Eur J Clin Pharmacol (1984) 27: 419–422

European Journal of Clinical Pharmacology

Haemodynamic Effects of Oral Molsidomine in Pump Failure Complicating Myocardial Infarction

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Summary. Haemodynamic monitoring, using a Swan-Ganz balloon catheter, was done in 14 patients with pump failure associated with acute myocardial infarction, before and for 8 h after single 6 mg oral dose of molsidomine. The following changes effects were found: HR fell by 1.6 to 4.7% (significant at 4th hour; $p < 0.05$); SBP was 8.4% lower after 1 h ($p < 0.05$); PCP was decreased by approximately 30%, a significant effect that lasted for 8 hours ($p < 0.002$). CI did not change significantly, although individual analysis showed it to have increased in 6 out of 12 cases. Stroke volume index was increased by about 6% (significant after 1 h, $p < 0.025$). The left ventricular stroke work index also increased from 9.8 to 24.5% (significant after 1 and 4 h, $p < 0.01$ and 0.025). These findings show the beneficial haemodynamic effects of molsidomine in pump failure complicating acute myocardial infarction.

Key words: molsidomine, myocardial infarction; haemodynamic effects, pump failure

Molsidomine [1, 2, 3] is a new vasodilator drug which acts predominantly on preload. This effect, due to its ability to produce dilatation of the peripheral venous system, has an estimated duration of 5 to 8 h. The drug has been found to be useful in the treatment of classic angina pectoris [4, 5] and, due to its haemodynamic properties [6], in patients with acute [7] and chronic [8] pump failure.

In Argentina, Aptecar et al. [9] reported on the effect of molsidomine in patients with uncomplicated acute myocardial infarction (AMI). In those patients, the drug produced a prolonged reduction of pulmonary pressure without change in cardiac index or heart rate.

In theory, patients with pulmonary congestion, whether alone or associated with a mild decrease in the cardiac index [10], may be helped by this type of drug. Accordingly, haemodynamic monitoring was undertaken of patients with AMI complicated by pump failure, using a Swan-Ganz balloon catheter, prior to and for 8 h after oral administration of 6 mg molsidomine.

Material and Methods

Fourteen cases with complicated AMI were studied on 16 occassions after administration of molsidomine (in 2 patients the study was performed twice, after 2 h of a drug-free period; denoted as Cases 1 a and b, and 8 a and b).

Patients were classified according to the haemodynamic criteria of Forrester et al. [10]. All of them presented a pulmonary capillary pressure exceeding 20 mmHg at baseline, and the majority belonged to Group II of that scheme (with a cardiac index equal to or exceeding 2.2 l/min/m^2).

Eleven patients were males and 3 were females; mean age 65.9 ± 9.7 years ($\bar{x} \pm$ SD), weight 76.5 ± 9.1 kg, height 1.65 ± 0.06 m, and body surface area 1.8 ± 0.1 m^2. In 8 patients the AMI was the second attack, and in the other 6 it was the first event. In 8 patients the site of infarction was anterior. All patients were admitted within 24 h of the beginning of symptoms. Seven patients were hypertensive. Three patients died in the Coronary Care Unit due to causes related to the acute infarction.

The diagnosis of AMI was made in accordance with the classical criteria of the MIRU [11]; (clinical data, enzymes, ECG) used in our Coronary Care Unit. All the patients were studied within 48 h of the appearance of symptoms. A triple lumen Swan-Ganz catheter [12] was inserted percutaneously by internal jugular or subclavian puncture for measurement or calculation of the following parameters:

1. Pulmonary capillary pressure (PCP)
2. Pulmonary systolic pressure (PSP)
3. Cardiac output by thermodilution method (CO)
4. Cardiac index (CI) CO/body surface
5. Stroke volume index = CI/pulse

