Türk Nefroloji Diyaliz ve Transplantasyon Dergisi/Office Journal of the Turkish Nephrology, Association 2000;1:44-49

EFFECTS OF SOMATOSTATIN AND OCTREOTIDE ON RENAL FUNCTION IN PATIENTS WITH POSTNECROTIC CIRRHOSIS

POSTNEKROTIK SİROZLU HASTALARDA SOMATOSTATIN VE OCTREOTİD'İN BÖBREK FONKSİYONLARI ÜZERİNE ETKİLERİ

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ÖZET

Somatostatin ve oktreotid splenik damarlarda kontraksiyon yaparak splenik sahadaki kanı genel dolaşıma döndürebilmededir. Bu çalışmada, postnekrotik sirozlu hastalarda her iki ilacın böbrek fonksiyonları üzerine etkileri araştırıldı. Hastaların böbrek fonksiyonlarını bozan ek bir hastalık yoktu. Oktreotid (100 pg) 21 hastaya 3 gün üst üste cilt altı olarak verildi. İlacın erken ve geç etkilerini gözlemlemek amacı ile ilacın son alımından hemen sonra ve 2 gün sonra ölçümler tekrarlandı. Aynı hastalar arasından rasgele seçilmiş olan 10 hastaya somatostatin (250 pg) intravenöz bolus olarak verildi. Ölçümler tekrarlandı. Oktreotid erken yanıt olarak günlük idrar çıkışını, idrar sodyumunu (Nα), fraksiyonel sodyum atılımını (FeNa) arttırdı. Plazma aldosteron ve antidiüretik hormon (ADH) düzeyinin ise azaldığı görüldü. ADH düzeyindeki azalma ilacın kesilmesinden 2 gün sonra da devam etti. Somatostatin ise idrar Nα, plazma kreatinin düzeylerini, plazma renin aktivitesini artırdı. Plazma Nα ve glomerider fütrasyon oranı ise azaldı. Günlük idrar miktarında ve aldosteron düzeylerinde anlamlı olmayan azalma saptandı.

Bu sonuçlar, octreotidin postnekrotik sirozlu hastaların böbrek fonksiyonları üzerinde kötü etkisinin olmadığını, hatta idrar çıkışını ve idrar Nα arttırarak yararlı olabileceğini gösterdi. Somatostatin ise böbrek fonksiyonları bozuk olan sirotik hastalarda dikkat/i kullanılmalıdır.

Anahtar Kelimeler: Somatostatin, Oktreotid, Renal Hemodinami, Postnekrotik Siroz

SUMMARY

// was proposed that somatostatin and octreotide can drive the splanchic blood into general circulation by constricting the splanchnic vessels and may ameliorate impaired functions in cirrhotic patients by their inhibitory effects on vasoconstricting hormones and mediators. We investigated the effects of both drugs on the renal functions of the patients with postnecrotic cirrhosis. No patient had an additional systemic disease deteriorating renal functions. Octreotide (100 pg t.i.d) was administered subcutaneously for three consecutive days to 21 patients. To observe the immediate and late effects of the drug, measurements were performed immediately and two days after the last administration of the drug and compared with initial results. Three weeks later somatostatin (250 pg i.v. bolus) was administered to ten patients randomly chosen from the same patients. Same measurements with octreotide were performed before and immediately after the administration of this drug. The immediate responses to octreotide were increased daily ***urine output,*** *urine sodium (Nα), fractional excretion of sodium (FeNa) and decreased plasma aldosterone and antidiuretic hormone (ADH). Prolonged decrease in ADH was observed two days after cessation of the drug. Somatostatin increased urine Nα, FeNa, plasma creatinine, plasma renin activity (PRA) and decreased urine creatinine, creatinine clear ence (Cer), plasma Nα and glomerular filtration rate (GFR). Unsignificantfalls in daily urine output and aldosterone level were also observed. These results indicate that octreotide has no considerable adverse effects on the renal functions in the patients with postnecrotic cirrhosis and even may be beneficial by virtue of increasing daily urine output and urine Nα excretion. Somatostatin should be used with caution in cirrhotic patients who have impaired renal functions.*

Key Words: Somatostatin, Octreotide, Renal Hemodynamics, Postnecrotic Cirrhosis

INTRODUCTION

It is suggested that the administration of somatostatin and its analogue octreotide to cirrhotic patients with functional renal failure induce splanchnic vasoconstriction, and depress increased sympathetic activity. As a result, renal blood flow may increase and renal functions improve (1,2). But the true impact of somatostatin and octreotide on renal functions in cirrhotic patients still remain controversial. We compared the efficacy and safety of octreotide and somatostatin on various indices of renal function in cirrhotic patients on different stages.

