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Comparison of the effects of I.C.I. 50172 and propranolol on the cardiovascular responses to adrenaline, isoprenaline and exercise

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1. The intravenous infusion of I.C.I. 50172 in doses up to 20 mg reduced, although not significantly, the increase in heart rate produced by the infusion of isoprenaline in healthy volunteers; the response to adrenaline was significantly reduced. The infusion of 1 mg propranolol abolished these responses

2. After the pre-treatment of subjects with atropine or hexamethonium, I.C.I. 50172 produced a significant reduction in an isoprenaline tachycardia. This reduction was not competitive and did not exceed 50%.

3. The intravenous injection of 4 mg I.C.I. 50172 reduced an exercise tachycardia; its effect was less than that of 4 mg propranolol. This difference became greater as the doses of the two drugs were increased. The dextro isomer of propranolol had no effect on the exercise tachycardia; I.C.I. 45763 reduced it to the same extent as propranolol.

4. The intravenous injection of I.C.I. 50172 reduced the increase in heart rate produced by tilting a normal subject from the supine to 80° head-up position. After the administration of atropine, I.C.I. 50172 almost abolished the response. In the presence of atropine, I.C.I. 50172 was as active as propranolol in reducing the increase in heart rate on tilting.

5. The reason for the differences in the effects of I.C.I. 50172 on the increases in heart rate brought about by the three procedures is not clear.

6. The increase in forearm blood flow produced by the infusion of isoprenaline into the brachial artery was not reduced by the intra-arterial administration of I.C.I. 50172.

During the past 10 years several compounds have been described which block adrenergic β receptors. Although the properties of all these compounds have been clearly established in animal studies, detailed observations in man of their adrenergic blocking activity have only been made with pronethalol (Dornhorst & Robinson, 1962), propranolol (Brick, Glover, Hutchison & Roddie, 1966; Harris, Schoenfeld, Brooks & Weissler, 1966), and to a lesser extent with I.C.I. 45763

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(Shanks, Wood, Dornhorst & Clark, 1966) and H 56/28 (Johnson, Norrby, Solvell & Ablad, 1966). These compounds have adrenergic β receptor blocking activity in man, for they reduce or abolish the cardiac chronotropic and the peripheral vasodilator action of adrenaline and isoprenaline. Propranolol has been shown to be effective in the treatment of angina pectoris, various cardiac arrhythmias and hypertension, but is contraindicated in patients with obstructive airways disease because it blocks sympathetic bronchodilator activity and may lead to a worsening of their condition (McNeill & Ingram, 1966).

A new compound, I.C.I. 50172 [4-(2-hydroxy-3-isopropyl-aminopropoxy) acetanilide], has become available. In animals it blocks adrenergic β receptors in the heart but not in the smooth muscle of the bronchi or peripheral blood vessels (Dunlop & Shanks, 1968). On this basis I.C.I. 50172 may be of value in patients who have airway obstruction but who require an adrenergic β receptor blocking compound for angina or control of an arrhythmia. Initially it is necessary to determine the activity of this compound in blocking adrenergic β receptors in man. In this paper we describe the effects of I.C.I. 50172 on the cardiovascular actions of adrenaline and isoprenaline and on the changes in heart rate produced by exercise and by tilting, and compare these with the effects of propranolol. Some of these results have been described to the British Pharmacological Society (Brick, Hutchison, Roddie & Shanks, 1968).

Methods

Observations were made on healthy subjects who volunteered their help.

Infusions of catecholamines

Forearm blood flow was measured using water filled plethysmographs (Greenfield, 1954), and the limb volume changes were measured using a Statham pressure transducer (P23 BB) as described by Hyman & Windsor (1966). Arterial blood pressure was measured intermittently through a catheter in the left brachial artery connected to a Statham pressure transducer (P23 AA). The length of the catheter was adjusted to give approximately 64% critical damping (Cliffe, 1966). Instantaneous heart rate was measured using a cardiotachometer triggered by the *R* wave of the electrocardiogram. The output from the tachometer was integrated electrically over 30-sec periods and was recorded on another channel. Recordings of the experiments were made on a Beckman Type R Dynograph. Dilutions of the drugs were prepared in a mixture of ascorbic acid (0.003%) and saline (0.9%) and infused intravenously or intra-arterially using a mechanically driven syringe.

Exercise studies

Lead 11 of the electrocardiogram was recorded on a direct writing electrocardiograph (Cardiomat, Siemens) at a paper speed of 25 mm/sec. The heart rate was obtained by determining the time taken for five complete cardiac cycles. Heart rate was recorded with the subject standing, before and within 7 sec of completion of a 3-min period of exercise which consisted of stepping on and off a box 15 in. (38 cm) high at the rate of 30 times/min. The subjects rested for 25 min between each period of exercise. On each day the subjects exercised six times. The first two runs were used to familiarize him with the exercise. Five minutes before the third period of exercise heart rate was recorded and 5 ml. of saline injected intra-

venously. Heart rate was recorded before and after exercise. The same procedure was used during the three succeeding periods of exercise when the test drugs were administered. Drugs were injected intravenously over a period of 2–3 min.

