Effect of Metoclopramide on Portal Blood Flow in Patients with Liver Cirrhosis

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Summary: *Current interest in the pharmacological manipulation of portal flow on the metoclopramide. We used pulsed doppler ultrasonography to assess the effects of metoclopramide. The measurement of the portal blood flow and velocity, blood pressure were made at 0,15,30 minutes (min). Intravenous (iv). administration of metoclopramide markedly reduced the portal blood velocity and flow, systolic and diastolic blood pressure when to compare with basal values. After administration of metoclopramide portal blood velocity fell by 19.7% at 15 min (p<0.05), 20.8% at 30 min (p<0.05), portal blood flow 32% at 15 min, 37.5% at 30 min (p<0.001) systolic blood pressure 3% at 15min, 3.5% at 30 min (p<0.01) and diastolic blood pressure 6% at 15 min (p<0.01), 4.5% at 30 min (p<0.05). The maximal diameter of the portal vein remained unchanged.*

In conclusion, in this study clearly has demonstrated that an iv. administration of metoclopramide results in a significant reduction in portal blood flow, systolic and diastolic pressure in patients with cirrhosis of the liver.

Key Words: Metoclopramide, portal blood flow, portal blood velocity, portal hypertension, liver cirrhosis

Bleeding from oesophageal varices is a serious complication of portal hypertension. The mortality of the first bleed, even when actively treated in specialised units is approximately 30% (1,2). and may be considerably more in other centres. One of the most demanding aspects of treatment is the arrest of active variceal bleeding. The most effective methods are seldom available outside specialised centres, and even then have an appreciable morbiditiy. Therefore, we have examined a new approach to this difficult clinical problem

Up to now, the pharmacological treatment of portal hypertension has been based on the use of vasoactive drugs that reduce pressure and blood flow within the portal venous system, such as vasopressin (3), somatostatin (4) and propranolol (5,6). A different approach may be the use of pharmacological agents that increase the lower esophageal sphincter (LOS) pressure. It has been suggested (7) that the pharmacological increase of LOS pressure may reduce the inflow of blood into the submucous venous plexus of the esophagus and hence into the esophageal varices. This suggestion is supported by the findings of portographic studies showing that blood flow to the esophageal varices is reduced after the administration of these drugs (8-10).

Several portographic studies have shown a decrease in the istamited superior portosystemic circulation after administration of metoclopramide (11) and domperidone (12) two substances known to increase the LOS pressure (13,14). Moreover (15) some investigators recently demonstrated that metoclopramide administration may be of some assistance in arresting acute bleeding from oesophageal varices.

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Table I: Clinical features of the patients.

Clinical features	No
No	7
Sex M/F	5/2
Age (yr)	
Range	51-62
Mean	55±3
Varices	
F_1	4
F_2	3
F_3	0
Child classification	
A	0
B	1
C	6

F_1: Straight
F_2: Enlarged tortuous
F_3: Largest

The pulsed doppler system combined with B-mode scan ultrasonography was recently introduced, and physiologic measurements of portal blood flow have become possible (16,17). This study is intended to evaluate the effect of acute metoclopramide administration on portal blood flow measured by the pulsed doppler system in cirrhotic patients with portal hypertension.

MATERIAL and METHODS

Seven adult patients with portal hypertension assessed (Table: 1). In all of these patients, the primary disease was liver cirrhosis, and esophageal varices were noted endoscopically in most. Details such as age, sex are shown in Table 1.

All patients were aged between and years and had been haemodynamically stable for at least 7 days prior to the study. The patients with a history of cardiac disease, diabetes mellitus or renal disease, and those taking vaso-active drugs, were excluded.

The patients were assessed by full physical examination, urinalysis an measurement of full blood count; coagulation screen; liver function tests, and plasma protein, gamma glutamyl-transferase and cholesterol levels. Chest x-ray and 12-lead eletrocardiograph were performed.