MATERIALS AND METHODS

This study was performed in 21 postnecrotic cirrhotic patients hospitalized from February 1993 to December 1995 in The Department of Internal Medicine at Gevher Nesibe Hospital of Erciyes University Medical Faculty.

All of the patients had mild ascites due to postnecrotic cirrhosis and had normal renal functions. The diagnosis of postnecrotic cirrhosis was based upon history, physical examination, biochemical indices, ultrasound, gastrointestinal endoscopy, liver biopsy (when possible), detection of either Hbs Ag or Anti - HCV. No patient had a history of alcohol abuse.

Seventy of cirrhosis was assessed according to Child - Pugh classification. Patients had no evidence of gastroenteritis, upper gastrointestinal bleeding, bacterial peritonitis, paracentesis, hepatic encephalopathy during last 15 days or a history of hepatocellular carcinoma, arterial hypertension, cardiovascular disease, chronic obstructive lung disease, genitourinary disease, diabetes mellitus. Approval of the protocol was obtained by the Ethical Committee of the Erciyes University Hospital. All patients gave informed consent before entering the study.

All medicines were ceased ten days before the study. Daily fluid intake was restricted to 1000 ml, controlled with daily body weight measurements. Patients were put on a low sodium diet.

Octreotide 100 μg was administered subcutaneously three times for three consecutive days. To observe the immediate and late effects of the drug respectively, the following measurements were obtained before the first administration and immediately and two days after the last administration. Urine volume, urine osmolality, sodium and creatinine in urine, serum osmolality, creatinine, sodium, aldosterone, PRA, ADH in blood. Ccr, FeNa, and GFR were calculated using standard formulas.

Three weeks later 250 g of somatostatin (i.v. bolus) was administered to ten patients with normal renal functions randomly chosen from these 21 cirrhotic patients. The same procedures mentioned above were performed just before and immediately after the administration of this drug.

Biochemical parameters were measured in RA-XT autoanalyzer (Technicon, Ireland) and Encore II autoanalyzer (Baker Instruments, USA). Plasma and urinary osmolality were measured from osmometric depression of the freezing point (Auto-Osmometer 030-D, Gonatec, West Germany). Aldosterone and ADH were measured by radioimmunoassay (Diagnostics Systems Laboratories Inc, USA). PRA was determined by radioimmunoassay (RENCTK. P2721, Sorin Biomedica Diagnostics, Italy). Hormonal parameters were measured in Multi-Crystal Gamma Counter LB 2111 (Berthold, West Germany). GFR was calculated scintigraphically by using diethylenetriamine pentaacetic acid in Digital Gamma Camera GCA 60RA/5A (Toshiba, Japan).

For the statistical analyses; Student's t - test, Wilcoxon signed rank test and Mann - Whitney u - test were performed. Changes were reported as significant if $p < 0.05$.

RESULTS

Table 1 shows the main demographic and clinical features of the patients at entry.

Table 1: The main demographic, and clinical features of the patients.

Patients	
Number	21
Mean age (years)	50,24 ± 10,72
Male / Female	14/7
Child class (a / b / c)	7/7/7

The early responses to octreotide assessed immediately after the last administration were increased urine sodium, FeNa, and decreased plasma levels of aldosterone and ADH ($p < 0.05$). Persistence of decreasing ADH levels was the delayed action observed two days after cessation of the drug ($p < 0.05$). Meanwhile, other changed parameters returned to the baseline levels. There were non significant decrease in urine osmolality and increase in Ccr two days after the cessation of octreotide ($p > 0.05$). The early and late effects of octreotide on renal functions are summarized in Table 2.

Table 2: Effects of octreotide on renal functions.

