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COMPARISON OF THE EFFECTS OF LABETALOL AND PROPRANOLOL IN HEALTHY MEN AT REST AND DURING EXERCISE

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1 Oral labetalol and propranolol have been compared in healthy men with regard to the effects on heart rate, blood pressure and peak expiratory flow rate (PEFR) at rest and the changes induced by exercise.

2 Labetalol caused a dose-related reduction in standing diastolic pressure at rest whereas propranolol did not but neither drug altered standing systolic pressure at rest.

3 In the doses compared, propranolol was consistently more potent than labetalol in influencing blood pressure changes induced by exercise, in lowering heart rate at rest and reducing PEFR at rest.

4 Labetalol and propranolol are both β-adrenoceptor antagonists and the observed differences in the profiles of the two drugs are probably directly related to the additional α-adrenoceptor blocking property of labetalol not possessed by propranolol. Because of these differences labetalol may be expected to have advantages in the treatment of hypertension.

Introduction

Propranolol has been used for over ten years in the treatment of angina pectoris and hypertension and its therapeutic value is believed to be due to β-adrenoceptor blockade.

Labetalol (AH 5158) blocks both α- and β-adrenoceptors (Farmer, Kennedy, Levy & Marshall, 1972) and it has been used intravenously and orally to treat hypertensive patients (Prichard, Thompson, Boakes & Joekes, 1975). It is a more potent antagonist of β-adrenoceptors than α-adrenoceptors, and after oral administration the potency ratio of α : β antagonism is approximately 1 : 3 (Richards, Tuckman & Prichard, 1976).

We have shown that oral labetalol modifies the cardiovascular but not the respiratory effects of exercise in healthy volunteers (Richards, Woodings, Stephens & Maconochie, 1974). In that investigation we used an exercise test procedure to increase endogenous sympathetic drive, and measured effects after labetalol which appeared to be due to beta adrenoceptor blockade. In order to obtain more information on the relative importance of the additional α-adrenoceptor blocking property of labetalol we decided to use the same exercise test procedure to compare and contrast labetalol and propranolol. On the basis of preliminary reports from clinical trials in hypertensive patients (Pugsley, Armstrong, Nassim & Beilin, 1976) we assumed that the potency ratio of propranolol : labetalol was approximately 2.5 : 1.

Method

Six healthy male subjects aged 21-34 years, weighing 65-81 kg took part in this study. Each subject came to the laboratory on six mornings after having had light breakfasts without tea or coffee. There were intervals of at least 1 week between visits. Heart rate was measured from chest electrodes using a Narco biosystems biotachometer, and was recorded on a Devices 2 channel recorder. Blood pressure was measured by the same observer throughout the study using an Accoson aneroid sphygmomanometer. Measurements of peak expiratory flow rate were taken using a Wright Peak Flow Meter.

Each subject sat quietly until the heart rate was steady and this was taken as the measure of resting heart-rate. After standing for 1 min the resting blood pressure was recorded followed by a measurement of resting peak expiratory flow rate (PEFR). Each then exercised on a Quinton treadmill for 2 min at a predetermined level which was

sufficient to increase heart rate to at least 150 beats/min. All subjects exercised at 4 m.p.h., two against an incline of 17° and four against an incline of 15°. Further measurements of PEFR were taken after 60 s and 120 s without interrupting the exercise. Heart rate was recorded throughout the exercise and the rate during the last 15 s of exercise was taken as the exercise heart rate. The exercise blood pressure was measured with the subject standing immediately after the exercise finished. After sitting quietly until the heart rate returned to the resting level the whole exercise procedure was repeated in order to establish that the responses to exercise were reproducible.

Each subject then took one of the drugs by mouth and the exercise procedure was repeated at hourly intervals for 4 h. Between the periods of exercise the subject sat at rest. A regular fluid intake was allowed but none likely to influence the cardiovascular system and no solid food was consumed during the experiment.

