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THE INFLUENCE OF MOLSIDOMINE ON INFARCT SIZE: AN ACUTE POST-INFARCTION PILOT STUDY WITH 303 PATIENTS

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SUMMARY. **In a multicenter, randomized and double-blind study, the efficiency of molsidomine on infarct size has been examined in 303 patients suffering from a first myocardial infarction and compared with a placebo. According to previous enzyme studies, and in order to detect a 20% reduction in infarct size with conventional levels of risk, $\alpha = 0.05$ and $\beta = 0.20$, the recommended sample size was 264 patients. Thirty-three patients initially selected were excluded for protocol violation and, among the 270 patients definitively included, 133 were allocated to molsidomine and 137 to placebo, without any difference concerning age, delay of treatment, infarct location, and initial blood pressure. Test drugs were both initiated within the 6 first hours and administered orally at decreasing doses for 10 days: 16 mg on the first day, 12 mg on the second day, and 6 mg daily from the third to the tenth days.**

There was not a significant difference between the molsidomine and placebo groups regarding the enzyme evaluation of infarct size, neither for CK dosage (101.72 ± 74.76 gram equivalents vs. 92.71 ± 65.91 gram equivalents, NS) nor for its MB fraction (67.34 ± 50.07 gram equivalents vs. 63.50 ± 43.01 gram equivalents, NS). Moreover, changes in the Q- or R-wave sum during the 10 days of follow-up were strictly identical. However, in-hospital mortality was lower in the molsidomine group than in the placebo group (4.5% vs. 8.0%), but this reduction was not statiscally significant. During the study, there were few side effects, mainly headaches, without withdrawal of the treatment.

KEY WORDS. **Infarct size, vasodilating drug, enzymatic evaluation, mortality, creatine kinase, molsidomine, acute myocardial infarction**

Vasodilating drugs have been mainly used at the acute phase of myocardial infarction, and several studies have demonstrated that intravenous nitroglycerin is effective in relieving ischemic pain and improving left ventricular function. A number of arguments suggest that molsidomine could be helpful in the same circumstances.

1. Molsidomine, like nitroglycerin, is a powerful vasodilating drug, exerting predominant effects on the venous side of the circulation and on the large epicardial coronary arteries [1]. It may play a beneficial role during myocardial infarction in reducing the infarct size, the severity of cardiac failure, the incidence of ventricular fibrillation [2], and, finally, the in-hospital mortality.
2. In vitro, molsidomine inhibits platelet aggregation [3]. In vivo, in an animal model of coronary artery thrombosis, it has been shown to delay or prevent the development of a thrombus [4]. This property might be of additional benefit in myocardial infarction.
3. Molsidomine is an inactive prodrug. However, transformation to its active metabolite is very fast, and therapeutic effects occur with a short delay, less than 1 hour after oral administration [5].
4. Over the past few years, recent observations on patients who received sustained high-dose infusions of intravenous nitroglycerin showed complete vascular tolerance within less than 24 hours [6]. As development of tolerance was never seen with oral molsidomine in any doses or regimen, and in spite of a limited experience in acute myocardial infarction, molsidomine may really be an improvement.

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The principal aims of this study were to assess the efficacy of early delivery of oral molsidomine at the acute phase of myocardial infarction and especially to test its ability to reduce the infarct size.

Materials and Methods

A multicenter trial coordinated by Hoechst Laboratories, Paris, with the participation of 30 French centers, was undertaken to compare two parallel groups of patients suffering from an acute myocardial infarction, randomized as molsidomine versus placebo and treated on a double-blind basis for 10 days.

The selection of patients involved two stages. Initially, patients aged less than 75 years and suffering from a first infarct as suggested by a characteristic chest pain lasting more than 15 minutes and persistent abnormalities of repolarization, were pre-included and allocated at random to treatment with either molsidomine or placebo. In all cases, the treatment was started less than 6 hours after the onset of symptoms. However, the confirmation of inclusion was achieved in a second step and based upon enzyme criteria with two possibilities: either raised levels of creatine-kinase (CK) and/or its MB fraction at twice normal range in the first sample or an increase of these enzyme levels in the first two samples. Patients with recurrent infarctions, patients in shock, patients with an uninterpretable ECG, and those initially treated by electrocardioversion were excluded, as well as patients who had received in the days just before entering the study or were likely to receive during the trial, some form of treatment forbidden by the protocol: nitrates, beta-blockers, calcium antagonists, and thrombolytics. All patients gave their informed consent.