Measurement of portal blood flow and haemodynamic variables. Portal vein anatomy and doppler flow factors were evaluated by means of a system that combined an ultrasonic ector scanner with a 3.5-MHz transducer and a pulsed doppler apparatus (Toshiba SAL-50A). Patients fasted overnight before the study. All measurements were performed while patients were lying quietly in a prone position and holding their breath in maximal expiration. Portal vein diameter had the angle between the doppler beam and the long axis of the portal vein were measured from a B-scan image showing beam direction with the portal vein in its long axis. An anterior subcostal approach that provides optimal visualization of the portal vein walls was used because it provides axial resolution for a more accurate diameter measurement. Portal vein diameter was measured at a location 1 to 2 cm proximal to its bifurcation, assuming that at this site the elliptic shape of the portal vein converges towards a circle (16).

Doppler signals were obtained from a sample volume located at the centre of the portal vein. After the maximal portal vein diameter and highest mean velocity were recorded, the portal blood flow rate was obtained by multiplying the blood velocity by the cross-sectional area of the vessel, calculated on the basis of the inner diameter, assuming circular geometry (16,17).

All measurements were performed by two independent, equally skilled investigators during two consecutive mornings. Interobserver variations in portal blood velocity measurements were always lower than 10%. The aver-

Table II: The measurement of portal blood velocity and flow, blood pressure were made after iv. administration of metoclopramide (mean±SEM).

Time (min)	Treatment	Velocity (ml/sec)	Blood flow (ml/min)	SBP (mmHg)	DBP (mmHg)	PVD
0. min	Metoclopramide	0.178±0.006	42.91±6.32	113.88±4.06	74.44±3.37	17.65±1.43
15. min	Metoclopramide	0.143±0.008	29.04±4.59	110.55±4.20	70.00±2.88	17.52±1.32
	%	19.7	32	3.0	6.0	1%
	P	<0.01	<0.0001	<0.01	<0.01	N.S
30. min	Metoclopramide	0.144±0.007	26.84±3.76	110.00±4.48	71.11±2.60	17.28±1.31
	%	20.8	37.5	3.5	4.5	1%
	P	<0.05	<0.0001	<0.01	<0.05	N.S.

SBP: Systolic blood pressure
DBP: Diastolic blood pressure
p: Significan different from basal value
NS: No significant
PVD: Portal vein diameter

age estimated portal blood flow rate varied always within± 10%.

Study design. After an overnight fast, mean volume of portal blood flow and haemodynamic variables were measured in all patients, and subsequently 20 mg metoclopramide (Metpamid amp. Sifar, Turkey) was administered intravenously for 10 min. Maximal diameter of the portal vein, portal blood velocity, portal blood flow, systolic and diastolic blood pressures, were monitored continuously 0,15 and 30 min after metoclopramide administration.

Statistical Analysis

The results are expressed as means ± SD. Two-way analysis of variance with replication and Student's t test for paired data were used for statistical comparison. Results were considered significant at $p<0.05$.

RESULTS

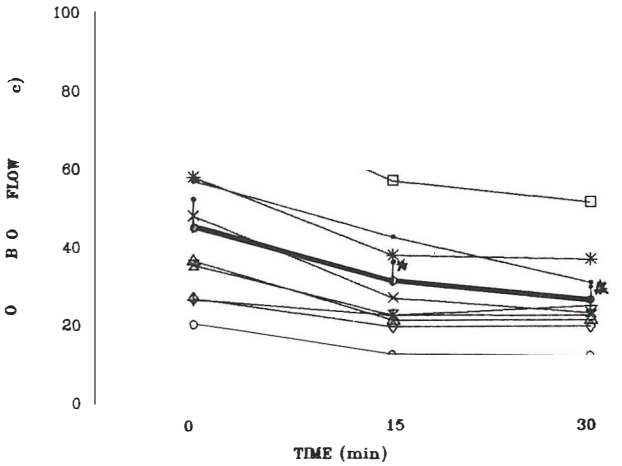
The effect of metoclopramide on portal blood flow, the maximal diameter of the portal vein, and some cardiovascular haemodynamic variables was studied in nine patients with cirrhosis of the liver and portal hypertension. The results presented in Table: 2. Metoclopramide significantly altered the volume of portal blood flow in all patients. Portal blood velocity and portal blood flow decreased significantly from 42.91±6.32 to 29.04±4.59 cm/sec (32%) and from 0.178± 0.006 to 0.143±0.08 ml/min (19.7%) respectively ($p<0.0001$ and $p<0.01$), within 15 min after metoclopramide administration and remained 26.84±3.76 cm/sec and 0.144±0.007 ml/min, at 30 min (37.5% and 20.8 %) ($p<0.0001$, $p<0.05$) respectively (Table: 2, Figure 1,2).

