EVALUATION OF THE EFFECTS OF OCTREOTIDE ON PORTAL HEMODYNAMICS USING PULSED DOPPLER ULTRASONOGRAPHY IN PATIENTS WITH CHRONIC LIVER DISEASE

(Received 8 March, 1993)

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SUMMARY

Intensive clinical investigations on Somatostatin have been being carried out in recent years. Somatostatin and its synthetic analogues were initially used in the treatment of endocrine tumors. Today, they are being studied in the treatment of gastrointestinal diseases and successful results are being obtained.

20 chronic liver disease (CLD) patients (10 chronic active hepatitis (CAH) and 10 cirrhosis), and 10 controls were included in this study. Effects of Octreotide on portal venous flow velocity were investigated using Pulsed Doppler technique. All the patients were given 100 mcg Octreotide (SC), after the determination of baseline values of blood pressure; pulse rate; blood glucose, urea, creatinin, Na, K and portal venous flow velocity. These criteria were determined again in the 15, 30, 45, 60, 120 and 180th minutes after the injection.

In the patients with CAH, portal venous flow velocity was changed from 11.8+2.6 cm/sec. to 9.9+2.5 cm/sec. in the 15th min. ($p<0.01$); to 8.7+1.9 cm/sec. in the 30th min. ($p<0.01$); to 8.6+2.1 cm/sec. in the 45th min. ($p<0.01$); to 8.7+2.0 cm/sec. in the 60th min. ($p<0.01$); to 9.0+2.2 cm/sec. in the 120th min. ($p<0.05$); and to 9.1+2.3 cm/sec. in the180th min. ($p<0.05$). In the cirrhotic patients and in controls, portal venous flow velocity showed similar changes and we observed that the efficacy of the drug continued until the 180 th minute.

The results of this study revealed that Octreotide had caused reduction in portal venous flow velocity with a rate of 30-35 % in controls, and 20-25 % in patients with CLD.

These significant changes observed in portal hemodynamics observed using pulsed doppler tecnique suggest that Octreotide could be used in emergency treatment of variceal gastrointestinal bleedings in patients with CLD.

Key Words: Octreotide, portal hypertension, variceal bleeding, portal venous flow velocity.

INTRODUCTION

Octreotide is a long-acting synthetic analogue of somatostatin. It is an octapeptide composed of 8 aminoacids. Its plasma half-life is 90 minutes. After its subcutaneous injection, it reaches a peak value in 15-30th minutes and 100 % biological activity is obtained (1).

Somatostatinergic neurons are found diffusely in central and peripheric nervous system and in gastrointestinal system especially in antrum and duodenum, as well (2).

Somatoastatin and its synthetic analogues have their effects basically on splanchnic blood flow (3-6), gastrointestinal endocrine (7,8) and exocrine (9-11) functions and motility (12,13).

Vasoconstrictive effects of Octreotide on splanchnic area have been shown to reduce portal blood flow and pressure in animals (14,15). Therefore its use is recommended in the initial treatment of hemorrhage from esophageal varices secondary to portal hypertension (16,17). Mechanism of its effect on portal hemodynamics has not been clarified yet, but its vasoconstrictive effect on the splanchnic area plays the most important role.

In this study effect of Octreotide (100 mcg subcutaneously) on portal venous flow velocity was investigated using pulsed doppler tecnique in patients with chronic liver disease (CLD) and in controls.

METHODS

Twenty patients (10 chronic active hepatitis and 10

cirrhosis of the liver) and 10 controls were included in this study. Patients who had had heart failure, hypertension and those who had been on medications known to effect portal venous flow and pressure (beto blockers, isosorbit dinitrate etc.) were excluded from the study. Controls were chosen among healthy young men. The clinical data of the patients and controls are summarized in table - I. The severity of liver cirrhosis was classified according to Child's classification.

All the patients were admitted to the hospital. The diagnosis of CLD was confirmed histopathologically, by liver biopsies performed using Menghini technique. All the patients underwent upper gastrointestinal endoscopy (Olympus GIF K-20) to reveal endoscopic findings of CLD.

The drug was given to patients at 09.00 a.m. who had not eaten anything after 09.00 pm the night before. After the determination of the baseline values of portal venous flow velocity, arterial blood pressure, pulse rate, blood urea, glucose, creatinin, Na,K levels, Octreotide (Sandoz Pharma Ltd. Basel, Switzerland) (100 mcg,S.C.) was injected to all patients. The drug had been kept at room temperature for 30 min. not to create pain at the injection site. The criteria, baseline values of which had been determined before, were repeatedly determined in the 15th, 30th, 45th, 60th, 120th and 180th minutes. Blood urea, glucose, creatinin, Na, K levels were determined only in the 60th and 180th minutes. Portal venous flow velocities (cm/second) were measured using an ultrasonic Sector Scanner and pulsed Doppler apparatus with a 3.5 MHz transducer (Toshiba 160-A Sonolayer) with anterior subcostal approach on 2-3 cm proximal to portal venous bifurcation while the patients were on supine position and keeping them at maximum expirium (Fig.1).

