

phase" there were no method failures, but a progestogen was given with or without an oestrogen every two to three months to induce vaginal bleeding. Galactorrhoea was induced in all but four of the women, and drowsiness and sedation were common. In this study we found that the combination of a progestogen with a dopamine receptor blocker was more effective than either drug given alone. This may be because sulpiride, by sensitising the hypothalamic-pituitary axis, rendered the action of norethisterone more effective. This combination may offer a new approach to contraception, and it may be possible to reduce the doses of both the dopamine antagonist and the progestogen considerably while still retaining a satisfactory contraceptive effect. It must be remembered that the progestogen only pill contains less progestogen than the combined pill, and a further reduction in progestogen content would be desirable after the doubts raised about its safety.<sup>14</sup> Thus it may be possible to overcome the traditional problems of poor control of cycles and reduced effectiveness associated with progestogen only contraception. Reduction in dosage may reduce or eliminate the side effects associated with this combination, although the drugs were on the whole well tolerated.

Another potential use of this approach of combining the progestogen only pill with a dopamine antagonist would be its use during lactation. Badraoui and Hefnawi used sulpiride as a contraceptive with some apparent success during lactation.<sup>15</sup> An improved supply of milk during lactation has been reported with administration of sulpiride,<sup>16</sup> and a treatment regimen that acted as both a galactagogue and a contraceptive would be highly attractive. Because sulpiride is transferred in the breast milk its widespread use in lactating women cannot be recommended until more is known about its effects on the nursing infant. Further studies are required to determine the optimum dosage regimen and the possible side effects of this potentially promising new approach to contraception.

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# Effect of isosorbide dinitrate, verapamil, and labetalol on portal pressure in cirrhosis

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## Abstract

The effects on portal pressure of the vasodilatory drugs isosorbide dinitrate and verapamil and of an  $\alpha$  and  $\beta$  blocking agent, labetalol, were assessed in 21 patients with cirrhosis and portal hypertension. The wedged hepatic venous pressure gradient (wedged minus free hepatic venous pressures) was used as an index of portal pressure and was not significantly changed by treatment with labetalol ( $n=5$ ) but was significantly decreased by verapamil ( $n=6$ ;  $p<0.05$ ) and isosorbide dinitrate ( $n=10$ ;  $p<0.01$ ). Long term administration of isosorbide dinitrate also had a significant effect ( $p<0.01$ ).

## Introduction

Since the finding that propranolol lowers portal pressure<sup>1</sup> there has been much interest in the pharmacological manipulation of pressure in the portal vasculature. The efficacy of propranolol in preventing variceal haemorrhage is controversial,<sup>2</sup> and the bradycardia induced by propranolol may be potentially dangerous during acute episodes of bleeding. Nitroglycerin, a vasodilator, also lowers portal pressure when given both orally and intravenously but has a short half life.<sup>3,4</sup> In this study we assessed the effect of the vasodilatory drugs isosorbide dinitrate and verapamil and an  $\alpha$  and  $\beta$  blocking agent (labetalol) on portal pressure in patients with cirrhosis with portal hypertension.

## Methods and results

All patients had histologically confirmed cirrhosis and oesophageal varices. The wedged hepatic venous pressure gradient was used as an index of portal pressure and was measured by passing a catheter (Cordis No 8) into the right hepatic vein under fluoroscopic control. Wedged and free hepatic venous pressures were measured, the difference giving the wedged hepatic venous pressure gradient.

After suitable wedging of the catheter the patient was given one of the drugs under investigation. All drugs were given intravenously as a

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bolus injection: isosorbide dinitrate 10 mg, labetalol 100 mg, and verapamil 10 mg. Wedged and free hepatic venous pressures were measured at intervals of five minutes until the pressure gradient fell and rose again, or until the test was abandoned because no change in portal pressure occurred. Before and during administration of the drug pulse, blood pressure, and heart beat were continuously monitored. One group of patients underwent repeat determination of portal pressure after one month of treatment with oral isosorbide. The determination was carried out three to four hours after the morning dose of the drug. The results were analysed statistically using the paired *t* test.

We studied 21 patients, of whom six received verapamil, five labetalol, and 10 isosorbide dinitrate. The mean wedged hepatic venous pressure gradient was 18 (SD 3.7) mm Hg. Administration of labetalol did not significantly change the wedged hepatic venous pressure gradient (table). Verapamil produced a small but significant fall in pressure ( $p < 0.05$ ). Isosorbide dinitrate significantly decreased the

## Discussion

This study shows that both short term and long term administration of isosorbide dinitrate significantly decreases portal pressure. Sublingual isosorbide dinitrate also results in a fall in portal pressure,<sup>5</sup> and the drug probably decreases portal pressure by relaxing smooth muscle in the portal vasculature. In contrast to the bradycardia produced by  $\beta$  blockade, the fall in portal pressure with oral isosorbide was not associated with any haemodynamic embarrassment. Propranolol also lowers cardiac output and plasma renin concentration, which could precipitate the hepatorenal syndrome in patients with cirrhosis with ascites. Isosorbide does not appear to have such drawbacks, and a controlled trial of its efficacy in preventing episodes of bleeding in patients at high and low risk is required.