Tilt studies

The subjects were placed on a tilt table and heart rate measured as in the exercise studies. Heart rate was recorded with the subject in the supine position. He was then tilted to the position of 80° head up to the horizontal. Heart rate was recorded until it had become constant, when he was returned to the supine position. There was an interval of 10 min between each tilting. Each subject was tilted 2–3 times before any observations were made to familiarize him with the procedure. Drugs were injected intravenously.

The following drugs were used: (±)-propranolol ("Inderal," Imperial Chemical Industries), (+)-propranolol (Imperial Chemical Industries), (±)-I.C.I. 50172, (±)-I.C.I. 45763—all as the hydrochloride; (−)-adrenaline hydrochloride (British Drug Houses); (±)-isoprenaline sulphate (Boots); atropine sulphate (British Drug Houses); hexamethonium bromide ("Vegolysin," May and Baker). All drugs were administered as the salt. Doses are expressed in terms of the salt with the exception of adrenaline, isoprenaline and atropine, which are expressed in terms of the base.

Results

Responses to the intravenous infusion of adrenaline

In six subjects adrenaline was infused at 5 μg/min for 3 min and 4 min later at 10 μg/min for 3 min. The responses to adrenaline were recorded before and 5 min after the intravenous administration of 5 mg and 20 mg of I.C.I. 50172 in three subjects, and before and after 1 mg of propranolol in three subjects. I.C.I. 50172 and propranolol were infused intravenously during a 5-min period. The average results are given in Fig. 1 and those for I.C.I. 50172 in Table 1. Although the administration of 5 mg of I.C.I. 50172 reduced resting heart rate, it did not affect the increase in heart rate produced by adrenaline. After 20 mg, the increase produced by adrenaline 5 μg/min was significantly reduced; the effect of 10 μg/min was also reduced but not significantly. The increase in forearm blood flow in response to adrenaline was still obtained afer the two doses of I.C.I. 50172. Adrenaline produced little change in arterial pressure before or after the blocking compound. The administration of adrenaline after 1 mg of propranolol decreased heart rate and forearm blood flow, and increased systolic and diastolic arterial pressure (Fig. 1).

Responses to the intravenous infusion of isoprenaline

The intravenous infusion of isoprenaline, 3.0 μg/min for 3 min, increased heart rate and forearm blood flow and reduced arterial diastolic pressure (Fig. 2). The effects of the intravenous infusion of I.C.I. 50172, given over a period of 5 min, on these responses in five subjects are given in Fig. 2 and in Table 1. After 5 mg of I.C.I. 50172, the increase in heart rate produced by isoprenaline was reduced but the change was not significant. Although there was no further reduction in the increase in heart rate after 20 mg of I.C.I. 50172, the maximum heart rate in response to isoprenaline was reduced from 83 to 75 beats/min due to a decrease in resting heart rate from 69 to 62 beats/min. A relationship between the resting heart rate and the response to isoprenaline has not been established, so we feel it

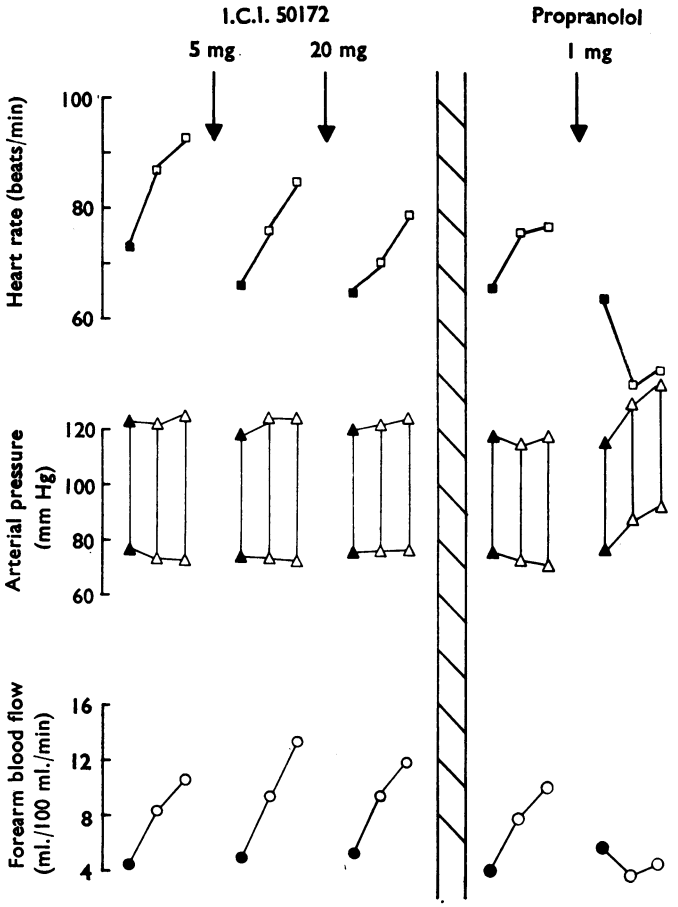

FIG. 1. Comparison of the effects of the intravenous infusion of I.C.I. 50172 and propranolol on the responses to adrenaline. Mean of observations in three subjects for each drug. Solid symbols denote resting levels; the first and second sets of open symbols denote the effect of the intravenous infusion of adrenaline at 5 and 10 μg/min respectively for 3 min.

