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INFLUENCE OF INTRINSIC SYMPATHOMIMETIC ACTIVITY OF β-ADRENOCEPTOR BLOCKERS ON THE HEART RATE AND BLOOD PRESSURE RESPONSES TO GRADED EXERCISE

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1 The relationship between plasma concentration and effect on heart rate and blood pressure at rest and at three levels of exercise were examined for four β-adrenoceptor blocking drugs having differing pharmacological properties.

2 Four doses of each drug were administered, the highest doses producing maximum effects of the work-heart rate and work-blood pressure relationships.

3 Pindolol and oxprenolol, which have intrinsic sympathomimetic activity (ISA) differed from timolol and metoprolol (which do not) in having a smaller effect on resting heart rate at each dose.

4 During exercise the four drugs had similar maximum effects on slope of the work–heart rate relationship suggesting similar suppression of *reflex* enhancement of sympathetic activity during exercise by each drug. The higher heart rate after drugs with ISA at rest was therefore still present at each level of exercise, e.g. maximum reduction of heart rate at 0.5 maximum work capacity was 20.5, 20.8. 24 and 28% for pindolol, oxprenolol, metoprolol and timolol respectively ($P < 0.01$ for difference between drugs with and without ISA).

5 The relationship between plasma concentration and reduction of heart rate at 0.5 maximum work capacity was qualitatively similar for each drug and was adequately described by a sigmoidal relationship wtih half-maximal effects at 4.4, 22, 35 and 5 ng/ml for pindolol, oxprenolol, metoprolol and timolol respectively whilst maximal effects occurred at approximately 30, 150, 100 and 30 ng/ml.

6 The results suggest that differences with exercise heart rate due to ISA are mainly due to effects on resting heart rate. The dose-response relationship of β-adrenoceptor blockers reaches a plateau at higher doses, irrespective of whether or not they possess ISA.

Introduction

The role of intrinsic sympathomimetic activity (ISA) of β-adrenoceptor blocking drugs on the exercise–heart rate response or on blood pressure has been the subject of much anecdotal discussion. However, to our knowledge the topic has been addressed specifically in only one major study: McDevitt *et al.* (1976) found that there were differences in the relationship of dose-inhibition of tachycardia at near maximum levels of exercise between β-adrenoceptor blocking drugs with ISA (i.e. that also had so-called partial agonist effects in addition to their major action as antagonists) compared with β-adrenoceptor blocking drugs without this property (i.e. 'pure' antagonists). At higher doses there was more inhibition of the exercise tachycardia with the latter drugs than with β-adrenoceptor blockers that also had ISA. Since resting heart rate was not measured, it is not known whether the observed differences in the dose-response curves represent differences between the drugs in their ability to inhibit the increase in heart rate due to exercise or whether it is the result of differences in the levels of resting heart rate which occur after β-adrenoceptor blockers with ISA.

It therefore seemed worthwhile to analyse in more detail the dose-response curves and re-examine the differences in the same subjects. We have studied the dose-response relationships of pindolol and oxprenolol (which both have ISA) and of metoprolol and timolol (which do not have ISA); in addition, metoprolol is a so-called β_1 cardioselective antagonist (Ablad *et al.*, 1975). The responses studied were the heart rate responses and the effects on systolic blood pressure at rest and during graded 'steady-state' exercise. This is in contrast to the protocol of McDevitt *et al.* (1976) who assessed the different β-adrenoceptor blocking drugs only from the differences in heart rate at a single level of exercise.

Methods

Six normal subjects participated in the study (four male and two female). Their average age was 20 years (17–23) and weight 65.3 kg (52–78). The subjects attended the laboratory on each study day following a light breakfast.

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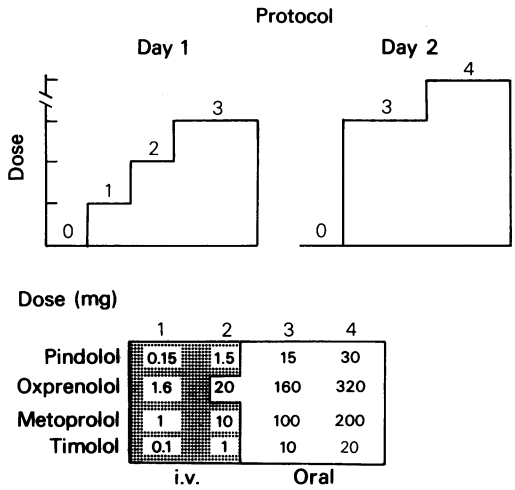

Figure 1 Protocol of the study (see text). Doses within the shaded area were given intravenously and the remaining doses orally. Exercise tests were performed 30 min after intravenous, and 1 h after oral doses.

