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Effects of Metoclopramide and Domperidone on Azygos Venous Blood Flow in Patients with Cirrhosis and Portal Hypertension

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The effects of pharmacological manipulation of the lower esophageal sphincter pressure on the esophageal circulation in patients with cirrhosis and portal hypertension were investigated in 33 patients by measuring the azygos venous blood flow, which is an index of blood flow through esophageal varices and periesophageal collaterals draining into the azygos venous system. Measurements were performed in baseline conditions and after the blind administration of metoclopramide (20 mg i.v.) (12 patients), domperidone (10 mg i.v.) (12 patients) and placebo (9 patients).

Both metoclopramide and domperidone caused a significant reduction of azygos blood flow, that decreased by 11.5% ($p < 0.01$) and 15.6% ($p < 0.02$) respectively, while no change was observed in patients receiving placebo (+1.4%, not statistically significant). Reduction of azygos blood flow represents a selective effect of metoclopramide and domperidone on the esophageal circulation, since portal pressure, hepatic blood flow, cardiac output, heart rate and arterial blood pressure were unchanged by the administration of metoclopramide, domperidone or placebo.

These results indicate that the administration of drugs that increase the lower esophageal sphincter pressure may reduce the inflow of blood into the esophageal varices in cirrhotic patients with portal hypertension.

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 (1), somatostatin (2) and propranolol (3, 4). A different approach may be the use of pharmacological agents that increase the lower esophageal sphincter pressure (LESP). It has been suggested (5) that the pharmacological increase of LESP 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 (6–8).

Recently, it has been shown that, in patients with portal hypertension, measurement of the azygos venous blood flow provides a quantitative estimation of blood flow through gastroesophageal collaterals and esophageal varices draining into the azygos venous system (9, 10). In order to characterize further the effects of drugs that increase LESP on the esophageal circulation in portal hypertension, the effects of metoclopramide and domperidone (11, 12) on the azygos venous blood flow were investigated in a series of patients with cirrhosis and esophageal varices.

PATIENTS AND METHODS

Thirty-three patients with cirrhosis of the liver were included in this study. All had severe portal hypertension, as evidenced by the presence of esophageal varices, demonstrated by endoscopy. Twenty patients had previously bled from varices, and 18 had ascites (Table 1). Cirrhosis was alcoholic in 28 patients and nonalcoholic in 5. There were 26 males and 7 females, and the mean age was 52 ± 3 years (mean ± SE). Additional clinical information on these patients is given in Table 1.

The protocol was approved by the Clinical Research Committee of the Hospital Clinic i Provincial in October, 1983. Patients gave their consent to participate after a full explanation of the nature and purpose of the study. Patients were selected among those submitted to hemodynamic investigations for the evaluation of portal hypertension. Criteria for selection were: presence of esophageal varices on endoscopy; willingness to cooperate in the study, and that portal hypertension was due to micronodular cirrhosis. Patients with portal vein thrombosis, as evidenced by ultrasonography and/or angiography, as well as those with known macronodular cirrhosis, were excluded because in these patients, hepatic vein catheterization may not adequately reflect portal pressure. After fasting overnight, two venous catheter introducers (USCI International, Inc., Mass.) were placed in the femoral vein (under local anesthesia) by the Seldinger technique. One was used to advance a catheter under fluoroscopy into the azygos vein, where it was kept in the same place, as checked by fluoroscopy, for the whole study, and the

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other was used alternatively to advance a Swan-Ganz catheter (Edwards Laboratory, Los Angeles, Calif.) into the pulmonary artery, for the measurement of cardiopulmonary pressures and cardiac output (thermaldilution) or a 7F balloon-tipped catheter (Medi Tech, Cooper Scientific Corp, Watertown, Mass.) into the main right hepatic vein (2). Repeated measurements of wedged (occluded) and free hepatic venous pressures were obtained by inflating and releasing the balloon (2). Portal pressure was expressed as the gradient between wedged and free hepatic venous pressures [hepatic venous pressure gradient (HVPG)]. The azygos venous blood flow was measured by continuous thermal dilution according to a previously described technique (9, 10, 13). Briefly, the azygos vein was catheterized with a preshaped, double thermistor catheter (Webster Laboratories, Altadena, Calif.). Azygos blood flow was measured during a constant infusion of 5% dextrose used as indicator. The rate of indicator infusion used in these measurements ranged between 45 and 90 ml per min. Azygos blood flow was calculated by the continuous thermal dilution equation:

