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STUDIES OF CARDIOSELECTIVITY AND PARTIAL AGONIST ACTIVITY IN β-ADRENOCEPTOR BLOCKADE COMPARING EFFECTS ON HEART RATE AND PEAK EXPIRATORY FLOW RATE DURING EXERCISE

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1 The effects of β-adrenoceptor antagonists given in single doses by oral or intravenous routes were examined in two double-blind controlled studies performed in healthy volunteers. Heart rate and peak expiratory flow rate (PEFR) were measured at rest and during standardized exercise.

2 Propranolol 80 mg and metoprolol 100 mg orally tended to reduce, and propranolol and metoprolol 0.2 mg/kg intravenously did reduce the physiological increase in PEFR during exercise; oxprenolol 80 mg orally and 0.2 mg/kg intravenously did not. Practolol 200 mg orally reduced this increase, but practolol 1 mg/kg intravenously did not.

3 In a third study of similar design, pindolol 0.05 mg/kg intravenously did not affect exercise-induced increase in PEFR.

4 Heart rate during exercise was reduced to a comparable extent at different times by all the active treatments.

5 Oxprenolol and pindolol share with practolol the property of partial agonist activity, which might contribute to their apparent lack of effect on airways resistance. A further possibility is that α-adrenoceptor blockade helps to maintain exercise-induced increase in PEFR.

Introduction

Patients with conditions such as angina pectoris or hypertension, for which treatment with a β-adrenoceptor blocking drug would normally be indicated, may also suffer from airflow obstruction. In this situation the physician may prescribe a cardioselective β-adrenoceptor blocking drug on the grounds that non-selective drugs are more likely to provoke bronchoconstriction. A previous study from this department examined the effects of β-adrenoceptor blocking drugs given intravenously to healthy volunteers (Kumana, Marlin, Kaye & Smith, 1974). The experimental method used depends on the high level of sympathetic activity during vigorous standardized exercise giving optimal conditions for assessing β-adrenoceptor blockade. Analysis of the changes in exercise heart rate and exercise peak expiratory flow rate (PEFR) after relatively small doses of β-adrenoceptor antagonists and placebo, permitted (a) the differentiation of β-adrenoceptor antagonists from placebo and (b) the differentiation of the selective drug practolol from the non-selective drug propranolol.

However, clinical experience has shown that even cardioselective drugs may worsen airflow obstruction in some patients (Waal-Manning & Simpson, 1971), perhaps because selectivity is lost when conventional therapeutic doses are given. There is experimental evidence showing that such a loss of selectivity occurs with practolol (Lertora, Mark, Johanssen, Wilson & Abboud, 1975).

It has been suggested that partial agonist activity may be more important than cardioselectivity in preventing exacerbation of airflow obstruction by β-adrenoceptor antagonists (Ablad, Brogard & Ek, 1967; Paterson, 1971). The studies reported here were designed to discover whether selective and non-selective β-adrenoceptor blocking drugs with and without partial agonism, given orally and intravenously in single doses, could be distinguished by their effects on exercise-evoked increase in PEFR in healthy volunteers. The selective drugs were practolol and metoprolol; the non-selective drugs were propranolol, oxprenolol and pindolol. Practolol, oxprenolol and pindolol have partial agonist activity, whereas propranolol and metoprolol do not (McDevitt, 1977).

Methods

The subjects were healthy men and women aged 21–31 years (mean age 25 ± 4.8 years) who had given their informed consent. Their mean weight was 65 ± 8.0 kg. They had no history or physical signs of cardiovascular disease or airflow obstruction, and were normotensive. All subjects had normal blood urea levels and creatinine clearances, and normal ECGs.

Each study was a double-blind within-subject comparison; treatment order was balanced using Latin square designs. Treatments within each study were given weekly.

In the first study, five men were given practolol 200 mg, propranolol 80 mg, metoprolol 100 mg, oxprenolol 80 mg or matched placebo orally in tablet form.

In the second study, four women and two men were given oxprenolol 0.2 mg/kg, metoprolol 0.2 mg/kg or isotonic saline intravenously over 5 min.

In the third study, the six subjects from the second study and two others (one man and one woman) were given practolol 1.0 mg/kg, propranolol 0.2 mg/kg, pindolol 0.05 mg/kg or isotonic saline intravenously over 5 min.

Smoking and caffeine or cola drinks were forbidden on the day of each experiment. Subjects fasted overnight before the oral study, but were allowed a light breakfast before the intravenous studies.

Measurements were made before and 2, 3, 4 and 6 h after treatment in the first and third studies; in the second study the 6 h readings were omitted. The subjects rested in the supine position for at least 5 min before heart rate was recorded on an ECG over 30 s. Forced expiratory volume in one second (FEV_1) was measured on a Vitalograph and the best of three readings taken. Peak expiratory flow rate was measured with a Wright peak flow meter, and the two best readings averaged. The subjects were then exercised for 3 min on a Monark bicycle ergometer against loads which had been shown in individual tests

Table 1 Mean ± s.e. mean values of resting and exercise heart rate, FEV_1, and resting and exercise PEFR for five subjects in the first study before and after each oral treatment