The protocol for the study is summarized in Figure 1. On each day a cumulative dose-response curve was obtained with one drug to assess its effects at different plasma concentrations on the work–heart rate and work–blood pressure relationship (see below). Each drug was studied over a 200-fold range of doses. This necessitated intravenous administration for small doses and oral administration for larger doses. To allow for pharmacokinetic differences and differences in bioavailability between the drugs and their various doses plasma concentration was measured after each dose. Extensive pharmacokinetic data on all these drugs is available (see **Discussion**) and measurements of plasma concentration and exercise tests were performed after each dose when near maximal effects on exercise–heart rates were anticipated. A control exercise test was performed on each occasion. After 15 min the lowest dose of each drug was administered (*Dose 1*—Figure 1) intravenously in 10 ml of normal saline over 3 min. Forty-five minutes later 10 ml of blood was taken for subsequent analysis of drug concentration and the exercise protocol repeated. At the end of exercise, *Dose 2* was administered intravenously on pindolol, metoprolol and timolol study days as described for *Dose 1*, with blood samples and exercise test after a similar period. *Dose 2* of oxprenolol was 20 mg oral, one half of a 40 mg tablet ('Trasicor', Ciba). Intravenous oxprenolol was not used for *Dose 2* because it was not commercially available in a satisfactory formulation. One hour after all oral doses blood was collected for drug concentration analysis and the exercise protocol was repeated. *Dose 3* was one tablet containing either 15 mg pindolol ('Visken', Sandoz), 160 mg oxprenolol ('Slow Trasicor', Ciba), 100 mg metoprolol ('Lopresor', Geigy), or 10 mg timolol ('Blocadren', Frosst). To determine whether this dose produced maximum effects on the exercise parameters a still higher dose of each drug (*Dose 4*) was studied on another 4 days. A control exercise test was performed, *Dose 3* was repeated and an hour later the same amount was administered again so that the cumulative dose on the second study day for each drug was nearly twice that on the first.

Drug assays

Pindolol in plasma was measured using high performance liquid chromatography as described by Bangah, Jackman & Bobik (1980) whilst the other drugs were measured by g.l.c. procedures, specifically oxprenolol and metoprolol according to the method of Bobik *et al.* (1979) and timolol by the method of Tocco, Duncan & Delauna (1975).

Exercise protocol

Exercise was performed on an Elema Schonander bicycle ergometer. Heart rate was measured from the electrocardiogram using an Avionics Exerstress 3000 recorder. Blood pressure was measured with a sphygmomanometer and a microphone placed over the brachial artery.

On a day prior to the first drug study day each subject performed a 'sprint' exercise test, solely to determine maximum exercise capacity (Wmax). Work was increased by 100 kilopond metres each minute, beginning at zero workload until further exercise was prevented by fatigue or discomfort.

Effects of β-adrenoceptor blockers were tested using an exercise protocol as described in detail by Jennings *et al.* (1979). Briefly, this consisted of three consecutive 4 min periods of 'steady-state' exercise. The workloads were 0.25, 0.5 and 0.75 of the previously determined 'sprint' Wmax which averaged 1050 ± 84 kilopond metres.

Exercise at 0.75 Wmax during steady state exercise is close to the maximum workload for sustained exercise (Bailey *et al.*, 1976; Jennings *et al.*, 1979) and the maximum heart rates attained during the present study were similar during steady state exercise at 0.75 Wmax (169 ± 3 beats/min) and sprint exercise at Wmax (171.3 ± 1.5 beats/min).

