Br. J. clin. Pharmac. (1979), **8**, 143–148

THE EFFECT OF β-ADRENOCEPTOR BLOCKADE ON FACTORS AFFECTING EXERCISE TOLERANCE IN NORMAL MAN

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1 We have studied the effects of single oral doses of 80 mg propranolol and 100 mg metoprolol on the cardiovascular and respiratory responses to progressive exercise in nine healthy men in double-blind, placebo-controlled experiment. As judged by their effects on exercise heart rate and cardiac output the doses of the two drugs used were equivalent.

2 β-adrenoceptor blockade reduced oxygen consumption by 3.5% over the whole work range with an increase in the respiratory exchange ratio of 0.056 units. Carbon dioxide production and exercise ventilation were unchanged. The two drugs had similar effects. Possible mechanisms for these observations are discussed.

3 Perceived exertion during exercise was increased by both the β-adrenoceptor blocking drugs and this may be of relevance to the symptom of fatigue reported by patients on these drugs. Endurance, assessed as either total work done or maximal work achieved, was reduced by 15%.

Introduction

One of the main therapeutic uses of β-adrenergic receptor blocking drugs has been in the management of angina pectoris. Many authors have reported improved exercise tolerance in these patients with delayed onset of both ischaemic pain and ECG abnormalities and reduced dependence on coronary vasodilators (Comerford & Besterman, 1976). β-adrenoceptor blocking drugs are also widely used in the control of hypertension, often in patients whose exercise tolerance is presumably normal. As adrenergic mechanisms play a major role in facilitating oxygen transport through their involvement in the control of cardiovascular and respiratory adjustments during exercise, it is important to establish the effect of β-adrenoceptor blockade on exercise tolerance, particularly as there is now evidence that the cardiovascular reserves of untrained but otherwise healthy people are more limited than generally appreciated (Wasserman, Whipp, Koyal & Beaver, 1973). Using normal individuals we have measured cardio-respiratory variables and the level of perceived exertion during a standard progressive exercise test. Nine subjects were exercised to exhaustion while taking either metoprolol, propranolol or placebo. In this way the effects of both non-selective and more cardio-selective β-adrenergic receptor blockade have been studied.

Methods

Nine healthy adult male volunteers with normal lung function were used as subjects. They were aged 25 to 42 years (mean ± s.d. 35 ± 7 years), and gave their informed consent to a protocol which had been approved by the Ethical Committee of the Department of Physiology and Pharmacology.

Identical tablets containing either 80 mg propranolol (Inderal, ICI) or 100 mg metoprolol (Betaloc, Astra) or lactose were used, and neither the subjects nor the experimenters were aware of the code used to identify the tablets. Three experiments were performed on each subject and at least 48 h elapsed between experiments on any individual. The order of the drugs was randomized between individuals to reduce bias due to any training effect of the procedure. Each experiment took 1.5 h and it started

10306–5251/79/080143–06 $01.00

2 h after a tablet had been taken on an empty stomach.

Measurements of ventilatory capacity (FEV_1, FVC using a Vitalograph; Peak expiratory flow rate (PEFR) using a Wright Peak Flow Meter) were made with the subject standing at rest at the start of the experiment and again less than 10 min after the exhausting exercise.

Cardiac output ($\dot{Q}$) was measured by an indirect Fick procedure at two steady-state moderate work loads (75 and 25 Watts) on a bicycle ergometer (Lode), each period lasting 10 to 15 min. Alveolar P_{CO_2} was estimated from end-tidal values, air being sampled continuously from the mouthpiece and passed through a URAS CO_2-meter, calibrated with standard mixtures analysed volumetrically and covering the physiological range. Mixed venous P_{CO_2} was estimated using the rebreathing method of Jones, Campbell, McHardy, Higgs & Clode (1967), and the rebreathing mixtures were made up on-line using mixing chambers connected directly to cylinders of CO_2 and O_2 whose outlet pressures could be adjusted quickly and easily. CO_2 production was measured using a 2-min Douglas bag collection immediately before or after the rebreathing procedure.

