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Transdermal nitroglycerin in cirrhosis. A 24-hour echo-Doppler study of splanchnic hemodynamics

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Background/Aims: **The present study was aimed to evaluate the 24-hour effect of transdermal nitroglycerin on splanchnic hemodynamics in cirrhotic patients.**

Methods: **Hemodynamic parameters (blood velocity and resistance indexes) were determined by means of pulsed echo-Doppler, a non-invasive method which proved to be useful to evaluate the effects of drugs on splanchnic vessels. Nine patients with biopsy-proven liver cirrhosis were studied. They were kept on a standard diet divided into 3 meals served at 8, 12 a.m. and 6 p.m. Echo-Doppler measurements were determined for 2 consecutive days at 7, 8, 9, 12 a.m, 1, 3, 6, 7, 9, 12 p.m. and again at 7 a.m. A transdermal nitroglycerin tape, capable of releasing 15 mg of the drug in 24 h, was applied to the skin of the chest at 7 a.m. of the second day.**

Results: **After nitroglycerin mean portal blood velocity and flow significantly decreased by 18 and 22%. Similarly superior mesenteric artery velocity decreased, while resistance indexes increased. ANOVA analysis showed a significant effect of the drug on superior mesenteric artery and portal flow, while the effect on hepatic artery flow and renal indexes were low.**

Conclusions: **This study shows that nitroglycerin, given as transdermal long-acting system, significantly influences portal hemodynamics in liver cirrhosis. Its use, favoured by easy administration, may be proposed for long-term clinical studies to test its efficacy in preventing gastrointestinal bleeding.**

Key words: **Cirrhosis; Echo-Doppler; Nitroglycerin; Portal flow; Splanchnic hemodynamics.**

BETA-BLOCKER agents constitute the most important medical approach to the prevention of upper gastrointestinal bleeding in cirrhotic patients (1). Treatment reduces portal pressure in approximately 2/3 of patients, the remaining being refractory to β-blockade. Other types of drugs have been proposed in non-responders and also in responders to potentiate the effects of β-blockers.

Several hemodynamic and clinical studies have recently evaluated the effects of vasodilators on portal hypertension in cirrhosis (2–8) testing their clinical effectiveness as single treatment or in association with β-blockers (8–11). Organic nitrates are usually administered orally, and the patients' compliance may be influenced by, in addition to other therapies, the overall high number of tablets that they have to ingest.

In a recent short-term hemodynamic study, transdermal nitroglycerin significantly reduced portal pressure in cirrhotic patients (12), but its long-term efficacy has never been tested.

The present study was aimed to evaluate the 24-h effect of transdermal nitroglycerin on splanchnic hemodynamics in cirrhotic patients. For this purpose we utilized pulsed echo-Doppler, which proved to be useful to evaluate, non-invasively, the effects of drugs on splanchnic vessels (3,11,13). The simultaneous evaluation of several Doppler hemodynamic parameters may also be of help in identifying the mechanism by which organic nitrates exert their action on splanchnic flow.

Patients and Methods

The study was performed on nine patients with biopsy-proven liver cirrhosis, whose clinical and laboratory data are reported in Table 1. They were

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TABLE 1

Clinical and biochemical parameters in the nine cirrhotic patients. Values are reported as mean±SD or median (range)

Sex (m/f)	5/4
Age (years)	61* (43–72)
Etiology (viral/alcoholic)	7/2
Albumin (g/dl)	3.56±0.29 (2.96–3.98)
Gammaglobulin (g/dl)	2.10±0.46 (1.60–3.14)
Aspartate transaminase (U/l)	64±27 (29–158)
Prothrombin time (%)	68±9 (53–81)
Cholesterol (mg/dl)	157±26 (118–211)
Total bilirubin (mg/dl)	1.46±0.49 (1.10–3.85)
Child-Pugh score	6* (5–8)
Esophageal varices (grade I/II/III)	3/3/3

* Median

The Child-Pugh score was calculated as reported in (14).

Esophageal varices at upper gastrointestinal endoscopy were graded according to Beppu et al. (15).

selected from a group of 12 consecutive patients; three had to be excluded because of poor echo-Doppler visualization of deep abdominal vessels due to ascites and/or meteorism. The nine patients admitted to the study were without ascites at the time of examination; three of them had previously suffered from gastrointestinal hemorrhage from bleeding varices or congestive gastropathy.

