# The effect of somatostatin analogue ( SMS 201-995) on renal function in patients with decompansated cirrhosis and healthy volunteers

## Dekompanse sirozlu hastalar ve sağlıklı gönüllülerde somatostatin analoğunun (SMS 201-995) renal fonksiyonlara etkisi

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**ÖZET:** *Bu çalışmada, SMS 201-995'in sağlıklı gönüllüler ve dekompanse karaciğer sirozu saptanan olgularda renal parametreler üzerine etkisi test edildi. Plasebo her iki gruba 1 cc serum fizyolojik puşeyi takiben 24 saatlik 500 cc serum fizyolojik infüzyonu şeklinde uygulandı. Plasebo sonrası renal biyokimyasal parametreler çalışıldıktan sonra 24 saat beklenerek SMS 201-995, 50 mcg bolus ve bunu takiben 100 mcg/24 saat şeklinde uygulandı.*

*Plaseboya göre SMS 201-995 tedavisinden sonra, sağlıklı gönüllülerde kan üre nitrojeni (BUN), serum kreatinin (Cr) ve idrar volümü anlamlı olarak artarken (p<0.05-0.01), idrar BUN, idrar Cr, idrar Na, idrar K, idrar klor, idrar osmolalitesi ve kreatinin klerensi anlamlı olarak azaldı (p<0.05-0.01).*

*Child C grubu dekompanse karaciğer sirozu olgularında ise SMS 201-995 tedavisinden sonra idrar Cr, idrar volümü ve kreatinin klerens artış gösterdi (p<0.05). Buna karşılık idrar osmolalitesinde anlamlı bir azalma ortaya çıktı (p<0.05).*

*Sonuç olarak sağlıklı bireylerde SMS 201-995 kullanımının böbrek fonksiyonlarını olumsuz etkileyebileceği buna karşılık dekompanse karaciğer sirozlu olgularda renal fonksiyonlarda düzelmeye neden olabileceği düşünüldü.*

Anahtar kelimeler: **Somatostatin, renal function, karaciğer sirozu**

**SUMMARY:** *The effect of SMS 201-995, a synthetic octapeptide analogue of somatostatin, has been tested on the renal parameters of 10 healthy subjects and 10 patients with decompansated liver cirrhosis. Placebo was administered as a 1 cc i.v. saline bolus followed by infusion for 24 hours of 500 cc saline. Twenty-four hours after completion of the placebo administration, 50 mcg of SMS 201-995 was given as i.v. bolus, folluwed by its infusion at a dose of 100 mcg/24h.*

*After the SMS 201-995 treatment, the blood urea nitrogen (BUN), serum creatinine (Cr) and urine volume increased (p<0.05-0.01) whereas a decrease has been observed in urine BUN (U-BUN), urine creatinine (U-Cr), urine sodium (U-Na), urine potassium (U-K), urine chlor (U-CI), urine osmolality (U-osm) and creatinine clearance (CCr) in healthy subjects as compared to plasebo (p<0.05-0.01). In patients with decompansated liver cirrhosis with a Child C score U-Cr, urine volume, and CCr values increased whereas U-osm decreased (p<0.05) after SMS 201-995 treatment.*

*In conclusion, SMS 201-995 caused deleterious effects on renal function of healthy subjects probably by reducing the renal blood flow. On the contrary, the drug affected renal functions affirmatively in patients with decompansated cirrhosis. These different effects may be as a result of the suppression of vasopressor activity, which increase in patients with decompaseted cirrhosis.*

Key words: **Somatostatin, renal function, liver cirrhosis**

SOMATOSTATIN, (SS) is a peptide having different physiological inhibitor effects mainly on central nervous system, hypophysis, hypothalamus, gastrointestinal system and pancreas (1,2).

SMS 201-995 (octreotide, Sandostatin-Sandoz Ltd.), an analogue of SS can be used in the treatment of many clinical conditions, mainly in oesophageal varriceal hemorrhage and in some malignancies (1).

Geliş tarihi: 14.4.1995, Kabul tarihi: 12.1.1996



In this clinical study, effects of SMS 201-995 on renal function in healthy subjects and in patients with decompansated liver cirrhosis have been tested.