After a period of rest long enough to return the heart rate close to its resting value, a progressive bicycle exercise test was performed. The work loads started at 25 or 50 Watts, and increased in 25 Watt steps at 2 min intervals until the subject stopped because of exhaustion. The Douglas bag method was used for the measurement of expired ventilation ($\dot{V}_E$), oxygen consumption ($\dot{V}_{O_2}$), and carbon dioxide production ($\dot{V}_{CO_2}$) during the second minute of the 2-min period spent at each work load. Heart rate was calculated from a continuous ECG record obtained from Praecordial electrodes (V-trace). At the end of each period the subject was asked to indicate his subjective impression of the difficulty of that work on an integer scale (Borg, 1970) which runs from '7 very, very light' to '19 very, very hard'. This scoring of subjective impression began only when moderate exercise levels had been reached, usually about 100 Watts, although the precise level of work at which scoring began was not always the same in different experiments on any individual to minimize any effect of remembering the score in the earlier experiments.

Statistical comparisons have been made with paired *t*-tests. Multiple regression in groups has been calculated using the method of Armitage (1971).

Results

Cardiovascular effects of the two β-adrenoceptor blocking drugs

The effectiveness of the β-adrenoceptor blockade can be assessed as the depression of heart rate at the work load which in the unblocked state gives rise to a heart rate of 150 beats/min, this being the level at which vagal tone is minimal. The mean ± s.e. mean reduction in heart rate following propranolol was 35 ± 2 beats/min, and following metoprolol was 35 ± 3 beats/min. This shows that in this respect the two β-adrenoceptor blocking drugs in the doses used were equipotent. Both drugs also had the same effect on steady-state cardiac output, there being a 12% increase in stroke volume on average as compared to placebo, which was not sufficient to compensate for a 22% reduction in heart rate, so that cardiac output fell by 12%. These results are summarized in Table 1.

Ventilatory capacity

Neither propranolol nor metoprolol caused any change in peak expiratory flow rate, forced expiratory volume in 1 s or forced vital capacity at rest. After exhausting exercise, none of these variables differed from the resting values.

Gas exchange, respiratory exchange ratio and ventilation

Figure 1 shows the relation between oxygen consumption and work for three experiments in one

Table 1 The effect (mean ± s.e. mean) of β-adrenoceptor blockade on steady-state stroke volume, heart rate and cardiac output in nine subjects, at two work loads. The β-adrenoceptor blocked column represents combined data from experiments with propranolol and metoprolol on separate occasions.

		Placebo	*β-adreno-ceptor blocked*	*Difference*	t	P
25 Watts	SV (ml)	100 ± 6	113 ± 5	+13 ± 5	2.40	<0.05
	HR (beats/min)	93 ± 5	73 ± 4	−20 ± 2	8.16	<0.001
	$\dot{Q}$ (l/min)	9.1 ± 0.6	8.2 ± 0.6	−0.9 ± 0.4	2.25	NS
75 Watts	SV (ml)	118 ± 9	130 ± 4	+12 ± 7	1.82	NS
	HR (beats/min)	114 ± 7	88 ± 4	−26 ± 4	7.39	<0.001
	$\dot{Q}$ (l/min)	13.2 ± 0.7	11.5 ± 0.5	−1.7 ± 0.6	3.04	<0.02

