The calcium-channel blocker, verapamil, does not improve portal pressure in patients with alcoholic cirrhosis

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1 Recently the calcium-channel blocker, verapamil, has been reported to decrease portal pressure in rats with experimental cirrhosis and in patients with liver cirrhosis.

2 In eight patients with alcoholic cirrhosis the effect of verapamil (5 mg i.v.) on systemic and splanchnic haemodynamics was investigated.

3 Mean arterial pressure, wedged hepatic venous pressure, hepatic venous pressure gradient, and verapamil plasma concentrations were measured before and at 10, 20, 30 min following 5 mg i.v. administration of verapamil. At 30–40 min cardiac output, systemic vascular resistance and hepatic blood flow were also measured.

4 Verapamil plasma concentrations averaged 47.9 ± 52.0 , 36.5 ± 36.3 , 31.3 ± 33.9 ng ml⁻¹ at 10, 20, 30 min respectively: mean arterial pressure and systemic vascular resistance decreased significantly (–9% and –14% respectively), and cardiac index increased significantly (+8%). Wedged hepatic venous pressure and hepatic venous pressure gradient remained unchanged, variations never exceeding 0.2 kPa. Hepatic blood flow increased significantly by 12%.

5 These results show that i.v. administration of 5 mg verapamil does not decrease portal pressure in alcoholic cirrhosis. This lack of effect is probably the consequence of a balance between decrease in porto-hepatic vascular resistance and increase in splanchnic blood inflow.

Keywords verapamil liver cirrhosis liver circulation portal hypertension

Introduction

It is well established that two pathphysiological determinants, namely increase in portal blood inflow and in outflow resistance to portal blood flow, are responsible for the development of portal hypertension in patients with cirrhosis (Benoit & Granger, 1986).

In the past few years vasodilators have been suggested as possible therapeutic agents for portal hypertension in patients with cirrhosis (Halleman *et al.*, 1983; Groszmann *et al.*, 1982; Freeman *et al.*, 1985; Merkel *et al.*, 1987). This approach stems by the fact that nitroglycerin, isosorbide dinitrate and sodium nitroprusside have been shown to decrease portal pressure by

decreasing portal blood inflow, probably through a baroreceptor-mediated reflex (Kroeger & Groszmann, 1985), and also by decreasing intrahepatic resistance to portal blood flow by a direct effect on intrahepatic vessels (Bhathal & Grossman, 1985).

Recently the calcium-channel blocker, verapamil, has been reported to decrease portal pressure in rats with experimental cirrhosis (Reichen *et al.*, 1986) as well as in few patients with cirrhosis (Freeman *et al.*, 1985; Kong *et al.*, 1986), and therefore its therapeutic use was suggested.

In our patients with cirrhosis and portal hyper-

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Table 1 Clinical and biochemical data in the eight patients with cirrhosis

Case	Age (years)	Ascites	Oesophageal varices degree (*)	Child's grade	Albumin ($\mu\text{mol L}^{-1}$)	Bilirubin ($\mu\text{mol L}^{-1}$)	Prothrombin time (%)
1	59	–	F3	B	421	18.8	48
2	26	–	F1	B	624	27.4	39
3	50	–	F3	A	609	15.4	56
4	38	–	F3	B	537	49.7	46
5	34	+	F1	C	421	149.0	31
6	50	–	F2	B	479	18.8	47
7	46	–	F3	B	508	24.0	61
8	58	–	F2	A	522	25.7	59

* According to the Japanese classification (*Jap. J. Surg.*, 10, 84, 1980).

tension we observed a lack of effect of verapamil on portal pressure, and therefore undertook this study to investigate the mechanism for this lack of effect.

Methods

Eight patients with biopsy proven alcoholic cirrhosis were studied. All patients admitted to have drunk at least 100 g day⁻¹ of alcohol for 5 years or longer. At the time of the study all patients had oesophageal varices; none had clinical signs of hepatic encephalopathy or ascites; five had previous gastrointestinal bleeding which occurred at least 1 month before the study. Informed consent to the procedure after full explanation of the procedure was obtained from all subjects. Main clinical and biochemical data are given in Table I.

