

Gallbladder Motility With The Long-Acting Somatostatin Analogue (SMS 201-995) in Human

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Özet: UZUN ETKİLİ SOMATOSTATİN ANALOĞU-NUN (SMS 201-995) İNSANLARDA SAFRA KESESİ KONTRAKSIYONUNA ETKİSİ.

Uzun etkili somatostatin analogu octreotidin (SMS 201-995) normal insanlarda safra kesesi kontraksiyonuna etkisi ultrasoundla ölçüldü. İncelemeler 12 saatlik açlığı takiben yapıldı. 20 gönüllü 2 ye ayrıldıktan sonra bir gruba 100 µgr SMS, diğer gruba placebo (saline) verildi ve safra kesesi volümleri 1 saat süre ile 15 dakika aralarla ölçüldü. Aynı istemler standart test gereğinden sonra da tekrarlandı.

Açlık döneminde bir saat süreyle izlenen kontrol ve SMS gruplarının safra kesesi volümleri sırasıyla 19.9 ± 5.2 ; 19 ± 6.8 ; 20.3 ± 5.4 ; 18.4 ± 6.2 cm³ ve 19.8 ± 4 ; 23.3 ± 4.7 ; 23.2 ± 5.7 cm³ idi. SMS grubunun safra kesesi volümleri kontrol grubuna göre anlamlı ölçüde (%17-21.6) büyüktü ($p < 0.05$). Post prandial dönemde her iki grubun safra kesesi volümleri sırasıyla 14.3 ± 7 ; 11 ± 6.5 ; 8.7 ± 5.6 ; 8.4 ± 5.7 cm³ ve 23.1 ± 6.8 ; 22 ± 7.2 ; 22 ± 4.1 ; 20.2 ± 4.2 cm³ idi. SMS grubunun safra kesesi volümleri kontrol grubuna göre anlamlı ölçüde (%60-155) büyüktü ($p < 0.001$). Diğer taraftan kontrol grubunun post prandial perid volümleri baseline göre anlamlı ölçüde (%28-57) azalmıştı ($p < 0.05-0.001$). Ancak tokluk dönemi SMS grubunun 75 dakikadaki safra kesesi volümü %16 oranında baseline göre hala büyükken 90.105 ve 120 dakikalarda safra kesesi volümleri baseline ile aynı düzeylere geldiği saptandı.

Bu sonuçlar safrakesesi volüm ve kontraksiyonun 100 µgr SMS enjeksiyonu ile tamamen bozulduğunu göstermektedir.

Summary: The action of the long-acting somatostatin analogue (octreotide SMS 201-995) on human gallbladder contraction measured by ultrasound in normal subjects. Scans were performed in the morning after a 12 hour fasting period. Then, the volunteers received subcutaneous injections of either 100 µg SMS 201-995 or placebo (saline) and the gallbladder was rescanned 15 min intervals for 60 min. End of this period the volunteers received standart liquid test meal (ensure, 375 Kcal), and sacns were performed again.

In the fasting period, the mean of fasting gallbladder volumes in the control and SMS groups which were followed for one hour period were 19.9 ± 5.2 , 19 ± 6.8 , 20.3 ± 5.4 , 18.9 ± 6.2 and 19.8 ± 4 , 23.8 ± 6 , 23.3 ± 4.7 , 23.2 ± 5.7 cm³ respectively. Gallbladder volumes of the SMS 201—995 group were significantly greater than those of the control group except baseline value ($p < 0.05$). In the postprandial period, the mean of gallbladder volumes of control and SMS group which were followed for one hour period were 14.3 ± 7 , 11 ± 6.5 , 8.7 ± 5.6 , 8.4 ± 5.79 and 23.1 ± 6.8 , 22 ± 7.2 , 22 ± 4.1 , 20.2 ± 4.2 cm³ respectively. Gallbladder volumes of SMS 201-995 group were significantly greater (60-155%) than those of the control group ($p < 0,001$). In addition, gallbladder volumes of the control group of the postprandial period as compared to that of the baseline were significantly lower between 28-5 % ($p < 0,05 - 0,001$). However postprandial gallbladder volume of SMS 201-995 group was still significantly greater 16% than that of baseline at the 75th minute, while volumes of gallbladder were unsignificantly greater than that of baseline at the 90th, 105th and 120th minutes.

These results suggest that gallbladder contraction is completely abolished after injection of 100 µg of SMS 201-995.

Anahtar kelimeler : Somatostatin, Safra kesesi kontraksiyonu

Key words: Somatostatin, gallbladder motility.