Test drugs were either molsidomine or a placebo, both administered in an identical form at decreasing doses for 10 days; initially 2 mg of an oral form and 2 mg of a sublingual form were administered. Thus, the total daily doses were 16 mg on the first day, 12 mg on the second day (2 mg six times a day), and 6 mg (2 mg three times a day) from the third to the last days.

Four criteria were used for assessing the results:

1. Enzyme criteria: A blood sample for dosage of CK with its MB fraction was drawn every 4 hours within the first 24 hours, then every 6 hours on the second day, and twice daily for the last 8 days. According to the method of Sobel [2] with the correction of Tansey [7], infarct size is the product of a proportionality constant K, body weight, and enzyme release measured by the area under the curve of the serial enzyme concentration dosages. The K values are, respectively, 5.9×10^{-1} for total CK and 4.1 for MB fraction.
2. Electrocardiographic criteria: Infarct size was also evaluated on the basis of the 12-lead ECGS taken from patients before therapy, then on the third, seventh, and tenth days. Tracings with bundle branch block and paced rhythm were not analyzed. According to a method derived from Maroko [8], the summated Q-wave depths and R-wave heights—in leads II, III, and aVF for inferior infarction and leads V_1 to V_6 for anterior infarction—were compared between the molsidomine and placebo groups.
3. Hospital mortality at ten days, with analysis of its causes.
4. Some clinical data obtained during the 10 days follow-up, such as presence or absence of cardiac failure according to the Killip classification, documented arrhythmias or recurrence of angina. The theoretical sample size for this study was derived from results of previous studies. According to Cairns [9], the recommended sample size was 264 patients in order to detect a 20% reduction in infarct size with conventional levels of risk of $\alpha = 0.05$ and $\beta = 0.20$.

Results

Among the 303 patients initially selected, 33 were subsequently excluded for protocol violation, 19 in the molsidomine group and 14 in the placebo group. Reasons for these secondary exclusions were the following: nonconfirmation of diagnosis of infarction by enzyme measurements in 19 cases; recurrent infarction in three cases; seen later than 6 hours in seven cases; and prolonged and unjustified treatment with intravenous nitroglycérin in four cases. These causes of exclusion are equally distributed in both groups. For these reasons, all the analysis based upon the intention-to-treat principle did not change the results, whether using the initially-selected patients or the finally-included sample.

Finally, 270 patients fulfilled the eligibility criteria and were definitively included in the analysis. One hundred and thirty-three were allocated to molsidomine group and 137 were given placebo. Comparison between the two treatment groups (molsidomine vs. placebo) did not show any difference regarding age ($55,4 \pm 9.9$ vs. 57.1 ± 10.3), sex ratio (114 M:19 F vs. 124 M:13 F), delay from the onset of symptoms to the

Table 1. Enzyme data

	Molsidomine	Placebo	p
CREATINE KINASE	n = 122	n = 125	
Size of necrosis (Gr Eq CPK)	101.72 ± 74.76	96.71 ± 65.91	NS
T max (MN)	1273.8 ± 863.3	1206.1 ± 500.1	NS
C max (IU/L)	1.745 ± 1.191	1.658 ± 1.127	NS
AUC	4137 ± 2666	3855 ± 2401	NS
MB CREATINE KINASE	n = 122	n = 123	
Size of necrosis (Gr Eq CPK)	67.34 ± 50.07	63.50 ± 43.01	NS
T max (MN)	1131.0 ± 829.8	1129.0 ± 681.3	NS
C max (IU/L)	1.48 ± 0.9	1.40 ± 0.8	NS
AUC	3020 ± 1570	2910 ± 1270	NS

T max = latent period before enzyme peak; C max = height of the enzyme peak concentration; AUC = area under the curve

beginning of treatment (3 h 57± 2 h 21 vs. 3 h 45 ± 1 h 22), infarct location (anterior 57 vs. 55, inferior 73 vs. 80, and anterior plus inferior 3 vs. 2), or systolic and diastolic blood pressure at initial measurement (133/85 vs. 129/83 mmHg).

