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Comparative Study of the Haemodynamic Effects of Oral Molsidomine and Isosorbide Dinitrate in Man

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Summary. The haemodynamic effects of oral molsidomine 4 mg and sustained-release isosorbide dinitrate (ISDN) 40 mg have been compared in 10 patients recovering from acute myocardial infarction. After both drugs pulmonary arterial, pulmonary capillary wedge and systemic arterial blood pressure were reduced to about the same extent. The maximum effect was reached 1.5 to 2 h after ingestion of both drugs, but the effect of molsidomine declined during the following 2 h and control values were almost reached after 4 h. After ISDN there was no rebound during the observation period of 6 h. Unlike molsidomine, ISDN reduced total peripheral resistance, so cardiac output and stroke volume index remained constant despite the reduction in cardiac preload. It is concluded that sustained release ISDN 40 mg and molsidomine 4 mg are about equieffective doses in terms of reduction of cardiac preload, but that the effect of molsidomine is of shorter duration. Since molsidomine alone causes venous pooling, cardiac output and stroke volume index are reduced, which may be an untoward side effect in patients with severe heart failure.

Key words: molsidomine, heart failure; sustained release ISDN, haemodynamics, antianginal drugs, pulmonary artery pressure, pulmonary wedge pressure

Molsidomine is a newly developed drug, recently introduced in the therapy of angina pectoris. Its main effect is a reduction in cardiac preload mediated by venous pooling [1–7]. For clinical use the drug is an alternative to the nitrates, which have quite similar haemodynamic effects [8, 9]. The present study was designed to find the dose of molsidomine equieffective to isosorbide dinitrate 40 mg (ISDN) given orally in a sustained-release preparation. This is a standard dose used routinely in the therapy of angina pectoris. It seemed reasonable to compare the effect of this dose to that of oral molsidomine 4 mg.

A second aim of the study was to compare the duration of effect of molsidomine and ISDN. This information is necessary for evaluation of the optimal time interval for administration of the drug during long-time therapy.

Materials and Methods

Patients

The study was performed in 10 patients (8 male, 2 female) recovering from acute myocardial infarction in the Coronary Care Unit; their mean age was 57.9 ± 8.4 (mean ± SD) years. Patients gave informed consent for their participation in the study.

The trial was started when the serum CK-level had reached normal values after the acute stage of infarction. None of the patients was treated with catecholamines, β-blocking agents, calcium antagonists or vasodilator drugs during the observation period. Parenteral therapy with nitroglycerine was discontinued at least 6 h before beginning the trial.

Measurements

The ECG was monitored by three chest electrodes. Arterial blood pressure was determined by the Riva-Rocci method. Mean arterial blood pressure was calculated by the formula $P_{diast} + (P_{syst} - P_{diast}) \times 0.4$.

A 7F Swan-Ganz flow-directed catheter was introduced through a cubital vein and placed into the right or left pulmonary artery under fluoroscopic control. It was connected to a Statham pressure transducer to measure pulmonary artery pressure, pulmonary capillary wedge pressure and right atrial pressure. All pressure recordings were made during respiratory arrest in expiration, and the values were output onto a multichannel recorder (Hellige).

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Table 1. Mean (± SD) control values of all parameters and maximum percent change produced by molsidomine and ISDN. The control values are HR = heart rate [beats/min]; RR = mean arterial blood pressure [mmHg]; PA = mean pulmonary artery pressure [mmHg]; PC = pulmonary capillary wedge pressure [mmHg]; RA = right atrial pressure [mmHg]; CI = cardiac index [l/min/m^2]; TPR = total peripheral resistance [dyn × sec × cm^{-5}]; PAR = pulmonary artery resistance [dyn × sec × cm^{-5}]; SVI = stroke volume index [ml/m^2]. t is the time after drug administration, when the maximum change was observed

	Molsidomine			ISDN			Difference
	control	Δ %	t [h]	control	Δ %	t [h]	
HR	88.1 ± 14.0	+ 9.1 ± 11.2[a]	1.5	84.8 ± 14.3	+ 3.5 ± 7.9	2	[a]
RR	91.5 ± 10.3	−11.2 ± 8.0[b]	1.5	93.8 ± 6.8	− 7.1 ± 6.6[b]	1.5	ns
PA	18.6 ± 3.9	−20.3 ± 7.4[b]	1.5	19.1 ± 3.8	−15.5 ± 11.6[b]	2	ns
PC	10.7 ± 4.4	−23.0 ± 15.1[a]	2	11.5 ± 3.8	−16.5 ± 13.6[a]	1	ns
RA	5.5 ± 2.7	−19.2 ± 33.6	1.5	5.2 ± 3.5	−14.7 ± 33.0	2	ns
CI	4.11 ± 0.74	− 6.4 ± 5.8[b]	1	4.07 ± 0.99	+10.8 ± 12.8[a]	5	[a]
TPR	927 ± 191	− 5.4 ± 10.2	1.5	960 ± 18.8	− 9.9 ± 11.6[a]	1.5	ns
PAR	88 ± 17	−12.7 ± 18.5	1.5	87 ± 20	− 9.9 ± 20.0	1.5	ns
SVI	47.5 ± 10.1	−13.2 ± 8.1[b]	1.5	46.0 ± 6.9	+ 2.8 ± 6.8	1	[a]

[a] $p < 0.05$

[b] $p < 0.01$. The last column indicates significance of the difference between the drug effects of molsidomine and ISDN

Cardiac output was determined by thermodilution using a Fisher cardiac output computer. Each value was calculated as the mean of three consecutive injections of 0.9% saline 10 ml at 4 °C.