TABLE 1. *Average changes in heart rate, systolic and diastolic arterial pressure and forearm blood flow produced by adrenaline in three subjects and isoprenaline in five subjects before and after 5 mg and 20 mg of I.C.I. 50172*

Changes produced by adrenaline 5 (Δ5) and 10 (Δ10) μg/min intravenously

	Control			I.C.I. 50172 5 mg			I.C.I. 50172 20 mg		
	R	Δ5	Δ10	R	Δ5	Δ10	R	Δ5	Δ10
Heart rate (beats/min)	73	14	20	66	10	19	65	5*	14
Systolic pressure (mm Hg)	123	−1	2	118	6	6	120	2	4
Diastolic pressure (mm Hg)	76	−3	−4	74	−1	−2	76	0	0
Forearm blood flow (ml./100 ml./min)	4·5	3·9	6·2	5·1	4·5	8·8	5·4	3·9	6·4

Changes produced by isoprenaline 3 μg/min intravenously

	Control		I.C.I. 50172 5 mg		I.C.I. 50172 20 mg	
	R	Δ	R	Δ	R	Δ
Heart rate (beats/min)	69	21	69	14	62	13
Systolic pressure (mm Hg)	129	−1	125	+4	134	−1
Diastolic pressure (mm Hg)	74	−11	76	−9	82	−8
Forearm blood flow (ml./100 ml./min)	6·2	3·9	6·2	2·3	5·3	2·9

* $P<0.05$. The resting values are included.

is more appropriate to compare the increase in rate produced by the drug rather than the maximum heart rate. I.C.I. 50172 did not affect the reduction in diastolic pressure produced by isoprenaline although the increase in forearm blood flow was reduced but not significantly after 5 mg with no further change after 20 mg. In contrast, the intravenous infusion of 1 mg of propranolol blocked the effects of isoprenaline (Fig. 2).

The effect of I.C.I. 50172 on the responses to isoprenaline was studied in four subjects pre-treated with atropine. The average results are given in Fig. 3 and in Table 2. The typical responses produced by the intravenous infusion of isoprenaline (3.0 μg/min for 3 min) were obtained before and after the intravenous infusion of 2.5 mg of atropine although there was a marked increase in resting heart rate after atropine. I.C.I. 50172 was then infused intravenously at 2 mg/min for 5 min and significantly reduced the increase in heart rate produced by the subsequent administration of isoprenaline, but without altering any of the other responses. Similar observations were made in three subjects in whom the responses to isopren-

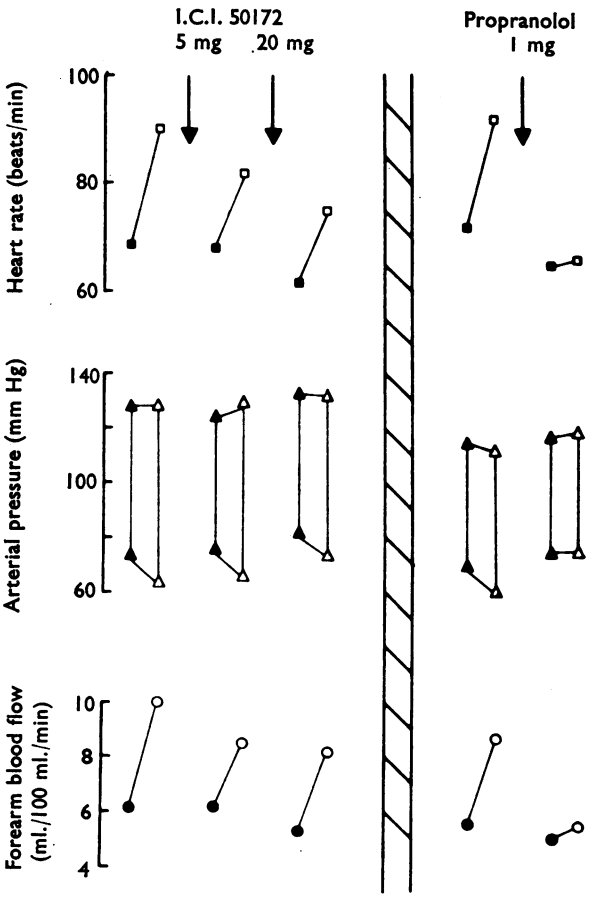

FIG. 2. Comparison of the effects of the intravenous infusion of I.C.I. 50172 and propranolol on the responses to isoprenaline. Mean of observations in five and three subjects respectively. Solid symbols denote resting levels and the open symbols denote the effect of the intravenous infusion of isoprenaline at 3 μg/min for 3 min.

aline were determined before and 20 min after the slow intravenous injection of 75–100 mg of hexamethonium. After the administration of 5 mg of I.C.I. 50172, the isoprenaline tachycardia was reduced significantly, but there was no further reduction after 20 mg. Both doses of I.C.I. 50172 had no significant effect on the changes is diastolic pressure and forearm blood flow produced by isoprenaline.