The doses of labetalol were 100 mg, 200 mg and 400 mg and those of propranolol were 40 mg 80 mg and 160 mg. Every subject received each dose under double-blind conditions. They received the two low doses first then the two middle doses and finally the high dose of each drug; the order of administration of labetalol and propranolol in each pair being randomized.

Analysis of results

For individual subjects a dose response curve of both drugs was plotted using the method of least squares. From these, mean dose response curves were constructed which were tested for non-parallelism (t-test) and where possible, dose ratios between the drugs were estimated. Where appropriate for both drugs at each of the paired dose levels a paired t-test was used to test for differences.

Results

Heart rate

The group mean pre-treatment resting heart rate was 71 ± 3 beats/min and the exercise heart rate was 156 ± 2 beats/min.

The effects of treatment on heart rate were assessed using the resting heart rates, the peak exercise heart rates and the exercise induced increases in heart rate at each hour. The individual results showed that these values were reduced after each treatment and the lowest values occurred at 2 or 3 h. The lowest values were used for comparing the effects of labetalol and propranolol (Table 1).

Table 1 Maximum effects of labetalol and propranolol on heart rate at rest and after exercise.

	Labetalol								*Propranolol*			
	100 mg		*200 mg*		*400 mg*		*40 mg*		*80 mg*		*160 mg*	
	Heart rate (beats/min)											
Subject	*Rest*	*Exercise*	*Rest*	*Exercise*	*Rest*	*Exercise*	*Rest*	*Exercise*	*Rest*	*Exercise*	*Rest*	*Exercise*
1	80	148	66	138	70	138	62	140	60	114	60	108
2	60	140	52	138	56	124	60	136	52	110	52	106
3	68	156	78	150	68	148	60	128	66	120	60	110
4	68	148	62	140	60	132	54	132	50	120	50	112
5	62	144	62	124	60	128	60	128	56	120	48	110
6	62	154	60	148	64	140	62	138	58	124	60	110
Mean	67	147	63	140	63	135	60	134*	57	118*	50	109*
s.e. mean	±3	±2.4	±3.5	±4.0	±2	±4.0	±1	±2	±2	±2	±2	±1

* $P < 0.05$ t-test for differences

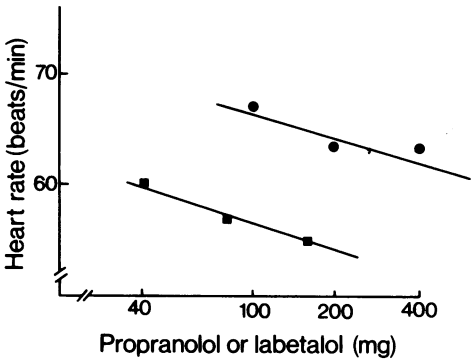

Figure 1 Maximum effect upon mean heart rate ($n = 6$) at rest after labetalol (●) and propranolol (■).

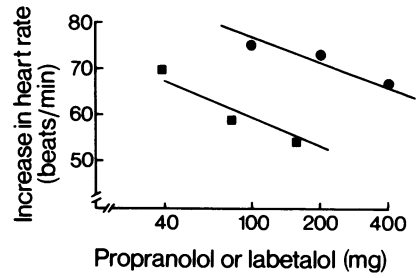

Figure 2 Maximum effect upon exercise-induced increases in mean heart rate ($n = 6$) after labetalol (●) and propranolol (■).

The mean resting heart rates were lower after propranolol than after labetalol. The calculated potency ratio propranolol : labetalol was 25.7 : 1 (Figure 1). The slopes obtained from the mean peak heart rates during exercise were not parallel and therefore no potency ratio could be calculated but the rate after each dose of propranolol was significantly lower ($P < 0.05$) than the rate after the paired dose of labetalol (Table 1). The mean increases in heart rate due to exercise were lower after propranolol than labetalol. The calculated potency ratio propranolol : labetalol was 6.2 : 1 (confidence limit 2.4-15.6) (Figure 2).