After overnight fast catheters were inserted into a hepatic vein, the pulmonary artery and a peripheral artery and the following parameters were measured: mean arterial pressure (MAP) as diastolic + 1/3 pulse pressure, wedged hepatic vein pressure (WHVP) and free hepatic vein pressure (FHVP) using a balloon catheter, and hepatic blood flow (HBF) using the ICG constant infusion technique (Caesar *et al.*, 1961). From WHVP and FHVP, hepatic venous pressure gradient (HVPG) was computed as index of portal hypertension. In six patients cardiac output was measured using the thermal dilution method and was expressed as cardiac index (CI) dividing cardiac output by the body surface area. Systemic vascular resistance index (SVRI) was computed as

$$\text{SVRI} = \text{MAP} \times 79.9/\text{CI}$$

Details of the procedure have been previously reported (Merkel *et al.*, 1986, 1987).

After baseline values were obtained, each patient received intravenously 5 mg of verapamil in 5 min, and MAP, WHVP and FHVP were measured after 10, 20, 30 min, CI after 30 min and HBF between 30 and 40 min. Verapamil plasma levels were measured at 10, 20, 30 min by a high performance liquid chromatographic assay according to Harapat & Kates (1980).

Results are given as mean $\pm$ s.d. Statistical analysis was performed using paired Student's *t*-test corrected for multiple comparison according to Bonferroni (Godfrey, 1985) and regression with the least square method. The null hypothesis was rejected at the 0.05 significance level.

Results

In the eight patients with alcoholic cirrhosis verapamil plasma levels averaged 47.9 ± 52.0 ng ml⁻¹, 36.5 ± 36.3 ng ml⁻¹, 31.4 ± 33.9 ng ml⁻¹ at 10, 20, 30 min, respectively, as shown in Figure 1. Average MAP significantly decreased from 97 ± 7 mmHg to 89 ± 9 mmHg, 91 ± 9 mmHg, 89 ± 7 mmHg at 10, 20, 30 min respectively, $P < 0.05$, 0.05, 0.025 respectively. Mean WHVP and HVPG remained unchanged at 10, 20, 30 min. following verapamil administration, and averaged 3.37 ± 0.65 kPa and 2.78 ± 0.72 kPa respectively before infusion, and 3.37 ± 0.64 kPa and 2.77 ± 0.72 kPa respectively both at 10 and 20 and 30 min after verapamil ($P > 0.6$). In any patient variations in WHVP or HVPG never exceeded 0.2 kPa.

Average CI significantly increased (from 4.50 ± 0.63 to 4.84 ± 0.68 l min⁻¹ m²; $P < 0.025$). Mean SVRI fell from 1701 ± 181 to 1457 ± 152 dyn s cm⁻⁵ m²; ($P < 0.01$). Mean HBF increased significantly from 1315 ± 427 to 1486 ± 419 ml min⁻¹ (+ 12%; $P < 0.05$). Increase in HBF was logarithmically correlated to increase in CI ($r =$

Figure 1 Wedged hepatic vein pressure (WHVP), hepatic venous pressure gradient (HVPG), mean arterial pressure (MAP), and verapamil plasma levels before and 10–30 min following i.v. administration of verapamil. ▼ = $P > 0.6$; * = $P < 0.05$; ** = $P < 0.025$.

Figure 2 Cardiac index (CI, $1 \text{ min}^{-1} \text{ m}^{-2}$), systemic vascular resistance index (SVRI, $\text{dyn s cm}^{-5} \text{ m}^2$), hepatic blood flow (HBF, ml min^{-1}) before and 30–40 min following i.v. administration of verapamil. * = $P < 0.05$; ** = $P < 0.025$; *** = $P < 0.01$.

0.80; $P = 0.05$). Individual values are illustrated in Figures 1 and 2.

Discussion

This study shows that intravenous administration of 5 mg verapamil did not influence portal hypertension in patients with alcoholic cirrhosis.

Reichen *et al.* (1986), Freeman *et al.* (1985), and Kong *et al.* (1986) obtained results different from ours in animals and patients respectively. The difference between our results and those studies is not easy to explain. In the experimental study (Reichen *et al.*, 1986) portal pressure was measured by splenic puncture at laparotomy, and this may have resulted in leakage of ascites, with decrease in cardiac output and portal pressure. That this could be the mechanism is suggested by the fact that also three of the six animals receiving placebo exhibited a marked decrease in portal pressure. Kong *et al.* (1986) and Freeman *et al.* (1985) in their human studies used the same technique as in our study. However Kong *et al.* (1986) reported results obtained in a group of patients with post-necrotic cirrhosis. In this clinical situation HVPG is known to be a poor indicator of portal pressure, due to the presence of a substantial presinusoidal outflow block (Pomier-Layrargues *et al.*, 1985). Therefore changes in HVPG are unlikely to reflect changes in portal pressure. This interpretation is supported by the fact that all patients in that study had had bleeding oesophageal varices, but had a rather scanty elevation in HVPG, which in half of the subjects did not exceed 12 mm Hg. This is the threshold for the developing of bleeding varices in sinusoidal portal hypertension (Viallet *et al.*, 1975). These problems were not present in our study, since in alcoholic cirrhosis HVPG clearly reflects portal pressure (Boyer *et al.*, 1977; Pomier-Layrargues *et al.*, 1985; Bosch *et al.*, 1986). All our patients had elevated HVPG, mean values being approximately 50% higher than those reported by Kong *et al.* (1986).

