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THE EFFECTS OF A NEW BETA-ADRENOCEPTIVE RECEPTOR BLOCKING DRUG ON HEART RATE IN MAN

BY

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In 1906, Dale showed that although ergot was capable of preventing most of the excitatory effects of adrenaline and of sympathetic nervous stimulation it was unable to prevent their inhibitory actions. Ahlquist (1948) found that slight modifications of the adrenaline molecule could alter its pharmacological potency. He explained his and Dale's findings by postulating the existence of two types of adrenoceptive receptor which he named alpha and beta.

Activation of adrenoceptive alpha receptors results in man in excitatory responses, one of the most noticeable of which is peripheral vasoconstriction. Stimulation of beta receptors generally produces inhibitory responses, but in the heart, where the receptors are exclusively beta in nature, activation produces an excitatory response. Thus, sympathetic nervous stimulation or the administration of β adrenoceptive receptor stimulant drugs results in an increase in the heart rate and cardiac contractile force. Prevention of these responses would reduce the work of the heart and thereby provide a new approach to the management of many cardiac disorders so there has been an intense search directed towards the discovery of β receptor blocking agents. With the introduction of such compounds the problem has arisen of their assessment in man. One way in which this might be accomplished is by the examination of the effects of such drugs on naturally and artificially induced tachycardia.

Three experimental situations were therefore devised and the activity of a new β adrenoceptive receptor blocking drug 6,7-dimethyl-α-(isopropylamino)methyl-2-benzofuranmethanol hydrochloride (R_o3-3528) compared with propranolol, a β receptor-blocking drug which is known to be of therapeutic value in various cardiovascular disorders.

METHODS

Resting pulse rate

Six healthy male volunteers aged 22–25 yr were asked to sit quietly for 5 min before their heart rate was determined (from the radial pulse over 1 min) at hourly intervals for 6 hr. After two drug-free control sessions, each volunteer received in random order oral doses of propranolol (20 and 40 mg) and R_o3-3528 (50, 100, 125 and 150 mg).

Isoprenaline-induced tachycardia

Eight healthy male volunteers aged 22–25 yr were investigated. The method used was based on that of Chamberlain (1967). Each volunteer was given standardized inhalation of 2% isoprenaline administered at 8 l/min by a Wright nebulizer and the number of breaths required to cause a consistent rise in heart rate of between 30–40 beats/min was recorded. Heart rate was measured on a Cambridge direct writing electrocardiograph at a paper speed of 25 mm/sec and by determining the time taken for five complete cardiac cycles indicated by the *R* waves.

At the start of each experiment the volunteers were seated at rest for 5 min before records were taken. A resting pulse rate was obtained before they inhaled the number of breaths of isoprenaline which they required to produce a standard increase in heart rate. The heart rate was recorded every 15 sec for 2 min after cessation of inhalation of isoprenaline.

Exercise-induced tachycardia

Six healthy male volunteers aged 22–25 yr were investigated. The method used was based on that of Chamberlain (1967). On each occasion volunteers were seated at rest for 5 min before records were taken. Measurements of heart rate were made first at rest seated, second after they had been standing for 30 sec and subsequently during the last 10 sec of each of six 2 min periods of exercise taken consecutively and without a break for rest on a motor driven treadmill at the following speeds and inclines: 1, 2 and 3 m.p.h. on the flat, and 3 m.p.h. on a 3°, 6° and 9° incline.

Each volunteer was exercised twice without drugs and a mean heart rate for each 2 min period was obtained. On three subsequent occasions 2 hr before exercise they received, in turn, oral doses of propranolol (40 mg) and R_o3-3528 (100 and 150 mg). The order of administration was randomized in a latin square sequence. The minimum time between tests was 2 days.

RESULTS

Table 1 shows the mean pulse rate in beats/min (±S.E.) at hourly intervals for 3 hr after administration of R_o3-3528 (50, 100, 125 and 150 mg) and propranolol (20 and 40 mg). Maximum drug effects were obtained at 2 hr, pre-drug levels being reached again after 4 hr.

