Effects of I.C.I. 50172 in Man during Erect Exercise

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Brit. med. J., 1968, **1**, 213–215

Preliminary observations on the drug I.C.I. 50172 (4-(2-hydroxy-3-isopropylaminopropoxy) acetanilide) have shown it to block isoprenaline-induced tachycardia in the experimental animal (Barrett *et al.*, 1968) and also in normal volunteers (Brick *et al.*, 1968). In this paper we report the haemodynamic effects in man of the intravenous administration of 5 mg. of I.C.I. 50172 during submaximal exercise.

Materials and Methods

Observations were made on 10 patients whose ages ranged from 19 to 60. All had been referred for an exercise test, the indication being atypical chest pain in six and a systolic murmur in the others. Two patients had trivial pulmonary stenosis, with a gradient of 10–15 mm. Hg across the valve, and one had very slight aortic incompetence. The others had no demonstrable haemodynamic abnormality.

The present investigation was performed immediately after the diagnostic exercise study. Before proceeding, the nature and purpose of the investigation was explained to the patients, and their permission was sought before the drug was administered.

Right heart pressures were measured in six patients through a fine nylon catheter, which was introduced percutaneously into an arm vein and advanced to the pulmonary artery. In the three patients with minor valve lesions a No. 8 twin-lumen catheter was introduced and a routine right heart pressure and sample run performed before the start of the study. The catheter was then positioned with its tip impacted in the pulmonary capillary wedge position. Systemic arterial pressures were recorded through Teflon tubing (internal diameter 1.1 mm., external diameter 1.6 mm.) introduced into the brachial artery by the Seldinger technique, and advanced approximately 30 cm. to the subclavian artery.

Pressures were measured with Consolidated Electrodynamics strain-gauge transducers (type 4-326-L212) and a Sanborn (964) four-channel direct-writing recorder. The zero level for pressure measurement was taken as the insertion of the fourth rib into the sternum. Mean pressures were derived by electrical integration. The pulse rate was determined from an E.C.G. recorded simultaneously with the pressures.

Cardiac output was determined by the dye dilution technique. Indocyanine green (5 mg.) was injected into the right atrium or the pulmonary artery. Arterial blood was withdrawn from the brachial artery catheter by a Kipp and Zonen constant-rate pump through a Gilford densitometer cuvette, feeding a Honeywell wide-chart recorder.

The patients were exercised erect throughout the test on an Elema-Schönander bicycle ergometer. For the single patient who developed angina of effort in the initial exercise test, a level of 100 kpm./min. was used, while all the others exercised at 200 or 300 kpm./min. for approximately 15 minutes. Control pressure and cardiac output measurements were made two and four minutes after the start of exercise, and at five minutes 5 mg. of I.C.I. 50172 was given intravenously. Further measurements were made at two-minute intervals over the next 10 minutes.

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One patient proved to have angina of effort, the pain being provoked by a total work load of 1,200 kpm., and his results have therefore been excluded from the final analysis. One further patient experienced a feeling of heat in the arms after only 2 mg. of the drug had been given. The injection was stopped and the sensation passed off in less than a minute. The investigation was completed, but showed no haemodynamic changes. Since the full dose was not given, this patient's results have not been included in the analysis. Though directly questioned, none of the other patients experienced any subjective symptoms after administration of the drug.

Results

Resting Values.—There was no significant difference between measurements made two minutes and four minutes after the start of exercise. The mean of these two values was used in the calculation of the significance (Student's *t* test) of any change after administration of the drug.

Pulse Rate.—In all the patients there was a reduction in the pulse rate, which was apparent within two minutes of giving the drug. After four to six minutes it averaged 17 beats per minute (14%) and persisted until the end of the investigation ($P<0.01$).

Blood Flow.—The stroke volume rose in seven out of the eight patients, so that the cardiac output did not change significantly. The increase in stroke volume was statistically significant from two minutes after the administration of the drug until the end of the investigation ($P<0.01$).

Left Ventricular Ejection.—The ejection time increased in all cases, by an average of 0.04 sec. (20%) at four to six minutes ($P<0.01$). The mean systolic ejection rate calculated as the stroke volume divided by the ejection time remained unaltered.