The relationship between workload and heart rate or blood pressure was calculated from the resting value and the values at each level of exercise (see Figure 2). The relationship was linear and we assessed the effects of the drugs on resting heart rate, slope of the work–heart rate relationship and on heart rate at 0.5 Wmax (HR_{50}) predicted from the regression line. Blood pressure effects were expressed using similar systolic blood pressure parameters. Percent reduc-

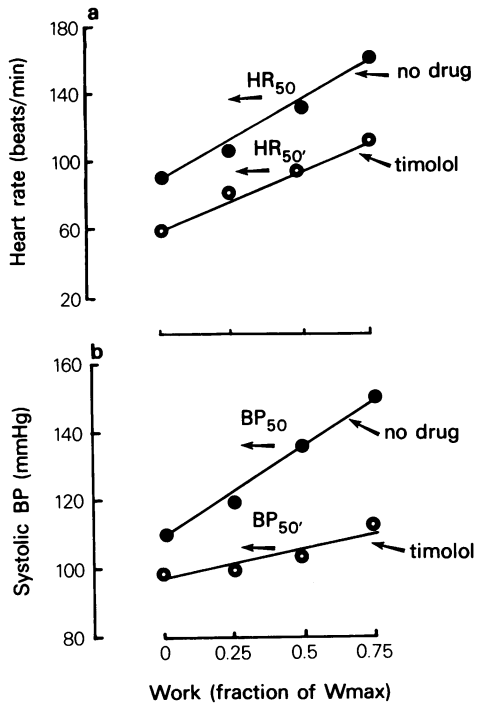

Figure 2 Representative example of the effects of a β-adrenoceptor blocker (timolol) on heart rate (a) and blood pressure (b) at different levels of exercise. HR_{50} is the heart rate at 0.5 Wmax predicted by the regression line relating work and heart rate. BP_{50} is the corresponding BP parameter.

tion of each variable was calculated as $(I\text{-}P'/P) \times 100$ where P = values before β-adrenoceptor blocker and P' = the value of β-adrenoceptor blockade (see Jennings *et al.*, 1979).

Analysis of variance was used throughout to assess differences between variables (Snedecor & Cochran, 1967). The standard error of the difference (s.e.d.) between any two drugs (within subjects) was $(2\ EMS/n)^{0.5}$ where EMS was the error mean square and n the number of subjects.

Effects on heart rate and blood pressure of beta blockers were related to their plasma concentration by the concentration–response equation of Wagner (1968):

$$E = Emax\ C_E^{\gamma}/(C_E^{\gamma} + C_{E(50)}^{\gamma})$$

where E is the intensity of the pharmacodynamic effect, Emax the maximum effect, C_E the plasma concentration, $C_{E(50)}$ the plasma concentration at 50% Emax and γ is a parameter which allows sigmoidicity of the C_E to effect relationship. Each plasma concentration–response relationship was defined using the non-linear least-squares regression program described by Parker & Waud (1971).

Results

The average results of each heart rate and blood pressure parameter are shown in Figure 3. For each drug the greatest reduction in the heart rate and blood pressure was attained after *Dose 3*. In four subjects it was confirmed that this corresponded to the maximum effect of each drug since no further fall in resting or exercise blood pressure was found one hour after *Dose 4* (Figure 3).

Control values varied slightly from day to day (Figure 3), but analysis of variance showed no significant difference between values on the different days of the experiment, nor were there differences between control values before the four different treatments. This suggests that the latin square method of allocating treatments was successful in minimising any bias due to differences in order of treatment. Results were therefore expressed as percentage reduction from the average values for that subject during the control tests.

To assess the maximum effect due to each drug the lowest value of each parameter after each drug was chosen and expressed as percentage reduction from the average values for that subject during the control tests (Figure 4).

All β-adrenoceptor blockers had similar maximum effects on slope of the work–heart rate relationship (Figure 4); but there were significant differences in the effects on resting heart rate and on HR_{50}. On average, resting heart rate was reduced slightly, but significantly less by drugs with ISA compared with drugs without this property (i.e. to 73 beats/min for both pindolol and oxprenolol *v* 70 beats/min and 67 beats/min for metoprolol and timolol respectively, $P < 0.005$). As there were no differences betwen the effects of drugs with and without ISA in their effect on slope of the work–heart rate relationship the difference in heart rate at rest was maintained at each level of exercise and consequently HR_{50} was also reduced less by pindolol and oxprenolol than by the other two drugs without ISA, Figure 5.

No differences were observed between the effects of the four drugs on blood pressure. There was a tendency for metoprolol to affect each blood pressure parameter less than the other drugs, but this difference was only significant for BP_{50} when the results for metoprolol were compared with the pooled results of the other three drugs. There were no significant differences between individual drugs.