Table 1. Haemodynamic values I

Time [h] / Parameter	Basal			1			4			8		
	$\bar{x}$	±SD	%	$\bar{x}$	±SD	%	$\bar{x}$	±SD	%	$\bar{x}$	±SD	%
HR [beats/min]	93.6	12.6	0	91.1	14.3	−2.7	89.2	15.6	− 4.7[b]	92.1	12.3	− 1.6
SBP [mmHg]	129.1	35.7	0	118.3	24.4	−8.4[b]	122.3	23.1	− 5.3	130.3	31.8	+ 0.9
DBP [mmHg]	78.8	23.2	0	74.3	13.4	−5.7	78.9	13.3	+ 0.1	83.0	16.9	+ 5.3
MAP [mmHg]	94.4	26.2	0	87.4	14.0	−7.4	93.3	15.9	− 1.2	99.4	21.4	+ 5.3
[a]SPP [mmHg]	41.6	10.1	0	32.7	8.0	−21.4[c]	33.3	7.2	−20.0[c]	32.9	10.1	−21.0[c]
PCP [mmHg]	26.9	7.1	0	18.9	7.0	−29.7[c]	20.3	5.5	−24.5[c]	18.8	6.3	−30.1[c]

[a] Systolic pulmonary pressure [b] $p < 0.05$ [c] $p < 0.002$

Table 2. Haemodynamic values II

Time [h] / Parameter	Basal			1			4			8		
	$\bar{x}$	±SD	%	$\bar{x}$	±SD	%	$\bar{x}$	±SD	%	$\bar{x}$	±SD	%
Cardiac output (CO) [l/min]	4.6	1.2	0	4.8	0.9	+ 0.4	4.6	0.9	0.0	4.9	1.0	+ 0.7
Cardiac index (CI) [l/min^2]	2.6	0.8	0	2.7	0.5	+ 0.4	2.6	0.6	0.0	2.8	0.7	+ 0.8
Stroke volume index (SVI)	27.8	6.7	0	29.4	5.6	+ 5.8[c]	29.4	7.5	+ 5.8	29.1	6.4	+ 4.7
Stroke work index (SWI)	26.5	13.7	0	29.1	11.9	+ 9.8[b]	31.5	14.1	+18.9[c]	33.0	13.2	+24.5
Systemic vascular resistance (SVR)	40.1	17.7	0	34.2	8.8	−14.7[a]	37.6	8.8	− 6.2	38.8	18.6	− 3.2
Pulmonary vascular resistance (PVR)	12.7	4.4	0	8.8	4.3	−31.0[b]	9.4	2.9	−26.0[b]	8.8	4.9	−30.5[b]

[a] $p < 0.05$ [b] $p < 0.01$ [c] $p < 0.02$

6. Left ventricular stroke work index (LVSWI) Stroke volume index × (MAP-PCP) × 0.0136
7. Total systemic resistance = MAP/CI
8. Total pulmonary resistance = MPP/CI.

The systolic (SBP) and diastolic (DBP) systemic blood pressures were measured by conventional sphygmomanometry. The mean arterial blood pressure (MAP) was calculated as MAP = DBP + 1/3 (SBP-DBP). Heart rate was derived from a conventional electrocardiographic record.

Protocol

After a stabilization period of 30 min, and before oral administration of 6 mg molsidomine, a first record of the measured parameters was obtained. Post-drug recordings were made 1, 4 and 8 h after molsidomine administration.

Due to technical problems, in three cases (nos. 2, 7 and 14) the cardiac output was not determined, and in Case 1b, no reliable value of cardiac output was obtained at 1 and 4 hours. Each determination was carried out three times and the results were averaged.

The data were analyzed by the *t*-test for paired samples.

Results

Mean values ($\bar{x} \pm SD$) of the results are shown in Tables 1 and 2.

The absolute and % changes compared to baseline values in the haemodynamic parameters 1 to 8 h after molsidomine administration are listed in Table 1. The most marked effect was on PCP, with a mean decrease of about 30%. SBP only fell by 8.4% at the most (1 h post-drug); HR also showed a modest though significant reduction (4.7%; $p < 0.05$). The mean cardiac index was not modified by treatment, ranging between 2.6 ± 0.8 l/min/m^2 at zero time, and 2.8 ± 0.7 l/min/m^2 at 8 h (Table 2).

