Acute effect of propranolol and isosorbide-5-mononitrate administration on renal blood flow in cirrhotic patients

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Abstract

Background—Propranolol and isosorbide-5-mononitrate (ISMN) are increasingly used in the prophylaxis of variceal haemorrhage in cirrhosis. However, recent studies have suggested that these drugs may compromise renal function, possibly by reducing renal blood flow.

Aims—To assess the acute effects of propranolol and ISMN on renal blood flow and other haemodynamic parameters in cirrhosis.

Patients and methods—Twenty six cirrhotic patients were given either 80 mg propranolol, 20 mg ISMN, or a combination of the two drugs. Unilateral renal blood flow (RBF), azygos blood flow (AZBF), hepatic venous pressure gradient (HVPG), mean arterial pressure (MAP), and heart rate (HR) were recorded prior to and one hour after drug administration.

Results—Propranolol caused a reduction in HR ($p < 0.005$), AZBF ($p < 0.01$), and HVPG ($p = 0.05$), but no change in MAP or RBF (454.1 (77.3) versus 413.9 (60.3) ml/min). ISMN reduced MAP ($p < 0.005$) and HVPG ($p < 0.01$), but had no effect on HR, AZBF, or RBF (302.5 (49.4) versus 301.7 (58.8) ml/min). Combined treatment reduced MAP ($p < 0.005$), AZBF ($p < 0.05$), and HVPG ($p = 0.002$), but HR and RBF (419.2 (62.6) versus 415.1 (61.1) ml/min) remained unchanged.

Conclusions—Despite the anticipated changes in other haemodynamic parameters, acute propranolol and/or ISMN administration did not reduce RBF. These drugs do not seem to compromise RBF in cirrhosis.

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Keywords: cirrhosis; portal hypertension; renal blood flow; propranolol; nitrates

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Propranolol is widely used in the primary and secondary prophylaxis of variceal haemorrhage in cirrhotic patients. It reduces portal pressure and collateral blood flow in cirrhosis and numerous studies have confirmed its efficacy as prophylaxis against portal hypertensive related gastrointestinal bleeding.¹⁻⁵ Isosorbide-5-mononitrate (ISMN) is a long acting venodilator that reduces portal pressure and hepatic vascular resistance.⁶⁻⁸ It has been shown to reduce the risk of variceal bleeding,^{9,10} and can be used as an alternative treatment for patients

with portal hypertension who are intolerant to β blockade. More recently, reports have suggested that the combination of propranolol and ISMN may be the optimum treatment to reduce portal pressure and overcome the problem of non-response to propranolol.^{11,12}

Several recent studies have suggested that β blockers and particularly nitrates may compromise renal function in cirrhosis, possibly due to a reduction in renal perfusion secondary to the associated reduced systemic blood pressure.¹²⁻¹⁷ The aim of our study was to investigate the effect of propranolol, ISMN, and the combination of both drugs on renal blood flow and systemic and splanchnic haemodynamics in cirrhotic patients.

Patients and methods

Twenty six patients (12 female, mean age 51.1 years (range 33-70), mean Child-Pugh score (CPS) 9.2 (0.6)) with cirrhosis were studied. Eighteen patients had ascites at the time of study which was clinically graded as mild, moderate, or severe. Diagnosis of cirrhosis was based on liver biopsy (20 patients) or the presence of chronic liver biochemical abnormalities and endoscopically proven varices (six patients). Cirrhosis was alcohol related in 21 patients, and secondary to primary biliary cirrhosis in two, primary sclerosing cholangitis in one, sarcoid in one, and α_1 antitrypsin deficiency in one. No patient had biochemical evidence of renal dysfunction prior to study (serum urea greater than 6.6 mmol/l or serum creatinine greater than 150 μ mol/l) and none was receiving vasoactive medication at the time of study. In addition, no patient had suffered a gastrointestinal haemorrhage within the previous four months. All patients gave informed consent and the study was approved by the Lothian Ethics Committee.