The doses of each drug were such that it was possible to examine the various heart rate and blood pressure effects over a wide range of plasma concentrations for each drug. The relative potency of each

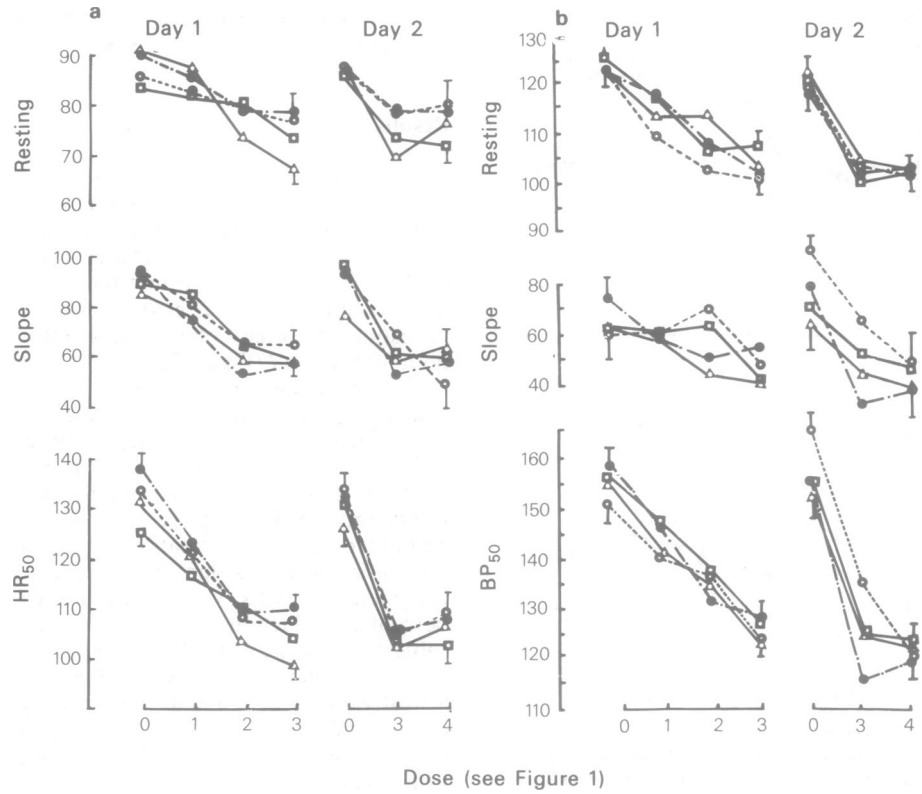

Figure 3 Resting heart rate, slope of the work-heart rate relationship and HR_{50} after doses, 1, 2, 3 and 4 (for explanation see Figure 1) of the various drugs (a). Corresponding systolic blood pressure parameters are shown in (b). ● pindolol, ○ oxprenolol, □ metoprolol and △ timolol.

drug in inhibiting the various heart rate and blood pressure parameters were apparent from their plasma concentration–effect relationships (Figure 6). To correct for the various differences between drugs in maximum effects described above, the effect on HR_{50} after β-adrenoceptor blocker was expressed as a percentage of the maximum effect due to that drug in each subject. The relationship was qualitatively similar for the four drugs with flattening of the dose–response relationship at higher doses. Half maximal inhibition ($C_{E(50)}$) of HR_{50} occurred at approximately 4.4 ng/ml, 22 ng/ml, 356 ng/ml and 5 ng/ml for pindolol, oxprenolol, metoprolol and timolol respectively. Maximum inhibition occurred at plasma concentrations above 30 ng/ml of pindolol and timolol, approximately 100 ng/ml of metoprolol and 400 ng/ml of oxprenolol. Analysis of effects on maximum heart rate (HR_{75}) produced similar plasma concentration-drug effect relationships.

Discussion

There was no difference in effects of pindolol, metoprolol, timolol and oxprenolol on the slope of the work–heart rate relationship during graded exercise. Slope of the work–heart rate relationship is determined by the increase in sympathetic effect on heart rate and the decrease in vagal effect which occurs throughout exercise. We have previously found that the contribution of vagal withdrawal during exercise to the slope of the work–heart rate relationship is unaffected by β-adrenoceptor blockade as the estimate of sympathetic inhibition obtained from the reduction of this parameter was similar after atropine (Jennings *et al.*, 1979). Maximum inhibition of slope of the work–heart rate relationship is thus a good measure of suppression of reflex enhancement of sympathetic activity during exercise. Hence, the results suggest that there is little difference between

