, the range of the anaerobic threshold (mean: 1.49 l/min VO₂) was constant, indicating no impairment of capacity for prolonged exercise.

Key words: Pindolol – clopamide – drug combinations – hypertension – exercise test

Introduction

The antihypertensive effects of beta-blocking agents are well established.^{8,10,17,19} The use of thiazide-type diuretics in combination with beta-blockers potentiates the antihypertensive effects and has the advantage of counteracting any tendency towards cardiac failure which the beta-blocker might cause.^{9,14,18,21}

Pindolol is a potent beta-adrenoceptor blocking agent with a weak quinidine-like effect, a receptor stimulation activity (intrinsic activity) but no effect on alpha-adrenergic receptors.^{1,2,5,15,16,20} Three mechanisms for the antihypertensive action of pindolol can be identified: a negative chronotropic effect on the heart, a decrease

in peripheral vascular resistance, and an increase in venous capacitance affecting the venous return.

The diuretic agent clopamide reduces the blood pressure by diminishing the vasopressor response of the vascular smooth muscles to changes in electrolyte concentration. Initially, the antihypertensive activity of the diuretic agent is caused by a fall in plasma volume.²⁰

Apart from blood pressure measurements at rest, a comprehensive evaluation of the effects of increased blood pressure on cardiovascular function should include data from quantified stress testing. Adequate restoration of abnormally high blood pressure values to normal should also consider the pressure regulation during physical work similar to that in which the patient is engaged during daily life.^{7,13}

This paper reports on a study carried out in mild to moderately severe hypertensive patients receiving long-term (12 months) treatment with tablets containing 10 mg pindolol plus 5 mg clopamide (VKB 105, 'Viskaldix'†). The aim was to assess blood pressure regulation and physical performance by ergospirometric stress testing after brief withdrawal of the patient-adjusted individual dose and also after acute administration of the beta-blocker combination.

Patients and methods

The study included 10 male and 5 female patients, aged 37 to 63 years (mean 53.1 years), with mild to moderate essential hypertension. The criterion for acceptance into the study was a blood pressure of 165/100 mmHg or more after a placebo pre-treatment period of at least 2 weeks. Patients were not included if, apart from hypertension, they had symptoms of other cardiovascular disease, diabetes, kidney or liver disease or other diseases which required special medication that might be expected to influence the result.

The mean initial dose of the pindolol/clopamide combination was 1.73 ± 0.10 tablets (median 2.0 tablets) daily. This dose was successively adjusted at 2-weekly intervals depending on the blood pressure response, the requirement being a lowering of the diastolic pressure by at least 20 mmHg or a blood pressure equal to or below 160/90 mmHg at rest without symptoms that could be attributed to the fall in blood pressure. The mean treatment period was 47.3 ± 2.2 weeks (median 49.5 weeks).

The ergospirometric stress tests were made at the end of the placebo period (A), after 2 months (B) and after about 12 months of treatment (C). Testing was performed twice, first without any therapy for 24 hours ('reference value' RV) and again 90 minutes after 1 tablet of the combination product. The patients were exercised on a electrically braked bicycle ergometer in the sitting position. The exercise protocol was based on the rectangular-triangular test procedure (2-min increment test). The examinations were carried out in exactly the same manner as during the placebo period. The stress tests were terminated at the same work load (92.9 ± 7.1 Watt; median 87.5 Watt; range 50 to 150 Watt) of approximately 60% (56.7 ± 3.0) of the predicted maximal load. The heart rate was taken from the ECG;

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the blood pressure was measured by auscultation. The systolic blood pressure refers to the value while the patient was exercising on the maximal load; the diastolic pressure was taken 1 minute after finishing the test. Primary ergospirometric parameters (oxygen uptake, 1-minute ventilation volume, tidal volume, oxygen pulse, respiratory quotient and others) were evaluated by means of an open air circuit system (Ergopneumotest mit EDV, Jäger BRD). By means of a computer-assisted on-line analysis, certain parameters of physical performance were documented by print-out and graphic display: anaerobic and aerobic power, the adaptation to work load increments and the anaerobic threshold. The parameter of metabolic acidosis (base excess) was calculated from blood gas analysis. The methods of computer assisted ergospirometric stress testing have been fully described elsewhere.^{11,12}