	Time (h) 0	2	3	4	6
Placebo					
Resting heart rate (beats/min)	73 ± 6	64 ± 5	83 ± 5	79 ± 4	79 ± 5
Exercise heart rate (beats/min)	166 ± 4	161 ± 2	172 ± 3	171 ± 5	168 ± 4
FEV_1 (l)	3.61 ± 0.23	3.66 ± 0.20	3.70 ± 0.22	3.71 ± 0.22	3.65 ± 0.50
Resting PEFR (l/min)	547 ± 14	550 ± 18	544 ± 16	539 ± 16	541 ± 14
Exercise PEFR (l/min)	569 ± 11	570 ± 16	570 ± 16	571 ± 15	564 ± 12
Practolol 200 mg					
Resting heart rate	70 ± 5	65 ± 5	74 ± 4	77 ± 4	75 ± 4
Exercise heart rate	163 ± 6	133 ± 4	134 ± 4	135 ± 4	137 ± 5
FEV_1	3.64 ± 0.22	3.62 ± 0.20	3.67 ± 0.21	3.65 ± 0.22	3.61 ± 0.26
Resting PEFR	548 ± 20	541 ± 19	545 ± 18	538 ± 20	534 ± 19
Exercise PEFR	574 ± 18	574 ± 19	562 ± 19	560 ± 22	554 ± 20
Propranolol 80 mg					
Resting heart rate	69 ± 5	59 ± 4	70 ± 4	69 ± 3	70 ± 5
Exercise heart rate	161 ± 5	124 ± 4	131 ± 5	139 ± 6	145 ± 5
FEV_1	3.60 ± 0.22	3.57 ± 0.21	3.60 ± 0.21	3.58 ± 0.20	3.61 ± 0.20
Resting PEFR	549 ± 17	549 ± 17	539 ± 13	542 ± 15	538 ± 11
Exercise PEFR	581 ± 21	575 ± 14	569 ± 11	574 ± 12	569 ± 12
Oxprenolol 80 mg					
Resting heart rate	73 ± 5	65 ± 5	77 ± 5	74 ± 5	76 ± 5
Exercise heart rate	169 ± 2	128 ± 3	138 ± 4	143 ± 4	157 ± 4
FEV_1	3.65 ± 0.18	3.64 ± 0.21	3.66 ± 0.21	3.69 ± 0.21	3.66 ± 0.24
Resting PEFR	549 ± 14	551 ± 16	548 ± 14	549 ± 19	541 ± 15
Exercise PEFR	578 ± 12	574 ± 10	584 ± 14	579 ± 16	570 ± 15
Metoprolol 100 mg					
Resting heart rate	69 ± 5	59 ± 5	70 ± 4	71 ± 4	72 ± 4
Exercise heart rate	166 ± 4	128 ± 5	138 ± 3	140 ± 2	145 ± 3
FEV_1	3.71 ± 0.25	3.53 ± 0.21	3.58 ± 0.22	3.60 ± 0.20	3.58 ± 0.20
Resting PEFR	541 ± 20	543 ± 22	546 ± 19	529 ± 21	534 ± 18
Exercise PEFR	575 ± 17	574 ± 20	564 ± 20	564 ± 21	565 ± 12

to be the smallest needed to produce, in the absence of drugs, a heart rate exceeding 160 beats/min in the last 30 s of cycling. The loads needed were from 825 to 1350 kilopond-metres/min (135 to 220 W). At least five readings of PEFR were taken during each exercise period, and the mean of the three highest was recorded. Consistent readings of FEV_1 could not be taken on a Vitalograph during vigorous exercise. Heart rate was derived from ECG records taken during the last 30 s of exercise.

Venous blood samples were taken just after each exercise period, on the hour, anticoagulated with lithium heparin and the plasma separated. Samples were always taken at 1 h after treatment, even if no measurements were made then. Concentrations of practolol were estimated by spectrophotometry (Turner, Burman, Hicks, Cherrington, MacKinnon, Waller & Woolnough, 1971), of propranolol and pindolol by fluorimetry (Shand, Nuckolls & Oates, 1970; and Pacha, 1969), and of oxprenolol and metoprolol by gas-liquid chromatography (Degen & Reiss, 1976).

The results obtained after each treatment were expressed as changes from pre-treatment values, and these changes examined by analysis of variance. For each subject, comparisons between the treatments were made when the reductions in exercise heart rate were most similar between drugs. In the second study, drug effects were compared when each pair of drugs reduced exercise heart rate in each subject by similar amounts.

Practolol and propranolol were not given in the second study. The effects of intravenous oxprenolol and metoprolol were therefore compared with those of intravenous practolol and propranolol given in the third study. This comparison between experiments is justified, since all subjects in the second study also took part in the third, and analysis of variance showed that there were no significant differences between the results obtained after placebo administration in each study.

Results

First study

Table 1 shows the mean values of resting and exercise heart rate, FEV_1, and resting and exercise PEFR.

Table 2 Analysis of variance, 2-tailed tests comparing each drug with placebo in the first study ($n=5$)

	Time (h)			
	2	*3*	*4*	*6*
	Probability levels			
Practolol v placebo				
Resting heart rate	NS	NS	NS	NS
Exercise heart rate	$P<0.001$	$P<0.001$	$P<0.001$	$P<0.001$
FEV_1	NS	NS	NS	NS
Resting PEFR	NS	NS	NS	NS
Exercise PEFR	NS	NS	NS	NS
Propranolol v placebo				
Resting heart rate	NS	NS	NS	NS
Exercise heart rate	$P<0.001$	$P<0.001$	$P<0.001$	$P<0.001$
FEV_1	NS	NS	NS	NS
Resting PEFR	NS	NS	NS	NS
Exercise PEFR	NS	NS	NS	NS
Oxprenolol v placebo				
Resting heart rate	NS	NS	NS	NS
Exercise heart rate	$P<0.001$	$P<0.001$	$P<0.001$	$P<0.001$
FEV_1	NS	NS	NS	NS
Resting PEFR	NS	NS	NS	NS
Exercise PEFR	NS	NS	NS	NS
Metoprolol v placebo				
Resting heart rate	NS	NS	NS	NS
Exercise heart rate	$P<0.001$	$P<0.001$	$P<0.001$	$P<0.001$
FEV_1	$P<0.01$	$P<0.05$	NS	NS
Resting PEFR	NS	NS	NS	NS
Exercise PEFR	NS	NS	NS	NS

Level of significance (α) = 0.05. NS = not significant.