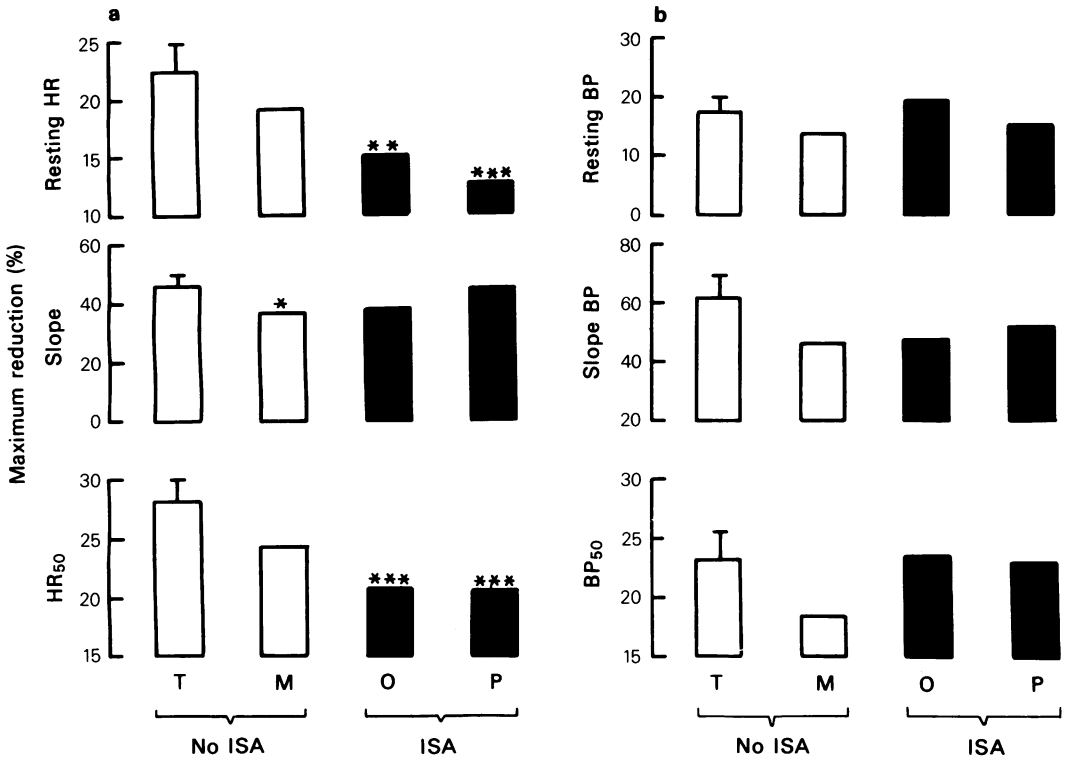

Figure 4 Maximum effects of the four drugs (T timolol, M metoprolol, O oxprenolol and P pindolol) on heart rate (a) and blood pressure parameters (b). Results are the average of six subjects. Error bars represent the standard error of the difference between any two columns from the analysis of variance, significant levels; $^{**}P < 0.01$, $^{***}P < 0.001$ for difference from results for timolol.

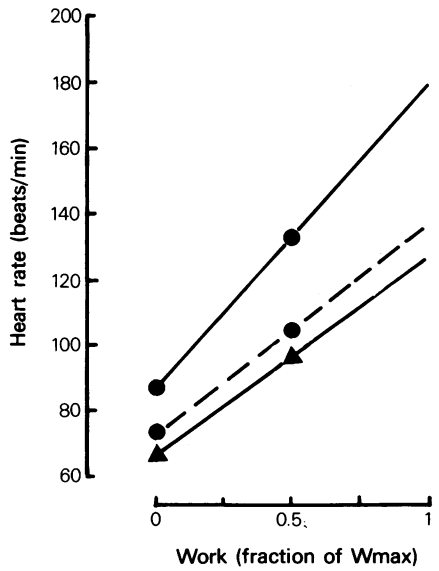

Figure 5 Effect of ISA on the heart rate at different levels of work. Average values ± s.e.d. are shown for resting heart rate and HR_{50}. The regression lines relating work and heart rate after pindolol (●- - -●, with ISA) and timolol (▲——▲, without ISA) at the highest doses were parallel, but heart rate at any given level of work was slightly lower after timolol due to the difference in intercept (resting heart rate) ●——● control values.