Studies were undertaken in the Department of Medicine catheter laboratory, on fasted patients in the supine position. Vascular catheters were positioned under fluoroscopic guidance via an 8.5 FG right femoral venous introducer (Baxter Healthcare Corporation, USA), inserted after local infiltration with 2% lignocaine. A balloon catheter (Sidewinder II, Cordis Corporation, USA) was inserted through the introducer to record both the free (FHVP) and wedged (WHVP) hepatic venous pressure. Hepatic venous pressure gradient (HVPG) was calculated as WHVP minus FHVP.

A double thermister, reverse thermidilution catheter (Webster Laboratories, California, USA) was then inserted through the introducer

Table 1 Patient characteristics

	Propranolol (n=9)	ISMN (n=8)	Combined treatment (n=9)
Age (y)	52.7 (2.3)	50.5 (2.8)	51.1 (1.9)
Child-Pugh score	9.2 (1.0)	9.4 (1.5)	9.1 (1.1)
No with ascites (mild or moderate/severe)	5/0	4/1	7/1
Serum creatinine ($\mu\text{mol/l}$), mean (range)	83.1 (63–136)	92.1 (65–142)	88.8 (66–126)
Aetiology (ALD/other)	8/1	6/2	7/2

ALD, alcoholic liver disease.

and positioned in the left renal vein. The proximal thermister was confirmed to be within the lumen of the renal vein by injection of 5 ml dilute contrast media (Conray 280, May & Baker Ltd, Dagenham, UK). Recordings of unilateral renal blood flow (RBF) were made using a custom built interface (B55724 type CF) and an IBM microcomputer processor (PS2–286) as previously reported.¹⁸ Mean blood flows were recorded over a 30 second period with the patient breathing normally at rest.

Finally, the reverse thermodilution catheter was positioned in the azygos vein and azygos blood flow (AZBF) recorded in a similar manner to RBF. The catheter was then left in position for the duration of the study.

When recruited for the study, patients were matched for age and CPS for each therapeutic regimen (table 1). Nine patients were then given 80 mg oral propranolol, eight patients 20 mg oral ISMN, and nine patients both treatments. One hour later AZBF was again recorded, then the reverse thermodilution catheter was manoeuvred back into the initial position in the left renal vein and repeat RBF measurement made as described above. Finally, repeat measurements of the WHVP and FHVP were recorded using the balloon catheter. The sheath was then removed and firm pressure applied until haemostasis was ob-

tained. Heart rate (HR) and mean arterial pressure (MAP) were also recorded for the duration of the study and for four hours thereafter. In all patients, the duration of the study was less than 3.5 hours.

STATISTICAL ANALYSIS

Results are expressed as mean (SEM) or range where indicated. For parametric data, the paired Student's *t* test and Pearson's correlation were used. The Wilcoxon signed ranked test and Kendall correlation were used for non-parametric variables. A *p* value of less than 0.05 was taken to be significant.

Results

All patients completed the study without difficulty and no side effects were observed or reported. There was no statistical difference between the three therapeutic groups with regard to baseline RBF or other haemodynamic parameters. Baseline RBF did not correlate with CPS, HVP, or ascites severity. Table 2 shows changes in HR and MAP for each treatment group at one hour following medication.

Following administration of propranolol, there was a fall in HVP from 16.3 (2.2) to 12.9 (1.9) mm Hg (*p*=0.05) and in AZBF from 471.5 (85.8) to 293.4 (42.6) ml/min (*p*<0.01) (fig 1). There was no effect on RBF (454.1 (77.3) versus 413.9 (60.3) ml/min) (fig 2).

ISMN treatment led to a fall in HVP from 14.9 (1.9) to 11.0 (1.3) mm Hg (*p*<0.01), but had no effect on either AZBF (573.4 (183.1) versus 576.0 (145.1) ml/min) (fig 1) or RBF (302.5 (49.4) versus 301.7 (58.8) ml/min) (fig 2).

Following administration of the combination of propranolol and ISMN, HVP fell from 15.1 (1.8) to 8.9 (1.1) mm Hg (*p*=0.002) and AZBF fell from 612.5 (187.6) to 358.2 (57.0)

Table 2 Systemic haemodynamic effects

	Propranolol		ISMN		Combined treatment	
	Before	After	Before	After	Before	After
HR (bpm)	81.6 (3.9)	71.7 (4.2)*	86.8 (3.5)	91.0 (3.3)	79.9 (4.8)	71.4 (4.4)
MAP (mm Hg)	82.6 (3.4)	78.2 (3.3)	84.5 (3.3)	76.9 (3.6)*	78.1 (4.6)	68.7 (3.4)*

**p* < 0.005.

Figure 1 Changes in HVP and AZBF one hour after a single dose of (A) propranolol, (B) ISMN, or (C) combined treatment.

