Br J Clin Pharmacol 1996; **41**: 409–413

Haemodynamic effects of molsidomine and propranolol in patients with cirrhosis

JEAN-MARC COMBIS, JEAN-PIERRE VINEL, PHILIPPE BADIA, KARL BARANGE, JEAN-LOUIS PAYEN, FLORENCE COMBIS, HERVÉ DESMORAT & JEAN-PIERRE PASCAL
Service d'hépato-gastroentérologie, CHU Purpan, Toulouse, France

Propranolol and molsidomine have both been shown to decrease the hepatic venous pressure gradient in patients with cirrhosis. The present study aimed at assessing the effects of the combination of these two drugs on splanchnic and systemic haemodynamics of cirrhotic patients. Fifteen patients with biopsy proven alcoholic cirrhosis had haemodynamic measurements under basal conditions, 60 min after oral administration of 4 mg molsidomine then 15 min after intravenous administration of 15 mg propranolol. As compared with baseline values, molsidomine was found to decrease mean arterial pressure (−7.9%, $P<0.01$), cardiac output (−7.3%, $P<0.01$), pulmonary wedged pressure (−45.8%, $P<0.05$) and hepatic venous pressure gradient (−11.7%, $P<0.01$). Propranolol decreased heart rate (−21%, $P<0.01$), further decreased cardiac output (−20.6%, $P<0.01$) and hepatic venous pressure gradient (−10.5%, $P<0.01$). As a whole, molsidomine plus propranolol decreased mean arterial pressure (−8%, $P<0.01$), heart rate (−19%, $P<0.01$), cardiac output (−26.5%, $P<0.01$) and hepatic venous pressure gradient (−21%, $P<0.01$). Pulmonary wedged pressure, liver blood flow and hepatic intrinsic clearance of indocyanine green were not significantly changed by the association of molsidomine and propranolol. We conclude that in patients with cirrhosis, molsidomine and propranolol potentiate their effects on hepatic venous pressure gradient. Such a combination could therefore prove useful in the treatment of portal hypertension.

Keywords portal hypertension cirrhosis β-adrenoceptor blockers vasodilatators

Introduction

Non selective β-adrenoceptor blockers, namely propranolol and nadolol, have been shown to reduce the risk of variceal bleeding [1, 2] or rebleeding [3, 4] from œsogastric varices in patients with cirrhosis and portal hypertension.

Recently, it has been suggested that the coadministration of propranolol with other drugs could improve their beneficial effect. Vasodilators seem to be the most promising candidates [5, 6]. The haemodynamic efficacy of propranolol is secondary to the inhibition of both β_1-and β_2-receptors [7–10]. Among vasodilatators, molsidomine an antianginal agent of the class of sydnonimines, could offer several advantages. The haemodynamic effects of this drug are similar to those of organic nitrates with a peripheral venous pooling and a reduction of the cardiac preload induced by the relaxant effect on smooth vascular musculature of SIN1-A, the metabolically active product of molsidomine. This action is mediated by activation of guanylate cyclase and accumulation of cyclic guanylic acid. However, molsidomine may have potential advantages over nitrates since it does not induce tolerance and has little or no arterial pressure reducing effect in patients with normal liver function [11–13]. Molsidomine was reported to decrease portal pressure of cirrhotic patients [14, 15] and cirrhotic rats [16] by reducing porto-hepato-collateral resistance. The combination of these two drugs has not yet been investigated.

The aim of this study was to determine whether molsidomine and propranolol have additive effects on hepatic venous pressure gradient.

This work was presented to the annual meeting of the European Association for the Study of Liver Disease, August 1992, Vienna, Austria. It was published in an abstract form *(J Hepatol* 1992; **16**, suppl 1, P1, 76).

Correspondence: Dr J. M. Combis, Service d'hépato-gastro-entérologie, CHU Purpan 31059 Toulouse Cedex, France.

Methods

Patients

Fifteen patients (nine males and six females, mean age: 52.5 ± 11 years) with biopsy proven alcoholic cirrhosis and portal hypertension assessed by the presence of oesophageal varices were included in the study. Patients with a previous history of variceal haemorrhage or hepatocellular carcinoma, with contraindication to propranolol or molsidomine and patients treated with vasoactive drugs and/or diuretics were excluded from the study. The main clinical and biochemical characteristics of the patients are given in Table 1.

Written informed consent was obtained from each patient and the study was approved by the local ethics committee.

Methods

Patients were studied after an overnight fast. A vessel dilatator with a polypropylene sheath (Desilet; Vygon, Ecoen, France) was placed in the right jugular vein in order to permit passage of different catheters.