Table 3 Analysis of variance, 2-tailed tests comparing drugs with each other in the first study ($n=5$)

	Time (h)			
	2	*3*	*4*	*6*
	Probability levels			
Practolol v propranolol				
Resting heart rate	NS	NS	NS	NS
Exercise heart rate	$P<0.05$	NS	NS	$P<0.01$
FEV_1	NS	NS	NS	NS
Resting PEFR	NS	NS	NS	NS
Exercise PEFR	NS	NS	NS	NS
Practolol v oxprenolol				
Resting heart rate	NS	NS	NS	NS
Exercise heart rate	$P<0.01$	NS	NS	$P<0.01$
FEV_1	NS	NS	NS	NS
Resting PEFR	NS	NS	NS	NS
Exercise PEFR	NS	NS	NS	NS
Practolol v metoprolol				
Resting heart rate	NS	NS	NS	NS
Exercise heart rate	NS	NS	NS	NS
FEV_1	NS	NS	NS	NS
Resting PEFR	NS	NS	NS	NS
Exercise PEFR	NS	NS	NS	NS
Propranolol v oxprenolol				
Resting heart rate	NS	NS	NS	NS
Exercise heart rate	NS	NS	NS	NS
FEV_1	NS	NS	NS	NS
Resting PEFR	NS	NS	NS	NS
Exercise PEFR	NS	NS	NS	NS
Propranolol v metoprolol				
Resting heart rate	NS	NS	NS	NS
Exercise heart rate	NS	NS	NS	NS
FEV_1	NS	NS	NS	NS
Resting PEFR	NS	NS	NS	NS
Exercise PEFR	NS	NS	NS	NS
Oxprenolol v metoprolol				
Resting heart rate	NS	NS	NS	NS
Exercise heart rate	NS	NS	NS	$P<0.05$
FEV_1	$P<0.01$	NS	NS	NS
Resting PEFR	NS	NS	NS	NS
Exercise PEFR	NS	NS	NS	NS

Level of significance (α) = 0.05; NS = not significant.

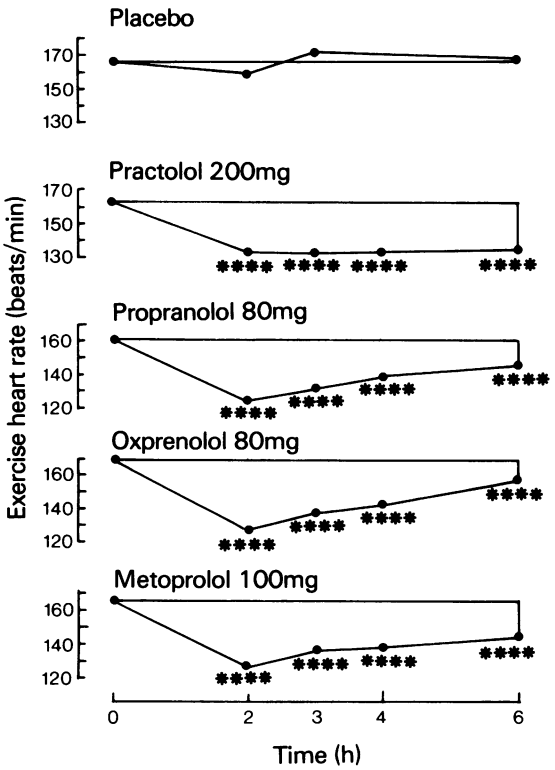

Figure 1 Mean changes in exercise heart rate after five oral treatments, with significance levels of comparisons of drugs with placebo, first study ($n=5$). ****$P<0.001$.

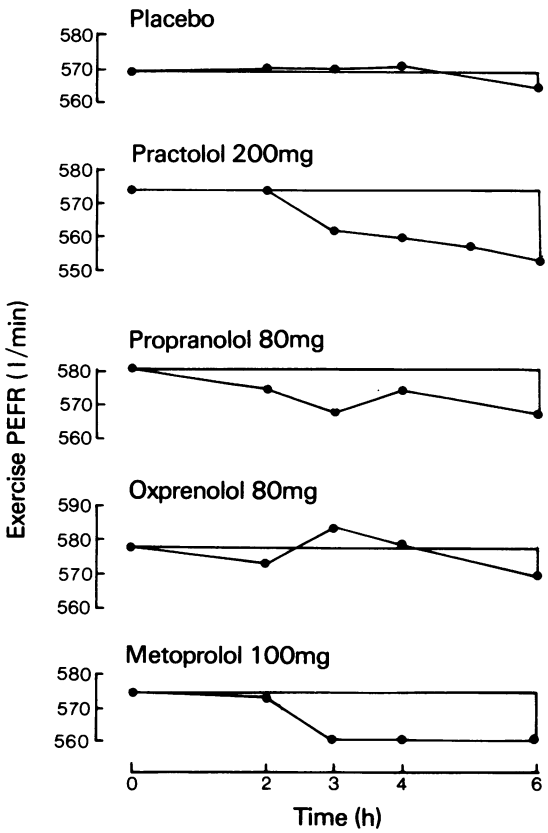

Figure 2 Mean changes in exercise peak expiratory flow rate after five oral treatments, with significance levels of comparisons of drugs with placebo, first study ($n=5$).

Figures 1 and 2 show the mean changes in exercise heart rate and PEFR after each drug, compared with placebo. Tables 2 and 3 show the probability levels for drug effects on each measurement, compared with placebo and with each other.

No marked effects on resting heart rate were noted after any treatment. Exercise heart rate was clearly reduced by all four drugs, but was unaffected by placebo; these reductions were similar at 3 and 4 h. Only metoprolol produced significant reductions in FEV_1 compared with placebo (2 and 3 h after treatment) and oxprenolol (2 h). No drug produced a significant change in resting or exercise PEFR, although practolol, propranolol and metoprolol tended to reduce exercise PEFR.

Figure 3 shows the mean plasma levels of the four drugs at various times after ingestion.

Second study

The results for practolol and propranolol were taken from the third study.

Table 4 gives the mean values of the five sets of measurements made after each treatment. Figures 4 and 5 show the mean changes in exercise heart rate and PEFR. Table 5 gives the probability levels for drug effects on each variable, compared with placebo. Table 6 shows the probability levels when drug effects were compared with each other, at times when each pair of drugs reduced exercise heart rate in each subject to a similar extent.

Resting heart rate fell after oxprenolol at 2 h, and after propranolol and metoprolol at 2 and 3 h. Metoprolol slowed resting heart rate more than practolol. Compared with placebo, all four drugs reduced exercise heart rate markedly. No drug changed FEV_1 significantly compared with placebo. Only propranolol reduced resting PEFR significantly. Exercise PEFR was reduced by propranolol at 3 and 4 h and by metoprolol at 4 h, but was unchanged by the other drugs, compared with placebo. Practolol was distinguished from both propranolol and metoprolol

by its clearly smaller effect on exercise PEFR. Similarly oxprenolol differed significantly from propranolol.

Figure 6 shows the mean plasma levels of the four drugs plotted against time after injection.