$$\text{Blood flow (ml/min)} = F_I \cdot 1.08 \cdot \left[\frac{T_B - T_I}{T_B - T_M} - 1\right]$$

in which F_I is the indicator infusion rate, 1.08 is a constant representing the ratio between the density and especific heat of 5% dextrose and blood, T_B is the baseline azygos blood temperature (°C), T_I is the temperature of the indicator (°C) and T_M is the temperature of the mixture of blood and indicator during indicator infusion (°C) (9). Normal values in our laboratory are 174 ± 29 ml per min (10).

The hepatic blood flow (HBF) was measured during a continuous infusion of indocyanine green (Serb, Paris) at a rate of 0.3 mg per min after a priming dose of 10 mg and an equilibration period of 40 min. A hepatic extraction above 0.1% and steady arterial indocyanine green levels were required for the calculation of the HBF (2, 14). These criteria were not met in six patients, two in each of the study groups. Arterial pressure was measured by sphygmomanometry, and heart rate was derived from the continuous ECG monitoring. Permanent tracings of all measurements were obtained with a multichannel recorder (Hewlett Packard, Model 1280 C, Waltham, Mass.).

After obtaining baseline measurements, 12 patients received domperidone (10 mg i.v.), 12 received metoclopramide (20 mg i.v.) and 9 patients received placebo (5% dextrose). Azygos blood flow was measured again 20 min after drug administration and also at 40 to 50 min. Several studies have demonstrated that the peak LESP response to intravenous metoclopramide (15, 16) and domperidone (17) is usually obtained within 20 min in subjects without liver disease. Cardiopulmonary pressures, cardiac output, HVPG and hepatic blood flow were measured again at 40 min. In each set of measurements, the same order of determinations was used: (a) simultaneous measurements of cardiac output, heart rate and arterial pressure; (b) simultaneous measurements of wedged hepatic venous pressure, free hepatic venous pressure, azygos blood flow and HBF. The choice of placebo, domperidone and metoclopramide was made at random, using closed envelopes. The drugs were prepared for administration in a separate room by a nurse not involved in the study and were given blindly. The code was not open until the final analysis of the results.

All measurements were made by triplicate in each period of the study. The results are given as mean ± S.E. The paired and unpaired Student's t test were used in the statistical analysis of the results (18).

TABLE 1. Summary of clinical data

	Placebo	Metoclopramide	Domperidone
No. of patients	9	12	12
Age (yr)[a]	51 ± 4	53 ± 2	53 ± 4
Sex (M/F)	8/1	9/3	9/3
Child-Campbell class			
A	5	6	5
B	4	5	6
C	—	1	1
Esophageal varices (n)	9	12	12
Previous variceal bleeding (n)	3	7	10
Ascites (n)	4	7	7
HVPG (mm Hg)[a]	18.9 ± 1.6	18.3 ± 1.2	17.4 ± 1.9
Azygos blood flow (ml/min)[a]	557 ± 68	608 ± 58	613 ± 82

Comparisons between the three groups showed no significant differences.

[a] Mean ± S.E.

RESULTS

All patients had severe portal hypertension, as demonstrated by the presence of esophageal varices and by an increased HVPG (Table 1). In these patients, values of HBF, cardiac output, mean arterial pressure and heart rate (Table 2) were similar to those observed in previous studies from our laboratory (2, 10, 13). As shown in Tables 1 and 2, there were no significant differences in baseline clinical and hemodynamic parameters between patients receiving placebo, metoclopramide or domperidone.