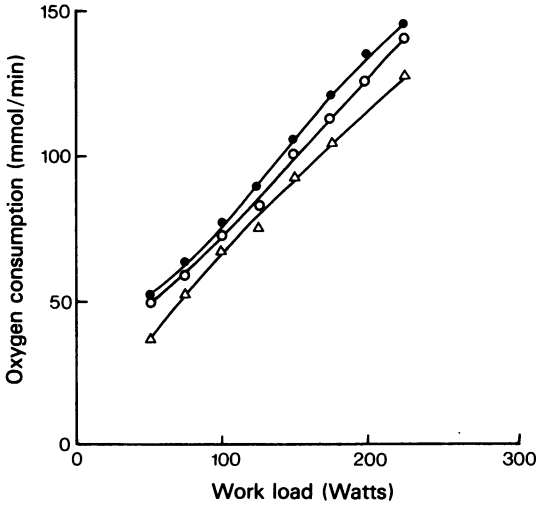

Figure 1 The relation between oxygen consumption and work load during progressive bicycle exercise in a single subject.
●, placebo; ○, metoprolol; △, propranolol.

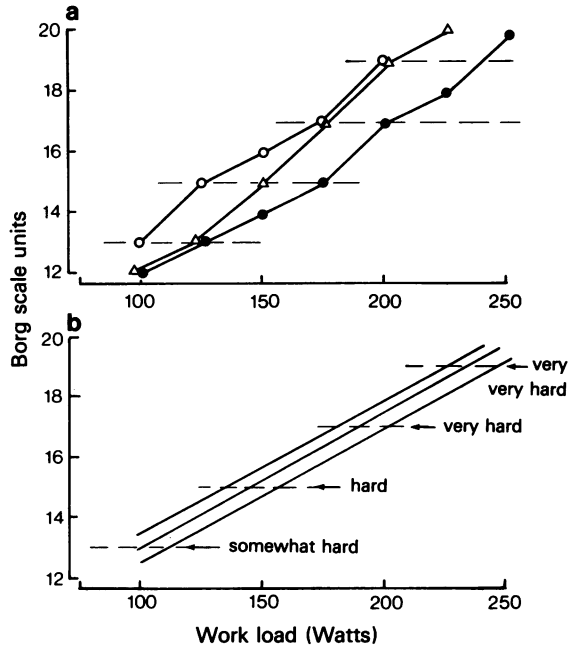

Figure 2 The relation between the perception of exertion (Borg scale rating) and work load:
(a) in three experiments on a single subject.
●, placebo; ○, metoprolol; △, propranolol.
(b) Parallel regression lines representing the effect of β-adrenoceptor blockade in the group of nine subjects. The upper line represents the relation with metroprolol and the middle line propranolol.

subject: the β-adrenoceptor blocking drugs reduce the oxygen consumption at given work levels. For the whole group of subjects, the multiple regression of oxygen consumption on work shows that β-adrenoceptor blockade significantly reduces the slope of the $\dot{V}_{O_2}$, work relation by 3.5% ($P<0.01$), corresponding to a fall of 84 ± 30 ml O_2/min at a work load of 200 Watts, but the intercept is not significantly reduced. The two β-adrenoceptor blocking drugs were indistinguishable in their effects. The results are summarized by the regression equation:

$$\dot{V}_{O_2}\ (\text{mmol/min}) = 17.39 + \{0.5444 \times \text{Work (Watts)}\} - [\{0.01867 \times \text{Work}\}\ \text{in β-blocked subjects}]$$

The relation between CO_2 production and work, on the other hand, is not influenced by β-adrenoceptor blockade. The simple regression equation:

$$\dot{V}_{CO_2}\ (\text{mmol/min}) = 2.18 + \{0.6365 \times \text{Work (Watts)}\}$$

adequately describes the results from all the experiments.

Because β-adrenoceptor blockade reduced oxygen consumption at given work levels without altering CO_2 production, the respiratory exchange ratio (RER) was raised. The two β-adrenoceptor blocking drugs do not differ in their effect which is to raise the RER by 0.056 units (s.e. mean=0.012) as compared to placebo ($P<0.001$) over the range of work loads studied.

The relation between ventilation and work was not affected by β-adrenoceptor blockade although higher levels of ventilation were seen on the β-adrenoceptor blocking drugs when this was plotted against oxygen consumption, as might be expected from the effects of these drugs on the oxygen consumption, work relation described above.