Left Ventricular Work.—The left ventricular minute work, calculated as the product of mean arterial pressure and cardiac output, did not show any significant change. The stroke work increased with the stroke volume.

Arterial Pressures.—There was no significant change in the pulmonary arterial pressures, available in five cases, or in the mean systemic arterial pressures. The wedge pressure was available in three cases: in two it was unchanged and in one it dropped by 1 mm. Hg.

The mean values for the group are given in the Table and individual data are shown in Fig. 1. The time course of events

Mean Values of Haemodynamic Data for the Group (Erect Position)

	Control	Minutes after Administration of I.C.I. 50172				
		0–2	2–4	4–6	6–8	8–10
Pulse rate (beats/min.)	124	112†	109†	107†	109†	104†
Cardiac output (l./min.)	9·3	9·3	9·3	9·4	9·0	9·3
Stroke volume (ml.) ..	77	85*	89†	92†	88†	89†
Ejection time (sec.) ..	0·20	0·23†	0·23†	0·24†	0·23†	0·22†
Mean systolic ejection rate (ml./sec.) ..	390	380	400	390	390	410
Systemic arterial pressure (mm. Hg)—mean	92	91	92	92	90	90
Peripheral resistance (units)	9·9	9·8	10·1	10·2	10·0	10·3
Pulmonary arterial pressure (mm. Hg) ..	16·5	16·0	16·0	16·5	16·5	16·5
Left ventricular work (kpm./min.) ..	11·7	11·5	11·6	11·7	11·0	11·4

* Significant at $P < 0.05$ level. † Significant at $P < 0.01$ level.

following the intravenous injection of 5 mg. of I.C.I. 50172 is shown in Fig. 2.

Discussion

In the present study the drug was given by rapid intravenous injection during continuous submaximal exercise rather than between two periods of exercise. This avoided the possibility that the effects observed were due to differences that may occur between such identical exercise periods in the absence of any therapeutic intervention (Burkart *et al.*, 1967). The absence of any significant difference between the two sets of control values shows that a steady state had been reached before the drug was administered, and is in keeping with the results of a previous investigation from our laboratory when identical techniques were used (Sowton and Burkart, 1967). The patients were thoroughly familiar with the apparatus at the start of the investigation, since they had all just completed a standard exercise test. Though this group of patients cannot be regarded as normal, the cardiac function was excellent in all but one case, and it seems likely that these findings are applicable to subjects without significant heart disease.

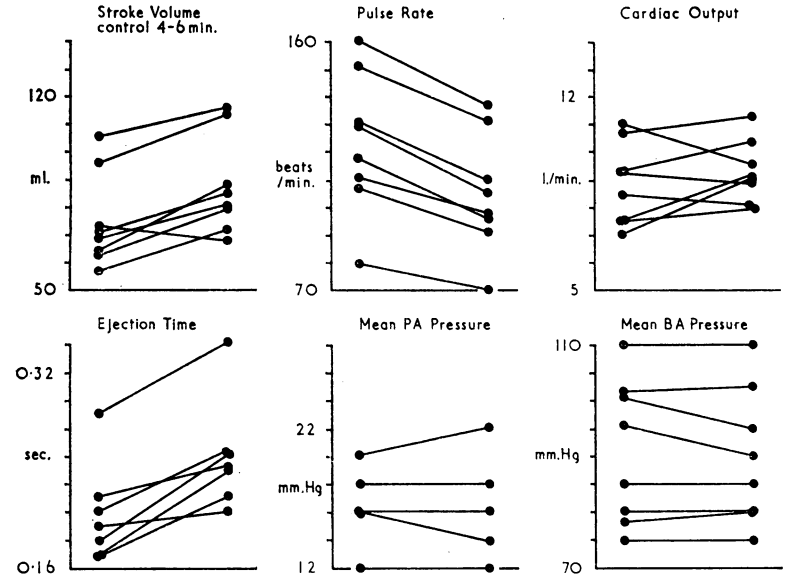

FIG. 1.—Haemodynamic data before and four to six minutes after intravenous administration of 5 mg. of I.C.I. 50172. PA=Pulmonary artery. BA=Brachial artery.