Placebo administration did not cause any significant change in HVPG, HBF, cardiac output, mean arterial pressure and heart rate (Table 2). Similarly, domperidone and metoclopramide had no significant effect on systemic and hepatic hemodynamics, indicating that at

TABLE 2. Effects of placebo, metoclopramide and domperidone on hepatic and systemic hemodynamics

	HVPG (mm Hg)	HBF (liters/min)	Cardiac output (liters/min)	Mean arterial pressure (mm Hg)	Heart rate (beats/min)
Baseline	18.9 ± 1.6	1.2 ± 0.8	7.9 ± 0.7	89 ± 5	92 ± 4
Placebo	18.6 ± 1.4	1.2 ± 0.7	7.7 ± 0.7	88 ± 5	88 ± 3
Baseline	18.3 ± 1.2	1.3 ± 0.5	7.9 ± 0.9	86 ± 2	84 ± 4
Metoclopramide	18.1 ± 1.3	1.4 ± 0.2	7.9 ± 0.8	85 ± 4	85 ± 4
Baseline	17.4 ± 1.9	1.2 ± 0.2	7.6 ± 0.8	84 ± 3	82 ± 2
Domperidone	17.0 ± 2.0	1.2 ± 0.3	7.6 ± 0.6	83 ± 3	81 ± 2

Values following the administration of placebo, metoclopramide and domperidone are not significantly different from baseline measurements.

the dose used in this study, these drugs have no significant circulatory effects in patients with cirrhosis (Table 2).

Azygos blood flow was increased in these series of portal hypertensive cirrhotics (Table 1). The mean values (557, 608 and 613 ml per min in patients receiving placebo, metoclopramide and domperidone, respectively) were much higher than those observed in a series of 11 subjects without portal hypertension studies in our laboratory (174 ± 29 ml per min) (10). There were no significant differences in the baseline azygos blood flow between patients receiving placebo, metoclopramide or domperidone (Table 3). Azygos blood flow did not change significantly 20 and 40 min after placebo administration (Table 3). The mean changes were −0.2 ± 5.1% and 1.3 ± 3.4%, respectively (Figure 1). In contrast, metoclopramide caused a significant reduction in azygos blood flow (Table 3) that fell an average of 10.0% at 20 min after drug administration and 11.5% at 40 min ($p < 0.01$), which is significantly different from the effect of placebo ($p < 0.01$; Figure 1). Domperidone also reduced the azygos blood flow by 8% at min 20 and by 15.6% at 40 min ($p < 0.02$) (Table 3). This change is significantly different from that observed after placebo administration ($p < 0.05$; Figure 1) but not from that caused by metoclopramide. Eight of the 12 patients receiving domperidone and six of those receiving metoclopramide experienced a reduction of azygos blood flow that exceeded 10% of baseline values (mean reductions = 27 and 19%, respectively).

No complications occurred, and there were no side effects following the administration of placebo, metoclopramide and domperidone.

DISCUSSION

Measurement of azygos blood flow by continuous thermal dilution is a recently introduced technique for the evaluation of portal hypertension that allows for a quantitative estimation of blood flow through gastroesophageal collaterals and esophageal varices draining into the azygos venous system (9, 10). It has been suggested that the main application of this technique is the evaluation of the effects of pharmacological agents on the esophageal circulation in patients with portal hypertension (9, 10, 19). We have previously shown that azygos blood flow, which is markedly increased in these patients, decreases significantly by the administration of vasopressin (10), somatostatin, (Bosch, J. et al., *Hepatology* 1983; 3:855, Abstract) and propranolol (13), vasoactive drugs that reduce portal pressure and that are currently used for the treatment of portal hypertension. In addition, in patients bleeding from esophageal varices, esophageal tamponade markedly reduces the azygos blood flow (10).

TABLE 3. Effects of placebo, metoclopramide and domperidone on azygos blood flow (ml/min)

	Baseline	20 min	40 min
Placebo	557 ± 68	541 ± 53	560 ± 69
Metoclopramide	608 ± 58	541 ± 44[a]	538 ± 48[a]
Domperidone	613 ± 82	534 ± 64	494 ± 62[b]

[a] $p < 0.01$ vs. baseline.
[b] $p < 0.02$ vs. baseline.