The simultaneous changes in PCP and CI in 12 patients from the baseline level to 1 h, after treatment are illustrated in Fig. 1. A significant reduction in PCP was observed in 11 cases. In the remaining subject (Case 13), PCP tended paradoxically to increase slightly with a concomitant drop in CI. In 6 of the 11 cases with a decrease in pulmonary wedge pressure, a mean increment in CI of approximately 0.3 l/min/m^2 was observed. No relevant changes were seen in 3 of the 5 remaining patients (Cases 1, 6 and 8a), whilst the other two (Cases 8b and 9)

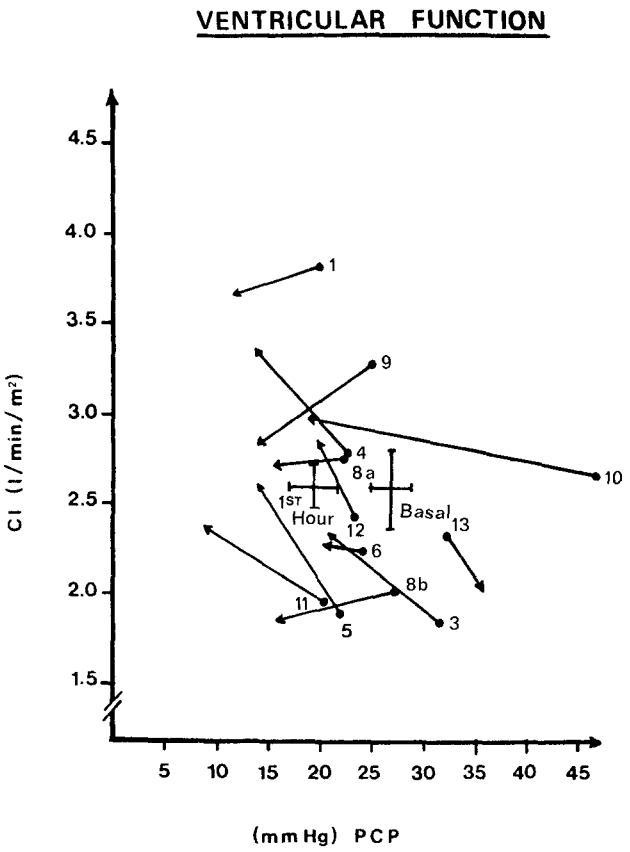

Fig. 1. Individual values before and 1 h after oral molsidomine 6 mg of pulmonary capillary pressure vs cardiac index (PCP vs CI). Mean (±SD) basal and 1st hour values are also shown ($n = 12$)

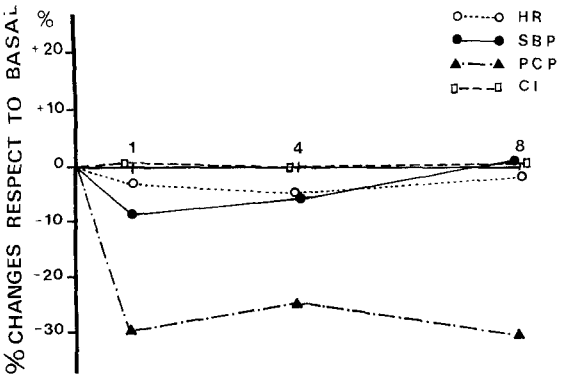

Fig. 2. Mean percentage changes in heart rate (HR), systolic blood pressure (SBP), pulmonary capillary pressure (PCP) and cardiac index (CI), 1 to 8 h after oral administration of 6 mg molsidomine

showed decreases in CI of 7.5% and 15%, respectively.

Changes in MAP, systemic and pulmonary vascular resistance and stroke volume after administration of 6 mg molsidomine are shown in Tables 1 and 2. One hour after starting treatment, a non-significant decrease in MAP, with a concomitant and significant drop ($p < 0.05$) in systemic vascular resistance was observed; the reduction in pulmonary resistance was larger (26% to 31%). On the other hand, the stroke volume index increased significantly ($p < 0.025$), by about +6% compared to the baseline value, and so did the left ventricular stroke work index (Table 2).

