Haemodynamic effects of a new β_1 -receptor agonist in acute myocardial infarction

A useful antidote to unwanted cardiac effects of β -blocking agents

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SUMMARY The haemodynamic effects of a new β_1 -receptor agonist, 1-(4 hydroxyphenoxy) 3-isopropyl-amino-2-propanol, were studied in 25 patients after acute myocardial infarction using non-invasive methods. The drug caused an increase in systolic blood pressure and pulse pressure, without change in diastolic blood pressure, and a slight increase in heart rate and reduction in the pre-ejection period. These changes were greater in patients without a history of left heart failure. It is suggested that this cardioselective drug possesses positive inotropic activity but only slight positive chronotropic activity. The substance has been further investigated as a possible antidote to unwanted cardiac side effects of the cardioselective β -blocker, metoprolol. The changes in the cardiovascular dynamics caused by metoprolol in patients with acute myocardial infarction were promptly reversed by this new β_1 -agonist. With its positive inotropic properties and its efficacy in reversing the effects of a cardioselective β -blocker, the drug is a potentially useful pharmacological agent to support an acutely depressed myocardium in patients on β -blocking agents.

Myocardial failure is an important if not a major cause of mortality in acute myocardial infarction, and is related to the size of the infarct (Bolooki *et al.*, 1971) and to the severity of the coronary artery disease (Wackers *et al.*, 1976). Until a definitive form of treatment becomes available, pharmacological support of the failing myocardium is necessary. Beregovich and co-workers (1972) reported that short-term administration of catecholamines improved myocardial contractility after myocardial infarction. These agents, however, may induce undue tachycardia, or arrhythmia (Loeb *et al.*, 1973) and may provoke further myocardial necrosis (Krasnow, 1971; Maroko *et al.*, 1971; Waldenström *et al.*, 1978). Hence, a cardiostimulant drug without these deleterious effects would be a welcome addition to the therapeutic armamentarium.

The substance racemic 1-(4 hydroxyphenoxy)-3-isopropylamino-2 propanol³ and its laevo form⁴, new compounds with β_1 -selective agonist activity, were investigated in animals by Carlsson *et al.* (1977) and in healthy volunteers by Johnsson *et al.* (1979) and Knaus *et al.* (1978). Preliminary investigations of their haemodynamic effects, using non-invasive methods in healthy subjects (Johnsson *et al.*, 1979), showed a significant shortening of the pre-ejection period (PEP), left ventricular ejection time (LVET), and electromechanical systole, and a rise in the systolic blood pressure. There were no great changes in heart rate or diastolic blood pressure when the racemic form was given as an intravenous infusion in doses up to 20 μ g per kg body weight or in oral doses of 2.5 to 20 mg. These findings indicate a selective inotropic action, making the substance a useful pharmacological agent to support a myocardium whose function has been depressed

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⁴H 133/22, AB Hässle (Astra Pharmaceuticals), Sweden; CGP-7760, Ciba-Geigy, Switzerland.

by myocardial infarction or myocardial depressant drugs.

Using non-invasive methods, the haemodynamic effects of the racemic form were studied in patients in a stable phase following acute myocardial infarction. The effects of the laevo form were also studied in patients with acute myocardial infarction after previous intravenous injection of the cardio-selective β -blocker metoprolol, to evaluate the drug as a possible antidote to unwanted cardiac effects of β -blocking agents.

Methods

With their informed consent, 25 patients with stable acute myocardial infarction were given 1-(4 hydroxyphenoxy)-3-isopropylamino-2-propanol, using non-invasive procedures. The laevo form of the compound (H 133/22) is twice as potent as the racemic form (H 80/62). The diagnosis of myocardial infarction was based on a typical clinical picture, definite electrocardiographic infarct patterns, and an increase in serum levels of cardiac enzymes (e.g. aspartate aminotransferase, AST). Patient data are shown in Tables 1 and 2.