Using the parameters mentioned above, it was possible to calculate the cardiac index (CI), total peripheral resistance (TPR), pulmonary artery resistance (PAR), and stroke volume index (SVI) from by standard formulae.

Experimental Protocol

All parameters were first determined at rest to obtain the control values. Then ISDN 40 mg or molsidomine 4 mg was given orally. Thereafter, all parameters were measured every 30 min up to 3 h after drug ingestion, and further measurements were performed after 4,5 and 6 h. On the following day the measurements were repeated before and after administration of the other drug. The sequence of the drugs was randomized, so that 5 patients received molsidomine first and ISDN second, and 5 patients were treated in the reverse order.

Statistical Analysis

Statistical analysis of the results was performed with Student's t-test for paired data. All data in the text are given as mean ± standard deviation.

Results

Control Values

The control values of all parameters observed were in the normal range (Table 1). There was no statistically significant difference in parameter between the control values in the molsidomine and ISDN observation periods.

Heart Rate

After molsidomine, heart rate increased significantly by 9.1 ± 11.2%, the maximum effect was observed 1.5 h after drug ingestion. After ISDN, heart rate showed a tendency to increase, but the change was not statistically significant.

The difference between the effect of molsidomine and ISDN was statistically significant ($p < 0.05$).

Arterial Blood Pressure

Both drugs significantly reduced mean arterial blood pressure by 7.1 ± 6.6% (ISDN) and 11.2 ± 8.0% (molsidomine); the maximum effect was reached 1.5 h after administration of either drug. The effect of molsidomine was slightly but not significantly more pronounced than that of ISDN, but the duration was shorter, so that the control value was almost reached 4 h after administration. In contrast, the fall in blood pressure after ISDN lasted throughout the observation period of 6 h (Fig. 1).

Pulmonary Vascular System

Mean pulmonary artery and pulmonary capillary wedge pressures were significantly decreased by both drugs. The maximum effect was observed 1–2 h after administration. Again, molsidomine caused a slightly more pronounced effect than ISDN, but it was of shorter duration. Control values were almost

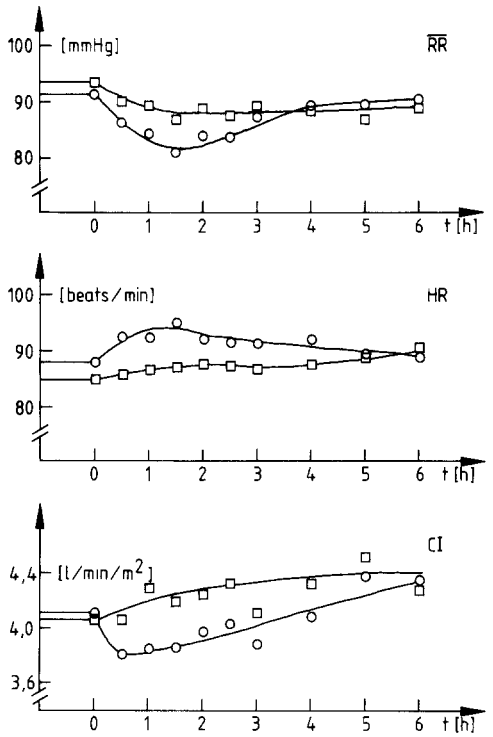

Fig. 1. Time course of mean arterial blood pressure ($\overline{RR}$), heart rate (HR), and cardiac index (CI) after molsidomine and ISDN given p.o. at time zero. The mean values in the 10 patients before and after molsidomine are shown by circles, and those after ISDN by squares

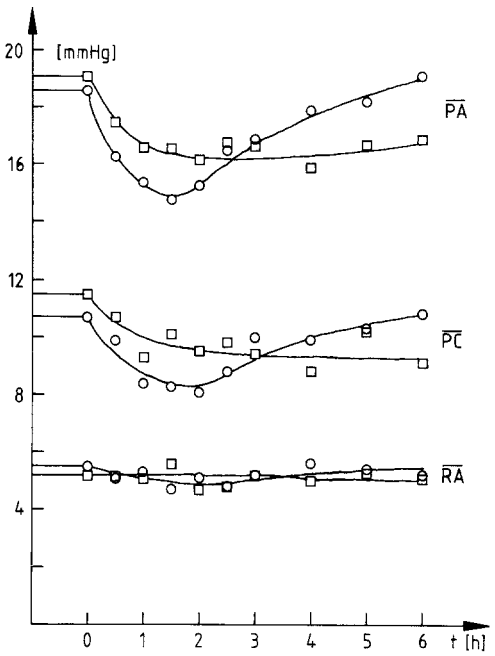

Fig. 2. Time course of changes in the pulmonary circulation after molsidomine and ISDN. $\overline{PA}$ = mean pulmonary artery pressure, $\overline{PC}$ = mean pulmonary capillary wedge pressure, $\overline{RA}$ = mean right atrial pressure. ○ = molsidomine, □ = ISDN

reached 4 h after molsidomine, whereas there was no rebound in the 6 h after ISDN.