Third study

Table 7 shows the mean values of the five sets of measurements after each treatment. Figures 7 and 8 show the mean changes in exercise heart rate and PEFR. Tables 8 and 9 give the significance levels for drug effects compared with placebo and with each other.

Propranolol slowed resting heart rate at 2, 3 and 4 h; pindolol increased it at 2, 3 and 6 h. As in the other studies, the three active drugs reduced exercise heart rate to a highly significant degree; these reductions were comparable until 4 h after administration, beyond which the effects of propranolol and pindolol declined. FEV_1 was reduced by propranolol at 2, 4 and 6 h, and by pindolol at 2 and 6 h. Only propranolol reduced resting PEFR significantly compared with placebo.

Table 9 shows that practolol is distinct from propranolol in its effects on four variables: resting heart rate at 2, 3 and 4 h, FEV_1 at 4 h, resting PEFR at 2 h and exercise PEFR at all times after drug administration. Similarly pindolol is distinct from propranolol in terms of resting heart rate at all times, resting PEFR at 2 h and exercise PEFR at 2, 3 and 6 h.

Figure 9 shows the mean plasma levels of the three drugs plotted against time.

Figure 10 shows the mean plasma levels of practolol and propranolol after oral versus intravenous adminstration, with the significance levels for the differences between these two routes of administration.

Table 4 Mean ± s.e. mean values of resting and exercise heart rate, FEV_1, and resting and exercise PEFR for six subjects in the second study before and after each intravenous treatment

	Time (h)			
	0	*2*	*3*	*4*
Placebo				
Resting heart rate (beats/min)	69 ± 4	67 ± 3	67 ± 3	74 ± 4
Exercise heart rate (beats/min)	165 ± 1	161 ± 2	161 ± 1	164 ± 3
FEV_1 (l)	3.91 ± 0.30	3.90 ± 0.32	3.90 ± 0.32	3.94 ± 0.33
Resting PEFR (l/min)	543 ± 50	541 ± 45	554 ± 46	555 ± 46
Exercise PEFR (l/min)	572 ± 48	572 ± 46	579 ± 46	584 ± 48
Practolol 1.0 mg/kg				
Resting heart rate	72 ± 5	64 ± 2	71 ± 2	72 ± 3
Exercise heart rate	169 ± 2	133 ± 3	135 ± 3	137 ± 2
FEV_1	3.98 ± 0.31	3.95 ± 0.30	3.97 ± 0.31	4.01 ± 0.32
Resting PEFR	553 ± 47	559 ± 45	557 ± 44	563 ± 44
Exercise PEFR	585 ± 47	585 ± 47	585 ± 47	593 ± 50
Propranolol 0.2 mg/kg				
Resting heart rate	76 ± 5	60 ± 3	64 ± 4	66 ± 3
Exercise heart rate	169 ± 2	130 ± 2	133 ± 2	138 ± 3
FEV_1	3.99 ± 0.30	3.94 ± 0.32	3.95 ± 0.31	3.98 ± 0.29
Resting PEFR	552 ± 49	530 ± 48	541 ± 48	539 ± 47
Exercise PEFR	586 ± 51	569 ± 50	575 ± 51	574 ± 50
Oxprenolol 0.2 mg/kg				
Resting heart rate	75 ± 2	61 ± 2	68 ± 2	73 ± 3
Exercise heart rate	164 ± 1	134 ± 2	139 ± 2	147 ± 4
FEV_1	3.84 ± 0.31	3.83 ± 0.32	3.84 ± 0.31	3.89 ± 0.33
Resting PEFR	553 ± 44	550 ± 43	557 ± 42	556 ± 47
Exercise PEFR	571 ± 49	572 ± 47	580 ± 48	580 ± 48
Metoprolol 0.2 mg/kg				
Resting heart rate	75 ± 2	59 ± 2	64 ± 2	68 ± 4
Exercise heart rate	165 ± 3	136 ± 4	140 ± 4	150 ± 3
FEV_1	3.96 ± 0.33	3.85 ± 0.32	3.91 ± 0.29	3.90 ± 0.30
Resting PEFR	559 ± 43	557 ± 46	559 ± 44	557 ± 43
Exercise PEFR	586 ± 50	578 ± 51	582 ± 49	583 ± 48

Table 5 Analysis of variance, 2-tailed tests comparing each drug with placebo in the second study ($n=6$)

	Time (h)		
	2	*3*	*4*
	Probability levels		
Placebo v practolol			
Resting heart rate	NS	NS	NS
Exercise heart rate	$P<0.001$	$P<0.001$	$P<0.001$
FEV_1	NS	NS	NS
Resting PEFR	NS	NS	NS
Exercise PEFR	NS	NS	NS
Placebo v propranolol			
Resting heart rate	$P<0.02$	$P<0.01$	NS
Exercise heart rate	$P<0.001$	$P<0.001$	$P<0.001$
FEV_1	NS	NS	NS
Resting PEFR	NS	NS	$P<0.01$
Exercise PEFR	NS	$P<0.01$	$P<0.001$
Placebo v oxprenolol			
Resting heart rate	$P<0.02$	NS	NS
Exercise heart rate	$P<0.001$	$P<0.001$	$P<0.001$
FEV_1	NS	NS	NS
Resting PEFR	NS	NS	NS
Exercise PEFR	NS	NS	NS
Placebo v metoprolol			
Resting heart rate	$P<0.002$	$P<0.01$	NS
Exercise heart rate	$P<0.001$	$P<0.001$	$P<0.001$
FEV_1	NS	NS	NS
Resting PEFR	NS	NS	NS
Exercise PEFR	NS	NS	$P<0.05$

Level of significance (α) = 0.05; NS = not significant.