During the study period, patients were kept on a standard diet of 1800 kcal, divided into three meals served at 8 a.m., 12 a.m. and 6 p.m. Patients were allowed to walk freely within the Department, but they were asked to refrain from any physical exercise.

Heart rate, systolic and diastolic arterial pressure and echo-Doppler parameters of deep abdominal vessels were determined for 2 consecutive days at 7, 8, 9, 12 a.m., 1, 3, 6, 7, 9, 12 p.m. and again at 7 a.m. Measurements performed at 8 a.m., 12 a.m. and 6 p.m. were taken just before the meal.

A transdermal nitroglycerin tape, releasing 15 mg of the drug in 24 h, was applied to the skin of the chest at 7 a.m. of the 2nd day.

Echo-Doppler measurements were obtained using equipment which combines a real-time electronic sector scanner and a pulsed Doppler unit (Esaote-Hitachi AU 590 Asyncronous). To avoid interobserver variability of the results the echo-Doppler examination was always performed by the same investigator, who had more than 5 years of experience in Doppler examination of deep abdominal vessels. All data were collected and registered by an independent investigator, who also took care in keeping the same Doppler setting (Θ angle, PRF, wall filter) for each measurement. Patients were examined after a 10-min rest in the supine position and, during the Doppler recording, were asked to hold their breath during normal respiration. In agreement with recent studies (16,17), the measurements were repeated until three consistent values were consecutively obtained, and the mean values were considered for statistical purposes.

The portal vein was scanned longitudinally, and the sample volume was positioned in the middle of the portal trunk, in the tract just underneath the hepatic artery, as previously described (16,18). Mean portal blood velocity was calculated automatically by the equipment, while portal blood flow was determined by multiplying blood velocity by the sectional area of the portal vein. The sectional area was determined on the basis of the caliber of the longitudinal section of the portal vein by considering the vessel of circular shape ($\pi \times r^2$).

The hepatic artery measurements were taken where a straight stretch runs parallel to the portal vein, some centimeters away from the celiac axis, while for the echo-Doppler study of the superior mesenteric artery, the sample volume was positioned in the tract of the vessel parallel to the aorta, 2–3 cm from its origin. Care was taken to maintain the θ angle (the angle between the ultrasonic beam direction and the blood flow direction) at 55° or just below (17).

The sectional area of the hepatic and of the superior mesenteric arteries were also determined on the basis of their caliber, while mean blood velocity was calculated by multiplying the average maximum velocity by 0.62, as suggested by Nakamura et al. (19). Hepatic and superior mesenteric artery flows were determined by multiplying the mean blood velocity by the sectional area of the artery. The resistance indexes of these arteries were calculated with the following formulas:

Resistive index (RI)=(Maximum systolic velocity – End diastolic velocity)/Maximum systolic velocity.

Pulsatility index (PI)=(Maximum systolic velocity – Minimum diastolic velocity)/Mean velocity.

The renal resistance indexes were evaluated in the right kidney by positioning the sample volume in the interlobar arteries. Easy identification of intrarenal arterial vascularization was obtained by color Doppler. The resistance indexes RI and PI were determined with the same formulas.

All subjects gave their informed consent to take part in the study, which was performed according to the Helsinki Declaration. The protocol of the study was approved by the Senior Staff Committee.

The data in the text and in the tables are expressed

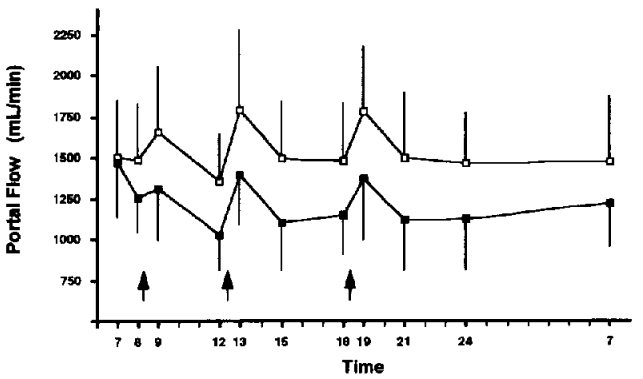

Fig. 1. 24-hour variation of portal blood flow. Empty square: 1st day, basal period; solid square: 2nd day, after transdermal nitroglycerin. Arrows indicate meals.

as mean±SD. The 24-h area under the curve (AUC) was determined with the trapezoidal rules and the time corrected mean values were determined.