Responses to the intra-arterial infusion of isoprenaline

In three subjects the changes in blood flow to the left forearm produced by the infusion of isoprenaline at 0.0125 μg/min into the left brachial artery for 3 min were recorded before and after the intra-arterial infusion of I.C.I. 50172 at 5, 25, and 125 μg/min for 5 min. The mean increase in blood flow during the control infusion of isoprenaline was 5.2 ml./100 ml. forearm tissue/min and after the three doses of I.C.I. 50172 was 6.2, 3.5 and 4.6 ml./100 ml./min, respectively. It had previously been shown that the infusion into the brachial artery of propranolol at 1 μg/min for 5 min reduced by 78% the increase in forearm blood flow produced by the intra-arterial infusion of a much larger dose of isoprenaline (0.25 μg/min) than used in the present experiments (Brick, Hutchison & Roddie, unpublished work).

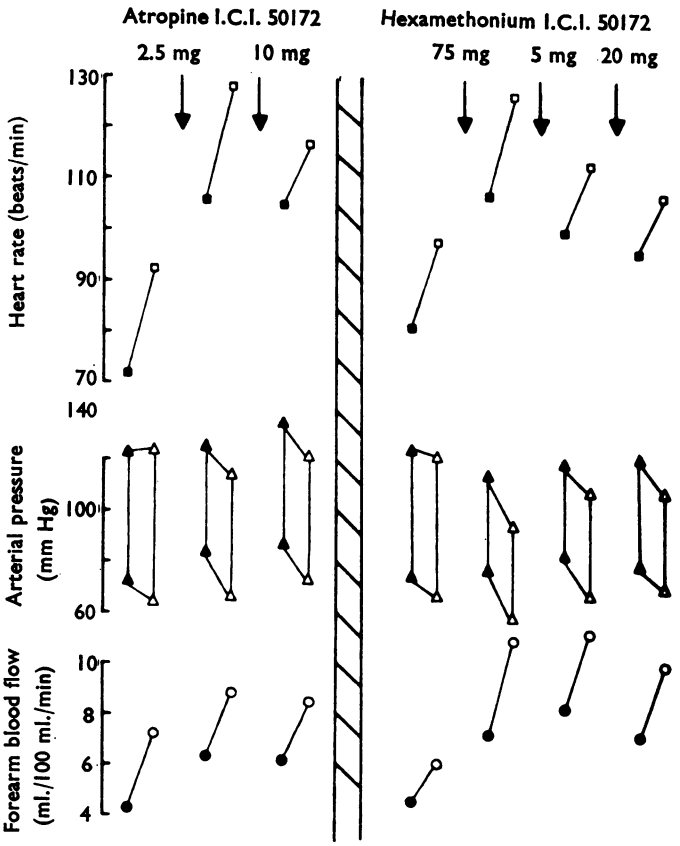

FIG. 3. Left-hand panel: Mean results from four subjects in which responses to isoprenaline were recorded before and after atropine and then after I.C.I. 50172. Symbols as in Fig. 2; all drugs were infused intravenously. Right-hand panel: Mean results from three subjects in which responses to isoprenaline were recorded before and after hexamethonium and then after two doses of I.C.I. 50172. Symbols as in Fig. 2; all drugs were infused intravenously.

Heart rate responses to exercise

The effects of the intravenous injection of three doses (4, 8 and 16 mg) of I.C.I. 50172 and of propranolol on the increase in heart rate produced by exercise were compared in five subjects. Observations were made on each subject on 2 different days; the drugs were administered in random order. The average results are given in Fig. 4 and in Table 3. There was little difference between the response to exercise on the control run and after the administration of saline on the 2 days. After 4 mg of each drug the increase in heart rate on exercise was reduced. The effect of propranolol was significantly greater than that of I.C.I. 50172 ($P<0.05$). After 8 and 16 mg of propranolol there were further reductions in the exercise heart rate. Although 8 mg of I.C.I. 50172 reduced the increase in heart rate on exercise to a greater extent than 4 mg, there was no further change after 16 mg. The difference between the effects of the two drugs was greater after 16 mg. Both drugs reduced resting heart rate to the same extent.