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Somatostatin analogue (SMS 201-995) administered 5 and 50 µg subcutaneously (sc) significantly suppressed postprandial release of gastrin, secretin, gastric inhibitory peptide, cholecystokinin (CCK), neurotensin, motilin, pancreatic polypeptide, glucagon, and insulin in man SMS 201-995 has been shown to inhibit both bile secretion and gallbladder contraction, and by inhibition of CCK release from the gut (1-5).

A single injection of 25 µg of SMS 201-995 in a shortlasting study in normal volunteers caused almost complete abolition of gallbladder contraction, CCK release, and pancreatic polypeptide (PP) secretion in response to a lundh test meal (6). Such data could be of importance because of the supposedly high incidence of cholelithiasis in patients with somatostatin-producing tumors and the role of bile stasis in the development of gallstones (7-11).

The aim of this study was to assess the effects of long acting SMS 201-995 on postprandial gallbladder contraction in human.

MATERIAL and METHODS

Twenty healthy volunteers (mean age 39 ± 12 years all within $\pm 12\%$ ideal body weight) agreed to participate in the study after the protocol and the test procedures had been explained them. All of the subjects completed the protocol. Gallbladder volumes were measured by using ultrasonography.

Scans were performed at 9 am after a 12 hour fast. After basal measurement received subcutaneous injections of either 100 µg SMS 201-995 (9 : 10) or placebo (saline) (n : 10) in the morning. One hour later, the gallbladder was rescanned 15 min intervals for 60 min. At the end of this period all of the volunteers received standart liquid test meal (ensure 375 cal/250 ml, protein 16.7%, fat 3%, carbonhydrate 53.3%) and scans were performed again.

Gallbladder volume and emptying were measured by using ultrasonography (12). Using a 3.5 or 5 MHz transducer real time ultrasound scans were obtained with Simens Sonoline SL-2 3.5 MHz Subjects were scanned supine in the right

anterior oblique position by a radiologist trained in ultrasonography. The gallbladder was visualized in the longitudinal and transverse planes, and measurements of maximum length, width, and height were taken in duplicate. The volume of the gallbladder was subsequently calculated using the ellipsoid method (volume = $0.52 \times \text{length} \times \text{width} \times \text{height}$) (13). The results were expressed as mean $\pm$ SEM unless otherwise stated. For statistical analysis, the Wilcoxon signed-rank test or the Mann Whitney U test was used where appropriate (14).

RESULTS

The fasting mean gallbladder volumes in the control and SMS groups which were followed up quarter hourly for one hour period were 19.9 ± 5.2 , 19 ± 6.8 , 20.3 ± 5.4 , 18.9 ± 6.2 and 19.8 ± 4 , 23.8 ± 6 , 23.3 ± 4.7 , 23.2 ± 5.7 respectively. The fasting mean gallbladder volumes of SMS group as compared to baseline was became significantly greater 20%, 20%, 17.6%, 16% respectively after the 15 th minutes of SMS injection. However control group showed any change for one hour period. Mean Volumes of SMS groups compared to control group were significantly greater 25%, 17%, 16.5%, 21.6% respectively except baseline volumes ($p < 0.05$).

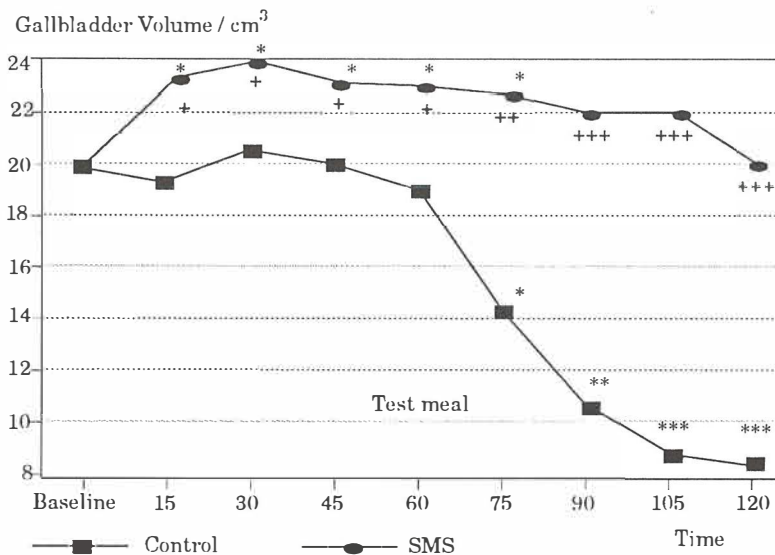
Postprandial mean gallbladder volumes in the control and SMS groups were 14.3 ± 7 , 11 ± 6.5 , 8.7 ± 5.6 , 8.4 ± 5.7 and 23.1 ± 6.7 , 22 ± 4.1 , 20.2 ± 4.2 cm³ respectively. In SMS group, mean volume of gallbladder was significantly greater 16% than that of baseline at the 75th. minutes while volumes of gallbladder were insignificantly greater than that of baseline at the 90th, 105th and 120th minutes. In control group, postprandial volumes were significantly lower 28%, 44%, 56%, 57% than that of baseline ($p < 0.05$ - $p < 0.001$) at the 75th, 90th, 105th and 120th minutes respectively. Mean postprandial gallbladder volumes of SMS group as compared to control group were significantly greater 60, 100, 155, 140% respectively between 75th-120th minutes (Figure 1, Table 1).