The first part of the study comprised 15 patients (Table 1), aged from 50 to 80 years, investigated at 2.5 to 21 days from the onset of chest pain. Nine of these patients had a previous history of left ventricular failure and were on diuretics and/or digitalis, but were not in heart failure at the time of the study. None was on β -blocker therapy. After a control period of 20 minutes, to achieve steady state conditions, H 80/62 was infused initially in a dose of 40 to 50 μ g per kg body weight. Later, 40 to 50 μ g per kg was infused, to give a total dose of 80 to 100 μ g per kg body weight. Heart rate was calculated from a continuous electrocardiographic recording, using an average rate during the last 5 minutes before the drug infusion as the control value. Heart rate after infusion of the drug was calculated as mean heart rate during a 5-minute period after completed drug infusion. The blood pressure was measured indirectly every 2 minutes with an ultrasound sphygmomanometer (Arterio-sonde 1217, Hoffman La Roche, Inc., Cranbury, USA), which has been shown to give readings which correlate well with the invasively measured blood pressure (Hochberg and Salomon, 1971; George *et al.*, 1975). The systolic and diastolic blood pressures and the pulse pressure were taken as the mean values during a 5-minute period after the completed infusion period. The pre-ejection period (PEP) was measured from simultaneous recordings of the electrocardiogram (lead II), phonocardiogram, and carotid pulse tracing, as previously described

Table 1 Clinical features of patients with acute myocardial infarction given H 80/62

No. of patients	15
Age (y)	50-80 (64.8)
Age of infarct (d)	2.5-21 (9.3)
Maximum AST level (IU/l)*	23-366 (148)
Heart size (ml per m ² BSA)	350-850 (496)
Site of infarction	No. of patients
Anterior	6
Inferior	8
Unknown	1
History of left heart failure	
Positive	6
Negative	9

* AST (SGOT) normal value $\leq$ 17 IU.

All values are shown as range and mean (in parentheses).

Table 2 Clinical features of patients with acute myocardial infarction given metoprolol and H 133/22

No of patients	10
Age (y)	36-69 (55.9)
Age of infarct (d)	4-8 (5.8)
Maximum AST level (IU/l)*	31-289 (156)
Heart size (ml per m ² BSA)	330-610 (474)
Site of infarction	No. of patients
Anterior	6
Inferior	3
Unknown	1

* AST (SGOT) normal value $\leq$ 17 IU.

All values are range and mean (in parentheses).

(Fabian *et al.*, 1972; Waagstein *et al.*, 1974) and was corrected for heart rate to derive pre-ejection period index (PEPI) (Weissler and Garrard, 1971; Weissler *et al.*, 1972) as an index of myocardial performance.

In the second part of the study, 10 patients with acute myocardial infarction (Table 2) were given a cardioselective β -blocking drug, metoprolol (Seleno[®], AB Hässle, Sweden), and the laevo form of the inotropic agent (H 133/22). The ages of the patients ranged from 36 to 69 years and they were studied 4 to 8 days after the onset of clinical symptoms of acute myocardial infarction during the stable phase of the disease. Other criteria for inclusion in this group were: (1) no β -blocking therapy within the previous 24 hours; (2) no clinical signs of cardiac failure; (3) systolic blood pressure above 100 mmHg; (4) no signs of poor peripheral circulation; (5) heart rate above 45 beats/minute; and (6) absence of atrioventricular conduction defects.

After a control period of 20 minutes, intravenous metoprolol was administered in 3 doses of 5 mg given at 2-minute intervals. Ten minutes after the metoprolol had been given, H 133/22 was infused

continuously for 5 minutes in a dose of 50 μg per kg body weight, using the Braun-Melsungen infusion pump. After the infusion was completed, the patients were monitored until their heart rate and blood pressure reached a steady state. Heart rate, systolic and diastolic blood pressures, pre-ejection period, and pre-ejection period index were measured in the control period, 10 minutes after metoprolol, and 15 and 60 minutes after the end of H 133/22 infusion. The cardiac output was estimated from heart rate and stroke volume, using impedance cardiography (Instrumentation for Medicine, Model 304 A), which has been found to give results which correlate well with those obtained by the Fick method (Naggar *et al.*, 1975). Electrocardiograms were recorded continuously in all patients. No arrhythmias or conduction defects were noted.