After completion of this comparison of I.C.I. 50172 and propranolol, the effects of 4, 8 and 16 mg of I.C.I. 45763 on resting and exercising heart rate was studied in the same five subjects. A strict comparison between the effects of the three drugs cannot be made because their administration was not randomized, resting heart rate

TABLE 2. *Average changes in heart rate, systolic and diastolic arterial pressure and forearm blood flow produced by isoprenaline*

(A)

	Control		After atropine		After I.C.I. 50172	
	R	Δ	R	Δ	R	Δ
Heart rate (beats/min)	72	20	106	21	105	11*
Systolic pressure (mm Hg)	123	1	125	−11	134	−13
Diastolic pressure (mm Ng)	73	−8	84	−18	87	−15
Forearm blood flow (ml./100 ml./min)	4·3	2·9	6·3	2·5	6·1	2·3

(B)

	Control		After hexamethonium		After I.C.I. 50172 (5 mg)		After I.C.I. 50172 (20 mg)	
	R	Δ	R	Δ	R	Δ	R	Δ
Heart rate (beats/min)	81	17	107	20	100	13†	96	11†
Systolic arterial pressure (mm Hg)	124	−2	114	−21	119	−12	120	−13
Diastolic arterial pressure (mm Hg)	74	−8	76	−21	82	−15	78	−10
Forearm blood flow (ml./100 ml./min)	4·1	1·6	7·1	3·8	8·1	3·0	7·0	2·8

* $P<0.02$. † $P<0.05$.

(A), changes produced in four subjects during a control period, after 2·5 mg atropine and then after 10 mg I.C.I. 50172; (B) changes produced in three subjects during a control period, after 75 mg hexamethonium and after 5 and 20 mg I.C.I. 50172. The resting values are included

TABLE 3. *Mean values from five subjects for the increase in heart rate produced by exercise after the intravenous injection of saline (control) and 4, 8 and 16 mg I.C.I. 50172, propranolol and I.C.I. 45763*

	Heart rate (beats/min)			
	Saline	4 mg.	8 mg	16 mg
I.C.I. 50172	70·2	55·8	50·2	51·0
Propranolol	67·0	43·6	39·2	36·4
I.C.I. 45763	58·4	48·0	41·6	35·4
Standard error of difference of means from two compounds	3·9	3·9	3·3	2·7

was greater and the increase in heart rate during the control exercise less when the subjects received I.C.I. 45763. The results which are given in Fig. 4 and in Table 3 suggest that there is probably no difference between the effects of 8 and 16 mg of I.C.I. 45763 and propranolol, but that there is a significant difference between the effects of these doses of I.C.I. 45763 and I.C.I. 50172 on the increase in heart rate on exercise.

Similar observations were made in four other subjects in which the effects of 4, 8 and 16 mg of D-propranolol on resting heart rate and on the increase produced by exercise were studied. The average results are given in Fig. 5 and show that D-propranolol had no effect on resting heart rate or on the increase produced by exercise.

Heart rate responses to tilting

Tilting a subject from the supine to the 80° head-up position increased heart rate. When this response had become constant in five subjects, 10 mg of I.C.I. 50172 was injected intravenously. When the subjects were tilted 5 min later, heart rate increased but the increase was significantly less than in the control period (Table 4). There was little further change in the increase in heart rate on tilting after the administration of 20 mg of I.C.I. 50172 (Table 4). In five different subjects, 2.4

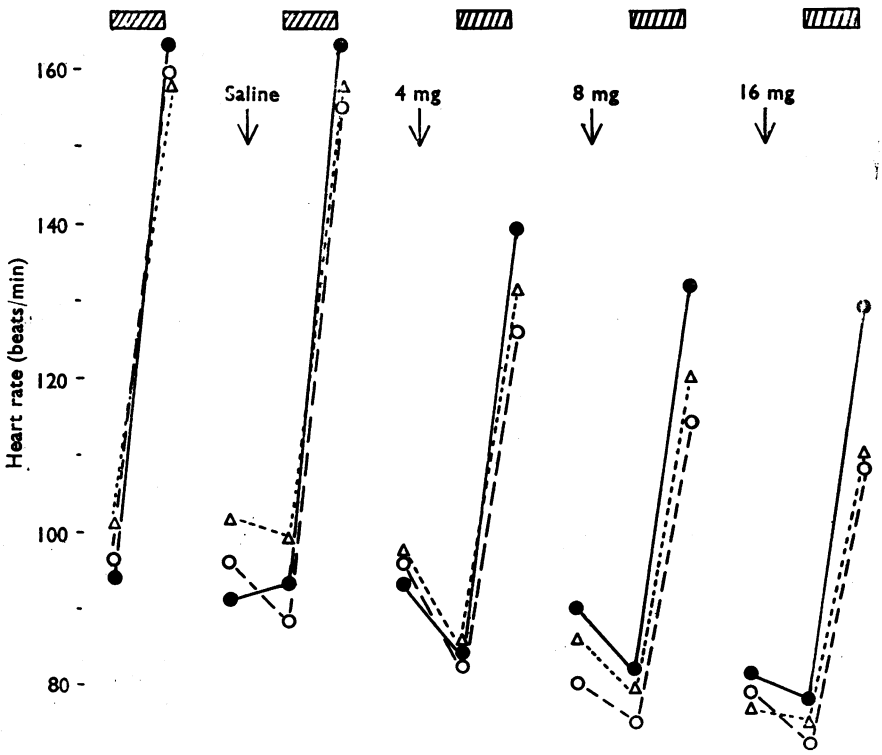

FIG. 4. Comparison of the effects of the intravenous injection of saline and of three doses of I.C.I. 50172 (●——●), propranolol (○- - -○) and I.C.I. 45763 (△- - -△) on heart rate at rest and at the end of a 3-min period of exercise (▨). Mean of observations in five subjects who received each drug on separate occasions. The left-hand set of responses were obtained during a control run.

mg of atropine was injected intravenously after obtaining the control response to tilting. Five minutes later resting heart rate was increased but on tilting there was a further increase in heart rate (Table 4). Five minutes after returning to the supine position 20 mg of I.C.I. 50172 was injected intravenously. When the subjects were again tilted the increase in heart rate was markedly reduced.

