Hemodynamic Evaluation of Molsidomine: A Vasodilator with Antianginal Properties in Patients with Alcoholic Cirrhosis

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Organic nitrates were reported to reduce portohepatic venous pressure gradient in patients with cirrhosis. However, these drugs lower arterial pressure and are well known to induce tolerance. The aim of the present study was to assess the hemodynamic effects of molsidomine, an antianginal agent, which does not induce tolerance and has little effect on arterial pressure in patients with normal liver, in 13 patients with alcoholic cirrhosis. Wedged hepatic vein pressure (−11%, $p < 0.01$), portohepatic venous pressure gradient (−15%, $p < 0.005$),hepatic blood flow (−17.4%, $p < 0.005$), mean arterial pressure (−13.5%, $p < 0.01$) and cardiac output (−17%, $p < 0.001$) were significantly reduced by molsidomine. Free hepatic vein pressure, intrinsic hepatic clearance indocyanin green, heart rate and systemic vascular resistances were not significantly modified. There was no correlation between the decrease in portohepatic venous pressure gradient and the reduction in mean arterial pressure on one hand and the decrease in cardiac output on the other hand. We therefore conclude that in patients with cirrhosis, molsidomine has effects similar to nitrates on systemic and splanchnic hemodynamics. (HEPATOLOGY 1990;11:239-242.)

Medical treatment of portal hypertension is based thus far on β blockers. Recently, organic nitrates (1-4) were found to reduce portal pressure, and their use in the treatment of patients with cirrhosis was advocated. However, these agents induce a decrease in mean arterial pressure correlated to the decrease in portal pressure. Such a phenomenon could induce untoward effects in cirrhotic patients, whose arterial pressure is usually lower than normal, and could therefore hamper the beneficial effects of these drugs on portal hemodynamics. Further, chronic administration of organic nitrates is well known to induce tolerance (5-8). Molsidomine, an antianginal agent belonging to the class of sydnonimines, is a vasodilator with a predominant effect on the venous system. It is a pro-drug metabolized by the liver in SIN-1A, an active metabolite that confers long-acting vasodilator properties on this drug; hemodynamic effects are still detectable 6 to 8 hr after oral administration (9-10). Like organic nitrates, nitroprusside and atrial natriuretic factor, molsidomine elicits vascular smooth muscle relaxation through activation of guanylate cyclase and accumulation of cyclic guanylic acid (11, 12).

Molsidomine was reported to induce venous pooling principally in the splanchnic territory (13). Accordingly, this drug could reduce portal pressure in patients with cirrhosis. It also has several potential advantages over organic nitrates. First, molsidomine was reported to have little or no (9, 14) arterial pressure–reducing effect in patients with normal livers. Second, this drug does not induce tolerance (15, 16).

We therefore undertook the present study aiming to assess the effects of molsidomine on systemic and portal hemodynamics in patients with alcoholic cirrhosis.

PATIENTS AND METHODS

Population. Thirteen consecutive patients with biopsy-proven alcoholic cirrhosis and portal hypertension were studied. Main clinical and biochemical characteristics were listed in Table 1.

All the patients gave their informed consent to participate in the study. The study was approved by the local ethical committee.

Methods. All the patients were studied after an overnight fast. A 7F Cournand catheter was inserted into the main right hepatic vein by the transjugular approach under fluoroscopic control. Indocyanine green (ICG; vert d'indocyanine, Laboratoire SERB, France) was infused through an antecubital vein at a constant rate of 0.15 $mg \cdot min^{-1}$ (0.19 $\mu mol/\cdot min^{-1}$) after a bolus injection of 10 mg. After an equilibration period of 30 min, simultaneous samples were drawn from a radial artery and from the hepatic vein at 2-min intervals for 10 min. Free and wedged hepatic vein pressures were measured with an electromagnetic manometer (Honeywell EB 200, Honeywell, Bois d'Arcy, France) by reference to a zero point situated at the level of the midaxillary line with the patient in the supine position.

A Swan-Ganz thermodilution catheter was used for measurements of cardiac output (COM .I, American Edwards Lab-

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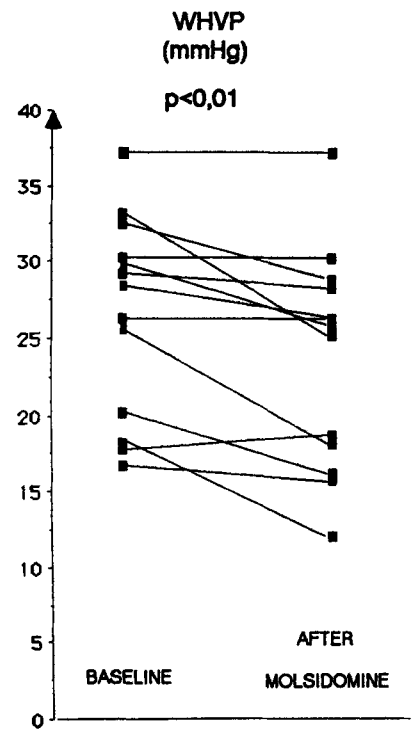

FIG. 1. Individual values of WHVP before and after oral ingestion of 4 mg of molsidomine.