### PATIENTS and METHODS

In this study, 10 patients (6 male, 4 female) with decompansated liver cirrhosis of C group according to Child classification who applied to our university hospital, section of gastroenterology between July and November 1992 (aged 52.68±15.3

**Table 1.** *Values of renal parameters and statistical comparison of healthy subjects after placebo and SMS 201-995 treatment*

| | | | A-P | A-SMS | p value |
|---|---|---|---|---|---|
| | BUN | (mg/dL) | 18.8 ± 7.7 | 19.7 ± 6.8 | <0.05 |
| SERUM | Cr | (mg/dL) | 0.80 ± 0.26 | 0.91 ± 0.23 | <0.05 |
| | Na | (meq/L) | 141.3 ± 1.41 | 141.1 ± 1.9 | – |
| | K | (meq/L) | 4.31 ± 0.28 | 4.40 ± 0.57 | – |
| | Cl | (meq/L) | 103.1 ± 1.4 | 103.2 ± 3.0 | – |
| URINE | BUN | (mg/dL) | 780 ± 215 | 712 ± 271 | <0.01 |
| | Cr | (mg/dL) | 98.3 ± 42.1 | 89.2 ± 46.6 | <0.01 |
| | Na | (meq/L) | 211 ± 90 | 193 ± 33 | <0.01 |
| | K | (meq/L) | 41.9 ± 22 | 38.3 ± 7.0 | <0.01 |
| | Cl | (meq/L) | 137.1 ± 87.2 | 135.0 ± 89.3 | <0.05 |
| Urine volume | | (mL/day) | 1350.2 ± 127.8 | 1455.1 ± 151.3 | <0.01 |
| U-Osm | | (osm/kg) | 0.682 ± 0.110 | 0.541 ± 0.122 | <0.05 |
| RFI | | | 1.86 ± 1.1 | 2.0 ± 1.4 | – |
| FENa (%) | | | 1.3 ± 0.7 | 1.4 ± 0.5 | – |
| CCr (mL/min) | | | 112.9 ± 34.0 | 95.1 ± 59.6 | <0.01 |
| BP (cystolic) | | (mmHg) | 112.1 ± 17.7 | 114.7 ± 7.9 | – |
| BP ( diastolic) | | (mmHg) | 71.2 ± 11.9 | 74.2 ± 8.7 | – |

A-SMS: After SMS 201-995 treatment, A-P: After Plasebo, –: Not statistically significant
BUN: Blood Urea Nitrogen, Cr: Creatinin, U-osm: Urine osmolality
CCr: Creatinin Clearence BP: Blod pressure

$$\text{FENa: Fraxione Na Excretion} = \frac{\text{Urine/serum Na}}{\text{Urine/serum Cr}} \times 100$$

$$\text{RFI: Renal Failure Index} = \frac{\text{Urine Na x serum creatinine}}{\text{Urine creatinine}}$$

years), and 5 male and 5 female healthy subjects (aged 41.76±18.1 years) are included. Treatment of patients with decompansated cirrhosis have been discontinued for 5 days and a similiar diet was given to all individuals prior to this study.

Placebo of 1 cc saline was given to healthy subjects and to patients with decompansated cirrhosis by intravenous (IV) route, following 500 cc saline for 24 hours as continuous infusion. Urine was collected during the treatment. At the twelth hour, serum creatinine (Cr), and at the end of the twenty-fourth hour, serum urea nitrogen (BUN), creatinine (Cr), Na, K, Cl, and urine BUN (U-BUN), creatinine (U-Cr), Na (U-Na), K (U-K), Cl (U-Cl) and osmolarity (U-osm) values in all cases were determined. Creatinine clearance (CCr), fractional Na extraction (FeNa) and renal failure index (RFI) have been calculated for the two groups. During the placebo treatment, systolic and diastolic blood pressure have been monitored in all subjects.

After 24 hours, SMS 205-991 has been given to all subjects as 50μ bolus, followed by a 24h infusion of 100 microgram SMS 205-991 in 500 cc saline. Urine volumes in the two groups were checked during the day, and all of the parameters mentioned above were repeated.