TABLE 1

MEAN PULSE RATE IN BEATS/MIN (± S.E.) IN SIX SUBJECTS AT HOURLY INTERVALS FOR 3 HR FOLLOWING ORAL ADMINISTRATION OF R_o3-3528 (50, 100, 125, 150 mg) AND PROPRANOLOL (20, 40 mg)

Hours		0		1		2		3	
Treatment		Beats/min	S.E.	Beats/min	S.E.	Beats/min	S.E.	Beats/min	S.E.
Control		78·8	3·99	70·4	2·03	70·2	3·40	72·8	4·55
R_o3-3528	50 mg	76·6	5·75	70·1	4·69	64·0	3·77	69·6	4·51
	100 mg	79·0	7·36	71·0	4·80	65·2	2·20	70·3	3·12
	125 mg	80·0	5·79	68·0	4·79	62·8	1·73	70·0	3·58
	150 mg	76·7	5·18	65·0	3·11	63·2	3·08	69·2	3·37
Propranolol	20 mg	73·2	4·15	63·2	3·11	59·3	3·56	63·7	3·16
	40 mg	74·6	1·31	64·2	4·06	61·2	3·03	66·4	4·32

Figure 1 shows the fall in resting pulse rate (R.P.R.) after 2 hr following the administration of R_o3-3528 (50, 100, 125 and 150 mg) and propranolol (20 and 40 mg). Significant differences ($P<0.05$) from the pre-drug resting pulse rates were shown with all doses used.

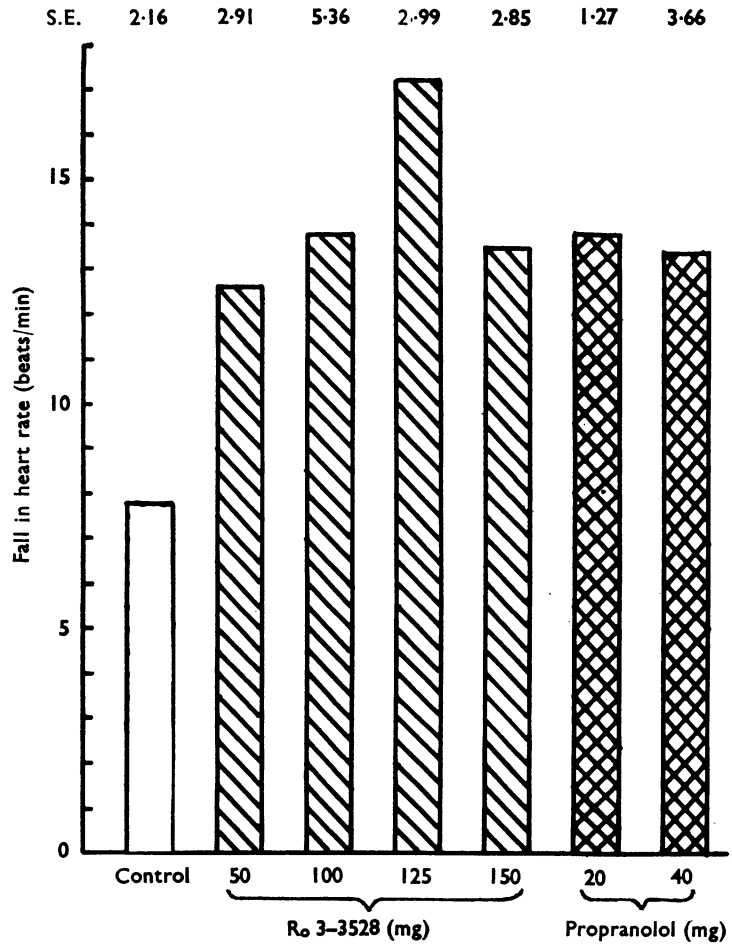

Fig. 1. Mean fall in resting heart rate (beats/min ± S.E.) in six subjects 2 hr after oral administration of placebo, R_o3-3528 (50, 100, 125 and 150 mg) and propranolol (20 and 40 mg).

If, however, the fall in R.P.R. after 2 hr in the control subjects is subtracted from the fall in R.P.R. after 2 hr after the administration of each treatment, then the mean difference in fall in R.P.R. between controls and each treatment can be plotted (Fig. 2).

When the results are expressed in this manner only one treatment (R_o3-3528 125 mg) produced a significant decrease over the control fall, but the resting rate with this dose (Table 1) was higher than with the other treatments and this may have produced an anomalous result.

Figure 3 shows the maximum pulse rate in beats/min (± S.E.) following inhalation of a 2% isoprenaline aerosol 2 hr after oral administration of R_o3-3528 (50, 100, 125 and 150 mg) and propranolol (10, 20 and 40 mg). A graded response was obtained, propranolol 40 mg being the most effective in inhibiting isoprenaline-induced tachycardia.