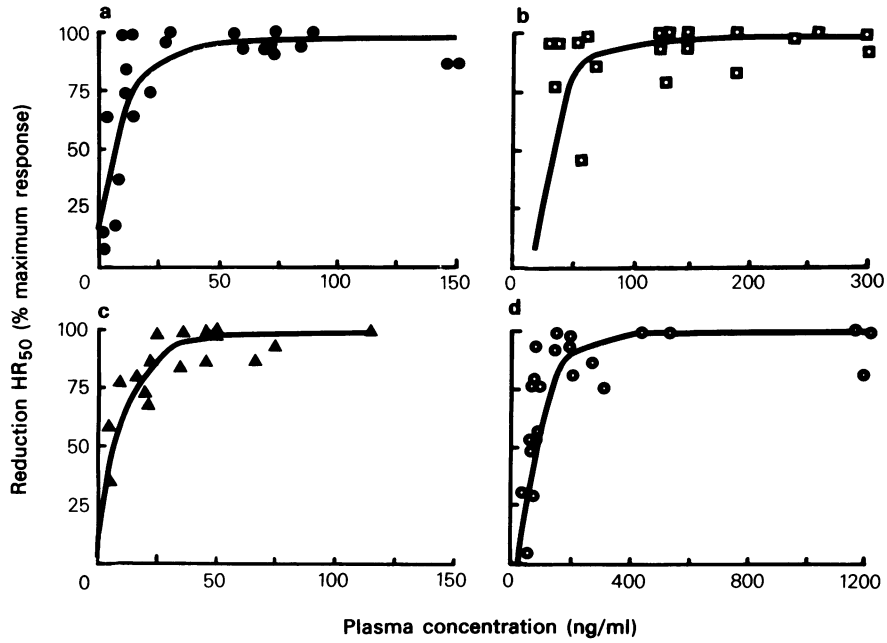

Figure 6 Relationship between plasma concentration (ng/ml) and reduction of HR_{50} expressed as a percentage of the maximum reduction of HR_{50} by each drug (a pindolol, b metoprolol, c timolol, d oxprenolol). Each point represents the effect of a single dose on a single subject.

the drugs with or without ISA in the amount of sympathetic inhibition during exercise. Resting heart rate and HR_{50} both provide estimates of the intercept of the work–heart rate relationship (Jennings *et al.*, 1979) and these were reduced less by the drugs with ISA. This is in accord with the findings of McDevitt *et al.* (1976) that ISA reduced the maximum suppression of exercise heart rate by β-adrenoceptor blockers. Their estimate is based on something similar to HR_{75} (heart rate at a single, near maximum workload) and thus provides information on the *intercept* of the regression line, but not about the slope which, as discussed previously, is probably the best indicator of reflex drive (Jennings *et al.*, 1979). The present results suggest that ISA has a small, but significant, effect on heart rate which remains virtually constant at all levels of work, and is most apparent at rest when sympathetic drive is least. The average effect at rest of ISA was 4–5% (or 15–20% of the maximum sympathetic suppression).

The differences in maximum effect on heart rate described above were not observed in the systolic blood pressure changes, which were similar after each drug. In particular, metoprolol which is relatively β_1 selective caused, if anything, a smaller reduction in exercise blood pressure than the other three drugs. Lack of blockade of β_2-receptors with β_1-selective antagonists might theoretically cause a smaller rise in blood pressure during dynamic exercise. The absence of any selective effect could be due to: (i) the systolic blood pressure changes during exercise being little influenced by β_2 mediated vasodilatation; (ii) loss of 'selectivity' of metoprolol at doses which produce maximum effect on heart rate; (iii) a component of the increased cardiac output during exercise due to the effect of adrenaline on the muscle vascular bed which is blocked by non-selective drugs, but not by metoprolol. These have not been investigated in the present study. Metoprolol is more 'β_1 selective' at doses which are submaximal in their effects on heart rate (Ablad *et al.*, 1975), but no differences were observed in slope-BP at lower doses. Changes in diastolic blood pressure were not measured here, but differing effects on diastolic blood pressure may have been observed if direct measurement of arterial pressure had been performed.