Systemic haemodynamic parameters were recorded using a Swan-Ganz pulmonary artery catheter (Baxter Healthcare Corporation, Edwards Critical-Care Division, Santa-Ana, CA, USA). Occluded pulmonary arterial pressure (OPAP) was measured with an electromagnetic manometer (Honeywell EB, Honeywell, Saint-Quentin en Yvelines, France) by reference to a zero point situated at the level of the midaxillary line with the patient in the supine position. Cardiac output (CO) was determinated by the thermodilution method using a COM I computer (American Edwards Laboratories, Santa-Ana, CA, USA). Heart rate (HR) was monitored by continuous electrocardiogram, arterial pressure by an external sphygmomanometer (Omega 1400, Hellige, Strasbourg, France).

A 7 F Cournand catheter was inserted into the right hepatic vein by the transjugular approach under fluoroscopic control. Free hepatic venous pressure (FHVP) and wedged hepatic venous pressure (WHVP) were measured using the same transducer as for the measurement of pulmonary pressures.

After an initial bolus injection of 10 mg, indocyanine green (ICG, vert d'indocyanine, Laboratoire SERB, Paris, France) was infused through an antecubital vein at a constant rate of 0.15 mg min^{-1} (0.19 μmol min^{-1}) until steady state plasma concentration was achieved. After a period of 30 min, blood samples were simultaneously drawn from the jugular vein and the hepatic vein at 2 min intervals for 10 min. Determination of plasma ICG concentrations was performed at the end of the investigation by spectrophotometry at 805 nm. Haematocrit was measured by centrifugation (Compur M1100, Compur electronic BH, Munich, Germany).

Table 1 Main clinical and biochemical characteristics of the patients

Age (years)	52.5 ± 11
Sex ratio (men/women)	9/6
Total bilirubin (μmol l^{-1})	48.4 ± 61.9
Albumin (μmol l^{-1})	378 ± 63.4
Prothrombin index (%)	59.7 ± 14.9
Ascites	9 (60%)
Encephalopathy	1
Child-Pugh score	9.5 ± 1.6

Calculations

The hepatic venous pressure gradient (HVPG) was calculated as the difference between WHVP and FHVP. Results were expressed as the mean of at least three measurements. Systemic vascular resistance (SVR) was calculated as (MAP-RAP) × 80/CO where MAP was mean arterial pressure, RAP right auricular pressure and CO cardiac output.

Hepatic extraction (HE) was calculated as (Cp-Ch)/Cp where Cp and Ch were mean concentrations of ICG in peripheral and hepatic veins, respectively. Hepatic plasma flow (HPF) was determined as I/(Cp-Ch) where I was the infusion rate of ICG. Hepatic blood flow (HBF) was calculated as HPF/(1-haematocrit). The intrinsic hepatic clearance (IHC) was calculated according to the sinusoidal model [17, 18] as $-\text{HBF}\ln(1\text{-E})$. HBF and IHC were calculated only when E was greater than 10%.

Experimental design

For each patient, systemic and splanchnic haemodynamic parameters were obtained at baseline, 60 min after oral administration of 4 mg molsidomine then 15 min after intravenous administration of 15 mg propranolol.

Statistical analysis

Results were expressed as mean ± s.d. Statistical comparisons were performed using Student's t-test and one way analysis of variance for repeated data. Statistical significance was established at $P < 0.05$.

Results

Effect of molsidomine and propranolol on systemic haemodynamics

Molsidomine significantly decreased MAP (86.6 ± 10.8 *vs* 79.7 ± 6.4, $P < 0.01$; [−7.9%]), OPAP (6.3 ± 3.9 *vs* 3.4 ± 3.6, $P < 0.05$, [−45.8%]) and CO (7.6 ± 2 *vs* 7 ± 1.7, $P < 0.01$; [−7.3%]); HR was unchanged. The addition of propranolol induced a further and significant reduction of HR (81.1 ± 16.4 *vs* 64 ± 11, $P < 0.01$; [−21.1%]) and CO (7 ± 1.7 *vs* 5.5 ± 1.4, $P < 0.01$; [−20.6%]) but MAP remained unchanged. These

changes were associated with an increase in OPAP (3.4 ± 3.6 *vs* 5.9 ± 4.5, $P < 0.05$; [+73.1%]). As compared with basal values, MAP (86.6 ± 10.8 *vs* 79.6 ± 9.1, $P < 0.01$; [−8.1%]), HR (79 ± 14.8 *vs* 64 ± 11, $P < 0.01$; [−18.9%]) and CO (7.6 ± 2 *vs* 5.5 ± 1.4, $P < 0.01$; [−26.4%]) were decreased by molsidomine plus propranolol; OPAP remained unchanged.