The enzyme data are listed in Table 1. The mean infarct size was 101.72 ± 74.76 CK gram equivalents in the molsidomine patients and 96.71 ± 65.91 CK gram equivalents in the placebo patients (NS) or 67.34 ± 50.07 MB CK gram equivalents in the molsidomine group and 63.50 ± 43.01 MB-CK gram equivalents in the placebo group (NS). The infarct size reduction was less than 5% and did not reach statistical significance. Similarly, there was not a significant difference in the electrocardiographic assessment of the infarct size. With regard to the sum of Q- or R-waves and the site anterior or inferior to the necrosis, amplitude and changes in the curves during the 10 days of surveillance were strictly identical in both groups (Figures 1 and 2).

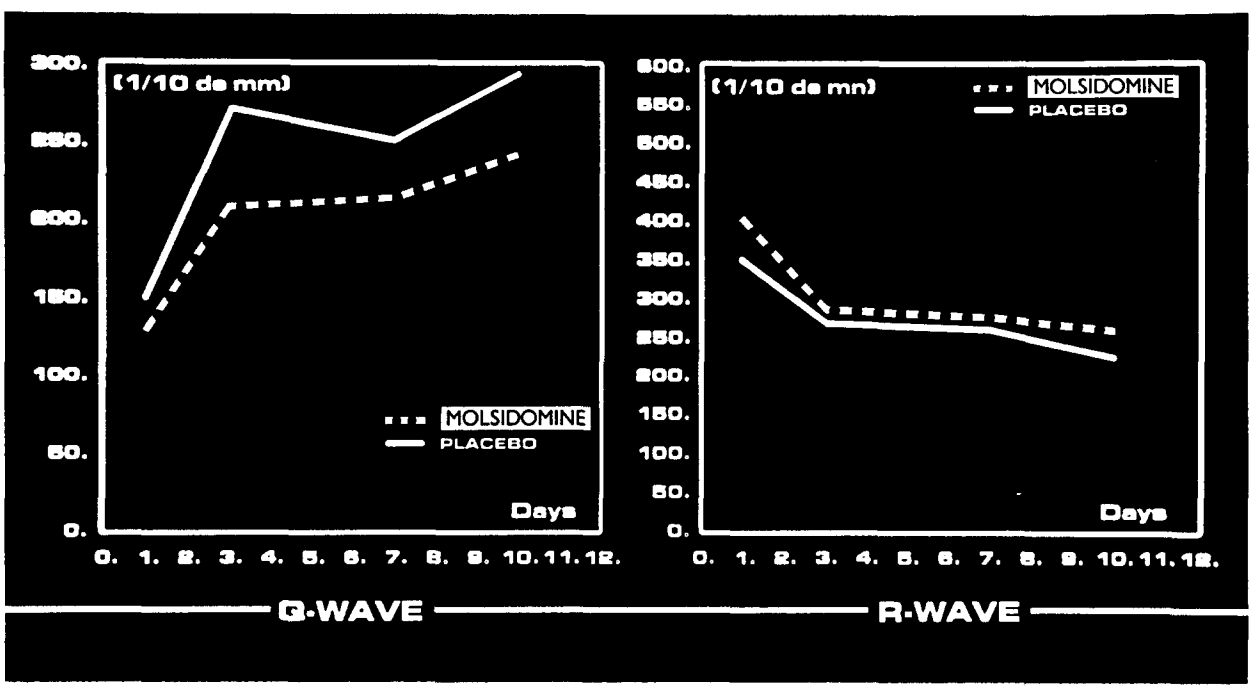

Fig. 1. ECG data in anterior infarction: the sum of the Q waves on left and the R waves on right are equal for molsidomine group and placebo.