Results

The mean daily dose was 1.43 tablets of the trial medication (14.3 mg pindolol + 7.2 mg clopamide) after 2 months of treatment and 1.23 tablets (12.3 mg pindolol + 6.2 mg clopamide) after 12 months of treatment, the medians being 1.5 and 1 tablet, respectively.

The resting heart rate and blood pressure data are given in Table I.

Table I. Influence of long-term treatment with pindolol/clopamide on blood pressure (mmHg) and heart rate (beats/min) at rest (seated): mean (\pm S.D.) values

Measurement	A	A+1	B	C
	End of placebo	After 1 week	After 2 months	After 12 months
<i>Blood pressure</i>				
Systolic	172.0 \pm 27.95	146.7 \pm 22.25**	133.0 \pm 13.67**	139.6 \pm 18.5*
Diastolic	114.3 \pm 13.7	103.8 \pm 9.5**	91.43 \pm 8.6**	94.33 \pm 9.7*
Heart rate	79.9 \pm 16.5	75.7 \pm 11.35 (N.S.)	68.6 \pm 6.7*	69.0 \pm 6.85 (N.S.)

Note: difference compared with A, N.S. = not significant, * $p < 0.01$, ** $p < 0.001$ (Wilcoxon's test for paired comparisons)

A significant reduction in blood pressure was seen after 1 week of treatment. The mean initial dose was 1.73 tablets (17.3 mg pindolol and 8.65 mg clopamide). At the end of the study, despite the reduction in the daily dose, the resting systolic (-18.8%) and diastolic (-17.5%) blood pressure remained significantly reduced.

The data on the stress tests are given in Table II. The mean load was 92.9 \pm 7.1 Watt, equivalent to 56.7% of the predicted maximal load. The data for the placebo period (A) have been compared both with the reference periods (withdrawal of therapy for 24 hours) and the exercise data after administration of 1 tablet of the combination. Compared to the placebo period, a single tablet of the beta-blocker combination initially (A) depressed the exercise heart rate (-17.3%) and the systolic blood pressure (-20.3%) to an extent that was not surpassed during the long-term

Table II. Influence of long-term treatment with pindolol/clopidamide on parameters of physical performance assessed by computer-assisted ergospirometry (mean max. load 92.9 Watt): mean (\pm S.E.M.) values for 15 hypertensive patients