It is likely that the magnitude of the partial agonist activity of a given drug is independent of the level of sympathetic activity. McDevitt *et al.* (1976) reported further reduction in exercise heart rate when drugs with ISA were administered after maximum blockade by drugs with ISA. They suggested that the former were causing more sympathetic inhibition, perhaps because the partial agonist activity was more

apparent at higher doses. An alternative explanation is that the additional effect was due to blockade of β-receptor stimulation due to intrinsic sympathomimetic activity. Such an effect has been observed by Kenakin & Black (1978) in isolated tissues. The magnitude of the additional effect thus estimates the ISA of the first drug. Our results suggest that the effect on exercise heart rate due to ISA is entirely dependent on changes in resting heart rate; hence the difference in effects on resting heart rate provides another estimate of ISA possessed by different drugs. McDevitt *et al.* (1976) did not provide information on resting heart rate in their study, but it is of interest that the additional effect on exercise heart rate of giving sotalol (without ISA) to subjects who had already received high doses of oxprenolol was a fall of 5.8 beats/min. This is closely similar to the difference in the effect on resting rate between oxprenolol and timolol of 5.5 ± 1.0 beats/min due to the ISA of oxprenolol in the present study.

The question arises to what extent the differences observed in the present study between drugs with and without ISA after cumulative doses can be applied to long term β-adrenoceptor blocker administration in man. The dose and route of administration of each drug were chosen solely in order to obtain a sufficiently wide range of plasma concentrations to accurately define their plasma concentration–effect relationship. This necessitated combining intravenous and oral dosage of each β-adrenoceptor blocker. It is unlikely that possible differences in metabolism between intravenous and oral doses have altered the findings in the light of previous studies showing similar plasma concentration response relationships after intravenous and oral doses of metoprolol (Johnsson, Regardh & Solvell, 1975) and pindolol (Jennings *et al.*, 1979). Other studies have shown that oxprenolol metabolites do not contribute significantly to the β-adrenoceptor blocking activity (Gartiez, 1971; Burke & Nelson, 1979). In previous studies with timolol we have examined whether possible discrepancies between concentration time and effect profiles influence the application of plasma concentration-effect relationships to chronic therapy. A similar relationship between peak plasma timolol and effect on HR_{50} to that of the present study was obtained after several single oral doses (Bobik *et al.*, 1979). The entire time course of effects on HR_{50} of the various single oral doses could be accurately predicted from the results at peak plasma concentration and the known pharmacokinetics of the drug when the data were fitted to the well known Hill equation (Wagner, 1975; Bobik *et al.*, 1981). In the same subjects the relationship was found to be similar when the same doses were given chronically.

In agreement with the present study maximal and half maximal effects on HR_{50} occurred at similar plasma timolol concentrations to the corresponding effects on BP_{50}. The plasma concentration–blood pressure effect relationship was also unchanged with chronic therapy and predicted the time course of effects on exercise blood pressure. Furthermore, in a clinical trial of timolol in patients with essential hypertension (Jennings, Bobik & Korner, 1979) there was good agreement between the duration and intensity of effects on blood pressure and those predicted from plasma timolol concentration by the dose response relationship in normal subjects (Bobik *et al.*, 1981). The other drugs in the present study have not been examined in this way. Pindolol, although differing from timolol in the property of ISA, has similarities with the latter in non-dose-dependent bioavailability and high potency. Plasma pindolol concentrations observed in out-patients on chronic therapy have also been found to be in agreement with the known acute pharmacokinetics (Bangah, Jackman & Bobik, 1980). Although the point requires further evaluation, it is therefore likely that the difference between heart rate effects of pindolol and timolol observed in the present study, and attributed to ISA would also hold for chronic therapy. The cumulative administration of intravenous and oral doses in the present study cannot be applied to long term beta-adrenoceptor therapy without qualification, but the results of our previous studies with timolol suggest some relevance. The further advantage of defining the dose response relationships in the present study was that they provide the most accurate assessment of the maximum effects of each drug.

Our results indicate that plasma concentration or dose–heart rate effect relationships of the various beta blockers are qualitatively similar. The main effect of ISA on the plasma concentration (dose)-HR_{50} relationship is to reduce the magnitude of the effect on exercise–heart rate. This effect could be attributed to the higher resting heart rate observed after administering β-adrenoceptor blockers with ISA. ISA has no apparent effect on dose–blood pressure relationships. These findings agree with therapeutic observations that effects of the various β-adrenoceptor blocking drugs on blood pressure in patients with hypertension are similar, although heart rate effects may be less if the drug possesses ISA (Waal-Manning, 1976).

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