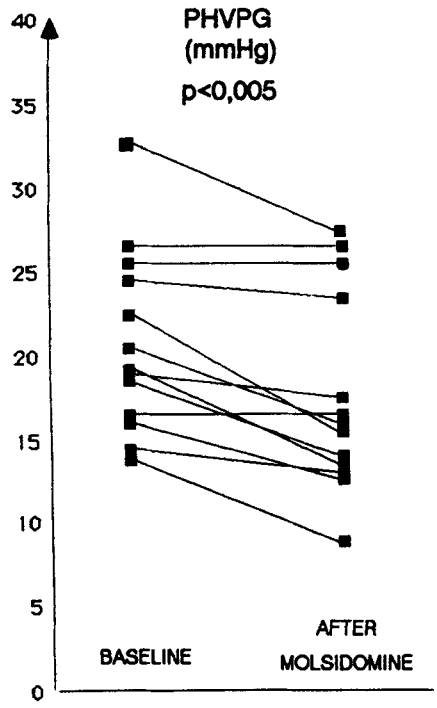

FIG. 2. Individual values of PHVPG before and after oral ingestion of 4 mg of molsidomine.

TABLE 1. Main clinical and biochemical characteristics of the patients

Characteristics	Patients (n = 13)
Age (yr)	56.7 ± 8.7[a]
Men	8 (62%)
Women	5 (38%)
Albumin ($\mu mol/L^{-1}$)	469.3 ± 76.2[a]
Total bilirubin ($\mu mol/L^{-1}$)	31.2 ± 23.1[a]
Ascites	10 (77%)
Encephalopathy	1 (8%)
Prothrombin index (%)	58.6 ± 10.0[a]
Child-Pugh score	9.4 ± 2.2[a]

[a]Mean ± S.D.

oratories, Santa Ana, CA). The arterial pressure was measured every 5 min using an external sphygmomanometer (Omega 1400, Hellige, Strasbourg, France). The heart rate was determined by continuous electrocardiogram monitoring.

The same measurements were repeated 60 min after oral administration of 4 mg of molsidomine.

Determination of ICG plasma concentrations was performed immediately at the end of the investigation by spectrophotometry at 805 nm. Hematocrit was measured by centrifugation (Compur M1100, Compur Electronic BH, Munich, West Germany).

Calculations. The portohepatic venous pressure gradient (PHVPG) was calculated as the difference between wedged hepatic vein pressure (WHVP) and free hepatic vein pressure (FHVP). Results were expressed as the mean of at least three measurements.

Hepatic extraction ratio (E) was calculated as $Cp\text{-}C_h/Cp$ where Cp and C_h were mean plasma concentrations of ICG in the arterial blood and in the hepatic venous blood, respectively. Hepatic blood flow and intrinsic hepatic clearance of ICG were calculated only when E was greater than 10%. Ten patients fulfilled this requirement. Hepatic plasma flow (HPF) was calculated as $I/ Cp\text{-}C_h$, where I was the infusion rate of ICG (0.15 $mg \cdot min^{-1}$) (17). Hepatic blood flow (HBF) was calculated as HPF/1-hematocrit. The intrinsic hepatic clearance (IHC) of ICG was calculated according to the sinusoidal model (18) as $-HBF \cdot In(1\text{-}E)$. Whether a steady-state concentration of ICG was achieved was assessed by determining the slopes of concentration vs. time curves during each sampling period. Systemic vascular resistances (SVR) were calculated as MAP/CO, where MAP was mean arterial pressure and CO was cardiac output.

Statistical Analysis. Results were expressed as mean ± S.D. Statistical comparisons were performed using the paired *t* test and two way ANOVA. Correlations were assessed using Spearman's correlation coefficient.

RESULTS

Molsidomine significantly diminished WHVP (−11.1% ± 13%), PHVPG (−15.4% ± 14%), MAP (−13.5% ± 13.5%) CO (−17.1% ± 1.7%) and HBF (−17.4% ± 11.2%) (Table 2, Figs. 1 and 2). Individual values of PHVPG before and after molsidomine ingestion are presented in Table 3.

FHVP, IHC of ICG, heart rate and SVR were not

TABLE 2. Hepatic and systemic hemodynamics before (A) and after (B) oral administration of 4 mg of molsidomine in 13 patients with alcoholic cirrhosis

	A	B	p value
FHVP (mm Hg)	6.4 ± 4.2	6.2 ± 4.6	NS
WHVP (mm Hg)	26.6 ± 6.7	23.6 ± 7.1	<0.01
HBF (ml · min · $^{-1}$)	1,336.5 ± 394.6	1,107.0 ± 360.7	<0.005
IHC (ml · min · $^{-1}$)	280.0 ± 162.9	269.0 ± 157.5	NS
MAP (mm Hg)	10.2 ± 1.2	8.8 ± 1.4	<0.01
CO (ml · min · $^{-1}$)	7,401.5 ± 1869.8	6,229.2 ± 1823.2	<0.001
SVR (dyn · cm · $^{-1}$)	1,488.5 ± 422.6	1,555.9 ± 469.3	NS
HR (beats · min · $^{-1}$)	89.9 ± 14.8	84.9 ± 9.7	NS

FHVP = free hepatic vein pressure, WHVP = wedged hepatic vein pressure, HBF = hepatic blood flow, IHC = intrinsic hepatic clearance, MAP = mean arterial pressure, CO = cardiac output, SVR = systemic vascular resistances, HR = heart rate, NS = not significant.