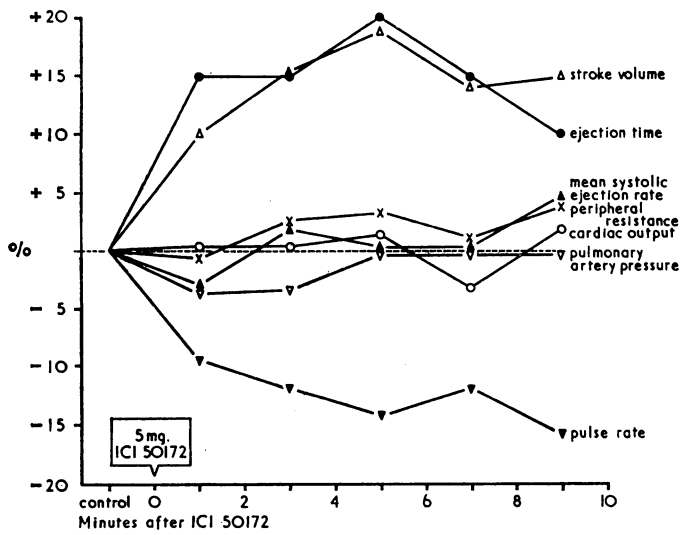

FIG. 2.—Percentage changes in mean values of haemodynamic variables after administration of 5 mg. of I.C.I. 50172.

Howitt (1967) observed that intravenous administration of I.C.I. 50172 caused a reduction in the resting pulse rate in man. The present study demonstrates that the drug also reduces the pulse rate during exercise. There was no change in cardiac output due to a reciprocal increase in the stroke volume, apparent within two minutes of giving the drug.

Preliminary observations in dogs have demonstrated that I.C.I. 50172 has a sympathomimetic effect on the ventricular myocardium (Barrett *et al.*, 1968). In the present study the increased stroke volume was accompanied by a significant prolongation of the left ventricular ejection time, with the result that the mean systolic ejection rate remained unchanged. This last quantity has been shown to decrease with positive inotropic stimuli (Braunwald *et al.*, 1958), and the lack of any change after I.C.I. 50172 provides indirect evidence against the drug having any such effect. It therefore seems likely that the increase in stroke volume was secondary to the change in pulse rate rather than to a further effect of the drug on left ventricular function. The similarity in time course between the drop in pulse rate and the increase in stroke volume also supports this relationship. The study gives no indication of the mechanism by which the cardiac output remains constant in the presence of a decrease in pulse rate: in particular, the peripheral resistance, the pulmonary arterial pressure, and the wedge pressure all remained constant.

Animal work with I.C.I. 50172 indicates that it has a selective action, blocking catecholamine effects on the heart but not on the peripheral vascular tree (Barrett *et al.*, 1968). This would allow sympathetic mediated reflexes to maintain arterial pressures despite alterations in cardiac state, and so no change in aortic pressure is to be expected after the drug. Similar reciprocal changes in stroke volume are seen when the heart rate is slowed by paired pacing of the atria with normal ventricular activation. Lister *et al.* (1967) demonstrated that when the heart rate was depressed by as much as 45% below the sinus rate there was no significant change in left ventricular work, cardiac output, or mean systemic arterial pressure.

The effects of 5 mg. of I.C.I. 50172 during submaximal exercise differ from those of the same dose of propranolol, which produces a drop both in pulse rate and in cardiac output (Epstein *et al.*, 1965; Sowton and Hamer, 1966). In addition, Epstein *et al.* (1965) showed a significant decrease in systemic arterial pressure, while in Sowton and Hamer's (1966) patients there was an increase in the pulmonary arterial pressure. The reduction in the cardiac output was attributed by Epstein *et al.* to the combined effects of a drop in pulse rate and the prevention of the normal augmentation of myocardial contractility occurring during exercise. It was therefore of interest that in the present series of patients slowing of the pulse rate was not accompanied by any change in the cardiac output or in the left ventricular minute work. It is possible that I.C.I. 50172 may have therapeutic value from an ability to antagonize the tachycardia produced by catecholamines without seriously impairing left ventricular function.