Figure 2 Unilateral RBF one hour after a single dose of (A) propranolol, (B) ISMN, or (C) combined treatment.

ml/min ($p < 0.05$) (fig 1). Again, there was no effect on RBF (419.2 (62.6) versus 415.1 (61.1) ml/min) (fig 2).

When the 18 patients with ascites were considered alone, there remained no effect on RBF of any treatment when these patients were grouped together, or when analysed in treatment subgroups.

Discussion

We undertook this study to assess the acute effect of propranolol, ISMN, and the combination of both drugs on RBF in cirrhotic patients. Despite the anticipated changes in other haemodynamic parameters, no change in RBF was detected.

Any reduction in renal function is critical in cirrhotic patients, because they are already at risk of renal impairment due to reduced RBF, glomerular filtration rate (GFR), and sodium and water excretion.¹⁹ Recent suggestions that β blockers and nitrates may have deleterious renal effects in cirrhosis include reports of reduced renal sodium excretion^{12 13 16} and reduced renal perfusion¹⁴⁻¹⁷ following administration of these drugs. This is important in view of their increasing use as prophylaxis against variceal haemorrhage.^{1-5 9 10}

Generally, autoregulation in the kidney maintains a constant RBF over a wide range of arterial blood pressures.²⁰ Henriksen and Ring-Larsen suggest that in cirrhosis, a pharmacologically induced fall in MAP may compromise renal perfusion and GFR, leading to a subsequent reduction in sodium and water excretion, partly due to a shift in this autoregulation.¹⁷

β Blockers are the most widely used drugs in the prophylaxis of variceal haemorrhage. Most investigators have studied propranolol in this role, although nadolol has been used by some researchers. In addition to their portal hypotensive action, these drugs reduce cardiac output and increase systemic vascular resistance but have less effect on MAP.²¹

The renal effects of β blockers are complex due to their haemodynamic and neurohumoral actions. Propranolol treatment leads to increased circulating concentrations of nor-adrenaline which can cause sodium and water retention²²; however, reduced levels of renin,

angiotensin, and aldosterone (β_1 blockade) are also observed which increase salt and water excretion.²³ In addition, renal vasoconstriction due to β_2 blockade has been suggested as a mechanism by which β blockers may impair RBF and GFR.²⁰ However, the clinical significance of these changes remains unclear and data on cirrhotic patients are limited.

β Blockers have been shown to reduce the frusemide stimulated increase in renal interlobular arterial flow,¹⁴ and reduce estimated RBF in cirrhosis as assessed by Doppler ultrasonography.¹⁵ However, Bataille *et al* found no effect on RBF of acute propranolol treatment when given to cirrhotic patients,²⁴ and no difference in creatinine clearance was detected between cirrhotic patients given diuretics alone and those given propranolol and diuretics.¹³ In addition, propranolol has been reported as having no effect on GFR in cirrhosis despite suppressing renin secretion,²⁵ and Bernardi *et al* found that propranolol actually increased GFR and natriuresis in ascitic cirrhotics with high sympathetic tone.²³ Other studies have reported both decreased¹³ and increased²⁶ natriuresis in cirrhotic patients in response to propranolol.

Up to 40% of cirrhotic patients do not have a reduction in portal pressure in response to propranolol despite a fall in AZBF and are termed "non-responders". In addition, approximately 15% of patients are intolerant of the drug.^{27 28} Therefore, nitrates are commonly used as an alternative treatment, or in combination with propranolol.