Perceived exertion and endurance

In the progressive exercise tests at work loads greater than 100 Watts, the β-adrenoceptor blocking drugs produced a significant increase of 0.73 scale units (s.e. mean=0.20) in the perceived exertion rating ($P<0.001$) for the group of nine subjects. There was no significant difference between the two β-adrenoceptor blocking drugs, though metoprolol had the greater effect. Figure 2a shows the relation between the Borg scale rating and work load for a typical subject, and Figure 2b illustrates the linear regression analysis for all nine subjects, comparing the two β-adrenoceptor blocking drugs with the control. That is, a given work load appears subjectively harder in the presence of β-adrenoceptor blocking drugs. A similar pattern is also seen if perceived exertion is plotted against oxygen consumption: over the whole range of oxygen consumptions, β-adrenoceptor blockade raises the perceived exertion rating by 1.0 scale units $P<0.01$). The levels

of perceived exertion are essentially the same at maximum exertion whether or not β-adrenoceptor blocking drugs had been taken.

Endurance can be assessed as the total work done during the progressive bicycle test which continued until the subjects stopped because of exhaustion. Assessed in this way, mean ± s.e. mean endurance on placebo was 145 ± 19 kJ, on propranolol 119 ± 15 kJ and on metoprolol 129 ± 10 kJ. Thus, endurance is 18% less on propranolol than on placebo, a significant reduction ($P < 0.05$), whereas the effect of metoprolol on endurance is less, producing a reduction of 11% which is not significant at the 0.05 level. A similar pattern of results is seen if the final work rate achieved is used as the index of endurance.

Discussion

The results to which we draw attention are the previously unreported effects of the β-adrenoceptor blocking drugs on oxygen consumption during exercise, and their effects upon perceived exertion and endurance.

The reduction in oxygen consumption and rise in respiratory exchange ratio might be a consequence of reduced muscle blood flow secondary to reduced cardiac output, so that a larger proportion of energy is derived from anaerobic metabolism as the work increases. However, the normal circulatory response to exercise includes vasoconstriction in regions such as the splanchnic area and skin (c.f. Rowell, 1974), so that changes in cardiac output after β-adrenoceptor blocking drugs do not necessarily equate with changes in muscle blood flow unless compensatory changes in other regional circulations can be excluded. It has been shown that the reduction in blood supply to the liver is more intense after β-adrenoceptor blockade (Trap-Jensen, Clausen, Noer, Larsen, Krogsgaard & Christensen, 1976), thereby presumably minimizing the effect on muscle blood flow of falling cardiac output. Furthermore, whilst it is generally assumed that fatigue is a function of local accumulation of metabolites and hence principally related to muscle blood flow, there is good evidence that fatigue is also related to neuromuscular mechanisms. Experiments on partially curarized subjects have shown that a given level of work is associated with a greater sense of fatigue after curare, which is not attributable to any change in cardiac output or arterial blood gases (Asmussens Johansen, Jorgensen & Neilsen, 1965).