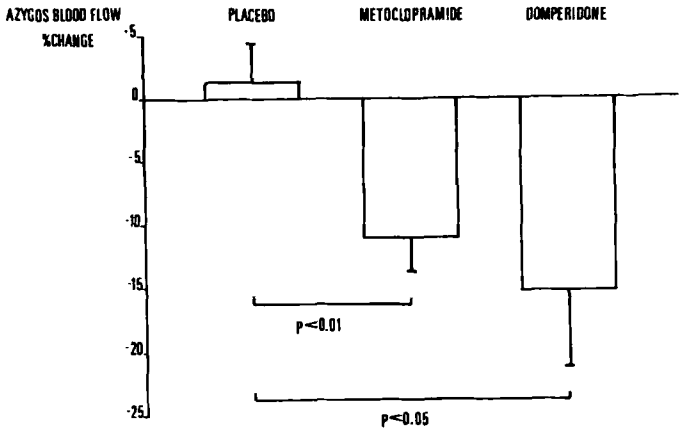

FIG. 1. Comparison of the effects of placebo (n = 9), metoclopramide (n = 12) and domperidone (n = 12) on azygos blood flow 40 min after i.v. administration (per cent change from baseline, mean ± S.E.). The reduction of azygos blood flow achieved by domperidone was not significantly different from that obtained with metoclopramide.

The present study demonstrates that administration of metoclopramide and domperidone, but not placebo, also causes a significant reduction of azygos blood flow in patients with cirrhosis and esophageal varices. These drugs, unlikely vasopressin (1, 2, 10), somatostatin (2) and propranolol (3, 13), have no significant effects on systemic and splanchnic hemodynamics, as shown by the lack of any significant change in cardiac output, mean arterial pressure, heart rate, HVPG and HBF. Therefore, reduction of azygos blood flow represents a selective effect of metoclopramide and domperidone on the esophageal circulation in patients with cirrhosis.

The mechanism by which metoclopramide and domperidone reduced azygos blood flow is probably related to its known effect of increasing LESP (11, 12): that reducing the inflow of blood into the submucous venous plexus will decrease blood flow in the esophageal varices. Our results are in accordance with previous observations of portographic studies in which the administration of drugs that increase LESP, including metoclopramide and domperidone (6–8), was shown to reduce the inflow of blood into the esophageal varices in some patients with portal hypertension (6–8).

Reduction of azygos blood flow was detected early after metoclopramide and domperidone administration, and was maintained after 40 min, suggesting a sustained effect. It is not clear why the maximal effect of metoclopramide and domperidone on azygos blood flow was noted at 40 min while it is known from studies in normal subjects that peak effects on LESP are usually reached within 20 min. It is possible that this is related to changes in the plasma half-life of the drugs in patients with cirrhosis. There was no significant difference between the reduction of azygos blood flow achieved by metoclopramide (11.5%) and domperidone (15.6%). Although the mean effect was moderate, in over half of the patients, reduction of azygos blood flow was more pronounced and similar to that observed with other drugs currently used

in the medical treatment of portal hypertension. Previous studies have shown that azygos blood flow decreases by 25% during vasopressin infusion (10) and by 34% following propranolol administration (13, 20).

It is important to note that measurement of azygos blood flow includes both blood flow from esophageal varices and from periesophageal collaterals draining into the azygos venous system (9, 10). It is difficult to ascertain how much of the reduction in azygos blood flow is contributed by a fall in variceal blood flow or in periesophageal collateral blood flow. However, since the effects of metoclopramide and domperidone on azygos blood flow appear to be related to their known effect of increasing LESP, it is likely that these drugs only can influence blood flow through the esophageal varices. Thus, the observed reductions in azygos blood flow probably reflect actual decreases in esophageal collateral blood flow. Moreover, since esophageal varices are often communicated with periesophageal collaterals (21, 22), it is possible that increases in LESP, by raising the inflow resistance into the varices, shift the collateral blood flow into the periesophageal veins. In that regard, it is worth noting that, in some patients, portographic studies have shown interruption of variceal blood flow with concomitant enhancement of periesophageal collateral blood flow after the administration of pentagastrin and domperidone (7).

These results may be of clinical relevance in the pharmacological treatment of portal hypertension. Both metoclopramide and domperidone have the advantage of being well absorbed after oral administration, which makes them adequate for prolonged oral treatment. However, whether moderate reductions of azygos blood flow, such as those achieved with metoclopramide and domperidone, may be of therapeutic benefit is still unclear. Therefore, the question of whether these drugs might eventually become useful agents in the treatment of portal hypertension should be specifically investigated by appropriate controlled clinical trials.

Finally, this study provides further evidence showing that measurement of azygos blood flow by continuous thermal dilution is an accurate and reproducible technique, as demonstrated by the lack of any modification in azygos blood flow following the intravenous, double-blind administration of placebo.

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