Table 6 Two-tailed tests comparing drugs with each other at times of similar reductions in exercise heart rate for each subject in the second study ($n=6$)

	Probability level		*Probability level*
Practolol v propranolol		*Propranolol v oxprenolol*	
Resting heart rate	NS	Resting heart rate	NS
Exercise heart rate	NS	Exercise heart rate	NS
FEV_1	NS	FEV_1	NS
Resting PEFR	NS	Resting PEFR	NS
Exercise PEFR	$P<0.02$	Exercise PEFR	$P<0.02$
Practolol v oxprenolol		*Propranolol v metoprolol*	
Resting heart rate	NS	Resting heart rate	NS
Exercise heart rate	NS	Exercise heart rate	NS
FEV_1	NS	FEV_1	NS
Resting PEFR	NS	Resting PEFR	NS
Exercise PEFR	NS	Exercise PEFR	NS
Practolol v metoprolol		*Oxprenolol v metoprolol*	
Resting heart rate	$P<0.02$	Resting heart rate	NS
Exercise heart rate	NS	Exercise heart rate	NS
FEV_1	NS	FEV_1	NS
Resting PEFR	NS	Resting PEFR	NS
Exercise PEFR	$P<0.01$	Exercise PEFR	NS

Level of significance (α) = 0.05.
NS = not significant.

Table 7 Mean ± s.e. mean values of resting and exercise heart rate, FEV_1, and resting and exercise PEFR for 8 subjects in the third study before and after each intravenous treatment

	Time (h)				
	0	*2*	*3*	*4*	*6*
Placebo					
Resting heart rate (beats/min)	74 ± 4	69 ± 4	72 ± 3	74 ± 3	75 ± 3
Exercise heart rate (beats/min)	166 ± 2	165 ± 3	163 ± 2	166 ± 2	164 ± 2
FEV_1 (l)	4.04 ± 0.30	4.06 ± 0.31	4.05 ± 0.29	4.07 ± 0.30	4.07 ± 0.31
Resting PEFR (l/min)	563 ± 37	568 ± 38	568 ± 38	570 ± 36	571 ± 38
Exercise PEFR (l/min)	593 ± 37	594 ± 39	592 ± 37	595 ± 37	600 ± 36
Practolol 1.0 mg/kg					
Resting heart rate	71 ± 4	65 ± 2	71 ± 2	73 ± 2	71 ± 3
Exercise heart rate	169 ± 2	134 ± 3	137 ± 2	140 ± 2	142 ± 2
FEV_1	4.08 ± 0.30	4.07 ± 0.28	4.07 ± 0.30	4.11 ± 0.30	4.07 ± 0.29
Resting PEFR	566 ± 39	572 ± 37	567 ± 38	570 ± 38	575 ± 36
Exercise PEFR	598 ± 38	598 ± 38	597 ± 38	603 ± 40	607 ± 41
Propranolol 0.2 mg/kg					
Resting heart rate	74 ± 4	60 ± 2	64 ± 3	65 ± 3	70 ± 4
Exercise heart rate	168 ± 2	131 ± 2	136 ± 2	139 ± 2	147 ± 2
FEV_1	4.06 ± 0.30	3.98 ± 0.30	3.99 ± 0.30	3.99 ± 0.30	3.98 ± 0.30
Resting PEFR	565 ± 40	547 ± 39	553 ± 39	556 ± 40	559 ± 42
Exercise PEFR	600 ± 41	584 ± 40	586 ± 40	590 ± 41	583 ± 40
Pindolol 0.05 mg/kg					
Resting heart rate	66 ± 4	66 ± 3	69 ± 2	70 ± 2	73 ± 2
Exercise heart rate	167 ± 2	131 ± 3	136 ± 2	141 ± 3	145 ± 3
FEV_1	4.10 ± 0.30	4.04 ± 0.31	4.06 ± 0.29	4.06 ± 0.27	4.04 ± 0.29
Resting PEFR	563 ± 37	557 ± 35	561 ± 36	562 ± 35	566 ± 36
Exercise PEFR	588 ± 37	587 ± 37	587 ± 36	588 ± 36	598 ± 37

Table 8 Analysis of variance, 2-tailed tests comparing each drug with placebo in the third study ($n = 8$)

	Time (h)			
	2	*3*	*4*	*6*
	Probability levels			
Practolol v placebo				
Resting heart rate	NS	NS	NS	NS
Exercise heart rate	$P < 0.001$	$P < 0.001$	$P < 0.001$	$P < 0.001$
FEV_1	NS	NS	NS	NS
Resting PEFR	NS	NS	NS	NS
Exercise PEFR	NS	NS	NS	NS
Propranolol v placebo				
Resting heart rate	$P < 0.01$	$P < 0.02$	$P < 0.01$	NS
Exercise heart rate	$P < 0.001$	$P < 0.001$	$P < 0.001$	$P < 0.001$
FEV_1	$P < 0.05$	NS	$P < 0.01$	$P < 0.01$
Resting PEFR	$P < 0.01$	NS	NS	NS
Exercise PEFR	$P < 0.02$	$P < 0.01$	$P < 0.05$	$P < 0.01$
Pindolol v placebo				
Resting heart rate	$P < 0.05$	$P < 0.02$	NS	$P < 0.05$
Exercise heart rate	$P < 0.001$	$P < 0.001$	$P < 0.001$	$P < 0.001$
FEV_1	$P < 0.05$	NS	NS	$P < 0.01$
Resting PEFR	NS	NS	NS	NS
Exercise PEFR	NS	NS	NS	NS

Level of significance (α) = 0.05; NS = not significant.

Table 9 Analysis of variance, 2-tailed tests comparing drugs with each other in the third study ($n=8$)

	Time (h)			
	2	3	4	6
	Probability levels			
Practolol v propranolol				
Resting heart rate	$P<0.01$	$P<0.01$	$P<0.01$	NS
Exercise heart rate	NS	NS	NS	$P<0.01$
FEV_1	NS	NS	$P<0.01$	NS
Resting PEFR	$P<0.01$	NS	NS	NS
Exercise PEFR	$P<0.02$	$P<0.02$	$P<0.01$	$P<0.01$
Practolol v pindolol				
Resting heart rate	$P<0.05$	NS	NS	$P<0.02$
Exercise heart rate	NS	NS	NS	$P<0.01$
FEV_1	NS	NS	NS	NS
Resting PEFR	NS	NS	NS	NS
Exercise PEFR	NS	NS	NS	NS
Propranolol v pindolol				
Resting heart rate	$P<0.001$	$P<0.001$	$P<0.001$	$P<0.001$
Exercise heart rate	NS	NS	NS	NS
FEV_1	NS	NS	NS	NS
Resting PEFR	$P<0.05$	NS	NS	NS
Exercise PEFR	$P<0.02$	$P<0.02$	NS	$P<0.001$

Level of significance (α) = 0.05; NS = not significant.