Parameters	**Before octreotide**	**Just after cessation of the drug**	P	**Second day free of octreotide**	P
U_v (ml/d)	1111.91±685.73	1414.29+769.73	**p< 0.01**	980. 00±457.48	P> 0.05
U. (mOsm/kg)	743.05+13.59	709.91 + 11.90	P> 0.05	740.29±8.00	P >0.05
U_{Na} (mm/1)	68.00±34.35	87.19+36.52	P< 0.02	57.10+10.15	P> 0.05
U_{cr} (mg/dl)	109.81+52.39	100.24±44.51	P > 0.05	120.62±59.74	P > 0.05
FeNa(%)	0.42+0.25	0.58±0.33	P< 0.01	0.34±0.18	P> 0.05
Ccr (ml/min)	87.38±27.78	95.48±20.79	P > 0.05	91.1021.09	P> 0.05
SOsm (mOsm/kg)	294.24+5.69	296.09±5.10	P > 0.05	**295.95*2.60**	P> 0.05
Aldosteron (ng/dl)	55.83±74.10	41.45+51.19	P< 0.02	44.75±52.64	P> 0.05
PRA (ng/ml/h)	2.477±3.646	2.14+4.01	P>0.05	2.57±3.29	P> 0.05
ADH (pg/ml)	3.123±1.081	2.686±0.664	**P<** 0.05	2.069+1.910	P< 0.005
GFR (mlmin)	79.12+ 19.37	75.83+ 20.87			

Note: UV. urine flow rate; Uosm, Sosm, UNa ,UCr urine osmolality; serum osmolality; urine sodium;urine creatinine

Administration of somatostatin increased urine sodium, FeNa, plasma creatinine, PRA and decreased urine creatinine, Ccr and GFR ($p < 0.05$). A fall in daily urine output and aldosterone level also observed but were not statistically significant ($p > 0.05$). The effect of somatostatin on renal functions are summarized in Table 3.

Comparison of the actions of the both drugs yielded that octreotide administration was associated with increased daily urine output, while Ccr remaining unchanged and somatostatin decreased Ccr. In addition, increased urine sodium and FeNa, an effect seen with both drugs was slightly more pronounced by somatostatin. Comparison of the actions of the drugs are shown in Table 4 and Table 5.

Tablo 3: Effect of somatostatin on renal functions.

Parameters	Before **Somatostatin**	**After Somatostatin**	**t**	P
U_v (ml/d)	1245.00±437.45	1060.00±230.70	23	p > 0.05
U_{rem} (mosm/kg)	**742.9Qt9.04**	741.60+12.30	26	p > 0.05
U_{Na} (mm/1)	97.50±53.83	**121.80+45.08**	8	p < 0.05
UJmg/dl)	105.90±38.92	77.60±32.97	7	p < 0.05
FeNa (%)	0.63±0.37	1.37+0.37	**1**	p < 0.005
C_{cr} (ml/min)	80.6±24.91	49.00± 16.59	0	p < 0.005
S_{Osm}(mOsm/kg)	297.30±3.43	296.30±5.03	24	P > 0.05
GFR(ml/m)	80.62+17.61	49.3+18.56	1	p < 0.05
Aldosteron(ng/dl)	60.18+91.73	57.38±82.79	26	p > 0.05
PRA(ng/ml/h)	2.14±2.40	3.23+3.56	4	p < 0.05
ADH(pg/ml)	5.53+1.52	4.04±1.21	12	p > 0.05

Note: UV, urine flow rate; Uosm, Sosm, UNa ,UCr urine osmolality; serum osmolality; urine sodium;urine creatinine

Table 4 : A comparison of the biochemical data obtained just after octreotide and somatostatin administrations.

	The first day after Octreotide (Median)	**After somatostatin (Median)**	u	p
U_v (ml/d)	1575(750-2250)	1075 (600-1400)	79.5	p < 0.05
U,™ (mosm/kg)	743.5 (725-754)	746 (726-760)	54.5	P > 0.05
U_{N}, (mm/I)	102.5(90-166)	131.5(5-166)	73.5	p < 0.05
U_{CR} (mg/dl)	94(42-170)	70(36-140)	66.0	p > 0.05
FeNa *(%)*	0.53 (0.23-0.9)	1.39(0.03-2.4)	85.0	p < 0.05
Ccr (ml/min)	105(83-133)	43.5 (30-80)	100.0	p < 0.005
S_{Osll}, (mOsm/kg)	297.5 (290-306)	297.5 (289-304)	54.0	p > 0.05
GFR(ml/m)	72.35(53.5-108.9)	47.65 (20.2-78.6)	84.0	p < 0.005
Aldosteron(ng/dl)	18.79(0.27-101)	19.64(7.35-260.93)	54.0	P > 0.05
PRA(ng/ml/h)	0.97(0.28-6.19)	1.87(0.14-11.52)	67.5	p > 0.05
ADH(pg/ml)	3.01 (1.83-4)	3.88 (2.46-6.02)	**76.0**	P < 0.05