Parameter	A: end of placebo		B: after 2 months		C: after 12 months		P minus RV(B)	P minus RV(C)	RV (B) minus RV(C)
	P	PC	RV	PC	RV	PC			
Blood pressure (mmHg):									
Systolic	202.1	161.1	181.7	166.3	186.1	160.0	20.5	16.1	-4.4
	± 9.3	$\pm 9.1^{***}$	± 6.0	$\pm 6.3^{***}$	± 5.2	$\pm 6.7^{***}$	$\pm 10.9^*$	± 10.6	± 8.0
Diastolic—1 min	105.7	99.3	98.3	93.7	93.6	88.3	7.4	12.1	4.8
	± 4.9	$\pm 5.0^{***}$	± 3.4	$\pm 2.7^{**}$	± 2.2	± 4.6	± 5.9	$\pm 5.3^{**}$	± 3.9
Heart rate (beats/min)	122.9	101.6	112.3	101.0	117.8	104.6	10.6	5.1	-5.5
	± 4.9	$\pm 2.2^{***}$	± 2.3	$\pm 2.4^{***}$	± 2.9	$\pm 2.8^{***}$	$\pm 5.3^*$	± 5.7	± 3.7
Minute ventilation volume (l/min BTPS)	42.2	39.2	40.9	41.5	43.7	44.2			
	± 2.4	± 2.6	± 2.4	± 2.5	± 2.6	± 2.3			
Tidal volume (l BTPS)	1.61	1.52	1.62	1.54	1.70	1.58			
	± 0.10	± 0.09	± 0.09	± 0.08	± 0.09	± 0.09			
VO ₂ —1 min (l/min STPD)	1.43	1.37	1.41	1.39	1.60	1.50	0.02	-0.17	-0.19
	± 0.06	± 0.06	± 0.08	± 0.06	± 0.09	± 0.06	± 0.10	± 0.10	± 0.12
VO ₂ —2 min (l/min STPD)	1.66	1.49	1.59	1.55	1.69	1.64			
	± 0.07	$\pm 0.08^{***}$	± 0.09	± 0.07	± 0.09	± 0.08			
VO ₂ (ml/kg/min)	20.0	18.2	19.6	18.9	21.0	20.0	0.45	-0.99	-1.44
	± 0.99	$\pm 0.76^{**}$	± 0.99	± 0.62	± 0.85	± 0.81	± 1.40	± 1.31	± 1.32
Oxygen pulse (ml VO ₂ /beat)	13.6	14.7	14.4	15.6	14.8	15.9	-0.81	-1.26	-0.45
	± 0.80	$\pm 0.76^{***}$	± 0.71	$\pm 0.66^*$	± 0.78	± 0.77	± 1.06	± 1.11	± 1.05
Respiratory quotient	0.91	0.90	0.96	0.97	0.89	0.89	-0.05	0.02	0.067
	± 0.02	± 0.03	± 0.02	± 0.01	± 0.02	± 0.03	± 0.03	± 0.03	$\pm 0.03^{**}$
Anaerobic power (kcal)	2.18	3.98	3.26	3.71	1.70	2.64	-1.07	0.38	1.55
	± 0.63	$\pm 0.62^{***}$	± 0.68	± 0.76	± 0.69	± 0.95	± 0.93	± 0.68	± 0.97
pH	7.34	7.33	7.35	7.38	7.36	7.35			
	± 0.01	± 0.02	± 0.01	± 0.01	± 0.02	± 0.01			
Base excess (mEq/l)	-4.4	-3.9	-4.5	-3.0	-3.5	-4.6			
	± 0.7	± 0.7	± 0.7	± 0.6	± 1.0	± 0.8			
Anaerobic threshold (lVO ₂ /min)					1.49	1.48			
					± 0.1	± 0.1			

Note: P=placebo period, PC=test 90 min after 1 tablet of pindolol/clopidamide, RV=reference value, withdrawal of therapy for 24 hours.

*p<0.10, **p<0.05 and ***p<0.01 (Student's t-test for paired data and mean values)

treatment. The diastolic pressure showed a progressive reduction from -5.7% (A) to -16.5% (C).

At comparable work loads the minute ventilation volume (VE) and the tidal volume (VT) remained unchanged.

The oxygen uptake at the first minute of the maximal load (VO_2 -1 min) was somewhat suppressed after beta-receptor blockade (at time A: -4.2% ; N.S.). After 1 year of treatment, the oxygen uptake increased somewhat faster comparing the placebo data to the reference values (A/C: $+11.9\%$; N.S.). The oxygen uptake at the second minute per load (VO_2 -2 min) was reduced significantly (-10.2%) by the first administration of the drug (Time A). The follow-up after 1 year of treatment demonstrated an improved capability to take up oxygen, but the VO_2 after acute beta-receptor blockade still remained below the reference level.

The on-line calculated oxygen/pulse ratio serves as an index of the stroke volume, as $O_2/\text{pulse} = VO_2/hf = SV \times avDO_2$ (a variation in the oxygen extraction – $avDO_2$ – may be ignored if no change is seen in the parameters of metabolic acidosis that indicate an increased oxygen extraction and consequently the onset of anaerobic processes in the muscles – see base excess). The oxygen/pulse ratio increased during the treatment period both after withdrawal and after administration of the drug combination (at Time C: placebo versus reference: $+8.8\%$; N.S.).