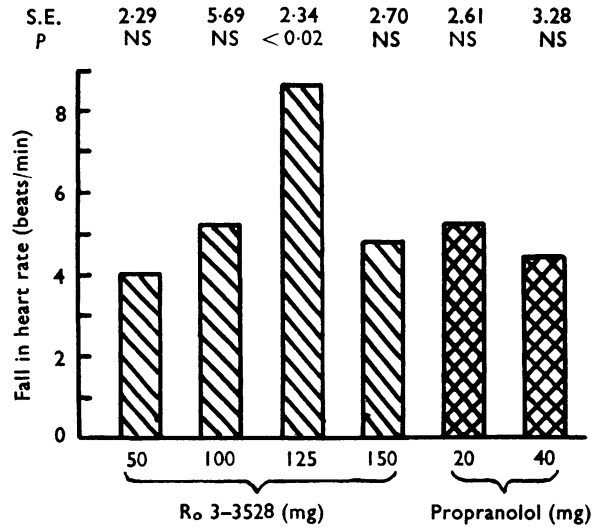

Fig. 2. Mean difference in fall in resting heart rate (beats/min ± S.E.) between placebo, $R_0$3-3528 (50, 100, 125 and 150 mg) and propranolol (20 and 40 mg) 2 hr after oral administration ($n=6$).

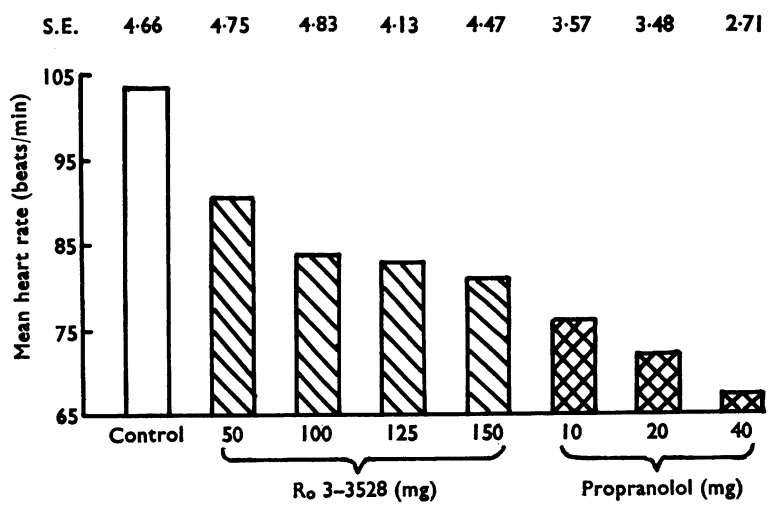

Fig. 3. Mean maximum heart rate in eight subjects (beats/min ± S.E.) following a standard inhalation of 2% isoprenaline solution 2 hr after oral administration of placebo, $R_0$3-3528 (50, 100, 125 and 150 mg) and propranolol (10, 20 and 40 mg).

The differences in maximum pulse rate between each dose of drug and all other doses was determined and the mean difference tested for statistical significance. The results are tabulated in Table 2.

TABLE 2

P VALUES FOR DIFFERENCES IN INCREASED HEART RATE INDUCED BY ISOPRENALINE IN EIGHT SUBJECTS AFTER PRETREATMENT WITH $R_0$3–3528 (50, 100, 125, 150 mg) AND PROPRANOLOL (10, 20, 40 mg) WHEN COMPARED WITH EACH OTHER AND CONTROL VALUES

	$R_0$3–3528				Propranolol		
Control	50	100	125	150	10	20	40
Control	<0·01	<0·01	<0·01	<0·01	<0·01	<0·001	<0·001
	50	<0·05	<0·05	<0·05	<0·01	<0·01	<0·001
		100	N.S.	N.S.	N.S.	<0·02	<0·01
			125	N.S.	<0·02	<0·001	<0·001
				150	<0·05	N.S.	<0·01
					10	N.S.	<0·05
						20	N.S.

All doses showed a significant fall in mean maximum pulse rate from the untreated control and also from the 50 mg dose of $R_0$3-3528. It was also evident that 10 mg of propranolol was about as potent as 100–150 mg of $R_0$3-3528 in inhibiting isoprenaline-induced tachycardia.