Effect of molsidomine and propranolol on splanchnic haemodynamics

Molsidomine administration caused a significant decrease in HVPG (19.1 ± 4.8 *vs* 16.8 ± 5.6, $P < 0.01$; [−11.7%]). Addition of propranolol further diminished HVPG by 10.4% (16.8 ± 5.6 *vs* 15.1 ± 5.5, $P < 0.01$). Finally, HVPG was decreased by 20.9% by the association of molsidomine and propranolol. This effect was mainly due to a marked fall in WHVP (24.7 ± 5.1 *vs* 21 ± 5.9, $P < 0.01$), without significant change in FHVP. Individual values of HVPG before then after molsidomine ingestion and after propranolol administration are presented in Figure 1.

In the 14 patients in whom the calculations were made, IHC and HBF were not modified by molsidomine, propranolol or by the association of the two drugs.

Discussion

The results of this study demonstrate that molsidomine and propranolol have a cumulative effect and lower portal pressure without causing deleterious systemic haemodynamic effect or metabolic dysfunction of the liver as assessed by ICG clearance. The combination of molsidomine and propranolol decreased HVPG by 21%; this diminution was 1.8 times greater than that generated by molsidomine alone. This was achieved without important effects on systemic haemodynamics. A decrease of HVPG under 12 mmHg was observed in seven patients. Feu *et al.* [19] have reported that a fall in HVPG greater than 20% was associated with a very low risk of bleeding. Accordingly, the association of propranolol and molsidomine could be more effective than propranolol alone in the prevention of the first bleeding episode in patients with cirrhosis.

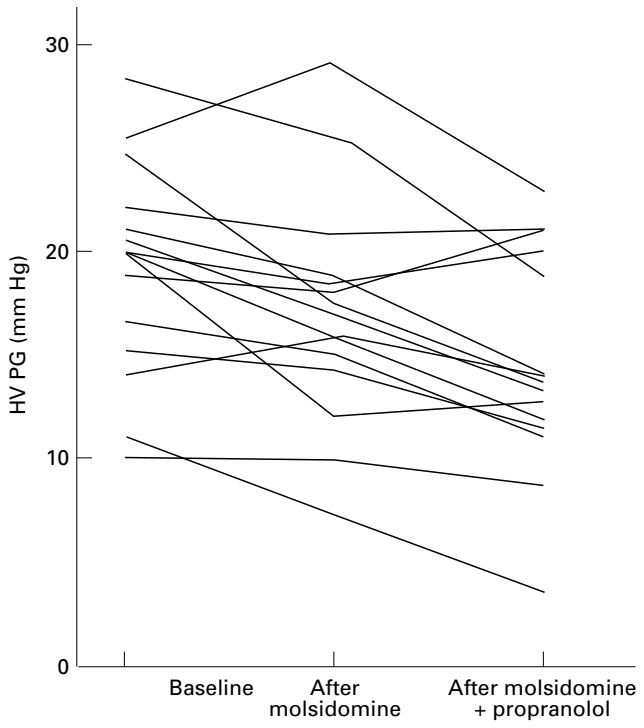

Figure 1 Individual values of hepatic venous pressure gradient (HVPG) before and after ingestion of 4 mg molsidomine, then after administration of 15 mg propranolol.

Several studies have shown that propranolol decreased intrinsic hepatic clearance of ICG [20, 21] thus suggesting that metabolic function of the liver was altered. In our work, neither molsidomine nor propranolol decreased hepatic intrinsic clearance of ICG. At least two explanations for this phenomenon can be proposed: (a) we cannot rule out a β-type error in statistical analysis; however should this be the case, the deleterious metabolic effect of the combination of molsidomine and propranolol would probably be too small to have any clinical relevance; (b) molsidomine could prevent the propranolol induced hepatic intrinsic clearance fall by decreasing intra-hepatic resistance [16]. Such an effect has been reported by Reichen *et al.* [22] and Bhathal *et al.* [23] with vasodilatators. Using isolated perfused cirrhotic rat livers, they demonstrated that the decrease of intra-hepatic resistance generated by the perfusion of vasodilatators was associated with an inprovement in liver metabolic function. Whether molsidomine acts in the same way still needs to be proved.