Discussion

The technique used in these studies was originally devised to assess cardioselectivity of β-adrenoceptor antagonists. When β-adrenoceptor blocking drugs were given intravenously in moderate doses which reduced exercise heart rate by similar amounts, non-selective drugs reduced the increase in PEFR evoked by exercise, whereas selective drugs did not. The results of the present studies show that this is an over-simplification. Only oxprenolol and pindolol were consistently without effect on exercise PEFR, and there is no evidence that these drugs are cardioselective. In contrast, propranolol and metoprolol, and practolol given orally, did reduce exercise PEFR although only propranolol is acknowledged to be non-selective. Practolol behaved as a selective drug only after intravenous administration.

Lertora *et al.* (1975), studying the effect of practolol on isoprenaline-induced increases in heart rate and forearm arterial blood flow, have shown that cardioselectivity is lost when high serum concentrations of the drug are attained in normal volunteers. In our studies (Figure 10), practolol 200 mg orally resulted in plasma concentrations 2–4.5 times greater than those after intravenous injection of practolol 1 mg/kg. The failure to show the selectivity of practolol is probably due to these higher plasma concentrations; the drug is cardioselective, not cardiospecific. Since practolol is not significantly metabolized during its 'first pass' through the liver (Scales & Cosgrove, 1970), it is unlikely that non-selective metabolites caused the observed lack of selectivity.

The effects of metoprolol were indistinguishable from those of the non-selective drug propranolol after both oral and intravenous administration. Although only conventional doses were given in these studies, it is likely that the resulting plasma concentrations were too high for the selectivity of metoprolol to be apparent. The pharmacological actions of the 'first pass' metabolites of metoprolol in man are negligible (Johnsson, Regardh & Solvell, 1975). These experimental findings are consistent with clinical experience, for it is well known that even cardioselective drugs may worsen airflow obstruction in some patients (Waal-Manning & Simpson, 1971; Johnsson, Svedmyr & Thiringer, 1975; Singh, Whitlock, Comber, Williams & Harris, 1976). Our data are in keeping with the findings of Harms (1976) and Newman (1976).

Both oxprenolol and pindolol failed to reduce the exercise-evoked increase in PEFR despite their marked effects on exercise heart rate. They behaved like a typical cardioselective drug such as practolol when it is given intravenously in relatively small doses. This finding is not easily explained, for there is no other evidence that either drug is cardioselective. Although the mechanism is obscure, the partial

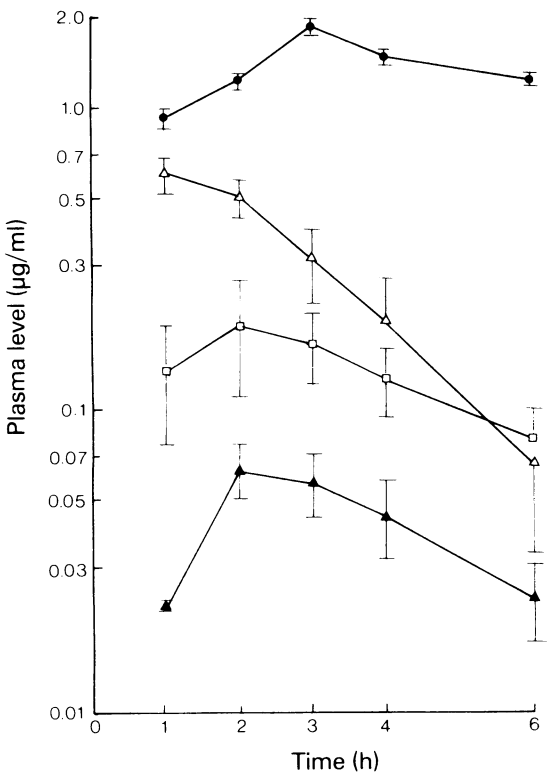

Figure 3 Mean ± s.e. mean plasma levels after oral administration of four drugs (● practolol 200 mg; △ oxprenolol 80 mg; □ metoprolol 100 mg; ▲ propranolol 80 mg), first study ($n = 5$).

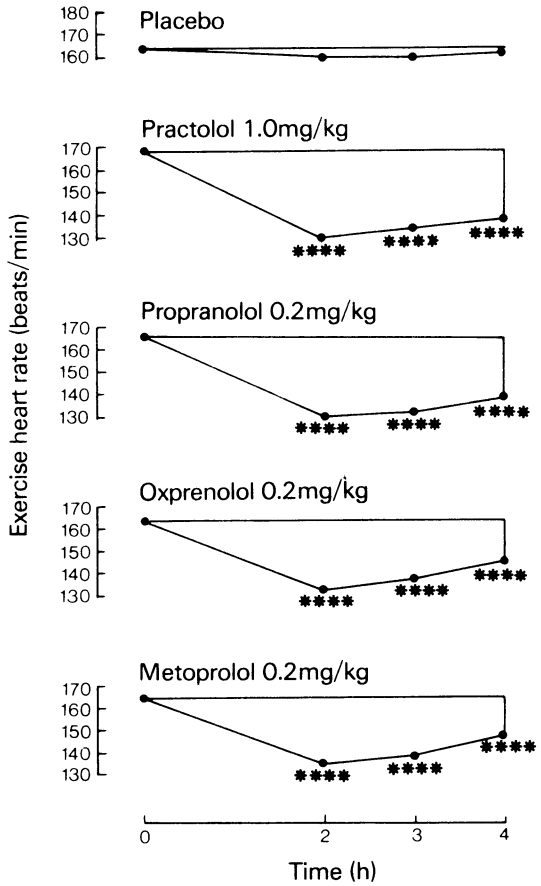

Figure 4 Mean changes in exercise heart rate after five intravenous treatments, with significance levels of comparisons of drugs with placebo, second study ($n = 6$). ****$P < 0.001$.

agonist activity which both drugs possess may protect the airways against the effects of β-adrenoceptor blockade. However, when oxprenolol and pindolol, both non-selective drugs with partial agonist activity, are compared with propranolol, a non-selective drug without partial agonism, only pindolol increased resting heart rate and resting PEFR without affecting FEV_1. Moreover, non-selective β-adrenoceptor antagonists have similar affinities for bronchial and cardiac receptors; the partial agonist effects of these drugs should therefore be similar in bronchi and heart. If partial agonism were to prevent the reduction by β-adrenoceptor blockade of exercise-induced increase in PEFR, it should also prevent the reduction of exercise heart rate by β-adrenoceptor blockade. Our data show clearly that oxprenolol and pindolol caused reductions in exercise heart rate similar to those caused by the other drugs. It is possible that the partial agonist activity of these drugs might selectively affect bronchial receptors, but there is no evidence for this.