Results obtained after placebo and SMS 205-991 treatments were given as the mean ± standard deviation, and statistical analysis was performed using Wilcoxon Signed Rank test, and differences were considered significant at $p<0.05$.

## RESULTS

Mean values of the parameters of healthy subjets after placebo and SMS 205-991 treatment, and statistical analysis of these are shown in Table 1, and those of the patients with decompansated liver cirrhosis in Table 2.

In healthy subjects; BUN, serum Cr, urine volume which were 18.8±7.7 mg/dL. 0.80±0.26 mg/dL and 1350.2±127.8 mL/day, respectively, after placebo increased to 19.7±6.8 mgr/dL, 0.91±0.23

**Table 2.** *Values of renal parameters and statistical comparison of a patients with decompansated liver cirrhosis after placebo and SMS 201-995 treatment*

| | | | P | SS | p value |
|---|---|---|---|---|---|
| | BUN | (mg/dL) | 15.6 ± 4.7 | 15.8 ± 6.3 | — |
| SERUM | Cr | (mg/dL) | 0.91 ± 0.21 | 0.90 ± 0.23 | — |
| | Na | (meq/L) | 134.1 ± 4.1 | 136.5 ± 4.0 | — |
| | K | (meq/L) | 4.30 ± 0.73 | 4.28 ± 0.54 | — |
| | Cl | (meq/L) | 103.0 ± 2.4 | 103 ± 2.2 | — |
| URINE | BUN | (mg/dL) | 750 ± 264 | 753 ± 277 | — |
| | Cr | (mg/dL) | 94.2 ± 13 | 97 ± 12 | <0.05 |
| | Na | (meq/L) | 55 ± 2.7 | 56 ± 2.6 | — |
| | K | (meq/L) | 47.8 ± 20.0 | 46.8 ± 37.2 | — |
| | Cl | (meq/L) | 98.9 ± 21.0 | 99.4 ± 25.0 | — |
| Urine volume | | (mL/day) | 1150 ± 168 | 1170 ± 143 | <0.05 |
| U-Osm | | (osm/kg) | 0.492 ± 0.100 | 0.473 ± 0.119 | <0.05 |
| RFI | | | 0.53 ± 0.29 | 0.52 ± 0.30 | — |
| FENa (%) | | | 0.40 ± 0.22 | 0.39 ± 0.21 | — |
| CCr (mL/min) | | | 83.4 ± 34.7 | 87.5 ± 22.9 | <0.05 |
| BP (cystolic) | | (mmHg) | 110 ± 8.7 | 100 ± 7 | — |
| BP ( diastolic) | | (mmHg) | 72 ± 9.1 | 68 ± 5 | — |

A-SMS: After SMS 201-995 treatment, A-P: After Plasebo, –: Not statistically significant
BUN: Blood Urea Nitrogen, Cr: Creatinin, U-osm: Urine osmolality
CCr: Creatinin Clearence BP: Blod pressure

$$\text{FENa: Fractional Na Excretion} = \frac{\text{Urine/serum Na}}{\text{Urine/serum Cr}} \times 100$$

$$\text{RFI: Renal Failure Index} = \frac{\text{Urine Na x serum creatinine}}{\text{Urine creatinine}}$$

mg/dL ($p<0.05$), 1455.1±151.3 mL/day ($p<0.01$) after respectively, SMS 201-995 treatment.

On the contrary, urine BUN (U-BUN), U-Cr, U-Na, U-K and CCr values which were 780±215 mg/dL, 98.3±42.1 mg/dL, 211±90 meq/L, 41.9±22 meq/L, 112.9±34.0 mL/min, respectively, after plasebo decreased to 712±271 mg/dL, 89.2±46.6 mg/dL, 193±33 meq/L, 38.3±7.0 meq/L, 95.1±59.6 mL/min, respectively, at the end of the SMS 201-995 therapy ($p<0.01$) respectively. In the healthy subjects U-Cl, U-osm, values, which were 137.1±87.2 meq/L and 682±110 mosm/kg, respectively, after plasebo decreased to 135±89.3 meq/L and 541±122 mosm/kg, respectively, at the end of the SMS 201-995 therapy ($p<0.05$).