Our results do not provide information about the mechanism by which the combination of molsidomine and propranolol decreases HVPG. However, since propranolol induced a further decrease in portal pressure, it is likely that the final decrease in HVPG observed after molsidomine and propranolol proceeded both from propranolol dependent splanchnic arteriolar vasoconstriction and from the decrease in hepatic resistance induced by molsidomine. There is a growing body of evidence that propranolol decreases collateral blood flow as assessed by azygos blood flow and enhances collateral resistances [24, 25]. The effect of molsidomine on collateral circulation remains obscure since azygos blood flow decreases in some cases and increases in others [14]. In a previous study from our group, Desmorat *et al.* [16] have shown that cirrhotic rats treated with molsidomine exhibited a trend towards greater collateral blood flow and smaller hepato-porto-collateral resistance. Further studies are clearly necessary to clarify the effect of the combination of molsidomine and propranolol on collateral circulation.

Among the 15 patients studied, five (33%) were 'nonresponders' to molsidomine, three of whom became responders after addition of propranolol; four (27%) were 'nonresponders' to propranolol, two of whom had previously responded to molsidomine; three (20%) were 'nonresponders' to both molsidomine and propranolol. Garcia-Pagan *et al.* [6] have evaluated the effect of the association of isosorbide-5-mononitrate and propranolol on portal hypertension. They have observed a similar

decrease in HVPG (−26.6%) as that obtained with molsidomine plus propranolol. However, in this work, all the patients exhibited a decrease in HVPG after isosorbide-5-mononitrate administration, even in 'nonresponders' to propranolol. The discrepency between our study and that of Garcia-Pagan *et al.* [6] could be accounted for by several reasons: (a) molsidomine is a prodrug which needs to be transformed by the liver to SIN 1 and SIN-1A to be active [11]; liver function impairment induced by cirrhosis could be responsible for a modification of the metabolism of molsidomine. However, the decrease of MAP observed in our work argues against this hypothesis; (b) we cannot rule out that the chronology of administration of the two drugs play a role since we have not investigated the haemodynamic effects of propranolol followed by the ingestion of molsidomine. The effects of propranolol on portal hypertension have been largely investigated while there are only scarce data on molsidomine. Thus, we have chosen to give molsidomine prior to propranolol in order to provide further information on the effects of molsidomine in this indication. Nevertheless it would be surprising that previous administration of β-adrenoceptor blockers modified the results we have obtained and made patients responders to organic nitrates while these drugs were not active in all the patients when given in monotherapy; (c) dosage of the drugs: this hypothesis seems to be irrelevant since heart rate was decreased by about 25% and MAP by 8%. Our work only provides evidence that cirrhotic patients can be 'nonresponders' in term of portal pressure either to propranolol, molsidomine or to both types of drugs. Nevertheless, the term 'nonresponders' could be irrelevant in clinical practice since in patients in whom propranolol did not modify HVPG, azygos blood flow or intra-variceal pressure were decreased, thus suggesting that haemorrhagic risk could be decreased [24, 26].

In conclusion, propranolol and molsidomine potentiate their effects on hepatic venous pressure gradient. The effect on the association of the two drugs on systemic haemodynamics were mild; hepatic blood flow and elimination capacity of the liver were not modified. Such an association could therefore prove useful in the treatment of portal hypertension.

References

1 Hayes PC, Davis JM, Lewis JA, Bouchier IAD. Meta-analysis of the value of propranolol in prevention of variceal haemorrage. *Lancet* 1990; **336**: 153–156.

2 Poynard T, Cales P, Pasta L, *et al*, Franco-Italian Multicentric Study Group. Beta-adrenergic-antagonist drugs in the prevention of gastrointestinal bleeding in patients with cirrhosis and esophageal varices. An analysis of data and prognostic factors from 589 patients from four randomized clinical trials. *N Engl J Med* 1991; **324**: 1532–1538.

3 Lebrec D, Poynard T, Hillon P, Benhamou JP. Propranolol for prevention of recurrent gastrointestinal bleeding in patients with cirrhosis: a controlled study. *N Engl J Med* 1981; **305**: 1371–1374.

4 Colombo M, De Franchis R, Tommasini M, Sangiovanni A, Dioguardi N. β-Blockade prevents recurrent gastrointestinal bleeding in well-compensated patients with alcoholic cirrhosis: a multicenter randomized controlled trial. *Hepatology* 1989; **9**: 433–138.

5 Kroeger R, Groszmann RJ. The effect of the combination of nitroglycerin and propranolol on splanchnic and systemic hemodynamics in a portal hypertensive rat model. *Hepatology* 1985; **5**: 425–430.

6 Garcia-Pagan JC, Navasa M, Bosh J, Bru C, Pizcueta P and Rodes J. Enhancement of portal pressure reduction by the association of isosorbide-5-mononitrate to propranolol administration in patients with cirrhosis. *Hepatology* 1990; **11**: 230–238.