Another explanation for the anomalous effect of oxprenolol and pindolol is that these drugs may have additional α-adrenoceptor blocking activity. Stimulation of α-adrenoceptors causes bronchoconstriction, and the α-adrenoceptor antagonist indoramin has been shown to prevent exercise-induced bronchospasm (Bianco, Griffin, Kamburoff & Prime, 1974; Kamburoff, 1976). Similarly the non-selective β-adrenoceptor antagonist labetalol, which has α-adrenoceptor blocking activity, did not worsen histamine-induced bronchoconstriction in normal subjects, in contrast to propranolol (Woodings, Maconochie & Richards, 1977). The same authors also showed that labetalol affected resting PEFR less than propranolol (Richards, Woodings & Maconochie, 1977). Exercise causes both α- and β-adrenoceptor stimulation in the airways, and a nett bronchodilator effect is seen. When this bronchodilatation is reduced by β-adrenoceptor blockade, a normal response might be restored by the addition of α-adrenoceptor blockade.

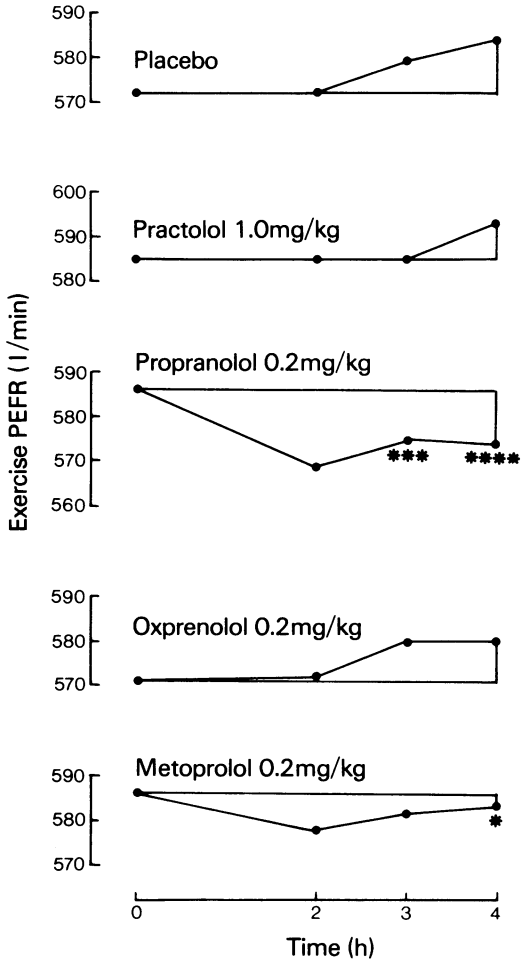

Figure 5 Mean changes in exercise peak expiratory flow rate after five intravenous treatments, with significance levels of comparisons of drugs with placebo, second study ($n=6$). *$P<0.05$; ***$P<0.01$; ****$P<0.001$.

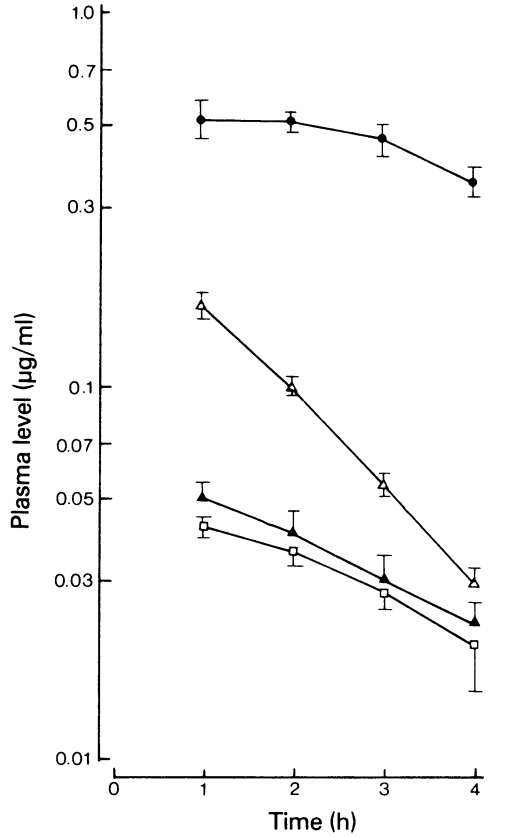

Figure 6 See legend below.

Figure 6 Mean ± s.e. mean plasma levels after i.v. administration of four drugs (● practolol 1 mg/kg; △ oxprenolol 0.2 mg/kg; □ metoprolol 0.2 mg/kg; ▲ propranolol 0.2 mg/kg), second study ($n=6$).

Figure 7 Mean changes in exercise heart rate after four intravenous treatments, with significance levels of comparisons of drugs with placebo, third study ($n=8$). ****$P<0.001$.