Differences in variables were studied for significance using a model of analysis of variance for repeated measurements (ANOVA) and Student's *t*-test for paired data. Whenever significant, the results of the analysis of variance were broken up into two components, the effects of time and those of treatment. Treatment effects are the differences in mean values between groups. Time effects are changes observed during each day, irrespective of nitroglycerin use. The interaction of time × treatment expresses the time changes in individual patients due to the specific treatment with nitroglycerin.

Results

In the basal state (7 a.m.) all the echo-Doppler parameters were fairly reproducible. Day-to-day variations were within 8% for portal flow measurements and within 15% for arterial flow measurements.

During the 1st day of the study, portal blood velocity and flow increased in the postprandial period by approximately 20% (Fig. 1), the mean velocity increasing from 12.7±2.0 cm/s at 12 a.m to 15.2±3.3 at 1 p.m., i.e. 1 h after lunch. Similarly, mean portal blood flow varied from 1352±460 ml/min to 1785±697. Similar results were obtained after dinner.

On the 2nd day, portal blood velocity and flow promptly decreased after transdermal nitroglycerin (Fig. 1), changing from 13.6±2.2 cm/s at 7:00 a.m. to 11.8±2.2 at 8:00 a.m., and from 1472±486 ml/min to 1257±415, respectively. All patients responded to transdermal nitroglycerin and the 1-h reduction on portal flow was on average 15% (range, 7–25%), being less than 10% in a single patient.

The increase in portal flow in the postprandial periods was maintained during nitroglycerin treatment, but the levels were always significantly lower than those observed during the 1st day. Time-corrected mean portal blood velocity and flow were lower after nitroglycerin (by 18 and 22%, respectively) (Table 2), and these data were confirmed by ANOVA analysis which showed an effect of the drug on the time course of hemodynamic parameters ($p<0.0001$ for both velocity and flow). The mean reduction in portal flow varied between 13 and 28%; in a single patient the average response was less than 15%, in two patients between 15–20%, and in the remaining six cases it exceeded 20%.

During the control day the hepatic artery velocity and flow slightly decreased in the postprandial state, while resistance indexes slightly increased after meals. After nitroglycerin, time-corrected mean velocity and flow decreased slightly, while PI increased (Table 2), but ANOVA analysis failed to detect any significant effect of the drug.

On the first day a significant decrease in resistance indexes was observed in the superior mesenteric artery after meal, which corresponded to an increase in blood velocity and flow of approximately 55–60%. The next day, the resistance indexes significantly increased soon after transdermal nitroglycerin, whereas blood velocity and flow decreased, but the effects of meals were maintained (Fig. 2). Time-corrected velocity and flow decreased, while PI and RI

TABLE 2

Time-corrected mean values±SD, calculated with the trapezoidal rules, of the hemodynamic parameters during the 2-day study period: 1st day: basal period; 2nd day: after transdermal nitroglycerin

	1st day	2nd day	*p*
Portal vein			
Velocity	13.7±2.3	11.3±1.7	0.0001
Flow	1520±519	1187±396	0.0001
Hepatic artery			
Velocity	47.4±10.3	41.9±11.3	0.0011
Flow	507±165	447±156	0.002
PI	1.44±0.26	1.52±0.32	0.0082
RI	0.72±0.05	0.73±0.06	0.1941
Superior mesenteric artery			
Velocity	49.7±9.7	41.8±8.9	0.0001
Flow	754±241	635±212	0.0001
PI	2.36±0.46	3.17±0.70	0.0001
RI	0.82±0.05	0.88±0.06	0.0001
Kidney			
PI	1.14±0.19	1.14±0.22	0.967
RI	0.66±0.05	0.64±0.06	0.010
Arterial pressure			
Systolic	144±14	136±11	0.0062
Diastolic	84±5	80±3	0.0023
Heart rate	70±9	72±8	0.0764