Freeman *et al.* (1985) did not provide the individual measurements of their results. However it is likely that changes in HVPG in their patients were not marked, since in a previous report on a smaller series of patients the same Authors claimed that verapamil did not decrease portal pressure (Freeman *et al.*, 1983).

Difference in dose and timing might also explain, at least in part, different results. In our study verapamil plasma levels showed a mean value of 47.9 ng ml⁻¹ at 10 min, and was associated with the systemic haemodynamic changes

typical of the calcium-channel blockers (Singh *et al.*, 1978). Furthermore the patient with a 10 min verapamil plasma level of 172.1 ng ml⁻¹ did not even exhibit decrease in portal pressure. Verapamil plasma levels are missing in the other reports on patients with cirrhosis (Freeman *et al.*, 1985; Kong *et al.*, 1986).

As already shown in normal man (Singh *et al.*, 1978), also in patients with cirrhosis verapamil decreased MAP and SVRI and increased CI. These effects are due to decrease in arteriolar resistance in the systemic circulation because of inhibition of the calcium flux in the smooth muscle cells of the arterial wall (Fleckenstein, 1977). Such effect is likely to happen also in the splanchnic arterial circulation, and it leads to the increase in hepatic blood flow we found in our subjects. The correlation between the increase in HBF and in CI is in agreement with this interpretation.

In isolated perfused rat liver verapamil was shown to decrease porto-hepatic vascular resistance (Reichen & Le, 1986), and this mechanism was claimed as responsible for the decrease in portal pressure reported in cirrhotic rats (Reichen *et al.*, 1986). We did not measure porto-hepatic vascular resistance. Nevertheless the increase in HBF associated to maintenance of HVPG strongly suggests a decrease in resistance, in agreement with results in experimental animals (Reichen & Le, 1986). However all mechanisms increasing cardiac output and splanchnic blood inflow also increase portal pressure in cirrhosis (Blendis, 1981; Vorobioff *et al.*, 1984; McCormick & Hegarthy, 1986); therefore arterial vasodilation induced by verapamil in the arterial part of the splanchnic circulation probably hinders the effect of the drug on porto-hepatic resistance and maintains portal pressure at the same level.

In conclusion verapamil did not decrease portal pressure in patients with alcoholic cirrhosis. This lack of effect is probably the consequence of the increase in splanchnic blood inflow which counterbalance the decrease in porto-hepatic vascular resistance. Therefore the ideal drug for the medical treatment of portal hypertension should decrease porto-hepatic, but not splanchnic arterial resistance.