Blood pressure

The group mean pre-treatment resting blood pressure was 117/75 ± 6/4 mmHg and the post exercise blood pressure was 158/64 ± 7/4 mmHg. The effects of treatment on blood pressure were assessed using the resting blood pressure, the exercise induced increases in systolic pressure and the exercise induced decreases in diastolic pressure at each hour. The lowest values after treatment occurred at two or three hours and these were used for comparing the effects of labetalol and propranolol (Table 2). The lowest values for blood pressure were chosen by the systolic readings and in most instances these coincided with the lowest diastolic reading. At rest the mean systolic pressures after each dose of both drugs were similar (Table 2). The mean resting diastolic pressures were lower after labetalol than after propranolol and these effects were dose related with labetalol but not after propranolol (Table 2). The mean value after labetalol (400 mg) was significantly lower than after propranolol (160 mg) ($P < 0.05$) but the paired values after the middle and low doses were not significantly different. The mean post exercise systolic pressures showed dose-related reductions after both labetalol and propranolol but the individual slopes were not parallel. The mean value after propranolol (40 mg) was significantly lower than that after labetalol (100 mg) ($P < 0.05$) but the paired values after the middle and high doses were not significantly different (Table 2). The mean exercise induced increases in systolic pressure were inhibited after both drugs and here the estimated potency ratio was propranolol : labetalol 3.8 : 1 (confidence limit 2.9-5.1) (Figure 3). After both drugs the post-exercise diastolic pressures were decreased in a dose related manner. The estimate of relative potency here was 2.2 : 1 propranolol : labetalol (confidence limit 1.2-4.0) (Figure 4).

Peak expiratory flow rate

The group mean pre-treatment PEFR at rest was 582 ± 2.3 litres/min. After 1 min of exercise the group mean PEFR was 595 ± 7.3 litres/min and after 2 min it was 609 ± 3.4 litres/min. The effects of treatment on PEFR were assessed using the data at rest and during exercise at each hourly interval and the mean of the hourly values after exercise for each treatment was analysed (Table 3). The mean PEFR at rest decreased after both drugs and the calculated ratio propranolol : labetalol was 14.9 : 1 (confidence limit 1.8-126.6). After 1 min of exercise the calculated potency ratio propranolol : labetalol was 9.2 : 1 (confidence limit 3.3-25.5). However, after 2 min of exercise the dose-related effect disappeared and this potency ratio could not be calculated.

Discussion

Therapeutic doses of β-adrenoceptor blocking drugs usually reduce the resting heart rate and excessive bradycardia sometimes restricts their use.

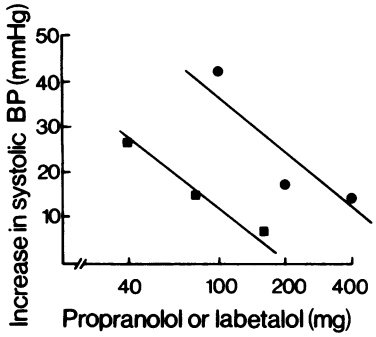

Figure 3 Maximum effect upon exercise-induced increases in mean systolic blood pressure (n = 6) after labetalol (•) and propranolol (▪).

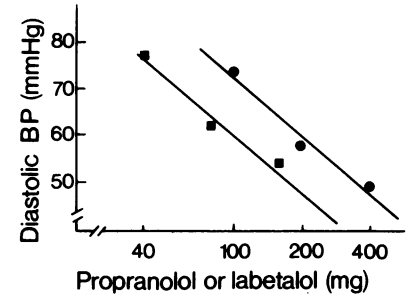

Figure 4 Maximum effect upon exercise-induced changes in mean diastolic blood pressure (n = 6) after labetalol (•) and propranolol (▪).