For the analysis of the data, the results were expressed as mean - SD and student's t-test was used to determine the significance of the results.

RESULTS

The results of the study are summarized in tables II and III. In the CAH and control groups blood pressure values showed no statistically significant differences during and after the study. The initial value of blood pressure (130±24/73±9.4 mmHg), fall to 112.5±21.2 / 64±6.9 mmHg in the 60th minute and this effect lasted until the end of the 180th minute (110±21.6 / 65±7.0 mmHg) ($p<0.05$), in the cirrhotic patients.

Portal venous flow rate was reduced in all groups, especially in the control group and this change was significant statistically (Table-II). The reduction in the flow rate was more impressive in the cirrhotic group compared to those of control and CAH groups. The reduction rate gradually increased and arrived to maximum in the 45th minute, and started to fall thereafter. The effect of the drug was seen until the 180th minute.

Blood flow rate changes in the control group was parallel to those in the other two groups. The maximum reduction occured in the 45th minute as well and the effect of the drug lasted until the 180th minute (Table-II, Fig. 2).

Side Effects: Previously reported side effects such as nausea, vomiting, pain at injection site, diarrhea, abdominal discomfort, headache and fatigue did not occur in any of our patients during the application of the drug and in the following 24 hours. The only side effect observed was hyperglisemia which occured in 5% of the patients. No statistically significant changes have occured in pulse rate, and in the plasma levels of urea, creatinin, Na and K during and after the study.

DISCUSSION

In this study we have shown that in patients with CAH and cirrhosis of the liver Octreotide administration significantly reduced the portal blood flow rate, and that this reduction could be evaluated using a pulsed Doppler ultrasography. Similar results have been reported by Ericksson et al (18), Jahren et al (5) and Lin et al (6). The observed reduction in hepatic blood flow is similar to those with somatostatin (18-20). In the study of Sonnenberg et al (3) somatostatin caused a reduction in normal controls, while no significant reductions were seen in cirrhotic patients. The results of other studies are on the contrary of this finding. The findings of Sonnenberg's study may be dose dependable and although some hepatic flow changes happened, they were not significant.

We preferred to conduct the study using an ultrasonography with sector scanner and pulsed scanner: because this is a simple, efficient, safe, non-radioactive and non-invasive way of determining blood flow rate (21).

In the study of Ericksson et al (18), it has been reported that, 15-30% ($p<0.01$-0.05) reduction in portal blood flow was observed in the first 15 minutes after the IV infusion of octreotide in 15 cirrhotic patients. In our study, portal venous blood flow velocity decreased 15.1% at the 15 th min.. 26.2% at the 30th min. and 27.7% at the 45th min. in the CAH group ($p<0.01$). The reduction in portal venous blood flow rate was more prominent in cirrhotic patients with portal hypertension (26.3 %, 24.5 % and 27.2 % respectively). ($p<0.01$).

In a placebo controlled study Burroughs et al have found that somatostatin is effective in the control of bleeding esophageal varices in 120 patients (17). This effect is thought to be related with decreased portal blood flow and with the reduction in wedge hepatic venous pressure. This study is of major importance, because it shows the efficacy of somatostatin in the clinical setting.

The dosage of the drug is different in various studies. In most studies the drug is given with bolus IV injection and/or infusions. We administered a total

Table - I Clinical characteristics of patients and controls

	Chronic Active Hepatitis	Cirrhosis	Controls
No. of Patients	10	10	10
Age	45 ± 11	52 ± 9	23 ± 2
Sex (M/F)	8/2	7/3	10/0
HCV (+)	-	3	-
HBsAg (+)	5	4	-
AntiHBs	1	2	-
ALT (U/L)	57.0 ± 44.9	87.9 ± 67.1	24.5 ± 5.4
AST (U/L)	42.4 ± 34.3	99.6 ± 50.9	22.8 ± 8.2
Child A/B/C		2/4/4	
Splenomegaly	9	10	-
Hepatosplenomegaly	7	4	-
Ascites	-	4	-
Esophageal Varices	-	10	-
Alcohol	-	1	-
Cryptogenic	-	2	-
Wilson	1	-	-

Table - II Portal venous blood flow rates (cm/second) before and after octreotide was injected