Right atrial pressure showed no significant change after molsidomine or ISDN although after both drugs there was a tendency to decrease (Fig. 2).

Cardiac Index (CI)

Cardiac index decreased significantly after molsidomine, by 6.4 ± 5.8% after 30 min, and then slowly returned to its control level. After ISDN, CI slightly increased, with a maximum effect of 10.8 ± 12.8% 5 h after treatment. The difference between the effects of the two drugs was statistically significant ($p < 0.05$) (Fig. 1).

Stroke Volume Index (SVI)

Resulting from the decrease in CI and increase in heart rate, there was a clearcut fall in SVI after molsidomine of 13.2 ± 8.1% after 90 min. The effect slowly decreased subsequently and CI returned to the control value after 5 h. In contrast, ISDN had no significant effect on SVI at any time during the observation period (Fig. 3).

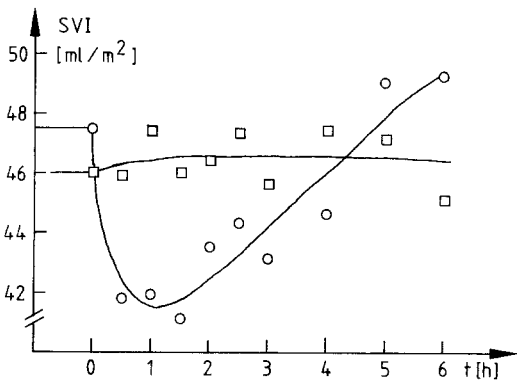

Fig. 3. Mean responses of stroke volume index to molsidomine (○) and ISDN (□). Molsidomine clearly reduced SVI, whereas it remained constant after ISDN

Vascular Flow Resistances

ISDN caused a significant decrease in total peripheral resistance which was maximal 90 min after ingestion. It showed no tendency to return to the control level during the 6 h of observation. After molsidomine, there was a tendency of TPR to decrease, but the change was not statistically significant.

The pulmonary artery resistance showed a tendency to decrease after both drugs, but due to the large standard deviations the change was not statistically significant.

Discussion

The results show that molsidomine 4 mg and sustained release ISDN 40 mg both induce a reduction of cardiac preload by venous pooling. The fall in pulmonary arterial and pulmonary capillary wedge pressure was about the same after both drugs. The effect of molsidomine seemed to be slightly more pronounced, but the difference was not statistically significant. There was, however, a difference in the duration of the actions, since there was almost a return to the since the control values 4 h after molsidomine, whereas there was no tendency to return to control levels in the 6 h after ISDN.

The time course of the molsidomine effect closely reflects that of its plasma levels, as described by Ostrowski [10], who found the peak level 1 to 1.5 h after oral intake, which had decreased to about 25% after 4 h.

It is concluded, that molsidomine 4 mg and sustained-release ISDN 40 mg are equieffective doses as far as the reduction in cardiac preload is concerned, but molsidomine would have to be given at shorter intervals (approximately every 4 h) to obtain a continous effect.

A qualitatively different action of the two drugs on peripheral arterial resistance was observed, as it fell significantly after ISDN and was not affected by molsidomine. Thus, the reduction in preload leads to a significant decrease in cardiac index after molsidomine, whereas after ISDN there is a simultaneous reduction in afterload and CI remains constant or may even increase slightly. For the same reason, the stroke volume index was clearly reduced by molsidomine whereas it remains unchanged after ISDN.

Similar haemodynamic effects of molsidomine have been described by Majid et al. [11] after intravenous administration of the drug. Contrary to the measurements at rest, however, they found no decrease in cardiac index during exercise.

The present clinical observations confirm the experimental results in anaesthetized dogs of Grund et al. [12], who observed more pronounced venous pooling relative to the arterial effect after molsidomine than after nitroglycerin.

The effect of both drugs on arterial blood pressure was about the same, since after ISDN the peripheral resistance decreased and CI was constant, and after molsidomine CI decreased and TPR was constant.

In conclusion, molsidomine 4 mg and sustained-release ISDN 40 mg are about equieffective doses as far as the reduction in cardiac preload is concerned, but in addition ISDN reduces cardiac afterload. We consider, therefore, that ISDN may be of greater value in the therapy of angina pectoris than molsidomine. In addition, sustained-release ISDN elicits longer lasting haemodynamic effects, and patient compliance will be better, since the interval between administration may be prolonged to 6 h, whereas molsidomine ought to be given every 4 h.

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