Effect of Sublingual Isosorbide Dinitrate in Portal Hypertension

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Abstract
Nitrates decrease portal pressure by decreasing portal venous inflow and resistance. We studied over 20 minutes the effect of 10 mg isosorbide dinitrate sublingual on intranssplenic pulp pressure, mean arterial pressure and heart rate, in 13 patients with cirrhotic or non-cirrhotic portal hypertension. The pulp pressure fell progressively over 20 minutes, from mean 43.6 ± 2.4 (SEM) to 35.6 ± 1.8 cm H₂O (p < 0.01). This was accompanied initially by a significant fall in mean arterial pressure (85.8 ± 1.9 to 80.4 ± 2.7 mm Hg at 4 minutes; p < 0.01) and rise in heart rate (92.5 ± 5.0 to 102.6 ± 5.9 per minute at 6 minutes; p < 0.02), following which these parameters remained stable. One patient developed dizziness due to hypotension at 15 minutes. We conclude that sublingual isosorbide dinitrate decreases pulp pressure in cirrhotic and non-cirrhotic portal hypertensives, but this is initially accompanied by significant hemodynamic changes.

Key words: Intrasplicenic pulp pressure, nitrates, transcutaneous nitroglycerin.

Introduction
Portal hypertension could be the result of increased blood flow, increased resistance, or both. The pressure can be decreased by lowering either of these factors. The effect of isosorbide dinitrate (ISDN) on portal pressure can be interpreted as the net sum of various hemodynamic effects induced by the drug. At low doses (dose of mean arterial pressure by less than 10%), venous effects predominate. Though cardiac output remains unchanged, the portal venous inflow is decreased probably because of reflex splanchnic arterial vasodilation and pooling. At higher doses, generalised arterial vasodilation occurs, in addition to venous dilatation, and the further decrease in portal pressure is accompanied by systemic hypotension. Vasodilators like nitrates, when administered to portal hypertensives already on vasodilator (arterial vasodilator), not only prevent the deleterious cardiovascular effects of vasodilator, but additionally decrease portal pressure.

Drugs that reduce portal pressure could theoretically be useful in the prevention and treatment of variceal hemorrhage.

The present study was undertaken to evaluate the acute effect of 10 mg ISDN sublingual on portal pressure (measured as intrasplicenic pulp pressure - ISPP) and systemic hemodynamics in patients with cirrhotic or non-cirrhotic portal hypertension.

Material and Methods
Patients with portal hypertension who underwent splenomectomy during evaluation for shunt surgery were taken for the study. After informed consent, 10 mg ISDN sublingual was given to 12 patients (8 men, 4 women; aged 50-66 years, mean 53.1) with portal hypertension (cirrhosis-5, including 4 in Child's A category and 1 in Child's B; non-cirrhotic portal fibrosis-6: congenital hepatic fibrosis-3). The patients had no evidence of any other systemic disease.

After an overnight fast, with the patient supine, under local anesthesia, a needle was passed transcutaneously into the splenic pulp under fluoroscopic guidance. The position of the needle was confirmed by injection of contrast material. The basal ISPP, blood pressure and heart rate were measured. After a stabilization period of 10 minutes, the patients received 10 mg ISDN sublingual. The ISPP, blood pressure and heart rate were measured at 2, 4, 6, 10, 15 and 20 minutes after administration of the drug. The patients were asked to report any discomfort, palpitations or giddiness. At the end of 20 minutes, a splenoportogram was performed, and the needle was withdrawn. Mean arterial pressure (MAP) was calculated as diastolic pressure - 1/3 pulse pressure.

Statistical analysis: Analysis of difference in values of individual parameters before and after administration of the drug was done by the two-tailed paired t test. Values are expressed as mean ± SEM.

Results
Intrasplenic pulp pressure (Fig): The basal ISPP was 43.6 ± 2.4 cm H₂O (range 30-59). The fall in ISPP was apparent at 2 min after administration of the drug, but reached significant levels only at 4 min, when the value was 39.9 ± 1.9 cm H₂O (range 29-51) (p < 0.05). At 20 minutes, the ISPP fell further to 35.6 ± 1.8 cm H₂O (range 29-50) (p < 0.01 as compared to 4 min). Thus, at 20 minutes, the ISPP had fallen overall by 17.2 ± 2.8% (p < 0.001). In three patients, the ISPP fell by less than 10%.