Student's *t* test for paired observations was used for statistical comparisons; values of $P < 0.05$ were considered significant.

Results

I: EFFECTS OF H 80/62 IN PATIENTS WITH ACUTE MYOCARDIAL INFARCTION

Intravenous infusion of the drug led to a significant rise in systolic blood pressure without change in the diastolic blood pressure, thus increasing the pulse pressure (Fig. 1 and 2; Table 3). There was

Fig. 1 Changes in systolic blood pressure (SBP), diastolic blood pressure (DBP), and pulse pressure (PP) in 15 patients with acute myocardial infarction after infusion of H 80/62. All values are shown as mean $\pm$ SE. * $P < 0.01$; ** $P < 0.001$; *** $P < 0.005$.

Fig. 2 Effects of H 80/62 on pulse pressure in 15 patients with acute myocardial infarction. ● = acute myocardial infarction with previous left heart failure; ○ = acute myocardial infarction with no previous left heart failure; $\bar{x} \pm \text{SE}$.

a significant but small rise in heart rate and in 2 patients a greater increase was seen (Fig. 3 and 4; Table 3). The pre-ejection period was shortened significantly from the control value (Fig. 5 and 6; Table 3). These changes were already evident at the lower concentration but were larger at the higher dose level. The absence of change in the diastolic blood pressure suggests that the drug has no significant peripheral effect. The decrease in the pre-ejection period corroborates the previous findings in healthy human subjects and indicates positive inotropic activity.

The responses of the patients with acute myocardial infarction with a history of left heart failure (group 2) were compared with those of patients without left heart failure (group 1) after a dose of 40 to 50 μg per kg body weight of the drug (Table 4). In group 1 there was a significant increase in the pulse pressure and a shortening of the pre-ejection period without significant increase in heart rate. In group 2, however, an increase in the pulse pressure was seen without shortening of the pre-ejection period. Heart rate in this group was significantly increased. The higher dose, 80 to 100 μg per kg

Table 3 Haemodynamic changes in 15 patients with acute myocardial infarction after infusion of H 80/62

	Control	<i>P</i> <	H 80/62 ($\mu\text{g per kg body weight}$) 40-50	<i>P</i> <	80-100
Heart rate (beats/min)	81.1 $\pm$ 3.8	0.05	84.8 $\pm$ 4.5	0.02	86.2 $\pm$ 4.9
Systolic blood pressure (mmHg)	110.7 $\pm$ 4.4	0.01	115.2 $\pm$ 4.5	0.005	117.2 $\pm$ 4.3
Diastolic blood pressure (mmHg)	72.5 $\pm$ 2.7	NS	72.9 $\pm$ 2.7	NS	73.0 $\pm$ 2.6
Pre-ejection period (ms)	104.3 $\pm$ 4.1	0.01	99.7 $\pm$ 3.9	0.001	97.8 $\pm$ 4.6
Pulse pressure (mmHg)	37.6 $\pm$ 3.6	0.001	43.0 $\pm$ 3.8	0.001	44.1 $\pm$ 4.0

All values are shown as mean $\pm$ SE. Significance of differences between control and values after administration of 480/62 are shown (*P*).

Fig. 3 Changes in heart rate in 15 patients with acute myocardial infarction after infusion of H 80/62. All values are shown as mean $\pm$ SE. * *P* < 0.05; ** *P* < 0.02.

Fig. 5 Changes in pre-ejection period (PEP) in 15 patients with acute myocardial infarction after infusion of H 80/62. All values are shown as mean $\pm$ SE. * *P* < 0.01; ** *P* < 0.001.