The respiratory quotient (RQ) was not significantly changed. The on-line calculated index of the anaerobic power increased significantly at Time A after beta-blockade due to the suppression of the ability to take up oxygen ($+82.5\%$). Nevertheless, the variation remained small in absolute terms, as the parameter of metabolic acidosis (see base excess) was not affected. In other words, the anaerobic threshold (anTH, defined in $l/\text{min } VO_2$), which indicates the onset of a considerable degree of anaerobic metabolism in order to support a given load, was unchanged by beta-receptor blockade (anTH at Time C: 1.49 versus 1.48 $l/\text{min } VO_2$; the anaerobic threshold was calculated from ergospirometric data with the help of a computer programme to define the range of the endurance performance).

Discussion

In determining the necessity for antihypertensive treatment, investigation of blood pressure regulation should not only include measurements at rest but also during physical stress, including dynamic and static work, to provide for a 'profile tensionnelle'.^{7,13} A standardized ergometer test, therefore, is useful in assessing the efficacy of any antihypertensive treatment in reducing the abnormal pressure load on the cardiovascular system.¹¹

The results presented in this paper indicate that the combination of the beta-blocker pindolol with the diuretic agent clopamide can produce a rapid and significant reduction in blood pressure both at rest and during moderate and heavy work. During 1 year of treatment with an individually adjusted dose of the antihypertensive combination, a brief withdrawal of the drug for 24 hours did not lead to a loss of protection against an abnormal increase in the blood pressure during physical stress.

It was never necessary to stop the test because of excessively high blood pressure except during the placebo period.

During long-term treatment, the acute administration of 1 tablet of the combination caused a reduction in maximal exercise heart rate and in the systolic blood pressure equal to the effect seen on the first administration of the drug. We also showed a progressive reduction in the diastolic pressure – the readings were taken 1 minute after termination of the exercise test – despite a reduction of the mean maintenance dose in the course of treatment.

The rapid onset of the antihypertensive action of the combination can partly be attributed to the haemodynamic situation found in mild to moderate hypertension – hypercirculatory state^{4,8} – which responds favourably to the beta-blocker. On the other hand, the diuretic agent clopamide may induce a rapid reduction in blood pressure by reducing the plasma volume. The hypotensive effect of the beta-blocker pindolol is initially brought about by a decrease in cardiac output while a decrease in vascular resistance seems to be more important after long-term treatment.

The combination reduced the heart rate during work which was followed by a small but insignificant reduction in the oxygen uptake at the first and second minute per load. There was a gradual increase in the on-line computed anaerobic energy compartment which contributed to the ability to perform the given work loads. In absolute terms, however, the anaerobic energy release was negligible with regard to adjustment to submaximal work rates in bicycle ergometry since the criterion of metabolic acidosis (base excess) showed no evidence of clinically relevant change. In our experimental set-up, the oxygen uptake at the first minute per load is accepted as a criterion of adequate adaptation of the cardiac output to the demand working muscles.^{3,11} After beta-receptor blockade by pindolol, the increase in oxygen uptake was only slightly reduced despite a considerable fall in the exercise heart rate. The rise in oxygen/pulse supports the findings of haemodynamic investigations in the sitting position¹⁶ that the increase in the stroke volume prevents a further reduction in the cardiac output. Despite a considerable suppression of the exercise heart rate, the adaptation to increasing work during daily activity is unlikely to be affected by pindolol if symptoms of impaired myocardial function are absent. This conclusion is supported by the observation that the anaerobic threshold, defined in l/min oxygen uptake, is not altered by the beta-receptor blockade of an agent with some agonist activity. In our study, patients suffering from essential hypertension showed neither a reduced capability of the cardio-circulatory system to adjust to work loads nor a reduced capacity to support prolonged work loads.

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