Patient Group	Initial Value (cm/sec.)	15. Min	30. Min	45. Min	60. Min	120. Min	180. Min
Control Group	13.7±1.3	11.5±1.6	9.2±1.9	8.7±1.4	8.7±1.2	8.7.1.1	9.2±1.4
Mean Reduction in blood flow (%)		16.1	32.9	36.5	36.5	36.5	32.8
Statistical Significance		p<0.01	p<0.01	p<0.01	p<0.01	p<0.01	p<0.01
CAH	11.8±2.6	9.9±2.5	8.7±1.9	8.6±2.1	8.7±2.0	9.0±2.2	9.1±2.3
Mean Reduction in blod flow (%)		16.1	26.2	27.7	26.2	23.7	22.8
Statistical Significance		NSD	p<0.01	p<0.01	p<0.05	p<0.05	p<0.05
Portal HT+ Cirrhosis	11.0±2.3	8.1±1.6	8.3±1.3	8.1±1.7	8.4±1.7	9.0±1.9	9.2±2.3
Mean reduction in blood flow (%)		26.3	24.5	27.2	23.6	18.1	16.3
Statistical Significance		p<0.01	p<0.01	p<0.01	p<0.01	p<0.05	NS.

NSD: Normal Standard Deviation.
CAH: Chronic active hepatitis.

dose of 100 mcg. S.C. to all patients. We preferred this route, because it is easy and the effect of the drug is longer with this usage. In both groups the effect of the drug was still detectable on the 180th min. (p<0.01 - p<0.05). We believe that subcutaneous application is responsible for the drug to act longer than its intravenous administration. In previous studies different doses of drug administration caused slight differences in portal blood flow which are statistically not significant (6,18).

The mechanism of action of somatostatin or its long acting analogue on portal blood flow is still not known. Animal studies proposed a reduction in the portal venous inflow as a result of the increase of splanchnic arteriolar resistance (15,22). It has been reported that the increase in circulating vasodilators, especially glucagon and reduced vascular sensitivity to endogenous vasoconstrictors (22,23) play the major role for the splanchnic hyperemia in chronic portal hypertension. It has also shown that octreotide decreases plasma glucagon levels (24). When these two findings are put together, it may be proposed that octreotide reduces splanchnic blood flow both by

decreasing circulating hormone (mainly glucagon) and by increasing splanchnic vascular sensitivity to vasoconstrictors in cirrhotic patients with portal hypertension.

We did not observe any side-effects such as pain at injection site, nausea, diarrhea, abdominal discomfort, headache and fatigue. We believe that keeping the drug at room temperature before the injection and injecting it slowly played a role in the painless injection. In previous studies hyperglisemia with a rate from 3-5 % to 10-20 % has been reported (4,24). In our patients hyperglisemia was observed about 5% without statistical significance. Plasma levels of Na, K, urea and creatinin and heart rate showed no changes.

Table- III Mean values of systolic / Diastolic blood pressure (mmHg)

Patient Group	Initial (Sys/Dias)	15. Min	30. Min	60. Min	180. Min
Control Group	117+6 71+7	115+5 74+6	110+10 72+5	106+9 70+6	109+11 70+6
Statistical Significance		NSD	NSD	NSD	NSD
CAH	116+16 74+6	110+14 69+7	106+4 69+7	108+14 68+6	108+16 67+7
Statistical Significance		NSD	NSD	NSD	NSD
Portal HT + Cirrhosis	130+24 73+9	121+25 73+9	114+21 66+9	112+21 64+7	110+21 65+7
Statistical Significanfe	NSD	NSD	NSD	p<0.05	p<0.05

NSD: Normal Standard Deviation.
CAH: Chronic Active Hepatitis.