Intravenous administration of metoclopramide reduced the systolic blood pressure from 113.88±4.06 mmHg to 110.55±4.20 mmHg (3%) ($p<0.01$), at 15 min and 110.00±4.48 mmHg (3.5%) ($p<0.01$) at 30 min, diastolic blood pressure from 74.44±3.37 mmHg to 70.00±2.88 mmHg (6%) ($p<0.05$) at 15 min, and 71.11±2.60 mmHg (4.5%) ($p<0.05$) at 30 min (Table:2, Figure 3,4).

No significant changes were noted in the maximal diameter of the portal vein (Table: 2).

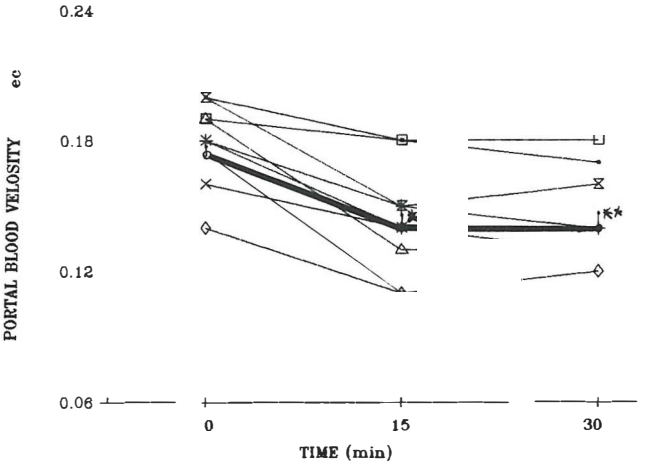
DISCUSSION

The present study demonstrates that administration of metoclopramide cause a significant



* p < 0.0001 significan different from basal value

Figure 1: The effect of intravenous metoclopramide administration on portal blood flow (ml/min) in patients with cirrhosis of the liver and portal hypertension.



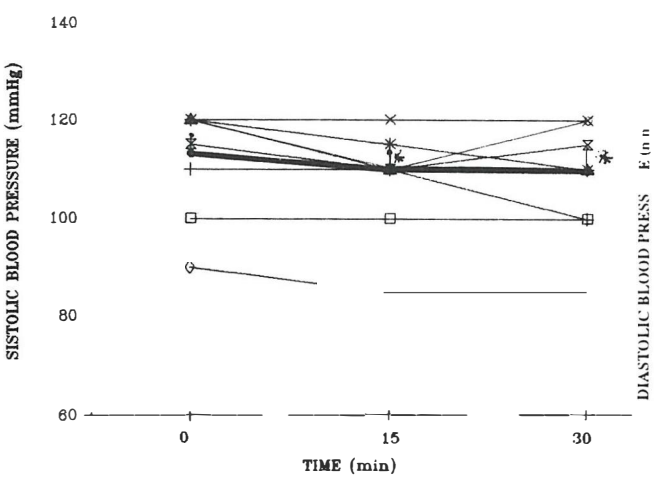
* p < 0.01

** p < 0.05 significan different from basal value

Figure 2: The effect of intravenous metoclopramide administration on portal blood velocity (ml/sec) in patients with cirrhosis of the liver and portal hypertension.

