Effect of Somatostatin Analogue (SMS 201-995) Administration on Portal Blood Flow in Patients with Liver Cirrhosis

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Summary: *Bleeding from oesophageal varices in serious complication of portal hypertension. Therefore, we have examined a new approach to this difficult clinical problem. This study is intended to evaluate the effect of acute long acting somatostatin analogue (SMS 201-995) administration on portal blood velocity measured by the pulsed Doppler system in cirrhotic patients with portal hypertention. The measurement of portal velocity, heart rate, blood pressure were made at 0, 15, 30, 45 and 60 minutes (min) after administration of SMS 201-995.*

7 cirrhotics were studied, 5 male and 2 female; mean age 55±3, range 51-62 years. First day, a bolus of 25 μg SMS was given followed by an intravenous infusion of 25 μg SMS over 1 hour. Second day, a bolus of 1 ml saline (SF) was given followed by intravenous infusion of 25 μg SMS over 1 hour. Portal blood velocity declined from a mean baseline value of 0.166±0.32 m/sec to mean of 0.130±0.02 m/sec at 5 minutes ($p<0.01$), a mean of 0.118±0.02 m/sec at 15 minutes ($p<0.01$), to mean of 0.121±0.03 at 30 minutes ($p<0.01$), to mean of 0.136±0.02 m/sec at 45 minutes ($p<0.05$) and mean of 0.140±0.01 at 60 minutes ($p<0.05$). This results of portal blood velocity was measured by pulsed doppler methot that is a noninvasive test suggestted that SMS exerts its main benefical effect on portal blood flow. And this suggest that SMS may be more effective when given as an intravenous bolus dose in patients with bleeding varices.

Key Words: Somatostatin analogue, portal flow, portal velocity, livercirrhosis

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Bleeding from oseophageal varices is serious complication of portal hypertension. The mortality of the first bleed even when actively treated in specialized units is approximately 3% (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. 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), propranolol (4,5) and nitroglycerin (6).

Somatostatin, in addition to its inhibiting action on the secretion of several gastrointestinal hormones, has been reported to decrease hepatic venous pressure gradient-a reflection of portal pressure-and has been proposed in the treatment of variceal bleeding in patients with cirrhosis (7-16). However, hemodynamic and clinical studies have shown widely divergent results. The effect of somatostatin on portal blood flow have been investigated by invasive methods as angiography. However the pulsed Doppler system combined with B-mode scan ultrasonography offers the advantages of being less invasive, was recently introduced, and physiologic measurements of portal blood flow have become possible (17,18). This study is intended to evaluate the effect of acute long acting somatostatin analogue (SMS 201-995) administration on portal blood velocity meas-

ured by the pulsed Doppler system in cirrhotic patients with portal hypertention.

MATERIAL AND METHODS

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

All patients were aged between 51 and 62 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 and measurement of full blood count; coagulation screen; serum urea and electrolyte concentrations; liver function tests, and plasma protein, gamma glutamyl-transferase and cholesterol levels. Chest x-ray and 12-lead electrocardiograph 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 sector 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 and 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

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	
	4
	3
	0
Child calssification	
A	0
B	1
C	6

F_1: Straight
F_2: Enlarged tortuous
F_3: Largest

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 (17).

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 (17,18).

Interobserver variations in portal blood velocity measurements were always lower than 10%. The average estimated portal blood flow rate varied always within 10%.

After an overnight fast, mean volume of portal blood flow and haemodynamic variables were measured in all patients, had subsequently 25mg SMS 201-995 (Sandoz Co.) or saline (SF) 0.02 ml/min was administered intrave-

Table II: Effects of SMS 201-995 infusion on hemodynamics.

Time (min)	Treatment	SBP	DBP	Pulse	Velocity
0.min	S	125±10	78±5	84±12	0.168±0.02
	SMS	123±12	79±4	84±8	0.166±0.03
	P	NS	NS	NS	NS
5.min	S	128±11	77±6	88±10	0.169±0.02
	SMS	128±13	80±5	82±10	0.130±0.02
	P	NS	NS	NS	<0.01
15.min	S	124±10	78±4	82-8	0.160±0.03
	SMS	124±11	80±3	78±10	0.118±0.02
	P	NS	NS	NS	<0.01
30.min	S	126±9	76±5	87±11	0.165±0.03
	SMS	125±8	77±4	80±7	0.121±0.03
	P	NS	NS	NS	<0.01
45.min	S	129±8	78±4	81±10	0.162±0.03
	SMS	127±10	81±4	82±8	0.136±0.02
	P	NS	NS	NS	<0.05
60.min	S	127±10	77±5	85±13	0.167±0.02
	SMS	126±9	78±6	79±11	0.140±0.01
	P	NS	NS	NS	<0.01

SBP: Systolic blood pressure
DBP: Diastolic blood pressure
NS: No significant

nously for 60 min. Maximal diameter of the portal vein, portal blood velocity, portal blood flow, systolic and diastolic blood pressures, and heart rate were monitored continuously 15,30,45 and 60 min after administration.