TABLE 3. Individual values of PHVPG

Patients	1	2	
1	21.8 ± 2.11	15.5 ± 1.3	
2	24.3 ± 0.6	23.7 ± 0	
3	18.8 ± 0.5	13.2 ± 1.67	
4	19.7 ± 0.6	16.1 ± 0.6	
5	15.7 ± 2.1	15.8 ± 1.5	
6	13.6 ± 0.9	8.3 ± 0.6	
7	25.0 ± 1.8	25.1 ± 3.6	
8	26.0 ± 2.0	26.3 ± 3.8	
9	14.3 ± 2.3	13.3 ± 0.6	
10	18.0 ± 1.0	13.4 ± 2.3	
11	18.2 ± 1.4	17.2 ± 4.3	
12	15.2 ± 1.0	12.5 ± 2.3	
13	30.7 ± 1.0	27.5 ± 0.6	
Mean ± S.D.	20.10 ± 5.17	17.53 ± 6.09	$p < 0.001$

Mean of three measurements ± S.D. in 13 patients with alcoholic cirrhosis before (1) and after (2) ingestion of 4 mg of molsidomine.

significantly changed after molsidomine ingestion (Table 2).

Decrease in PHVPG was greater than 20% in five patients, between 10% and 19% in two patients, below 10% in three patients and was not changed in three patients. There was no correlation between the decrease in PHVPG and the reduction in MAP ($r = 0.127$) on one hand and the decrease in CO ($r = 0.528$) on the other hand.

DISCUSSION

To investigate the effects of molsidomine on systemic and splanchnic hemodynamics, we studied 13 patients with alcoholic cirrhosis and portal hypertension.

Portal pressure was assessed using the WHVP, which has been shown to be very closely correlated with portal pressure in patients with alcoholic cirrhosis (19). Molsidomine reduced PHVPG by approximately 15%, mainly through reduction of WHVP because FHVP was not significantly changed. HBF was significantly decreased. However, HIC of ICG, which provides an estimation of the metabolic activity of the liver (20), was not modified. This indicates that, contrary to what was reported using vasoconstrictors (21-23), molsidomine reduces portal pressure without impairing liver elimination function.

CO was decreased by molsidomine, as expected. This effect is ascribed to a decrease in cardiac stroke volume resulting from venous pooling of blood. A contributing factor in our patients was the lack of reflex tachycardia. Similar results were reported using isosorbide dinitrate and were attributed to altered baroreceptor responsiveness in patients with cirrhosis (3).

Although molsidomine had been reported to have little or no arterial pressure–reducing effect (9, 14) in patients with normal livers, this drug induced a 13% decrease in MAP in our patients with alcoholic cirrhosis. However, SVR were not changed. This suggests that MAP reduction was accounted for by CO decrease and that molsidomine had little or no effect on arteriolar smooth muscle. PHVPG decrease was proportionately higher than MAP decrease and was not correlated with either MAP decrease or CO decrease. This suggests that molsidomine-induced PHVPG decrease must be at least in part ascribed to a direct action of the drug on splanchnic and portal resistances. This action could involve either a decrease in portal resistances or an increase in splanchnic resistances. Both effects were reported using nitrates. Decrease in portal resistances was attributed to a direct action of these vasodilating agents. On the contrary, increase in splanchnic resistances was supposed to be a result of sympathetic reflexes that would constrict the splanchnic vascular bed in response to venous pooling of blood (2). It is not possible from our data to assess the mechanism of molsidomine action. However, should baroreceptor sympathetic vasoconstricting reflexes be involved, one would have expected heart rate to increase, contrary to what was observed in our patients whose heart rate was unchanged.

Mean decrease in PHVPG was 15% in our patients. This figure obscures the fact that in three patients PHVPG was not changed by molsidomine. Three more patients exhibited only a minimal response. Should "nonresponders" be excluded, mean PHVPG decrease would have been 24%. We were unable to identify any clinical, biochemical, or hemodynamic factor that would differentiate "responders" and "nonresponders." MAP and CO decreased in every patient so that reduced absorption and liver activation of molsidomine could not explain this phenomenon. "Nonresponders" were also reported using propranolol and organic nitrates (4), in a proportion ranging from 30% to 50% (24, 25).

We conclude that in patients with alcoholic cirrhosis, molsidomine reduces PHVPG, MAP and CO. These effects are similar to those of organic nitrates. However,

molsidomine does not induce tolerance (15, 16) contrary to what was observed using organic nitrates (5-8). We therefore believe that molsidomine should be tested for long-term treatment of portal hypertension.

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