DISCUSSION

This study demonstrated that posprandial gallbladder contraction is completely abolished after the injection of 100 µg SMS 201-995.

	The Mean Volume (cm ³) in Different Time (min)								
	Baseline	15	30	45	60	75	90	105	120
Control	19.9 ± 5.2	19 ± 4.8	20.3 ± 5.4	20 ± 6.6	18.9 ± 6.2	14.3 ± 7	11 ± 6.5	8.7 ± 5.6	8.4 ± 5.7
SMS	19.8 ± 4	23.8 ± 6	23.9 ± 5.3	23.3 ± 4.7	23.2 ± 5.7	23.1 ± 6.8	22 ± 7.2	22 ± 4.1	20.2 ± 4.2
% difference from baseline in control group	----	- 4.5	+ 5	+ 5	- 5	- 28	- 44.7	- 56	- 57
P	----	US	US	US	US	< 0.05	< 0.01	< 0.001	< 0.001
% difference from baseline in SMS group	----	+ 20	+ 20	+ 17.6	+ 16	+ 16	+ 11	+ 11	+ 2
P	----	< 0.05	< 0.05	< 0.05	< 0.05	< 0.05	US	US	US
% difference according to control in SMS groups	- 0.5	+ 25	+ 17	+ 16.5	+ 21.6	+ 60	+ 100	+ 155	+ 140
P	US	< 0.05	< 0.05	< 0.05	< 0.05	< 0.001	< 0.0001	< 0.0001	< 0.001

US : Ultrasonography



* p < 0.05 difference from baseline
 ** p < 0.01 difference from baseline
 *** p < 0.001 difference from baseline
 + p < 0.05 difference from control
 ++ p < 0.001 difference from control
 +++ p < 0.0001 difference from control

Mean Gallbladder volumes of the SMS 201-995 group were significantly greater than those of the control group except baseline value. In the postprandial period, mean gallbladder volumes of SMS 201-995 were significantly greater (60-155%) than those of the control group. In control group of the postprandial period as compared to that of the baseline were significantly lower between 27-57%. However, postprandial mean gallbladder volume of SMS 201-995 group was still significant greater 16% than that of baseline at the 75th minute, while volumes of gallbladder were insignificant greater that of baseline at the 90th, 105th and 120th minutes.

In short-term studies, the inhibitory action of native SMS and SMS analog on gallbladder motility has been attributed to suppression of meal stimulated release of CCK (15,16). SMS 201-995 almost completely suppressed meal-stimulated plasma CCK release in healthy volunteers after six days of pretreatment with 25 µg twice daily (15,17,18). On the other hand, in this study re-

veals that integrated postprandial plasma CCK responses are not diminished in acromegalics pretreated for 6-32 months with the higher dose of 100 µg two to three times daily.

Despite the statistically significant rise of plasma CCK levels after the standard breakfast in the SMS study, no gallbladder contraction was observed, although the CCK increment required

for gallbladder contraction in response to exogenous CCK did exceed the threshold in response to exogenous CCK did exceed the threshold of 1.3 pmol/l previously determined in healthy volunteers (18).

Absence of a statistically significant direct correlation between plasma CCK levels and corresponding gallbladder volumes in the SMS support.

A direct effect of SMS to the gallbladder and level might account for this decreased sensitivity to CCK. Possibly, CCK receptors are down-

regulated directly by the SMS analog, although it has been demonstrated that the interaction between native SMS and CCK is of the noncompetitive type (20). In that same study, another possibly direct effect of SMS gallbladder motility was an observed progressive increase in gallbladder volume in response to increasing doses of the tetradecapeptide, suggesting an effect opposite that of CCK (20,21).

In conclusion, gallbladder contraction is completely abolished after injection of 100 µg of the SMS 201-995.

KAYNAKLAR

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