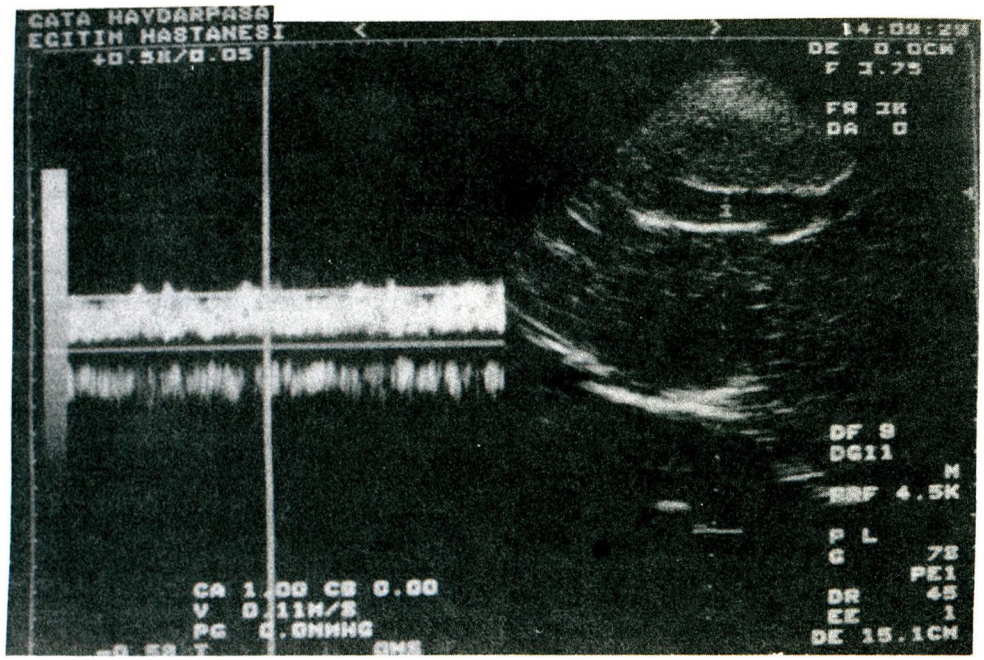

Fig.1. Portal venous bifurcation while the patient was in supine position and at maximum expirium.

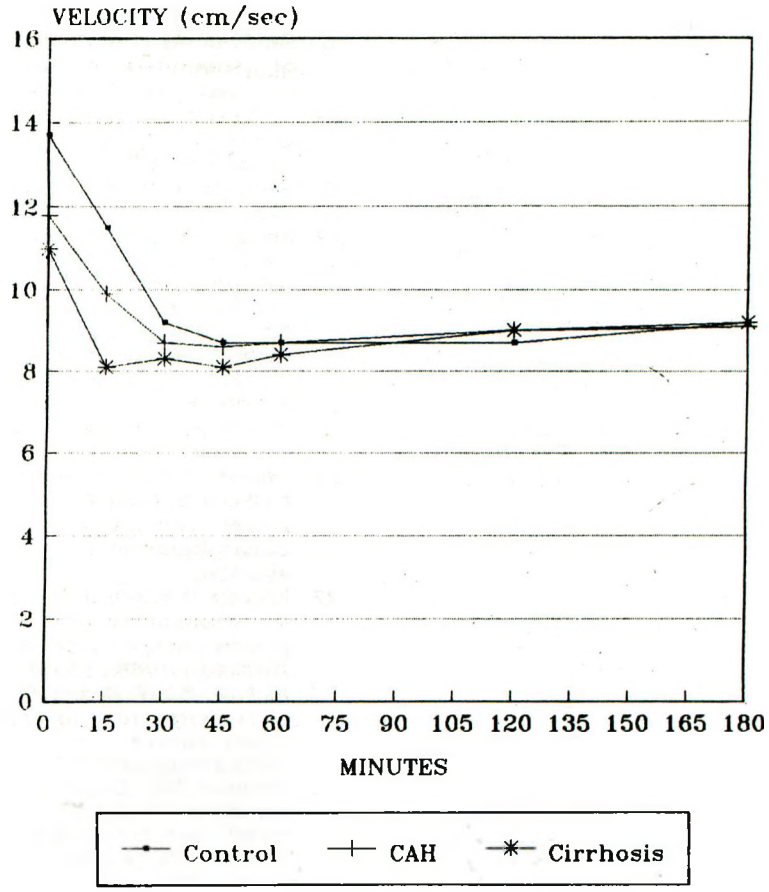

Fig.2. Effect of octreotide (100 mcg) on portal venous flow velocity

In this study, only in the cirrhotic patients both systolic and diastolic blood pressures decreased about 14% starting from the 60th minute until the end of the study. Changes in the pulse rate were not significant. In the study of Lin et al. although the heart rate, cardiac index and systemic vascular hemodynamics were not effected. 100 mcg/h infusion of Octreotide after an initial bolus of 100 mcg, caused a decrease in the mean arterial pressure (6). In other studies decreses of arterial blood pressure (13-14%) and cardiac output (19.7%) values were shown (5,19). Arterial blood pressure reduction in our cirrhotic patients is comparable to those which were dose dependable in the previous studies.

In conclusion:

1- 100 mcg. octreotide was seen to be effective to reduce portal blood flow 30-35% in the control group and about 20-25% in the CLD group beginning from the 15 th minute and this effect lasted at the end of the 180th minute. Early disappearence of the effect of the drug in cirrhotic patients must be kept in mind during the treatment of these patients.

2- We demonstrated that changes in the portal haemodynamics can be evaluated with the use of non-invasive pulsed-doppler technique instead of invasive techniques.

3- No side effects which limited the use of the drug were seen when octreotide was used 100 mcg SC.

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