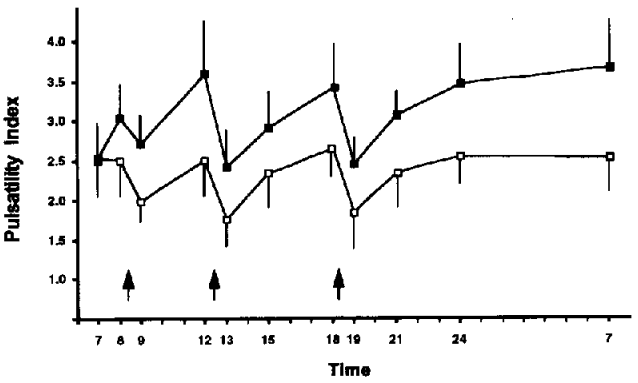

Fig. 2. 24-hour variation of superior mesenteric artery Pulsatility Index (PI). Empty square: 1st day, basal period; solid square: 2nd day, after transdermal nitroglycerin. Arrows indicate meals.

increased (Table 2). ANOVA analysis confirmed that transdermal nitroglycerin had a remarkable effect on all the hemodynamic parameters of the superior mesenteric artery ($p<0.0001$).

Regarding the resistance indexes of the kidney, nitroglycerin slightly decreased mean RI (Table 2), but the difference was not significant when tested by repeated measures (PI, $p=0.556$; RI, $p=0.529$; ANOVA analysis). No effects of meals were observed.

Mean heart rate increased slightly in response to transdermal nitroglycerin, while arterial blood pressure decreased (Table 2). Both systolic and diastolic arterial pressure were affected by the active drug ($p=0.0064$ and $p=0.020$; ANOVA analysis), but no correlations were observed between changes in arterial pressure (systolic, diastolic or mean) and changes in portal flow, both when acute effects (1-h) and 24-h changes were analyzed.

Discussion

This study shows that nitroglycerin, given as a transdermal long-acting system, causes a sustained and persistent decrease in portal flow in liver cirrhosis, mainly by increasing vascular resistances in the splanchnic arterial bed. The effect is confirmed to be present in all patients, with variable intensity (8). With regard to responsiveness to treatment, organic nitrates seem to be different from β-blockers, where a 25% unresponsiveness has repeatedly been demonstrated (1,9).

Nitroglycerin is a potent venous dilator and a mild arterial dilator (20) which has been shown to decrease portal pressure in animal models (21). In cirrhotic patients with portal hypertension, oral or sublingual administration of organic nitrates reduced portal pressure (2,4). Intravenous nitroglycerin also had a similar hypotensive effect on the portal trunk (22). At present some doubts still remain on the mechanism by which these drugs exert their action. It has been suggested that organic nitrates decrease portal pressure either by reducing portal blood flow or by reducing intrahepatic resistances and/or by portal-collateral dilatation. This is because reduced portal pressure was shown to be associated with both increased and decreased azygous venous blood flow (4,7,23,24).

The pharmacologic effects of nitroglycerin on splanchnic hemodynamics have so far been evaluated only by invasive techniques in short-term experiments (8,12,22). Iwao et al. (12), by means of portal and hepatic vein catheterization, have shown that transdermal nitroglycerin significantly reduces portal pressure in portal hypertensive cirrhotic patients after 1 h, but no data are available on the 24-h effect of the long-releasing formulation on splanchnic hemodynamics. Invasive methods cannot be used to determine the putative sustained response, which is expected to occur after administration of long-acting preparations of nitroglycerin, and cannot identify possible changes occurring in response to physiological events, such as meals or sleep.

In the present 24-h study we evaluated the effects of transdermal nitroglycerin on splanchnic vessels by means of pulsed echo-Doppler, a non-invasive technique, which, with the limits previously outlined (18,26), proved suitable for the measurement of splanchnic hemodynamics (3,11,13,25). The feasibility of the test is limited to approximately 80% of patients with cirrhosis, and patients with massive ascites cannot be included. Therefore, also the results obtained in our compensated patients cannot be extended to the whole population of patients with cirrhosis, although the inclusion of three patients with previous hemorrhage makes the group representative of patients who may take advantage of a primary or secondary prophylaxis for gastrointestinal bleeding.