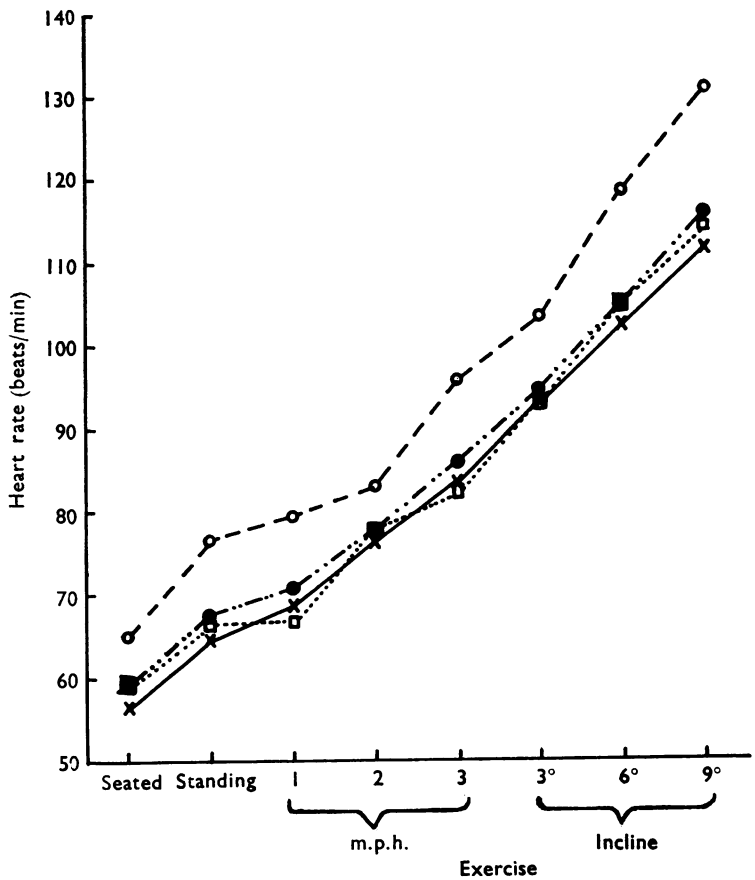

Fig. 4. Mean heart rate (±S.E.) in six subjects (beats/min) at rest, standing, and at the end of each of six consecutive 2 min periods of exercise 2 hr after oral administration of placebo (○----○); $R_0$3-3528 (100 mg) (●----●); $R_0$3-3528 (150 mg) (□·····□); propranolol (40 mg) (×——×).

Figure 4 shows the mean pulse rate in beats/min (±S.E.) plotted at the various exercise levels.

From Table 3 it can be seen that there is a statistically significant difference ($P<0.05$) between the pulse rate of the control and treated subjects. There was no statistically significant difference between the increase in pulse rate produced by any of the drugs at any of the exercise levels.

TABLE 3

DIFFERENCE AT 2 HR IN MEAN PULSE RATES (BEATS/MIN ± S.E.) AT INCREASING EXERCISE LOADS BETWEEN PLACEBO AND R_o3–3528 (100 AND 150 mg) AND PROPRANOLOL (40 mg) ($n=6$)

Treatment		Exercise level: Rest	Stand	1 m.p.h.	2 m.p.h.	3 m.p.h.	3°	6°	9°
Propranolol 40 mg	Diff.	8·2	12·0	10·7	6·7	12·7	10·7	15·8	18·4
	± S.E.	4·71	5·84	4·32	2·89	3·66	4·04	1·79	3·26
	P	≃0·05	N.S.	N.S.	N.S.	<0·02	<0·05	<0·001	<0·01
R_o3–3528 100 mg	Diff.	5·7	9·2	8·8	5·5	10·0	9·0	13·7	14·4
	± S.E.	3·39	2·99	2·05	3·7	3·50	3·70	4·23	4·09
	P	N.S.	<0·05	<0·02	N.S.	<0·05	≃0·05	<0·05	<0·02
R_o3–3528 150 mg	Diff.	7·7	9·5	12·1	5·3	13·3	10·3	13·5	16·3
	± S.E.	3·18	4·28	1·18	2·05	3·15	3·06	3·15	2·64
	P	N.S.	N.S.	<0·001	≃0·05	<0·01	<0·05	<0·01	<0·01