Note: UV, urine flow rate; Uosm, Sosm, UNa ,UCr urine osmolality: serum osmolality; urine sodium;urine creatinine

Table 5: A comparison of the biochemical data obtained 2 days after octreotide and immediately after somatostatin administrations.

Parameters	**2 days after Octreotide**	**after somatostatin**	u	p
UV (ml/d)	875(700-1250)	1075(600-1400)	68.0	p> 0.05
Uosm (mosm/kg)	741 (726-751)	746 (726-760)	58.0	p> 0.05
UNa (mM/L)	80 (30-136)	131 (5-166)	85.0	P< 0.05
Ucr (mg/dl)	120(60-187)	70(36-140)	75.5	P<0.05
FeNa(%)	0.28(0.15-0.62)	1.39(0.03-2.4)	89.0	p<0.025
Ccr (ml/m)	90(65-115)	43.5 (30-80)	96.0	p<0.005
Aldosteron (ng/dl)	24.22 (4.27-63.37)	19.64(7.35-260.93)	53.0	p<0.05
SOsm (mOsm/kg)	295.5(291-301)	297.5 (289-304)	51.0	p> 0.05
PRA(ng/ml/h)	1.81 (0.22-5.75)	1.87(0.14-11.52)	54.0	p> 0.05
ADH(pg/ml)	1.97(1.00-4.91)	3.88 (2.46-6.02)	86.0	p> 0.05

Note: UV, urine flow rate; Uosm, Sosm. UNa ,UCr urine osmolality; senim osmolality; urine sodium;urine creatinine

DISCUSSION

In liver cirrhosis low peripheral resistance, high cardiac index and arterial hypotension are very common because of splanchnic vasodilatation that leads to sequestration of blood within splanchnic area, severe hypoalbuminemia that contributes further to intravascular depletion by sequestering blood into the. third space and decreased response to vasoconstrictor mediators. As a result of decreased effective blood volume, renal perfusion decreases (3,4). In cirrhotic patients, overdiuresis, excessive paracentesis, gastrointestinal bleeding, hepatic encephalopathy, diarrhea and sepsis may lead to a functional renal failure in which kidneys are structurally normal (3). Hepatorenal syndrome is characterized functionally by renal vasoconstriction, decreased renal blood flow, GFR, and urinary output that contribute to the

azotemia. The intrarenal vasoconstriction seen in hepatorenal syndrome is due to an imbalance between vasoconstrictory and vasodilatory substances, such as decreases in prostaglandines PGE2, PGI2, and over production of tromboxane , platelet activating factor, endotelin (3,5).

Theoretically, a correct form of treatment should achieve an intrarenal vasodilatation together with increasing systemic vascular resistance and arterial pressure (3,4). Recently it was shown that ornipressin, an analogue of vasopressin administration to cirrhotic patients with impaired renal function induces splanchnic vasoconstriction, depresses increased activity of the sympathetic nervous system and of the renin angiotensin system. As a result, effective blood volume and renal blood flow increase. However, results in contrast to these were also reported (6).

It was shown that octreotide administration (10(^g/day sc) to healthy subjects reduces urine volume, urine sodium, and Ccr but increases urine osmolality for a few hours and within 10- 12 hours these observations return to baseline (7). Decreases in GFR and Ccr is thought to be due to the ability of octreotide to decrease glucagon and prostaglandins. Our results were in contrast with these observations. These differences may be due to that healthy people have not increased activity of vasoconstrictive system. It was thought that beneficial effects of somatostatin and its analogue may be due to a marked vasoconstriction of the splanchnic arteries which result in an increase of effective blood volume and renal blood flow as well as supression of the vasoconstrictor hormones and mediators (8,1). The effects of octreotide on renal blood flow and superior mesenteric arterial blood flow were recently studied in 11 • cirrhotic patients. It was shown that octreotide injection caused a pronounced reduction of the superior mesenteric arterial blood flow without significant changes in renal blood flow (9). These findings, like those of some others, confirmed a selective vasoconstrictive effect of octreotide on the splanchnic circulation which are not in agreement with the results obtained by somatostatin reported by Gines etal. (10).