Fig. 4 Effects of H 80/62 on heart rate in 15 patients with acute myocardial infarction. ● = acute myocardial infarction with previous left heart failure; ○ = acute myocardial infarction with no previous left heart failure; $\bar{x}$ = mean $\pm$ SE.

Fig. 6 Effects of H 80/62 on pre-ejection period (PEP) in 15 patients with acute myocardial infarction. ● = acute myocardial infarction with previous left heart failure; ○ = acute myocardial infarction with no previous left heart failure; $\bar{x}$ = mean $\pm$ SE.

Table 4 Comparison of effects of H 80/62 in patients with acute myocardial infarction without left heart failure (group 1) and with left heart failure (group 2)

	Control	P <	H 80/62 (μ g per kg body weight) 40-50	P <	80-100
Group I (n=6)					
Pulse pressure (mmHg)	40.8 $\pm$ 7.4	0.025	46.3 $\pm$ 8.5	0.025	49.6 $\pm$ 8.2
Heart rate (beats/min)	84.5 $\pm$ 7.8	NS	87.9 $\pm$ 9.8	0.05	91.8 $\pm$ 9.5
Pre-ejection period (ms)	92.4 $\pm$ 4.4	0.005	86.2 $\pm$ 3.3	0.025	85.4 $\pm$ 4.6
Group II (n=9)					
Pulse pressure (mmHg)	35.6 $\pm$ 3.6	0.025	40.7 $\pm$ 3.3	0.05	40.1 $\pm$ 3.8
Heart rate (beats/min)	78.8 $\pm$ 3.9	0.05	82.6 $\pm$ 4.1	NS	82.4 $\pm$ 1.7
Pre-ejection period (ms)	112.2 $\pm$ 4.7	NS	108.6 $\pm$ 3.8	NS	108.8 $\pm$ 4.8

All values are shown as mean $\pm$ SE. Significance of differences between control and values after administration of H 80/62 are shown (P).

body weight, induced further changes in all measurements in group 1 but not in group 2.

II: EFFECTS OF H 133/22 ON PATIENTS WITH ACUTE MYOCARDIAL INFARCTION TREATED WITH METOPROLOL

Metoprolol, a cardioselective β -blocker, in a dose of 15 mg given intravenously, reduced heart rate, systolic and diastolic blood pressures, and pulse pressure (Table 5). It prolonged the pre-ejection period by 9.8 per cent (Fig. 7; Table 5) and caused a reduction in cardiac output with no significant alteration in the stroke volume (Fig. 8 and 9). Fifteen minutes after the infusion of H 133/22 (50 μ g per kg body weight during 5 minutes), a significant reversal of the effects of metoprolol was achieved with an increase in heart rate, systolic and diastolic blood pressures, and pulse pressure, and a reduction of the pre-ejection period (Fig. 7; Table 5). Stroke volume was unchanged except in 2 patients (cases 1 and 4), who showed a large increase 15 minutes after the infusion; at 60 minutes the stroke volume returned to the previous level (after metoprolol) in these patients (Fig. 9). Cardiac output increased in all

Fig. 7 Changes in pulse pressure, heart rate, blood pressure, and pre-ejection period index (PEPI) in 10 patients with acute myocardial infarction after infusion of metoprolol (15 mg) (M) and H 133/22 (50 μ g per kg body weight) (H). All values shown as mean $\pm$ SE. * $P < 0.02$; ** $P < 0.01$; *** $P < 0.005$.

Table 5 Haemodynamic changes in 10 patients with acute myocardial infarction after metoprolol (15 mg) (M) and H 133/22 (50 μ per kg body weight) (H)