7 Hillon P, Lebrec D, Munoz C, Jungers M, Goldfarb G, Benhamou JP. Comparison of a cardioselective and a non selective β blocker on portal hypertension in patients with cirrhosis. *Hepatology* 1982; **2**: 528–531.

8 Westaby D, Bihari DJ, Gimson AES, Crossley IR, Williams R. Selective and non selective beta receptor blockade in the reduction of portal pressure in patients with cirrhosis and portal hypertension. *Gut* 1984; **25**: 121–124.

9 Kroeger RJ and Groszmann RJ. Effect of selective blockade of β2 adrenergic receptors on portal and systemic hemodynamics in a portal hypertensive rat model. *Gastroenterology* 1985; **88**: 896–900.

10 Mills PR, Rae AP, Farah DA, Russel RI, Lorimer AR, Carter D. Comparison of three adrenoreceptor blocking agents in patients with cirrhosis and portal hypertension. *Gut* 1984; **25**: 72–78.

11 Kokovetz WR, Holzmann S. Mechanisms of vasodilatation by molsidomine. *Am Heart J* 1985; **109**: 637–640.

12 Majid PA, De Feyter PJF, Van Der Wall EE, Wardeh R, Roos JP. Molsidomine in the treatment of patients with angina pectori: acute hemodynamic effects and clinical efficacy. *N Engl J Med* 1980; **302**: 1–6.

13 Jansen W, Eggeling T, Meyer L, Taucher M, Hilger HH. Acute and chronic effects of molsidomine on pulmonary artery pressure and work capacity in patients with coronary heart disease. *Eur Heart J* 1987; **8**: 870–877.

14 Ruiz Del Arbol L, Garcia-Pagan JC, Feu F, Pizcueta MP, Bosh J, Rodes J. Effects of molsidomine, a long acting venous dilatator on portal hypertension: a hemodynamic study in patients with cirrhosis. *J Hepatol* 1991; **13**: 179–186.

15 Vinel JP, Monnin JL, Combis JM, Cales P, Desmorat H, Pascal JP. Hemodynamic evaluation of molsidomine: a vasodilatator with antianginal properties in patients with alcoholic cirrhosis. *Hepatology* 1990; **11**: 239–242.

16 Desmorat H, Vinel JP, Lahlou O, *et al.* Systemic and splanchnic hemodynamic effects of molsidomine in rats with carbon tetrachloride induced cirrhosis. *Hepatology* 1991; **13**: 1181–1184.

17 Bass L, Keiding S, Winkler K, Tygstrup NJ. Enzymatic elimination of substances flowing through the intact liver. *J Theor Biol* 1976; **61**: 393–410.

18 Keiding S. Hepatic clearance and liver blood flow. *J Hepatol* 1987; **4**: 393–398.

19 Feu F, Cirera I, Garcia-Pagan JC, *et al.* Portal pressure response to drug therapy predicts the risk of rebleeding fron esophgeal varices. *J Hepatol* 1992; **16** (suppl 1): S37 (abstract)

20 Vinel JP, Caucanas JP, Cales P, Suduca JM, Voigt JJ, Pascal JP. Effect of propranolol on metabolic activity of the liver in patients with alcoholic cirrhosis. *J Hepatol* 1988; **7**: 186–192.

21 Braillon A, Jiron MI, Valla D, Cales P, Lebrec D. Effects of propranolol on hepatic blood flow in patients with cirrhosis. *Clin Pharmacol Ther* 1985; **37**: 376–380.

22 Reichen J, Le M. Verapamil favorably influences hepatic microvascular exchange and function in rats with cirrhosis of the liver. *J Clin Invest* 1986; **78**: 448–455.
23 Bhathal PS, Groszmann RJ. Reduction of the increased portal vascular resistance of the isolated perfused cirrhotic rat liver by vasodilatators. *J Hepatol* 1985; **1**: 325–337.
24 Bosh J, Mastai R, Kravetz D, *et al*. Effects of propranolol on azygos venous blood flow and hepatic and systemic hemodynamics in cirrhosis. *Hepatology* 1984; **4**: 1200–1205.
25 Cales P, Braillon A, Jiron MI, Lebrec D. Superior portosystemic collateral circulation estimated by azygos blood flow in patients with cirrhosis. Lack of correlation with esophageal varices and gastrointestinal bleeding. Effects of propranolol. *J Hepatol* 1984; **1**: 37–46.
26 Feu F, Bordas JM, Luca A, *et al*. Reduction of variceal pressure by propranolol: comparison of the effects on portal pressure and azygos blood flow in patients with cirrhosis. *Hepatology* 1993; **18**: 1082–1089.

(*Received 1 May 1995,*
accepted 22 November 1995)