Discussion

During the past few years, vasodilator agents, arterial, venous or mixed [13], have been increasingly used in cardiac insufficiency associated with AMI. They generally reduce left ventricular diastolic pressure and/or aortic impedance, which may be of benefit in diminishing myocardial oxygen consumption and improving ventricular function. The rational usage of these drugs depends on careful haemodynamic monitoring.

Due to the variability of initial haemodynamics in AMI, inconsistent results may be observed, even in the case of controlled trials with the same agent published simultaneously in the same journal [14, 15].

Molsidomine (N-ethoxycarbonyl-3-morpholin-sydnonimine) is a vasodilator drug, whose main haemodynamic effect is to reduce preload. It has been tested in early stages of AMI with and without pump failure [7, 9], and in cardiac insufficiency accompanying certain types of myocardiopathy [8]. In patients without pump failure, molsidomine produces a fall in systemic pressure levels on the right side, as well as a fall in the left ventricular end-diastolic pressure, measured indirectly with a Swan-Ganz catheter. A simultaneous, slight decrease in the cardiac index was observed in these patients. In both studies [7, 9], there was an insignificant adrenergic response as shown by a minimal effect on heart rate. A significant and prolonged decrease in PCP, without reflex tachycardia, as well as a mild reduction in systemic vascular resistance were observed.

The cardiac index increased in 6 out of the 12 cases examined and, as HR tends to be reduced by molsidomine, it is evident that the increase in CI was mainly due to an increase in the stroke volume. This would imply a particular effect on impedance, since the drug does not alter contractility [16]; (Fig. 2).

In the present study, as in the work of Bussman and his colleagues [2, 7], patients presented pump failure with a pulmonary pressure exceeding 20 mmHg. Almost all of them corresponded to Group II of the classification of Forrester et al. [10].

It was interesting here to note the difference in behaviour of the systemic and pulmonary vascular resistances. The reduction in the latter was between 26 and 31% of the basal value. The fall was persistent

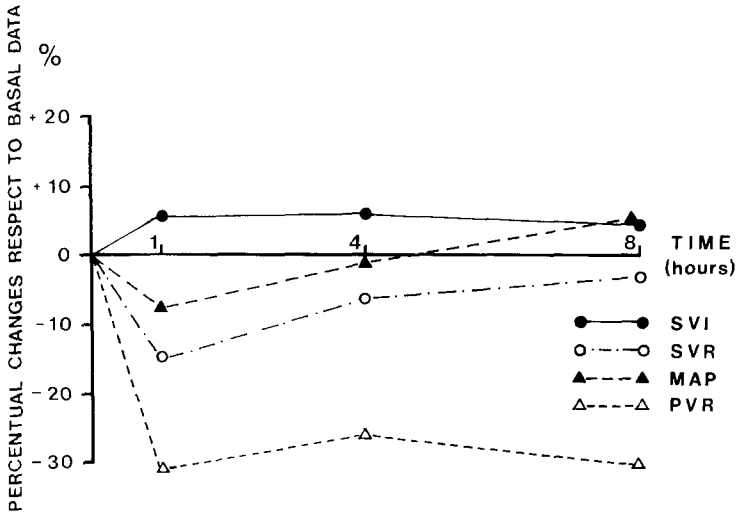

Fig. 3. Mean percentage change in stroke volume index (SVI), mean arterial pressure (MAP), systemic (SVR) and pulmonary (PVR) vascular resistances after oral molsidomine 6 mg

and lasted until the 8th hour of observation. On the other hand, the reduction in systemic vascular resistance was 3% to 15%, and was briefer as it declined after the 4th hour post-administration. The difference in the behaviour of the venous and arterial sectors shows that there was a predominant effect on the venous side, with a less important arteriolar component; (Fig. 3).

These findings indicate a beneficial haemodynamic effect of molsidomine in pump failure complicating AMI. The observed reduction in left ventricular wall pressure may also have a protective effect in ischaemic areas during the early stages of AMI [17], but this hypothesis requires further research.

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Received: October 24, 1983
accepted in revised form: May 25, 1984

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