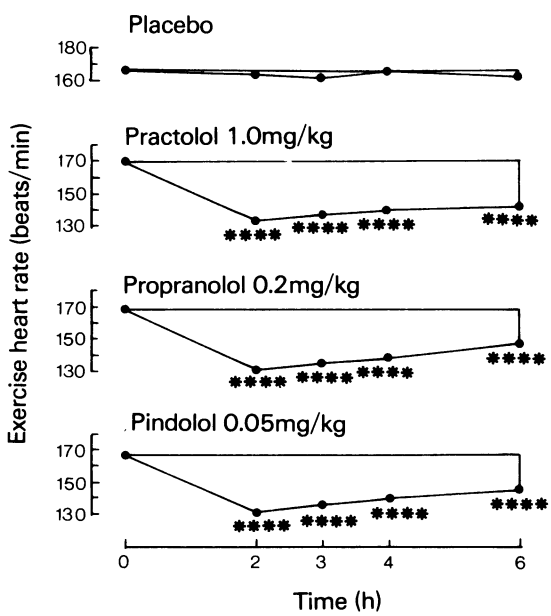

Figure 7

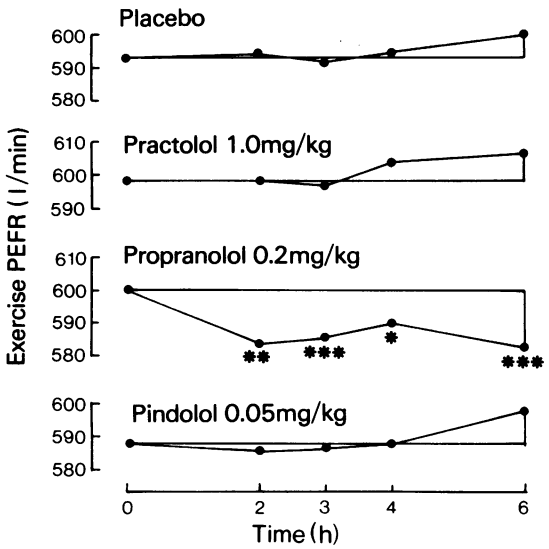

Figure 8 See legend below.

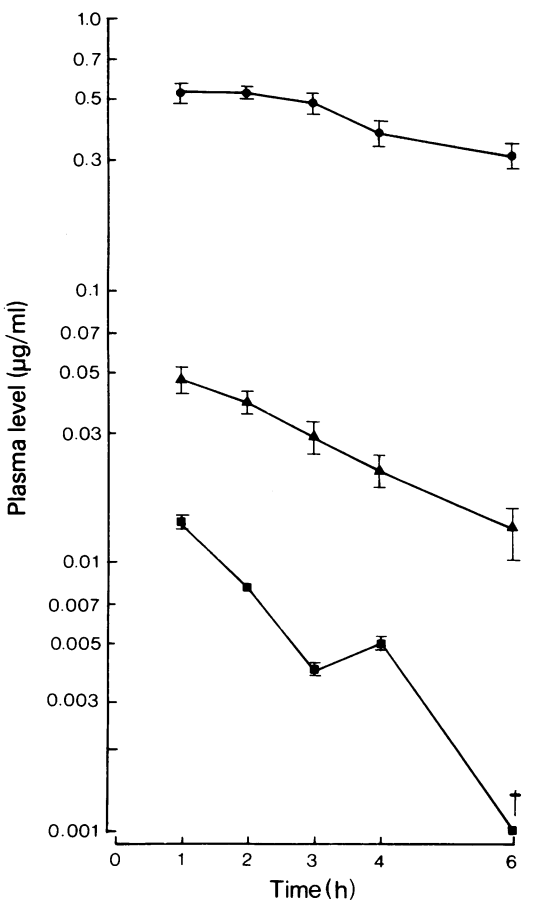

Figure 9

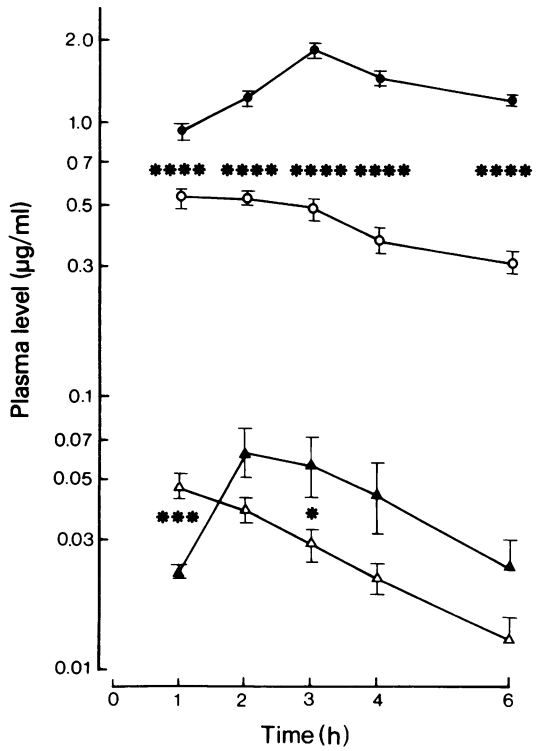

Figure 10 Mean ± s.e. mean plasma levels of practolol and propranolol. Oral route, first study, ($n=5$), (● practolol 200 mg; ▲ propranolol 80 mg). Intravenous route, third study, ($n=8$), (○ practolol 1 mg/kg; △ propranolol 0.2 mg/kg). *$P<0.05$; ***$P<0.01$; ****$P<0.001$.

Figure 8 Mean changes in exercise peak expiratory flow rate after four intravenous treatments, with significance levels of comparisons of drugs with placebo, third study ($n=8$). *$P<0.05$; **$P<0.02$; ***$P<0.01$.

Figure 9 Mean ± s.e. mean plasma levels after i.v. administration of three drugs (● practolol 1 mg/kg; ▲ propranolol 0.2 mg/kg; ■ pindolol 0.05 mg/kg), third study ($n=8$). † below the limits of detection.

Experiments with animal preparations have shown that oxprenolol has α-adrenoceptor blocking activity at concentrations within the range of therapeutic plasma levels (Rand, 1976), but pindolol has not been shown to have this property (Clark, 1977). If drugs like oxprenolol have α-adrenoceptor blocking activity, they may also act on inhibitory pre-synaptic α-adrenoceptors to give a nett increase in neurotransmitter output (Rand, McCulloch & Story, 1975). Further work in man is needed to clarify this point.

A third explanation is that the 'first pass' metabolites of oxprenolol and pindolol may have cardioselectivity, partial agonist activity or α-adrenoceptor blocking activity to account for their unexpected effect on exercise PEFR. Were this true, these drugs given intravenously should have reduced the exercise-evoked increase in PEFR: but they did not.

We do not suggest that any β-adrenoceptor antagonist can be given without risk to patients with airflow obstruction. However, the risks may be less with those drugs which, whatever the underlying mechanism, do not affect the physiological bronchodilatation that occurs on exertion.

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