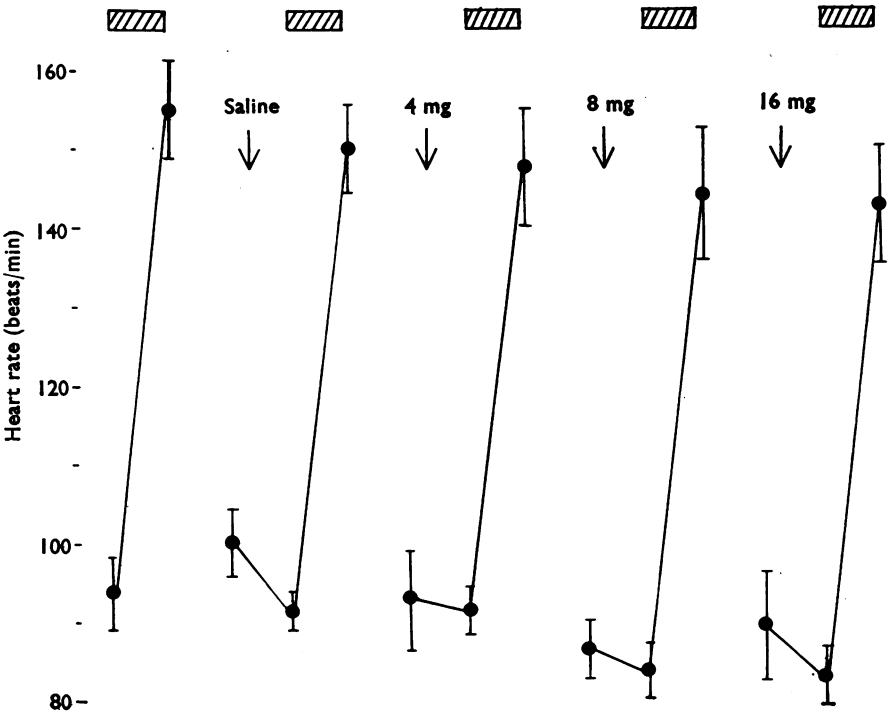

FIG. 5. Effects of the intravenous injection of saline and of three doses of D-propranolol on heart rate at rest and at the end of a 3-min period of exercise (▨). Mean of observations in four subjects; standard errors of the mean are included. The left-hand set of responses were obtained during a control run.

TABLE 4. *Increases in heart rate produced by tilting subjects from the supine to 80° head-up position*

(A) Effect of I.C.I. 50172 (10 mg and 20 mg)

No. of subjects	Control		After 10 mg		After 20 mg	
	Supine	Δ	Supine	Δ	Supine	Δ
5	60	28	59	19*	57	17*

(B) Effect of I.C.I. 50172 (20 mg) administered after atropine (2·4 mg)

No. of subjects	Control		After atropine		After I.C.I. 50172	
	Supine	Δ	Supine	Δ	Supine	Δ
5	62	25	116	19	110	6*

C) Comparison of effects of I.C.I. 50172 (25 mg) and atropine (2·4 mg) and of propranolol (15 mg) and atropine (2·4 mg) on the increase in heart rate on tilting in four subjects studied on two separate occasions

Control		After I.C.I. 50172 and atropine		Control		After propranolol and atropine	
Supine	Δ	Supine	Δ	Supine	Δ	Supine	Δ
57	29	115	4*	56	27	104	3*

* $0{\cdot}02 > P > 0{\cdot}01$.

The effects of I.C.I. 50172 and propranolol on the increase in heart rate on tilting were compared in four subjects who received each drug on different days. The effects of alterations in parasympathetic activity were greatly reduced by administering 2.4 mg of atropine along with I.C.I. 50172 and propranolol. The averaged results are given in Table 4. If it is assumed that the action of atropine was the same when given with the other two drugs, these results indicate that 25 mg of I.C.I. 50172 had the same effect as 15 mg of propranolol on the increase in heart rate on tilting.

Effect of I.C.I. 50172

The average resting values for heart rate, systolic and diastolic arterial pressure and forearm blood flow were determined in those subjects in whom they were measured before, and 5 min after, completion of the administration of each dose of I.C.I. 50172 or propranolol. These results are given in Table 5. In the normal subjects and in those pre-treated with hexamethonium, 20 mg of I.C.I. 50172 produced a significant reduction in resting heart rate. Although 5 mg reduced heart rate, the change was not significant. I.C.I. 50172 had no effect on arterial blood pressure or forearm blood flow. Propranolol (1 mg) had no effect on any of the parameters measured.