Mean arterial pressure: The basal MAP was 85.8 ± 1.9 mmHg (range 73-96.7). A decrease in MAP was observed after 2 min of sublingual ISDN, but became significant only after 4 min when the value was 80.5 ± 2.8 mmHg (range 60-96.7) (p < 0.01). Following
this, the MAP remained stable but significantly lower than basal till the end of 20 minutes. At 20 minutes, MAP had decreased by 6.9 ± 1.8% (p<0.01).

**Heart rate:** The basal heart rate was 92.5 ± 5.0 per minute (range 60-136). The heart rate increased after 2 min of ISDN, and reached a peak at 6 min (102.6 ± 5.9; p<0.02). At 20 minutes, the heart rate was 98.2 ± 5.5 per minute (range 82-124), an increase of 8.8 ± 5.2%.

One patient complained of dizziness when his MAP dropped to 60 mmHg at 15 minutes; he was asked to sit out the tablet remain, and recovered in the head low position within half an hour of discontinuing the drug.

**Fig:** Effect of 10 mg isosorbide dinitrate sublingual on mean arterial pressure (MAP) and heart rate over 20 minutes.

* p < 0.05, ** p < 0.01, *** p < 0.001, + p < 0.02 as compared to basal values.

**Discussion**

We studied over 20 minutes the effect of sublingual isosorbide dinitrate on patients with cirrhotic or non-cirrhotic portal hypertension. All the patients had a fall in ISPP after sublingual ISDN; in three patients, however, this fall was less than 10%. This fall was initially accompanied by significant systemic hemodynamic changes, which later stabilised while the ISPP continued to fall. One of our patients developed giddiness and hypotension. Our study was performed with the patient in the supine position, and compensatory mechanisms on standing were not tested.

Halleman et al. had shown that ISDN decreased hepatic venous pressure gradient significantly in cirrhotic patients and the decrease correlated well with the decrease in blood pressure. Dawson et al. found that intraduodenal ISDN (5 mg) did not decrease variceal pressure, but caused a significant decrease in systolic blood pressure, whereas Blei et al. found that MAP was a poor predictor of modification in hepatic venous wedge pressure. Navassa et al. found that the fall in portal pressure in cirrhosis on isosorbide-5-mononitrate 20 and 40 mg was associated with a decrease in MAP by 8% and 19%, respectively at the end of one hour. The fall in ISPP in our patients was accompanied by progressive systemic hemodynamic alterations only in the first few minutes; the later fall in ISPP was probably due to splanchnic venodilatation. An earlier study of nitrates in non-cirrhotic portal hypertensives was over a shorter duration, and details of hemodynamic changes were not mentioned.

In three of our patients, the ISPP decreased by less than 10%, following sublingual ISDN. Failure to respond to nitrates has also been observed, and a rise in the wedged hepatic venous pressure after sublingual ISDN was observed in 2 of 6 patients studied by Qureshi et al. 8

After an oral dose, only 25% of ISDN reaches the circulation as this drug undergoes extensive first pass metabolism in the liver. About twice the amount reaches the circulation following sublingual administration. 11 When nitroglycerine is administered transcutaneously, the onset of action is around 30 minutes; 12 steady-state values are reached in rats at 60 minutes at which time its effect on the systemic circulation is reported to be similar to that of intravenous nitrates. 13

We studied over 20 minutes the effect of 2% nitroglycerine transcutaneously on five patients with portal hypertension (unpublished data). We noticed a fall in the ISPP within 10 minutes in two of these patients, accompanied by a fall in MAP in one of them at 15 minutes; the other patients had no appreciable response over 20 minutes. The ease of administration of transcutaneous nitroglycerine makes it worthwhile to evaluate it for long-term therapy.

We conclude that sublingual ISDN may be used to acutely reduce portal pressure; hemodynamic parameters should be monitored simultaneously and caution should be exercised in patients who are already compromised hemodynamically.

**References**


**NITRATES IN PORTAL HYPERTENSION—BHATIA ET AL.**