Nitrates are venodilators that reduce cardiac output and MAP in cirrhosis.^{7 16 29} They are effective in reducing portal pressure and can convert propranolol non-responders into responders. This is consistent with our findings of only a mild reduction in HVPG following propranolol, but a significant reduction following ISMN and particularly the combination treatment. Recent studies have suggested that the combination of ISMN and β blockers may be the optimum treatment in portal hypertension.^{11 12}

There has been concern that nitrates may compromise renal function in patients with advanced liver disease, due to the associated fall in blood pressure and activation of the

sympathetic and renin-angiotensin-aldosterone systems. Vorobioff *et al* found that 57% of cirrhotic patients with ascites or a history of ascites developed worsening of ascites when given propranolol and nitrates, compared with no worsening of ascites in any patient given propranolol alone.¹² ISMN has also been shown to reduce renal plasma flow, GFR, and sodium and water excretion and increase renin and aldosterone values in cirrhosis.¹⁶ The fall in GFR and free water clearance was greater in those patients who had ascites.

However, Morrillos *et al* found no effect on inulin clearance, free water clearance, plasma renin activity, aldosterone concentration, or ascites outcome in cirrhotic patients given long term propranolol and ISMN, despite a reduction in blood pressure.³⁰ In addition, Merkel *et al* found no deterioration in renal function in cirrhotic patients given six months of ISMN and nadolol compared with patients given nadolol alone.³¹ Although there was a correlation between the fall in blood pressure and the rise in serum creatinine in the group as a whole, it was only the patients given combination treatment who had a reduction in their ascites.

More recently, Salerno *et al* reported that acute ISMN treatment in cirrhosis reduced diuresis and natriuresis, and reduced GFR in patients with ascites.³² However, the same study also showed that chronic administration of ISMN did not affect renal function if patients did not have ascites, but reduced diuresis and natriuresis in ascitic patients. No effect on GFR or renal plasma flow was detected.

It is clear that there are conflicting data in the literature on this subject which may be due to differences in the study populations or in the duration of treatment. Although we did not assess sodium and water excretion or GFR in this study, we found no change in RBF despite the expected changes in MAP, HVPG, and AZBF following administration of propranolol and/or ISMN. Despite the fact that all patients in our study had normal serum creatinine concentrations, it is possible that some may have had a degree of renal impairment not evident from their serum creatinine. However, when ascitic patients alone were assessed, there was still no effect on RBF. We assessed only the acute effect of these drugs on RBF, therefore we cannot draw conclusions regarding prolonged treatment. It is possible that administration of these drugs to cirrhotic patients may compromise renal function by mechanisms other than a reduction in RBF, such as neuro-humoral or tubular effects. However, the main concern of many of the above studies was a possible reduction in renal perfusion consequent on the systemic haemodynamic changes induced by these drugs.

In view of our desire to assess both AZBF and RBF in this study, we had to move the thermodilution catheter out of the renal vein between the two recordings of RBF. The initial position of the catheter in the left renal vein was recorded fluoroscopically and the catheter repositioned to the exact same position for the one hour recording of RBF using fluoroscopic

guidance. To ensure validity of these measurements, three other cirrhotic patients had multiple RBF recordings made over one hour, with the catheter moved in and out of the left renal vein under similar conditions. The coefficient of variation in RBF recordings was less than 10%.

Most studies assessing renal plasma flow and GFR rely on clearance of *p*-aminohippuric acid and inulin respectively, but such methods rely on high renal extraction of these substances. In the presence of sepsis or other pathological conditions leading to tissue hypoxia, microvascular abnormalities, and shunting of blood such as in cirrhosis, these methods are largely invalid.³³ Although thermodilution measurement of RBF has been shown to correlate well with half the renal blood flow as calculated from *p*-aminohippuric acid infusion,³⁴ thermodilution methods may be more accurate than clearance techniques in pathological states.

Using the thermodilution technique, we found no acute effect on RBF in patients given propranolol and/or ISMN. The possibility of a type II error exists, but the numbers studied produced significant results with regard to the other haemodynamic parameters, and particularly in the propranolol group, the patients with the lower initial RBF (whose renal function would be of most concern) actually had a rise in RBF following treatment. Although the patients given ISMN had slightly lower baseline RBF compared with those given propranolol or combination treatment, this difference was not significant, and as in the other therapeutic groups, these patients had no change in RBF after treatment.

In conclusion, we have detected no effect on RBF following acute administration of propranolol, ISMN, or a combination of the two drugs to cirrhotic patients, despite the anticipated changes in MAP, HVPG, and AZBF. Therefore any effect of these drugs on renal function in cirrhosis does not seem to be due to an acute reduction in RBF.

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