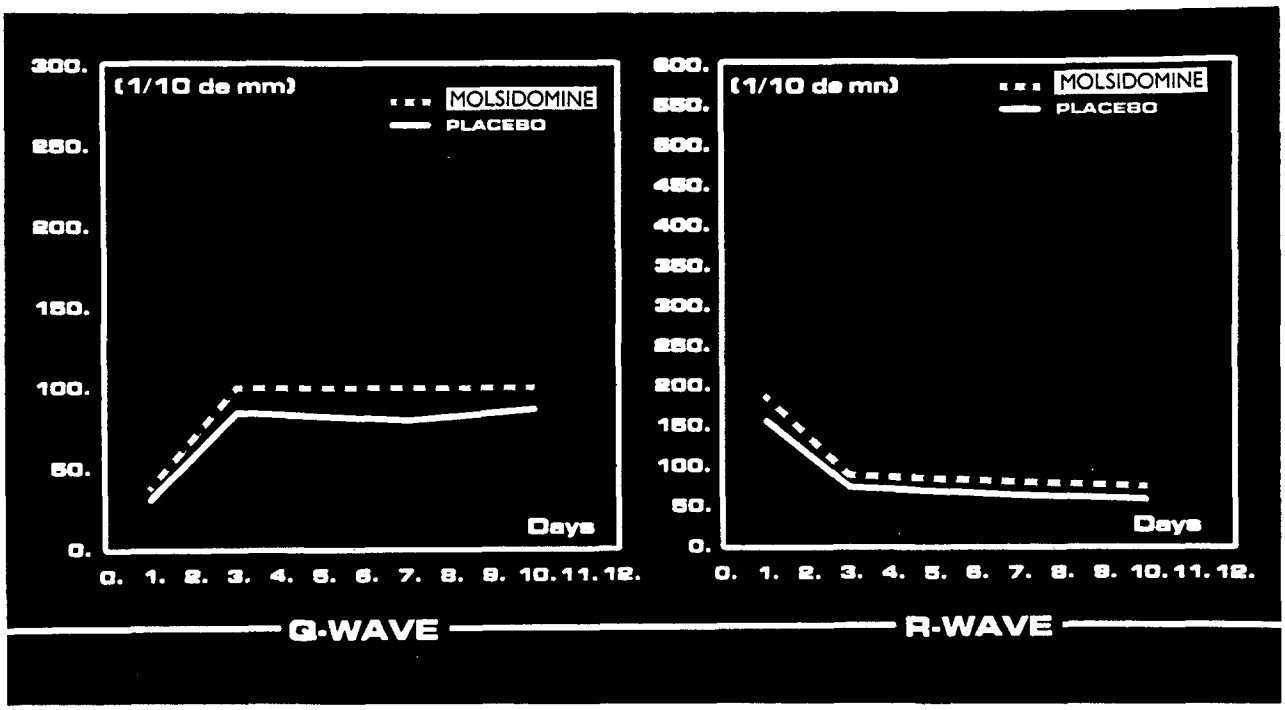

Fig. 2. ECG data in posterior infarction: the sum of the Q waves on left and the R waves on right are equal for molsidomine group in red and placebo group in yellow.

At the tenth day following infarction, mortality was six cases out of 133 in the molsidomine group (4.5%) and 11 cases out of 137 in the placebo group (8%). This difference, a reduction of 45% in favor of molsidomine, was not statistically significant ($p < 0.35$). Causes of death were, in all cases, cardiac: cardiac failure in six cases, external cardiac rupture in nine cases, and papillary muscle rupture in two cases. These are common causes of death at the acute stage of myocardial infarction. Their incidence was in the usual range and was the same in both groups, though one should bear in mind that only seven out of the 17 patients who died were autopsied.