*Effect of labetalol, verapamil, and isosorbide on gradient between wedged and free hepatic venous pressures. Figures are means (SD). (Changes in pressure after intravenous administration occurred within 30 minutes; those after oral administration occurred after one month of continuous treatment)*

Drug	No	Before treatment		After treatment	
		Wedged hepatic venous pressure gradient (mm Hg)	Free hepatic venous pressure (mm Hg)	Wedged hepatic venous pressure gradient (mm Hg)	Free hepatic venous pressure (mm Hg)
Labetalol (intravenously) 100 mg	5	16.3 (2.5)	5.1 (0.8)	14.2 (2.3)	4.4 (1.2)
Verapamil (intravenously) 10 mg	6	19.8 (3.3)	4.5 (1.8)	16.2 (3.9)*	3.9 (1.4)
Isosorbide dinitrate (intravenously) 10 mg	10	19.4 (2.5)	4.7 (2.5)	12.5 (3.0)**	3.9 (1.7)
Isosorbide dinitrate (orally) 20 mg four times/day	6	18.1 (2.9)	5.5 (0.4)	9.8 (1.9)**	4.4 (0.09)

\* $p < 0.05$ ; \*\* $p < 0.01$ .

pressure gradient (mean fall of 6.9 (2.4) mm Hg;  $p < 0.01$ ). Although both systolic and diastolic blood pressures fell after the administration of isosorbide, there was no significant correlation between the falls in these pressures and the fall in wedged hepatic venous pressure gradient. The fall in the pressure gradient produced by intravenous isosorbide dinitrate represented a 35% decrease in portal pressure. No significant changes in free hepatic venous pressure occurred with any of the drugs.

Oral isosorbide dinitrate 20 mg four times a day was well tolerated except by one patient, in whom headache necessitated a decrease in dosage to 10 mg four times a day. The wedged hepatic venous pressure gradient had fallen by 44% after one month of treatment (mean fall 8.3 (3.6) mm Hg;  $p < 0.01$ ).

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## 100 YEARS AGO

Our correspondent in Valencia writes, under date August 14th: Since my last, I am thankful to inform you that our terrible visitor, cholera, is showing us his heels. To-day's cemetery-report is sixteen burials of all deaths, which is about the average number when this city is in full health; and I may say the same of the various towns and villages of this Province. I regret I cannot say the same of the other Provinces and their towns—Alicante, Granada, Cartagena, Malaga, Seville, and Sarragossa. The daily account from all these quarters is both alarming and most heartrending on account of the panic among the well-to-do, their flight leaving the ill-paid, ill-fed, artisans and labourers without work or pay, to say nothing of the abject poor. All these, forming the great majority, are crying aloud to Government and the better classes of their people for help of every kind—food, medical men, medicines, and disinfectants—all of which seem to arrive late. The northern sea-ports of Bilbao, Santander (probably the filthiest in Spain), and the fashionable northern bathing-city San Sebastian, are now receiving a visit from the dire disease; and I feel sure that, if it get a footing in Santander and in San Sebastian, during this crowded season, the havoc will be great, especially in the former. We hear as yet nothing about the west or north-west coast being attacked, Vigo, Corunna, Pontevedra, Hijo, etc. This city has felt severely the cholera-shock in every way, and the best proof of that is the suspension of the great annual fair, held here for a fortnight at this time, and the greater annual bull-fight of choice bulls, held on three successive days; but, in exchange for the above, to-morrow there is the festival of the "Virgin of August," when young wild bulls will be slain to propitiate the above deity. There is still great trouble about the "cordones," "lazarettos," and "fumigaciones," between the Government, who orders all these to be abolished, and the Alcades and people, who seem determined in some places

to maintain them. A melancholy and fatal result of forced fumigation occurred on the Granada line, where five gipsies were done to death. The assaulting and insulting of the medical men still goes on in various parts of the country, including the capital and Valladolid; so that the Minister has published a decree ordering a heavy fine to be imposed on any one who insulted them. There was a great cholera-scare here two days ago, from thirty-five boys and girls, from 14 to 4 years old, being suddenly seized, in three streets near each other, with vomiting and purging, etc. The cause turned out to be that they had all been eating seeds of the castor-oil plant, which they had picked up near a public fountain. It seems that they were thrown there by a disgusted farmer, who had brought them in for sale, and, finding no buyer, he did not care about carrying them back with them. So far, there have been no deaths. Ferran and his "caldos" are now viewed with dread and terror by all the towns where the Government ordered him to follow up his "preventive cholera-inoculations;" so much so that, as soon as it became known he was to visit certain towns, the people rose with the Alcade and Municipality, and prevented him from entering the towns. So it happened in Denia, which was to be his "centre;" also in San Matero, Oliva, etc. I hope to be able to give you a clean bill of health from this city in my next.

In finishing the above, I was surprised by the account from a friend that a well-to-do family had started from Morella in the best of health and spirits, to return to their house here (situated in one of the best localities); that four out of the six who constituted the family were smitten with cholera, two dying in three hours, and the other two next day early. This has caused a great sensation. (*British Medical Journal* 1885;ii:358-9.)