Our results show that administration of octreotide produced marked decreases in ADH and aldosterone with no change in PRA, Ccr, GFR and increases in sodium excretion and urine flow. Prolonged decrease in ADH was observed two days after cessation of the drug. Other parameters returned to initial levels in a very brief duration. These results were similar to what Rodrigez- Perez et al found, in part. Rodrigez-Perez et al. showed that octreotide administration to 12 patients with ascites caused significant decreases in PRA and norepinephrine with an increase in Ccr (1). In another study, Mountakalakis et al. observed an increase of urinary volume, Ccr, and a decrease in urine osmolality with no change in sodium excretion caused by an infusion of octreotide (40 μg /h) in 9 cirrhotic patients (8). But we did not observe an increase of Ccr or a change in urine osmolality. Seizer and Dudley found that infusion of octreotide (50 Hg/h) in 11 patients with alcoholic liver cirrhosis is associated with decreased GFR, renal blood flow, free water clearance and PRA but increased renal vascular resistance. Addition of glucagon to infusion of octreotide reversed the detrimental effects of octreotide while preserving its beneficial effects (11). Our results with octreotide were against these, which were similar with our findings after somatostatin. Differences between results may be due to that all the patients in the study of Seizer and Dudley were alcoholic and a different dose and route of administration was used. Possible effects of alcohol on some hormones may explain these differences.

Octreotide induced natriuresis and increased urine flow may be apparently due to the decrease in ADH and aldosterone. These effects also may result from the vasoconstriction of splanchnic area that leads to an increase in effective blood volume and renal blood flow. But our lack of any change in GFR and Ccr is in contrast with this idea. Therefore, some additional mechanisms may interfere at this point. All these facts lead us to the hypothesis that octreotide also play a role in local hemodynamics of kidney, in addition to its known effects.

Our results show that somatostatin markedly increased urine flow, sodium excretion, and decreased Ccr and GFR but did not have any effect on ADH and aldosterone. Increase in PRA and decrease in GFR and Ccr after somatostatin are in contrast to the idea that somatostatin has a selective vasoconstrictive effect on splanchnic area. It may be possible that somatostatin has a vasoconstrictive effect on intrarenal arterial bed as well as on splanchnic arterial bed. Gines et al. also concluded that somatostatin administration (250-500 μg) to patients with and without ascites induced renal vasoconstriction and impaired GFR, reduced free water clearance, sodium excretion, urine prostaglandinF2 and ANF levels whereas it does not change aldosterone, and ADH levels. According to this report, somatostatin administration induces not only splanchic vasoconstriction but also renal vasoconstriction (10).

Comparison of the actions of both drugs in the patients with postnecrotic cirrhosis yielded that both drugs produced marked increases in sodium excretion and urine flow, but these increases are more prominent with somatostatin. Although ADH and aldosterone levels after somatostatin remained unchanged, PRA was increased, Ccr and GFR decreased. Administration of octreotide produced marked decreases in ADH and aldosterone. The different results between these drugs may be due to their different chemical structure, the dose, the route of administration, the time course of drugs.

However, not all changes in renal function after the drugs can be explained sufficiently by the improvement in the systemic blood volume. Therefore additional mechanisms appear to be of importance. All these facts led us to the hypothesis that octreotide and somatostatin also play some roles on local hemodynamics in kidneys in addition to their known effects. Impaired renal functions after somatostatin may be directly related to the alterations of local hemodynamics. This may, at least partially, explain why we found natriuresis and increased urine flow in patients administered somatostatin although aldosterone and ADH did not change while GFR and Ccr decreased.

Our results demonstrated that octreotide has no considerable adverse effects on the renal functions of the patients with postnecrotic cirrhosis. Moreover, the drug itself even may be beneficial by increasing sodium excretion and urine flow. Our results confirm that the use of somatostatin on cirrhotic patients with impaired renal function is obscure. We concluded that somatostatin should be used with caution in cirrhotic patients with impaired renal functions. Nevertheless, further investigation is required to fully define the use of somatostatin and its analogues in cirrhotic patients for their effects on local renal hemodynamics.

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