Discussion

In anaesthetized dogs and cats, I.C.I. 50172 produced competitive inhibition of the increases in heart rate elicited by isoprenaline and adrenaline (Dunlop & Shanks, 1968). I.C.I. 50172 had about one fourth the activity of propranolol in reducing these responses. In conscious dogs, I.C.I. 50172, unlike propranolol, had much less effect on isoprenaline tachycardia. To account for the difference between the effects of I.C.I. 50172 in conscious and anaesthetized dogs, it has been suggested that the

TABLE 5. *Effect of I.C.I.* 50172 *in (a) normal subjects, (b) after atropine* (3.0 *mg) and (c) after hexamethonium* (100 *mg) and of propranolol on resting heart rate, systolic and diastolic arterial pressure and forearm blood flow (averaged results)*

I.C.I. 50172

	(a) Normal subjects (number shown in brackets)			(b) After atropine Four subjects			(c) After hexamethonium Three subjects			
	Control	After 5 mg	After 20 mg	Control	After atropine	After 10 mg	Control	After hexamethonium	After 5 mg	After 20 mg
Heart rate (beats/min)	74 (12)	71 (10)	66 (10*)	72	106	105	81	107	100	96*
Systolic pressure (mm Hg)	127 (8)	122 (6)	128 (7)	123	125	134	124	114	119	120
Diastolic pressure (mm Hg)	75 (8)	75 (6)	79 (7)	73	84	87	74	76	82	78
Forearm blood flow (ml./100 ml./min)	5·6 (8)	5·6 (6)	5·5 (7)	4·3	6·3	6·1	4·5	7·1	8·2	7·0

Propranolol (six subjects)

	Control	After 1·0 mg
Heart rate (beats/min)	66	65
Systolic pressure (mm Hg)	116	117
Diastolic pressure (mm Hg)	74	76
Forearm blood flow (ml./100 ml./min)	4·7	4·8

* $P<0.05$.

increase in heart rate in response to isoprenaline in conscious dogs results from two mechanisms—a direct effect of the drug on the sino-atrial node and a reflex reduction in vagal inhibition in response to the fall in arterial pressure produced by isoprenaline (Barrett, Crowther, Dunlop, Shanks & Smith, 1968; Dunlop & Shanks, 1968). Because I.C.I. 50172 did not block the latter effect, it only produced a partial reduction in the isoprenaline tachycardia. Propranolol abolished the direct effect and the reflex effect and thus completely prevented the increase in heart rate. After treatment of conscious dogs with atropine or pempidine to abolish the reflex component of the isoprenaline tachycardia, I.C.I. 50172 produced almost complete blockade of the action of isoprenaline on the heart. In these conditions its activity was about one fourth that of propranolol (Barrett *et al.*, 1968; Dunlop & Shanks, 1968).

In the present experiments in man, 5 mg and 20 mg of I.C.I. 50172 reduced the increases in heart rate in response to isoprenaline although the changes were not significant. After the administration of atropine or hexamethonium in amounts which were probably large enough to abolish vagal and reflex effects on the heart (Chamberlain, Turner & Sneddon, 1967), I.C.I. 50172 produced a significant reduction in the isoprenaline tachycardia although the decrease was less than 50%. Increasing the amount of I.C.I. 50172 administered to 20 mg did not increase the antagonism of the isoprenaline tachycardia. From the present experiments the activity of propranolol and I.C.I. 50172 on an isoprenaline tachycardia in man could not be compared accurately but the results suggest that the former is at least 20 times more active.

Studies with four conventional β receptor blocking compounds, pronethalol, propranolol, I.C.I. 45763 and H 56/28, have shown that these block the cardiac actions of isoprenaline in animals and in man, and from the results it would appear that their ratios of activity are similar in both species (Black, Crowther, Shanks, Smith & Dornhorst, 1964; Shanks *et al.*, 1966; Forsberg & Johnston, 1967). The reason for the difference in the effects of I.C.I. 50172 on the increases in heart rate produced by isoprenaline in man and animals is not clear. In anaesthetized dogs and in conscious dogs treated with pempidine, I.C.I. 50172 produced competitive inhibition of the chronotropic action of isoprenaline. This did not occur in the present experiments in man either in normal conditions or after hexamethonium. In one subject treated with hexamethonium, the administration of 50 mg of I.C.I. 50172 reduced an isoprenaline tachycardia to the same extent as 5 mg. These observations indicate that I.C.I. 50172 can reduce the chronotropic effects of isoprenaline in man, but it is not clear why the dose-response curve is so much flatter than that of propranolol.