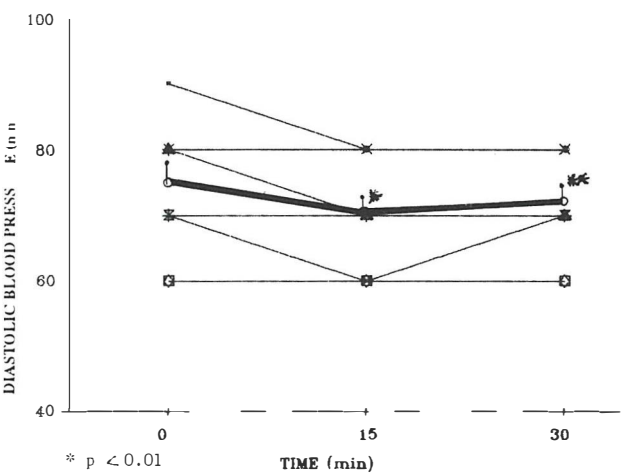
reduction of portal blood flow and velocity in patients with cirrhosis. In these patients metoclopramide administration led to significant reduction in the portal blood flow within 15 min, and after 30 min these that the maximal increase in LOS pressure, reached within approximately 15 min of intravenous metoclopramide administration (18), is probably associated with a maximal decrease in portal blood flow, directly supporting the possibility that changes in paravariceal blood flow may slightly influence the haemodynamics of portal blood flow. This results are in accordance with previous observations of doppler ultrasonic study in which the administration of drug that increase LOS pressure, including metoclopramide (19-22), was shown to reduce the inflow of blood into the eosephageal varices in some patients with portal hypertension.

A study shown that metoclopramide unlikely vasopressin (23-25), somatostatin (24) and propranolol (25,26) have significant effects on systemic and splanchnic haemodynamics, as



* p < 0.01 sienificant different from basal value

Figure 3: The effect of intravenous metoclopramide administration on sistolic blood pressure (mmHg) in patients with cirrhosis of the liver and portal hypertension.



* p < 0.01

** p < 0.05 significan different from basal value

Figure 4: The effect of intravenous metoclopramide administration on diastolic blood pressure (mmHg) in patients with cirrhosis of the liver and portal hypertension.

shown by the lack of any significant change in cardiac output, mean arterial pressure, heart rate. Therefore, reduction of portal blood flow represents a selective effect of metoclopramide on the esophageal circulation in patients with cirrhosis (19).

In contrast, in this study systolic and diastolic blood pressure decreased iv. administration of metoclopramide.

It is difficult to ascertain how much of the reduction in portal blood flow. Previous studies have shown the effect of LOS constriction on variceal blood flow to considerable. Portographic studies indicate that LOS constrictors such as domperidone, metoclopramide, and pentagastrin all reduce or even abolish blood flow in paraoesophageal varices (7,8) whilst not affecting flow in paraoesophageal varices. These findings are supported further by studies of azygous blood flow, where investigators showed in patients with varices that the some drugs reduce azygous blood flow without altering cardiovascular haemodynamics (19,27). It was concluded that the effect was the result of their constricting action on the LOS and resultant reduction of submucosal variceal flow. The results obtained from these two forms of investigation are not supported by our own portal blood flow studie.

The evidence of others suggested that pharmacological constriction of the LOS may be of sufficient force to compress varices so as to arrest active variceal bleeding. Metoclopramide has the advantage of being well absorbed after oral administration, which makes its aduquate for prolonged oral treatment. Current methods of arresting active variceal bleeding such as balloon tamponade (28), vasopressin with or without nitroglycerin (29), somatostatin (30) or emergency sclerotherapy (31) have limitations. These may be caused by lack of skilled nursing and medical personnel, side effects, cost of treatment, or lack of efficacy. Thus an effective, safe economic alternative is still required. The arrest of active variceal bleeding by metoclopramide appears to offer a genuine alternative to treatment altready mentioned.

Finaly, this study demonstrated that metoclopramide administration significantly, if only slightly, decreases the portal blood flow in patients with liver cirrhosis and portal hypertension.

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