	Control	P < ¹	10 minutes after M	P < ²	15 minutes after H	P < ³	60 minutes after H
Heart rate (beats/min)	76.9 $\pm$ 3.1	0.001	65.2 $\pm$ 2.4	0.001	74.1 $\pm$ 3.2	0.001	75.2 $\pm$ 3.3
Systolic blood pressure (mmHg)	119.0 $\pm$ 6.0	0.001	112.8 $\pm$ 6.4	0.001	120.7 $\pm$ 6.3	0.005	120.2 $\pm$ 6.4
Diastolic blood pressure (mmHg)	81.0 $\pm$ 3.7	0.02	78.5 $\pm$ 3.6	0.02	81.0 $\pm$ 3.0	0.05	83.3 $\pm$ 3.8
Pulse pressure (mmHg)	37.8 $\pm$ 3.3	0.001	33.9 $\pm$ 3.7	0.001	39.6 $\pm$ 4.3	0.005	39.2 $\pm$ 3.8
PEP (ms)	106.5 $\pm$ 2.5	0.001	117.0 $\pm$ 3.0	0.005	107.0 $\pm$ 3.5	0.02	109.5 $\pm$ 2.9
PEPI (ms)	136.0 $\pm$ 2.7	0.005	142.6 $\pm$ 3.0	0.02	136.4 $\pm$ 3.4	NS	139.1 $\pm$ 3.2
LVET (ms)	241.0 $\pm$ 7.3	0.001	255.0 $\pm$ 6.8	0.001	242.0 $\pm$ 7.0	0.005	245.4 $\pm$ 6.9
Stroke volume (ml/heart beat)	80.8 $\pm$ 4.3	NS	79.4 $\pm$ 4.4	NS	79.5 $\pm$ 4.9	NS	76.3 $\pm$ 4.4
Cardiac output (l/min)	6.17 $\pm$ 0.36	0.001	5.02 $\pm$ 0.33	0.005	5.87 $\pm$ 0.38	0.02	5.69 $\pm$ 0.33

All values are shown as mean $\pm$ SE.

P values refer to significance of differences between ¹ control and 10 minutes after M, ² 10 minutes after M and 15 minutes after H,

³ 10 minutes after M and 60 minutes after H.

Fig. 8 Changes in cardiac output in 10 patients with acute myocardial infarction after infusion of metoprolol (M) and H 133/22 (H), as given in Fig. 7. All values are shown as mean $\pm$ SE. * $P < 0.001$.

Fig. 9 Changes in stroke volume in 10 patients with acute myocardial infarction after infusion of metoprolol (M) and H 133/22 (H), as given in Fig. 7. All values are shown as mean $\pm$ SE.

patients after H 133/22 and the values after 15 and 60 minutes were not significantly different from those of the control period (before metoprolol)

(Fig. 8; Table 5). All other measurements were also the same 15 and 60 minutes after H 133/22 (Fig. 7-9) as during the control period.

III: ELECTROCARDIOGRAPHIC CHANGES AND SIDE EFFECTS

No arrhythmias or conduction abnormalities were observed in any of the patients before or after the administration of the inotropic compounds during continuous electrocardiographic recording. There were no signs of reinfarction in any of the patients as judged from symptoms, repeated daily electrocardiographic recordings, and enzyme analyses. The positive inotropic agent caused no other symptoms and was thus well tolerated.

Discussion

In the first part of this investigation, the haemodynamic effects of racemic 1-(4 hydroxyphenoxy)-3-isopropylamino-2-propanol (H 80/62) were studied on patients with acute myocardial infarction using non-invasive methods. The results showed an improvement in cardiac contractility, as shown by a reduction in the pre-ejection period, an increase in heart rate, and a rise in the systolic blood pressure and pulse pressure, effects similar to those of other β -adrenergic agonist compounds (Harris *et al.*, 1967; Krasnow, 1971; Weissler and Garrard, 1971). In contrast to isoprenaline, which has both cardiac (β_1) and peripheral (β_2) effects, H 80/62 did not affect the peripheral vessels, as shown by an unchanged diastolic blood pressure, as was noted by Carlsson *et al.* (1977) in the intact animal.