The changes in oxygen consumption and respiratory change ratio might also be the result of a change in the balance of free fatty acid and carbohydrate used as the energy source for exercise, since the calorific value of a litre of oxygen is greater for carbohydrate than for fat metabolism (Douglas & Priestley, 1948). In exercise the level of free fatty acid rises (Baru, Passmore & Strong, 1960), and rising free fatty acid levels inhibit the utilization of glucose by muscle (Randle, Garland, Hales & Newsholme, 1963). They also inhibit the breakdown of muscle glycogen (Hultman, 1967). Since catecholamine infusion promotes free fatty acid release from adipose tissue (Havel, Carlson, Ekelund & Holmgren, 1964; Eaton, Steinberg & Thompson, 1965) it is possible that β-adrenoceptor blockade may inhibit the normal rise in free fatty acid levels with exercise and increase the amount of carbohydrate used as fuel. Pronethalol has been shown to lower free fatty acid levels both at rest (Steinberg, Nestel, Buskirk & Thompson, 1964) and during exercise (Muir, Chamberlain & Pedoe, 1964). Propranolol given intravenously also produces significant falls in free fatty acid levels within 15 min (Imura, Kato, Ikeda, Morimoto & Yawata, 1971), and metoprolol is effective in inhibiting catecholamine-induced lipolysis in human adipose tissue (Frisk-Holmberg & Östman, 1977). Further support for such a mechanism underlying the fall in oxygen consumption and rise in respiratory exchange ratio seen in our experiments is provided by the drug nicotinic acid which also inhibits catecholamine-induced adipose tissue lipolysis (Carlson, 1963). Administration of this drug to man has been shown to lower free fatty acid levels in exercise, raise blood glucose levels and cause a rise in the respiratory exchange ratio of 0.05 units (Jenkins, 1965). However, more elaborate metabolic experiments, possibly incorporating measurements of muscle blood flow, will be necessary before we can explain with confidence the effects on oxygen consumption and respiratory exchange ratio in exercise produced by propranolol and metoprolol.

Both the β-adrenoceptor blocking drugs significantly increased the sense of fatigue during exercise when compared with placebo, and were indistinguishable in this respect. Although it has been reported previously that β-adrenoceptor blockade alters the relation between perceived exertion and heart rate (Ekblom & Goldbarg, 1971), it has not been shown before that they change the relation between perceived exertion and oxygen consumption. We accept that it is difficult to conduct double-blind experiments using β-adrenoceptor blocking drugs because of their effects on resting heart rate. The effects of bias were minimized by varying randomly the initial work load at which scoring of perceived exertion began from experiment to experiment, and by the time interval of at least 48 h between experiments on any individual. Questioning the subjects revealed that they could not recall accurately their initial score on the Borg scale in preceding experiments. Propranolol also produced a significant reduction in endurance as assessed by either total work done or maximum work achieved. Although the

effects of metoprolol on endurance were smaller and not significant at the 0.05 level the differences between the two β-adrenoceptor blocking drugs were not statistically significant.

The fact that β-adrenoceptor blockade did not change the relationship between ventilation and work load supports our earlier finding (Patrick, Tutty & Pearson, 1978) that these drugs do not modify the hypoxic drive to breathing, since it is known (Cunningham, Spurr & Lloyd, 1968) that a substantial proportion of the hyperpnoea of exercise has as its basis an increased hypoxic drive even in air-breathing man.

From the clinical point of view, many patients complain of lack of energy, fatigue and aching muscles while taking β-adrenoceptor blocking drugs. Our findings support this claim. Whilst this may not be of importance when angina is the limiting factor for muscular exercise, the increasing use of the β-adrenoceptor blocking drugs in the treatment of hypertension means that many people who may feel perfectly well untreated are becoming symptomatic on treatment. In the use of the drugs for treating hypertension, it is clearly the acceptability of the β-adrenoceptor blocking drugs as compared with alternative agents that is important for patient compliance, but within the group of β-adrenoceptor blocking drugs our results suggest that as far as fatigue is concerned there is probably nothing to be gained by the choice of a so-called cardioselective drug as compared with a non-selective drug. However, our experiments are all concerned with the acute effects of β-adrenoceptor blockade and some caution is necessary in extending this discussion to patients on drugs for long periods as adaptation to these drugs has been demonstrated by some workers (Tarazi & Dustan, 1972), though not by all (Lund-Johansen, 1974).

We acknowledge the willing co-operation of our subjects in these experiments; the supply of tablets from Astra Chemicals Ltd; the technical help of Mrs Shirley Dixon; and helpful comments on the typescript from colleagues in our departments. SBP is grateful to the Nottinghamshire Area Health Authority for a short period of study leave.

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(*Received October 4, 1978*)