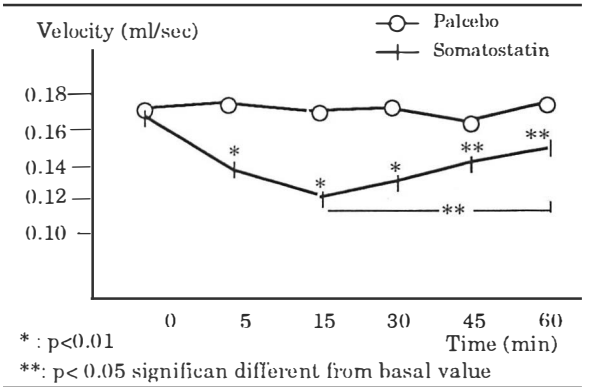
Statistical Analysis

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

RESULTS

The values obtained before and after the administration of SMS 201-995 and saline are listed in Table 2.

After iv. administration of SMS 201-995, portal blood velocity declined from a mean baseline value of 0.166±0.32 ml/sec to mean of



Graphic 1. The values of portal blood velocity after the administration of SMS 201-995 and saline.

0.130±0.02 ml/sec at 5 minutes ($p<0.01$), a mean of 0.118±0.02 ml/sec at 15 minutes ($p<0.01$), to mean of 0.121±0.03 at 30 minutes ($p<0.01$), to mean of 0.136±0.02 ml/sec at 45 minutes ($p<0.05$) and mean of 0.140±0.01 at 60 minutes ($p<0.05$) (Table 2, Graphic 1). Shows the changes in portal blood velocity with time in the two groups of patients. The heart pulse, blood pressure not changed significantly and no side effects were experienced by the patients who received SMS 201-995.

DISCUSSION

This study clearly has demonstrated that an intravenous infusion of SMS 201-995 results in a significant reduction in portal blood flow in patients with cirrhosis of the liver. The some reports with SMS 201-995 in cirrhosis has previously been published. But little work have been demonstrated by the pulsed doppler system is less invasive test.

The effects of somatostatin on portal hemodynamics remain controversial. Although most studies in animals (9-22) and human (9,11,12,14-16,23,24). have found decreases in portal tributary blood flow or pressure, others found no significant effect (10,13). This confusion is likely to be related to widely varying doses and the presence or absence of anesthesia.

The mechanism by which SMS 201-995 reduce portal pressure has not been clearly established.

Previous studies in the normal (21), pig (22) and rat (25) have found portal hemodynamic effects.

Somatostatin analogue is known to decrease levels of several vasodilatory hormones, including vasoactive intestinal polypeptide, pancreatic polypeptide, and glucagon (26,27). Benoit and colleagues have suggested that several humoral factors, in particular glucagon, may mediate chronic splanchnic hyperemia in portal hypertension (28). Recently, when glucagon antisera was given to rats to neutralize the effects of the native hormone, portal hypertensive rats, but not normal rats, responded with a 25% decrease in portal tributary flow (29).

It may thus be that the splanchnic vascular effects of somatostatin analogue in rats with portal stenosis or cirrhosis were due to a diminution of these splanchnic hyperemic humoral factors (25). Vasopressin, a "pure" vasoconstrictor, decreases portal blood flow in both normal and portal hypertensive animals (30). In contrast, somatostatin decreases portal blood flow only in portal hypertensive animals. This difference may be explained by the fact that vasopressin acts directly on the blood vessels, whereas somatostatin also acts indirectly by decreasing abnormal levels of vasoactive hormones in portal hypertensive animals (25).

In rats with portal hypertension, SMS 201-995 had a vasoconstrictive effect as evidenced by the increase in arterial pressure and total peripheral resistance. Some evidence suggests that SMS 201-995 also has a some investigated suggest direct vasoconstrictive action (21,23). That this factor may also play a role in the present results. Reflex splanchnic vasoconstriction subsequent to the fall in cardiac output is also a possibility, but the absence of correlation between the decrease in portal tributary flow and cardiac output tends to weigh against this idea (25).

In this study SMS 201-995 has been shown to have a significant effect on portal haemodynamics, with no significant effect on systemic haemodynamics. No side-effect was experienced.

The slight increase in arterial pressure was observed in some experimental and clinical studies (11,22,24). But a marked decrease in cardiac output was noted in only a few investigations (8,11,22,24).

In conclusion, decreasing effect of SMS 201-995 has been demonstrated on portal blood flow by the pulsed Doppler system.
The doppler method is simple and non-invasive and is particularly useful in studing changes in portal hemodynamics. These effects of SMS 201-995 may prove useful on menagement of variceal bleeding the patients with liver cirrhosis.

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