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References

- Benoit, J. N. & Granger, N. (1986). Splanchnic hemodynamics in chronic portal venous hypertension. *Sem. Liv. Dis.*, **6**, 287–298.
- Bhathal, P. S. & Grossman, H. J. (1985). Reduction of the increased portal vascular resistance of the isolated perfused cirrhotic rat liver by vasodilators. *J. Hepatol.*, **1**, 325–337.
- Blendis, L. M. (1981). Portal hypertension. In *Hepatic circulation in health and disease*, ed. Lauth W. W., pp. 329–350. New York, Raven Press.
- Bosch, J., Mastai, R., Kravetz, D., Navasa, M. & Rodés, J. (1986). Hemodynamic evaluation of the patient with portal hypertension. *Sem. Liv. Dis.*, **6**, 309–317.
- Boyer, T. D., Triger, D. R., Horisawa, M., Redeker, A. G. & Reynolds, T. B. (1977). Direct trans-hepatic measurement of portal vein pressure using a thin needle. *Gastroenterology*, **72**, 584–589.
- Caesar, J., Shaldon, S., Chiandussi, L., Guevara, L. & Sherlock, S. (1961). The use of indocyanine green in the measurement of hepatic blood flow and as a test of hepatic function. *Clin. Sci.*, **21**, 43–57.
- Fleckenstein, A. (1977). Specific pharmacology of calcium in myocardium, cardiac pacemakers, and vascular smooth muscle. *Ann. Rev. Pharmac. Tox.*, **17**, 149–166.
- Freeman, J. G., Barton, J. R. & Record, C. O. (1983). The effect of vasodilators on portal pressure in patients with portal hypertension. *European Association for the Study of the Liver*, Meeting 1983, Southampton, England, Abstracts p. 41.
- Freeman, J. G., Barton, J. R. & Record, C. O. (1985). Effect of isosorbide dinitrate, verapamil, and labetalol on portal pressure in cirrhosis. *Br. med. J.*, **291**, 561–562.
- Godfrey, K. (1985). Comparing the means of several groups. *New Engl. J. Med.*, **313**, 1450–1456.
- Groszmann, R. J., Kravetz, D., Bosch, J., Glickman, M., Bruix, J., Bredfeldt, J., Conn, H. O., Rodés, J. & Storer, E. H. (1982). Nitroglycerin improves the hemodynamic response to vasopressin in portal hypertension. *Hepatology*, **2**, 757–762.
- Halleman, R., Naeije, R., Mols, P., Melot, C. & Reding, P. (1983). Treatment of portal hypertension with isosorbide dinitrate alone or in combination with vasopressin. *Crit. Care Med.*, **11**, 536–540.
- Kong, C. W., Lay, C. S., Tsai, Y. T., Yeh, C. L., Lai, K. H., Lee, S. D., Juei, K. J. & Chiang, B. N. (1986). The hemodynamic effect of verapamil on portal hypertension in patients with post-necrotic cirrhosis. *Hepatology*, **6**, 423–426.
- Kroeger, R. J. & Groszmann, R. J. (1985). The effect of the combination of nitroglycerin and propranolol on splanchnic and systemic hemodynamics in a portal hypertensive rat model. *Hepatology*, **5**, 425–430.
- McCormick, P. A. & Hegarthy, J. E. (1986). Post-prandial changes in portal venous pressure in cirrhotic and non-cirrhotic patients with portal hypertension. *J. Hepatol.*, **3** suppl. 1, 53.
- Merkel, C., Finucci, G. F., Zuin, R., Bazzlerla, G., Bolognesi, M., Sacerdoti, D. & Gatta, A. (1987). Effects of isosorbide dinitrate on portal hypertension in alcoholic cirrhosis. *J. Hepatol.*, **4**, 174–180.
- Merkel, C., Sacerdoti, D., Finucci, G. F., Zuin, R., Bazzlerla, G., Bolognesi, M. & Gatta, A. (1986). Effect of nadolol on liver haemodynamics and function in patients with cirrhosis. *Br. J. clin. Pharmac.*, **21**, 713–719.
- Pomier-Layrargues, G., Kusielewicz, D., Willem, B., Villeneuve, J. P., Marleau, D., Coté, J. & Huet, P. M. (1985). Presinusoidal portal hypertension in non-alcoholic cirrhosis. *Hepatology*, **5**, 415–418.
- Reichen, J., Hirlinger, A., Ha, H. R. & Saegesser, S. (1986). Chronic verapamil administration lowers portal pressure and improves hepatic function in rats with liver cirrhosis. *J. Hepatol.*, **3**, 49–58.
- Reichen, J. & Le, M. (1986). Verapamil favourably influences hepatic microvascular exchange and function in rats with cirrhosis of the liver. *J. clin. Invest.*, **78**, 448–455.
- Reynolds, T. B., Ito, S. & Iwatsuki, S. (1970). Measurement of portal pressure and its clinical application. *Am. J. Med.*, **49**, 649–657.
- Singh, B. N., Ellrodt, G. & Peter, C. T. (1978). Verapamil: a review of its pharmacological properties and therapeutic use. *Drugs*, **15**, 169–197.
- Viallet, A., Marleau, D., Huet, M., Martin, F., Farley, A., Villeneuve, J. P. & Lavoie, P. (1975). Hemodynamic evaluation of patients with intra-hepatic portal hypertension. Relationship between bleeding varices and the porto-hepatic gradient. *Gastroenterology*, **69**, 1297–1300.
- Vorobioff, J., Bredfeldt, J. E. & Groszmann, R. J. (1984). Increased blood flow through the portal system in cirrhotic rats. *Gastroenterology*, **87**, 1120–1126.

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