The study was sequential, and did not follow a random crossover design, since any putative effect of transdermal nitroglycerin might have lasted longer than the 24-h observation period. This introduces a potential bias in the evaluation of the results, and a random crossover study, using a placebo tape and including a wash-out period, might theoretically be desirable. However, from a practical point of view, the effects of transdermal nitroglycerin on resistance indexes – mainly on mesenteric artery – were so large and prompt in the first observation period (from

07:00 to 08:00; 1st day, from −6% to +7%; 2nd day, from +12% to +39%) to make blindness impossible for an expert echo-Doppler operator.

In the first 24-h period we determined basal hemodynamics under controlled conditions in our patients. We confirmed that the postprandial increase in portal flow in cirrhotic patients is approximately 30%, which is considerably lower than that observed in control subjects (27,28). Postprandial splanchnic hyperemia returned to baseline values within 3 h in cirrhotic patients, and was not accompanied by any increase during the night, in contrast to a recent echo-Doppler study (29).

During the 2nd day, nitroglycerin promptly reduced portal blood flow in all patients, and the results were quantitatively similar to those invasively obtained by Iwao et al. (12). The effects on portal blood flow further increased in the following hours and persisted throughout the study period, showing that transdermal nitroglycerin maintains its efficacy for as long as 24 h. The 24-h reduction in portal blood flow and velocity between 15% and 25% is similar to that obtained by β-blockers (3,13).

On the basis of the echo-Doppler data of the superior mesenteric artery we speculate that nitroglycerin exerts its action on portal blood flow mainly by increasing arterial resistances in the splanchnic bed, thus reducing portal trunk inflow. Splanchnic vasoconstriction may be explained by a baroreceptor reflex which is activated by the reduction in arterial pressure (7,30), although we failed to demonstrate any significant correlation between changes in blood pressure and changes in resistance indexes in splanchnic area (not reported in detail).

Several previous reports showed that portal flow decreases after acute organic nitrates (8). Conflicting data are reported on total hepatic blood flow, determined by the Indocyanine Green clearance, which was reported to be reduced (8,31) or unchanged (8,12), suggesting a compensatory buffer response of hepatic artery inflow (32). Such a hypothetical effect on hepatic artery has never been proved *in vivo*. By contrast, in the present study a moderate, but significant, increase in PI and decrease in artery flow was observed, contributing to a reduction of total hepatic flow (i.e. sum of portal and hepatic artery flow). These results are perfectly in keeping with those recently obtained by Bolognesi et al. (11), who measured an increase in hepatic arterial resistances after organic nitrates by means of Doppler technique. Further studies are needed to elucidate the reasons for differences between Doppler results and clearance studies.

Unexpectedly, renal resistances were not affected by organic nitrates, in spite of a moderate decrease in arterial pressure. Salmeron et al. (33) showed that the response of renal resistances to organic nitrates in cirrhosis was different in relation to the presence of ascites, being increased in decompensated cirrhosis. We confirmed that, in the absence of ascites, no effect on renal resistances is expected after transdermal nitroglycerin, which was generally well tolerated. Only two patients complained of headache, but this symptom usually disappears during chronic use.

On the basis of the results of the present study, transdermal nitroglycerin may be proposed for long-term clinical studies, to test its efficacy in preventing gastrointestinal bleeding in liver cirrhosis both alone and associated with β-blockers. Transdermal patches are generally preferred to oral drugs and such treatment may increase compliance, which is a fundamental prerequisite for therapeutic effect. This further supports the use of transdermal formulation in patients who are subject to multidrug oral therapy to treat and/or to prevent complications of liver cirrhosis.

Long-term studies are also needed to verify whether long-term use of transdermal nitroglycerin is followed by decreased effectiveness on portal flow, due to adaptive mechanisms in chronically treated subjects. Tachyphylaxis is expected to be a minor problem in patients with cirrhosis, possibly in relation to abundance of sulfhydryl groups (8,34), but a short nitrate-free period remains a valid rule also in this condition (35).

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