DISCUSSION

Results obtained from animal experiments indicate that the compound R_o3-3528 is a potent adrenaline antagonist with a selective action on adrenoceptive beta receptors (Haefely, Hürlimann & Thoenen, 1967). The findings in this paper are based on preliminary investigations of the actions of R_o3-3528 on the heart rate in man in three experimental situations, and seem to confirm the results in animals. Haefely *et al.* (1967) found that in dogs R_o3-3528 in doses of up to 3 mg/kg orally had no significant effect on the resting heart rate. In man, however, a small fall was observed after oral administration of R_o3-3528 (50, 100, 125 and 150 mg) that was maximal at 2 hr. The greatest fall was only 8.6 beats/min more than the control fall and even this seems to be an anomalous value, probably resulting from the use of too few subjects. The chances of locating a statistically significant graded effect within the range 0–8.6 beats/min are remote when the number of subjects used is only six.

In the unanaesthetized dog with a chronically implanted catheter, increasing oral doses of R_o3-3528 had a graded effect on the amount of intravenous isoprenaline necessary to produce a standard increase in heart (Haefely *et al.*, 1967). At the higher dose levels of R_o3-3528, a 300% increase in dose required a 25% increase in isoprenaline to overcome the blockade.

In man, R_o3-3528 administered orally had a graded antagonistic effect on isoprenaline-induced tachycardia with a maximal action between 100–150 mg (1.3–2 mg/kg). Comparison with another beta receptor blocking drug propranolol indicated that R_o3-3528 was about 1/10–1/15 as active in this experimental situation. The resting pulse rates of the subjects just before isoprenaline inhalation showed falls consistent with those recorded in the resting heart rate experiment.

Tachycardia induced by exercise produced results similar to those obtained in unanaesthetized dogs (Haefely *et al.*, 1967). Both doses of R_o3-3528 used produced a statistically significant ($P<0.05$) fall in heart rate from the control values. They were, however, not significantly different from each other or from a dose of propranolol (40 mg) which was used for comparison. There was a tendency for an order of potency to be emerging at the more severe levels of exercise but many more subjects would be necessary before any definite judgement could be made. If results from previous experiments (Chamberlain, Turner & Sneddon, 1967) using this exercise technique are considered, it can be seen that 80 mg of propranolol administered orally does not produce any greater fall in the heart rate than the dose of 40 mg, either at rest or during any of the exercise periods. A maximal inhibitory effect on exercise-induced tachycardia is therefore seen with doses of 40 mg of propranolol and 100 mg of R_o3-3528.

A maximal effect on isoprenaline-induced tachycardia was also obtained using 40 mg of propranolol. The chief difficulty in obtaining a meaningful dose response relationship in exercise tachycardia is that the difference between control and maximum drug effect is so small. An increase in heart rates of more than 30 beats/min can be obtained after isoprenaline, however, and degrees of inhibition can be readily measured. It would appear, therefore, that the isoprenaline-induced tachycardia technique is the most sensitive to demonstrate a dose response relationship. It must be remembered, however, that it is an artificially induced situation unlike that involving exercise. How these results compare with those obtained in patients with various cardiovascular disorders remains to be seen but it seems that both the isoprenaline-induced and exercise-induced tachycardia techniques are of use in the preliminary investigations of the effects of beta adrenoceptive receptor blocking drugs on the heart whereas the resting heart rate method is of rather limited value because of the small changes involved, and hence the large number of subjects necessary to obtain a meaningful result.

SUMMARY

1. Three methods are described for investigating the actions of a new beta adrenoceptive receptor blocking drug R_o3-3528 on the heart rate in man.

2. No significant dose response effect was produced on the resting pulse rate with either R_o3-3528 or propranolol. The insensitivity of this method probably results in part from the small changes observed and the small number of subjects used.

3. A graded dose-response effect was observed with both R_o3-3528 and propranolol on the inhibition of isoprenaline-induced tachycardia. Results show that on this test R_o3-3528 is between 1/10 and 1/15 as active as propranolol.

4. There was no significant difference between the effect of R_o-3-3528 (100 mg) and propranolol (40 mg) in inhibiting exercise-induced tachycardia.

5. These results indicate that because large changes in pulse rates are obtained and because meaningful dose-response relationships can be demonstrated, the isoprenaline-induced tachycardia technique seems to be the most sensitive method of the three which have been described.

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