Summary

The intravenous injection of 5 mg. of I.C.I. 50172 during erect submaximal exercise in subjects with good cardiac function resulted in the following changes: heart rate fell by 16%, but stroke volume increased so that cardiac output remained constant; and left ventricular ejection time increased but left ventricular systolic ejection rate, left ventricular work, aortic

pressure, pulmonary artery pressure, and pulmonary capillary wedge pressure did not change significantly.

Supplies of 50172 were kindly provided through Dr. Desmond Fitzgerald, of I.C.I. Ltd.

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Haemodynamic Effects of I.C.I. 50172 in Patients with Ischaemic Heart Disease

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Brit. med. J., 1968, **1**, 215–216

Beta-adrenergic receptor blocking agents have had wide application since they were first introduced into clinical practice (Prichard *et al.*, 1963; Stock, 1966), particularly in the treatment of angina pectoris (Prichard *et al.*, 1963; Wolfson *et al.*, 1966; Gillam and Prichard, 1966; Hamer and Sowton, 1966). Unfortunately these drugs have had adverse effects on myocardial function in some instances (Chamberlain, 1966; Stephen, 1966), and this may often be due to the reduction in cardiac contractile force that they are known to produce (Shanks, 1966).

A drug with a similar action in angina but without the deleterious effects on myocardial function would be a most valuable addition to those currently available. I.C.I. 50172 (4-(2-hydroxy-3-isopropylaminopropoxy) acetanilide) has been shown in animal experiments to have approximately 40% of the inhibitory effect of the same dose of propranolol on isoprenaline-induced tachycardia, and mobilization of free fatty acids (Barrett *et al.*, 1968). It has, in addition, some intrinsic sympathomimetic action not shown by propranolol (Barrett, personal communication, 1967). Its haemodynamic effects in a group of patients with ischaemic heart disease are reported here.

Materials and Methods

Results were obtained from 14 male patients whose ages ranged from 36 to 67 years (mean 54.6). Five had proved myocardial infarction from one to six days previously and were being treated in the coronary care area of the National Heart Hospital. In all these patients haemodynamic monitoring was being performed in addition to the usual electrocardiographic monitoring, to provide information of immediate therapeutic value. The drug was given only when haemodynamic values had returned to the normal range. Nine subjects had typical severe angina pectoris and were being assessed for possible surgical treatment of their coronary artery disease by internal mammary artery implants. Included in this assessment was a study of cardiac function and degree of ventricular ischaemia which involved haemodynamic measurements, and the drug was given under these circumstances.

In all cases the technique of study was the same. The patients were studied in the morning after their usual breakfast and without premedication. Pulmonary artery pressure was recorded via either a fine nylon tube which was inserted percutaneously into an arm vein and guided by flow to the pulmonary artery or a No. 8 double-lumen catheter which was passed under fluoroscopic control so that the proximal lumen was in the pulmonary artery. A Teflon tube (outer diameter 1.6 mm., inner diameter 1.1 mm.) was inserted into the brachial artery percutaneously and passed to the aortic arch. Pressures were measured with Consolidated Electrodynamics strain-gauge transducers (type 4-326-L212) and recorded on a Sanborn (964) four-channel direct writer. Mean pressures were obtained by electrical integration. Cardiac output was measured by the dye dilution technique, 5 mg. of indocyanine green being injected into the pulmonary artery and blood withdrawn from the aorta with a Kipp and Zonen constant-rate pump through a Gilford densitometer, the output of which was fed into a Honeywell recorder. Stroke volume was obtained by dividing cardiac output by heart rate, total peripheral resistance by dividing mean aortic pressure by cardiac output, and mean systolic ejection rate by dividing stroke volume by systolic ejection time.

The above measurements were taken before and five minutes after the injection of 5, 15, or 25 mg. of I.C.I. 50172 into the pulmonary artery. Measurements were made in one patient at all three dosage levels and the others received only one dose, so that six patients were given 5 mg., four 15 mg., and six 25 mg. Student's *t* test was used for the statistical analysis.

Results

The results for patients with infarction and for those with angina were similar and so have been considered together. The mean levels of the various values for each dosage group are given in the Table. It can be seen that heart rate was significantly reduced in all three dosage groups. Systolic ejection time was, however, significantly prolonged only in the groups

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