The effects of I.C.I. 50172 on the increase in heart rate produced by adrenaline were similar to its effects on an isoprenaline tachycardia. In the present experiments the infusion of adrenaline increased heart rate, but little change in arterial pressure occurred. After 1 mg of propranolol, the effect of adrenaline on the heart was blocked and a bradycardia occurred. This can be attributed to a reflex increase in vagal activity (Glick & Braunwald, 1965) in response to the increase in arterial pressure which adrenaline produced as a result of propranolol blocking its peripheral vasodilator but not its vasoconstrictor action (Brick *et al.*, 1966). I.C.I. 50172 did not convert the effect of adrenaline on arterial pressure to a pressor response, so there was no reflex increase in vagal activity. Thus it is difficult to

compare accurately the effects of I.C.I. 50172 and propranolol on the chronotropic action of adrenaline in man, but it would appear that the former is much less active.

In contrast to its small effect on a catecholamine-induced tachycardia, I.C.I. 50172 had a much greater effect on the increase in heart rate produced by exercise. The tachycardia that occurs during severe muscular exercise results from a reduction in vagal activity, an increase in sympathetic activity and a non-nervous mechanism which has not yet been defined (Donald & Shepherd, 1965 ; Jose, 1966 ; Chamberlain *et al.*, 1967). The reduction in an exercise tachycardia produced by propranolol has been attributed to blockade of cardiac β receptor, for a similar effect is obtained by cardiac sympathectomy (Chamberlain, 1966). The present observations support this view and show that the local anaesthetic or quinidine-like action of propranolol (Morales-Aguilerá & Vaughan Williams, 1965 ; Levy & Richards, 1966), does not contribute to this effect because the dextro isomer had no effect on an exercise tachycardia. The dextro isomer has been shown to have little β blocking action, but has local anaesthetic and quinidine-like properties (Howe & Shanks, 1966 ; Brick, Hutchison & Roddie, unpublished ; Levy & Richards, 1966).

The effects of I.C.I. 50172 and propranolol on the exercise tachycardia differed. Although 4 mg of I.C.I. 50172 reduced the tachycardia, its effect was significantly less than that of propranolol. This difference between the effects of the two drugs became greater as the dose of each was increased, and thus it did not arise simply from I.C.I. 50172 being less active than propranolol. The greater effect of propranolol on the exercise response was not due to its local anaesthetic action, which is not possessed by I.C.I. 50172 (Dunlop & Shanks, 1968). The intrinsic sympathomimetic action of I.C.I. 50172 (Dunlop & Shanks, 1968) did not appear to account for the difference, as I.C.I. 45763 has this property (Shanks *et al.*, 1966) and it reduced an exercise tachycardia to a greater extent than I.C.I. 50172.

The dose-response curve in animals for I.C.I. 50172 for antagonism of catecholamine-induced changes in heart rate was much flatter than that for propranolol. As the reduction in an exercise tachycardia produced by I.C.I. 50172 and propranolol was due to blockade of adrenergic β receptors, the difference between the effects of the two drugs may to some extent arise from differences in the slopes of their dose-response curves.

The increase in heart rate on tilting a subject to the head-up position is reduced by propranolol and almost abolished by a combination of atropine and propranolol (Robinson, Epstein, Beiser & Braunwald, 1966), and thus arises from a combination of reduction in vagal activity and increase in sympathetic activity to the heart. In the present study the effect of I.C.I. 50172 on the response to tilting was the same as that described by Robinson *et al.* (1966) for propranolol. A comparison of the two drugs in a cross-over study in four subjects, who were given atropine to abolish the action of the vagus (Chamberlain *et al.*, 1967), showed that 25 mg of I.C.I. 50172 reduced the increase in heart rate on tilting to the same extent as 15 mg of propranolol. Allowing for the difference in dose, these observations indicate that I.C.I. 50172 is as active as propranolol in blocking the stimulation of cardiac adrenergic β receptors produced by changes in posture.

These studies show that I.C.I. 50172 blocked stimulation of adrenergic β receptors in the heart. Its activity, unlike that of propranolol, varied with different types of stimulation. Its effect was most marked on the increase in heart rate produced by tilting and least on the chronotropic action of catecholamines. The reason for the

differences in the effects of I.C.I. 50172 on the three types of response is not known. These observations indicate that the assessment in man of an adrenergic β receptor blocking agent must not be confined to a study of its effect on one type of response.

In animals I.C.I. 50172 did not block adrenergic β receptors in peripheral blood vessels, for it did not affect the fall in arterial diastolic pressure or the vasodilatation in the hind-limb of the dog produced by isoprenaline (Dunlop & Shanks, 1968). Most of the evidence in the present experiments in man confirm that I.C.I. 50172 does not block β receptors in the blood vessels of the human forearm. When given intra-arterially it had little effect on the vasodilatation produced by intra-arterial isoprenaline. In subjects treated with atropine or hexamethonium, I.C.I. 50172 given intravenously, in a dose which reduced the cardiac chronotropic response to isoprenaline did not reduce its peripheral vasodilator action. I.C.I. 50172 did not block the peripheral adrenaline vasodilatation. I.C.I. 50172 did, however, cause a slight reduction in the peripheral vasodilatation produced by the intravenous infusion of isoprenaline in subjects who had not been treated with atropine or hexamethonium.

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