Our results show that propranolol has much more effect than labetalol on resting heart rate and the potency ratio of 25.7 : 1 is far greater than that calculated from the other parameters. Heart rate at rest is controlled by the balance of modest sympathetic drive and vagal inhibitory effects so that blockade of cardiac β-adrenoceptors leads to vagal predominance and a slower heart rate. In addition, it may be that peripheral βadrenoceptor blockade allows a predominance of α-adrenoceptor activity and an increase in peripheral resistance causing a further reflex rise in the vagal inhibition of heart rate. One of the immediate effects of propranolol is to provoke an increase in total peripheral resistance (Prichard *et al.*, 1975). Furthermore it has been shown that propranolol allows an enhancement of responses to infused noradrenaline mediated through α-adrenoceptors (White & Udwadia, 1975; Imms, Neame & Powis, 1976. Similar effects are not seen with cardioselective β-adrenoceptor blocking drugs and in particular they usually have less effect than propranolol on resting heart rate (Johnsson, 1975). As there is no evidence that labetalol is cardioselective it seems probable that it differs from propranolol in its effect on resting heart rate because of its additional property of α-adrenoceptor blockade.

When heart rate exceeds 130 beats/min there is little or no vagal inhibition so that the heart rate becomes a fairly accurate index of sympathetic drive (Robinson, Epstein, Beiser & Braunwald, 1966) and a drug induced reduction in the exercise heart rate may be taken to indicate β-adrenoceptor blockade. We compared labetalol with placebo in a previous study and found that labetalol did cause a dose-related inhibition of peak exercise heart rate (Richards *et al.*, 1974). The results from the present study proved to be unsuitable in calculating the potency ratio using the effects of labetalol and propranolol on peak exercise heart rate and we compared instead their effects on exercise-induced increases in heart rate. Although this index is not simply a measure of sympathetic drive, it provides information which is probably relevant to the clinical situation. It showed that propranolol was approximately six times more potent than labetalol in inhibiting the increase in heart rate due to exercise. In a similar manner, exercise induced increases in systolic pressure may also be used as an index of β-adrenoceptor activity. Using this parameter we found that propranolol was approximately four times more potent than labetalol at inhibiting the increase in systolic pressure due to exercise. Thus both heart rate and systolic pressure indices suggest that propranolol is more potent weight for weight than labetalol in blocking β-adrenoceptors.

Resting diastolic pressure was reduced by labetalol but not by propranolol, which is a finding consistent with our previous report (Richards *et al.*, 1974). In addition, we have shown that labetalol (400 mg) reduced blood pressure in the 45° recumbent position whereas propranolol (80 mg) did not (Maconochie, Woodings & Richards, 1976). These data would indicate that labetalol differs from propranolol probably as a result of its additional α-adrenoceptor blocking effect. This is further supported by the findings that both drugs enhanced the exercise induced reduction in diastolic pressure but there however the estimate of potency between them narrowed to a two fold difference. This suggests that labetalol had a greater effect upon diastolic blood pressure during exercise than upon systolic pressure. Such an effect is likely to occur consequent upon blockade of α-adrenoceptors. The functional dissimilarity

Table 2 Maximum effects of labetalol and propranolol on blood pressure (standing) at rest and following exercise.

	Labetalol						Propranolol					
	100 mg		200 mg		400 mg		40 mg		80 mg		160 mg	
Subject	Rest	Exercise	Rest	Exercise	Rest	Exercise	Rest	Exercise	Rest	Exercise	Rest	Exercise
1	98/64	138/64	100/68	114/46	82/60	104/40	90/70	118/76	96/80	110/70	96/72	96/48
2	104/78	140/64	116/88	132/58	110/68	118/44	94/76	128/54	116/82	122/50	106/82	110/50
3	98/82	128/62	112/70	116/56	104/70	116/56	104/88	116/90	108/84	118/74	96/80	110/48
4	100/80	184/92	106/76	152/68	104/74	138/56	98/80	150/84	108/78	144/78	100/84	128/48
5	98/84	144/92	106/86	114/64	92/74	104/52	100/86	124/64	96/80	116/52	98/90	110/78
6	110/88	180/68	108/82	128/58	86/64	126/40	104/92	152/98	118/58	124/52	94/68	114/48
Mean	101/79	152*/74	108/77	126/58	96/68*	118/48	98/82	131/77	107/82	122/63	98/79	111/53
s.e. mean	±2/±3	±10/±6	±2/±3	±6/±3	±3/±2	±5/±2	±2/±3	±6/±7	±4/±4	±5/±5	±2/±3	±4/±5