Five patients in the placebo group who were in stage 2, 3 or 4 of cardiac failure according to the Killip classification at the time of inclusion in the trial worsened, while there were none in the molsidomine group. In contrast, no cardiac failure developed during the course of the trial in the placebo group, while molsidomine did not prevent stage 2 moderate impairment of the left ventricular function.

The actual incidence of arrhythmias during the course of the trial was not studied, since 24-hour electrocardiographic records were not obtained for the whole 10 days. Taking into account only those problems with clinical manifestations that were appropriately documented, there is no difference between the two groups (molsidomine vs. placebo) regarding ventricular tachycardia (9 vs. 5), ventricular fibrillation (4 vs. 1), atrial tachycardia (6 vs. 6), or atrioventricular bloc (8 vs. 11).

Finally, there was no statistical difference between the two groups concerning the most important clinical events occuring the first 4 days of the study: Infarct extension, pericarditis, collapsus, and cardiac rupture were equally frequent in both groups. Nevertheless, the frequency of recurrencies of anginal pain during the second and third days was lower in the molsidomine group, with 10 cases versus 19 cases in the placebo group. This slight difference is not significant (Table 2).

The tolerance of the treatment was usually good. Twenty-eight patients (21.0%) treated with molsidomine reported side effects, compared with nine patients (6.6%) given placebo. Headaches were more common in the molsidomine treated group (15 vs. 5), but adverse reactions caused the drug to be ceased in only one patient receiving placebo. There were 24 dropouts (10 molsidomine and 14 placebo). Among the reasons for withdrawal (Table 3), recurrent angina

Table 2. Clinical events

Day	1		2		3		4	
Test drug	M	P	M	P	M	P	M	P
n	133	137	132	131	131	130	131	130
Recurrence of angina	47	47	6	11	4	8	1	1
Infarct extension	1	3	4	1	2	2	1	—
Pericarditis	1	1	7	13	10	15	3	11
Collapse	6	2	—	1	1	—	—	2
Cardiac rupture	—	1	—	1	—	—	—	1
Death	1	6	1	1	—	—	—	1

M = molsidomine; P = placebo

Table 3. Reasons for withdrawal

	Molsidomine	Placebo
Pain recurrence	6	5
Coronary angiography and PCTA	1	1
Cardiac rupture	—	1
Collapse and shock	1	4
Severe heart failure	—	2
Sudden rise of blood pressure	1	—
Side effects	—	1 (nausea)
Nonmedical drop out	1	1

needing other drugs was the most common, but there was no difference between the two treated groups (6 molsidomine vs. 5, placebo NS)

Discussion

In contrast to the preliminary trial reported by Kipshidze [10], the favorable conclusion of which was based upon an acute decrease by the second hour in ST elevation and rapid normalization of enzymes with intravenous molsidomine, the study reported here failed to show any cardioprotective effect of molsidomine.

Despite very early therapeutic intervention, earlier than the sixth hour after the onset of symptoms, it was not possible to demonstrate any efficacy of oral molsidomine on the size of necrosis using noninvasive investigation techniques. Indeed, the administered form was not intravenous but oral, and the dose of 6 mg used from the third to the tenth day of the trial was probably too low. However, it was three times greater on the first day, during the only period where a possibility of infarct size reduction might have existed with other therapeutic techniques such as thrombolytic drugs or PTCA.

Furthermore, this study failed to demonstrate an efficacy of molsidomine on ventricular fribrillation, in contrast with conclusion of Cano based on animal experiments [2]. Since rhythm was not monitored continuously, we did not investigate nonclinical arrhythmias such as premature ventricular beats or nonsustained ventricular tachycardia. This study did not provide evidence for protection against early ischemic arrhythmias.

However, some of these results are encouraging, especially with regard to the in-hospital mortality. At 10 days, there were 6 deaths in the active treatment group and 11 deaths in the placebo group. This mortality reduction of 45% in favor of molsidomine is in the same range as observed with intravenous beta-blocking agents or thrombolytics. The studied population was small, and this difference was not statistically significant. To confirm this result, about 2000 patients would be necessary for a new study, with levels of risk $\alpha = 0.05$ and $\beta = 0.10$.

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