No statistical difference was found between placebo and SMS 201-995 in serum Na, K, Cl, RFI, FENa, systolic and diastolic blood pressures in healthy subjects ($p>0.05$).

In the patients with decompansated liver cirrhosis; U-Cr, urine volume and Ccr which were 94.2±13 mg/dL, 1150±168 mL and 83.4±34.7 mL/min, respectively, after plasebo, increased to 97±12 mg/dL, 1170±143 mL and 87.5±22.9 mL/min ($p<0.05$), respectively, at the end of SMS 201-995 therapy. On the contrary, U-osm, which was 492±100 mosm/kg after plasebo, decreased to 473±119 mosm/kg after SMS 201-995. Serum Cr, BUN, serum Na, K, Cl values, U-BUN. U-Na, U-K, U-Cl values, RFI, FENa, systolic and diastolic blood pressures have not displayed any significant difference ($p>0.05$).

## DISCUSSION

Effects of natural somatostatin (SS) and SMS 201-995 on renal function have been the topic of several studies, and contradictory reports are available in this subject in the literature.

The decrease in urine electrolytes, mainly in CCr, and the increase in serum Cr and BUN values in this study may be the result of the decrease in ef-

fective renal blood flow after infusion of SMS 201-995 in healthy subjects. Recent studies which were reported that SS and SMS 201-995 reduce renal blood flow and glomeruler filtration rate (3-7). The decrease in plasma renin, renin angiotensin system (RAS) activity are known after infussion of SMS 201-995 (8,9) and the suppression of this activity may reduce the glomeruler filtration rate and intraglomerular pressure(10). In additon, studies carried out on animals have shown that SS and SMS 201-995 have antagonized the effects of arginine vasopressin (AVP) (11,14). Our findings, also, suggest that SMS 201-995 may inhibit the AVP function of healthy subjects. Since we observed an increase in urine volume and a significant decrease in U-osm. On the other hand, it has been shown that the peptide has not affected the AVP levels (4). This effect might be connected to receptor blokage of AVP or to the direct inhibitor effect of SMS 201-995 on renal tubules (15). However there are some articles in the literature showing that in healthy subjects SMS 201-995 causes an antidiuretic effect (3,4,6,7,16). These contradictory reports may be due to differences in the hydration of subjects and the dose of SMS 201-995.

In conclusion, it is obvious that SS and its analogue SMS 201-995 may cause a list of negatory changes on renal parameters via some mechanisms, which are not fully understood in healthy subjects.

To the contrary of the normal subjects, it has been considered that an increase may appear in the renal blood flow, instead of a decrease, in the patients with decompansated liver cirrhosis due to the increase especially in CCr and urine volume. It is known that AVP, sympathetic nervous system (17) and RAS activity (18,19) are increased in patients with decompansated liver cirrhosis. It is, however, known that the basic pathology in cirrhosis which is complicated with hepatorenal syndrom is renal vasoconstriction (19). These vasopressor systems may be inhibited by SMS 201-995 and the inhibition of these systems may cause the different response of SMS 201-995 in decompansated liver cirrhosis as compared to healthy subjects. As a matter of fact, it has been known that SMS 201-995 might create an inhibitor effect on RAS and AVP (8,9,15,20). Our results that are obtained from the patients with decompansated cirrhosis are resembling the reports of Kallivretakis and Mountakalakis et al (15,20). The researchers in these two articles have reported that an improvement has occured in the renal functions through the SMS 201-995 application in physiological dose in the patients with decompansated liver cirrhosis. It was pointed out that CCr and urine volume has increased whereas U-osm has decreased by the effect of SMS 201-995 (15,20). This improvement in these patients might be due to the blocking of renal and mesengial receptors of AVP, or inhibition of vasoconstrictor system which is activated in decompansated liver cirrhosis, by SMS 201-995 (15,20).

## CONCLUSION

As a result of the study SMS 201-995 might affect the renal functions negatory in healthy subjects but affirmatively in the patients with decompansated liver cirrhosis. We consider that these two different effects can be the result of inhibition of the vasopressor activity, which is known to have increased in the patients with decompansated cirrhosis. More detailed studies are necessarry on this subject.

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