The insignificant reduction of pre-ejection period in patients with a history of left heart failure is probably the result of decreased sensitivity of β_1 -receptors mediating changes in contractility, as is seen in patients with chronic heart failure (Thomas and Marks, 1978). Some of these patients might need higher doses of the drug in order to respond with increased contractility. Some patients might not react at all to inotropic stimulation because of the severity of myocardial dysfunction. Dogs with failing hearts seem to react with an increased chronotropic response rather than an increased inotropic response to catecholamines, compared with controls (Newman, 1977). From the present study, it may be concluded that the drug possesses cardioselective agonist properties with only moderate chronotropic activity. These properties, in the absence of arrhythmic effects, may make the drug preferable to other sympathetic agonists for pharmacological support of the depressed myocardium.

In the second part of the study, the infusion of

50 μg per kg of H 133/22 completely reversed the effects of the β -blocking agent metoprolol (15 mg i.v.) in patients with acute myocardial infarction. In acute myocardial infarction, β -blocking drugs are administered to counteract the harmful effect of increased endogenous catecholamines on cardiac metabolism and cardiac work (Maroko *et al.*, 1971; Videbaek *et al.*, 1972; Waagstein and Hjalmarson, 1975; Waldenström *et al.*, 1978). Under certain circumstances, however, an unexpected depression of cardiac performance may occur, resulting in a drop in blood pressure and cardiac output, requiring immediate treatment. It has been found that β -blocking drugs are effective in controlling angina pectoris (Ekelund *et al.*, 1976), reducing ischaemic injury (Maroko *et al.*, 1971; Reimer *et al.*, 1973; Waagstein *et al.*, 1974; Gold *et al.*, 1976), controlling hypertension and certain arrhythmias (Jewitt and Singh, 1974), and in treatment of hyperkinetic circulatory states (Frohlich, 1971). An increasing number of patients on chronic β -blocker treatment will therefore be seen in emergency situations, such as acute myocardial infarction during surgical procedures. Sudden withdrawal of the β -blocker removes its protective effect on the ischaemic myocardium and its preventive effect against arrhythmias. The sudden withdrawal of β -blockers may be harmful (Miller *et al.*, 1975). The present investigation indicates that β -blocker treatment does not necessarily have to be withdrawn abruptly in these patients in emergency situations since an effective antidote is available for prompt reversal of the unwanted depression of cardiac function by β -blockade.

Isoprenaline and noradrenaline have been widely used to reverse the adverse effects of β -blocking agents. In a recent study it was found that dobutamine could reverse all the effects of the β -blocking agent metoprolol in patients with acute myocardial infarction (Waagstein *et al.*, 1978). From animal experiments (Robie *et al.*, 1974) it is known that dobutamine, in addition to its β_1 -stimulating action, also has α -receptor and β_2 -receptor stimulating effects. Low or moderate doses of dobutamine have balanced effects on vasoconstriction and vasodilatation with small changes in peripheral vascular resistance (Akhtar *et al.*, 1975; Loeb *et al.*, 1975). However, in situations where very high doses of dobutamine have to be given to overcome the adverse effects of β -blockade, the peripheral action of dobutamine could be of importance. During treatment with nonselective β -blocking agents, α -receptor effects of dobutamine may be unmasked, resulting in a large increase in peripheral vascular resistance. For this reason, a β_1 -stimulating drug such as H 133/22, with no peripheral action, is

preferable to drugs like isoprenaline, noradrenaline, dobutamine, and dopamine, especially when this is given to counteract adverse effects of a non-cardioselective β -blocker.

The effective reversal of the cardiovascular effects of metoprolol by H 133/22 makes it valuable in counteracting the cardiodepressant effect of β -blockers, especially β_1 -blocking agents. Because of its greater inotropic than chronotropic effect, it may be of value also in the treatment of congestive heart failure and hypotension. The combination of digitalis and H 133/22 with balanced effects on heart rate and optimal positive inotropic stimulation seems promising for the long-term treatment of patients with heart failure. The lack of arrhythmogenic properties also makes it useful in the treatment of extreme bradycardia and atrioventricular conduction. A special advantage of this inotropic agent compared with others available is that the drug can be given orally. Studies of the clinical value of the drug in acute and long-term treatment are in progress.

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