* $P < 0.05$ difference from propranolol (160 mg)

Table 3 Effects of labetalol and propranolol on mean peak expiratory flow rate ($n = 6$) at rest and exercise over a 4 h period

	Labetalol									Propranolol								
	100 mg			200 mg			400 mg			40 mg			80 mg			160 mg		
	PEFR (litres/min)																	
	Rest	Exercise 1 min	Exercise 2 min	Rest	Exercise 1 min	Exercise 2 min	Rest	Exercise 1 min	Exercise 2 min	Rest	Exercise 1 min	Exercise 2 min	Rest	Exercise 1 min	Exercise 2 min	Rest	Exercise 1 min	Exercise 2 min
Mean	595	619	618	577	597	603	580	594	607	580	606	600	562	588	587	554	567	571
s.e. mean	20	22	23	15	17	18	23	19	25	21	19	24	15	16	18	14	14	12

between labetalol and propranolol allows observations about the therapeutic use of the two drugs

The greatest use of propranolol is in the treatment of angina pectoris and hypertension. Although Boakes & Prichard (1973) demonstrated that labetalol significantly increased exercise tolerance in anginal patients, it did not do so on a dose-related basis and as such compared unfavourably with propranolol in the same patients. They suggested the reason for this was due to the increasing dose related reduction in blood pressure seen after labetalol but not propranolol. Data presented from our study would support their findings. On the other hand, it has been established in man that labetalol induces dose-related reductions in resting blood pressure after single oral doses (Richards *et al*, 1974) and more particularly produces marked reductions in blood pressure in hypertensive patients after intravenous injection (Rosei, Trust, Brown, Lever & Robertson, 1975). Prichard *et al.*, (1975) have shown that the oral drug is antihypertensive in long term treatment. In the present study our data suggests that in comparable β-adrenoceptor blocking doses in hypertensive patients, labetalol could be expected to produce greater falls in blood pressure at rest than propranolol and possibly greater reductions especially in diastolic pressure after exercise. Greater reductions with labetalol after exercise have been shown in a study of hypertensive patients receiving both propranolol and labetalol (Pugsley *et al.*, 1976). From these data therefore it may be inferred that the major therapeutic role for labetalol is likely to be in the treatment of hypertension.

In another study in healthy volunteers Kumana, Marlin, Kaye & Smith (1974) have shown that propranolol when compared with placebo, significantly reduces both peak expiratory flow at rest and following exercise. In our study following propranolol we showed a similar effect. We have previously reported no change in resting and exercising peak expiratory flow after single oral doses of labetalol 100 mg, 200 mg and 400 mg when compared against placebo (Richards *et al.*, 1974). In the present study the highest dose of propranolol produced greater reductions at rest and during exercise than the highest dose of labetalol. Kumana, Marlin, Kaye & Smith (1974) reported a difference in effect between propranolol and practolol which they attributed to the cardioselectivity of practolol. As there is no evidence from any previous study to suggest that labetalol is similar to practolol in being cardioselective it may well be that the differences between labetalol and propranolol are due to the additional α-adrenoceptor blocking effect of labetalol (Skinner, Gaddie & Palmer, 1975).

Overall the effects of both drugs on heart rate, blood pressure and peak expiratory flow rate were qualitatively similar but quantitatively dissimilar. The predominant effect of labetalol is reflected in changes in blood pressure whereas that of propranolol is upon heart rate. Thus in equipotent β-adrenoceptor blocking doses in hypertensive patients labetalol may be expected to reduce blood pressure to a greater extent.

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