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Gallbladder motility with the long-acting somatostatin analogue (Octreotide SMS 201-995) in human

Uzun etkili somatostatin analogunun (SMS 201-995 Octreotide) insanlarda safra kesesi kontraksiyonuna etkisi

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ÖZET: *Uzun etkili somatostatin analoğu Octreotide (SMS 201-995) normal insanlarda safra kesesi kontraksiyona etkisi ultrasound ile ölçüldü. İncelemeler 12 saatlik açlığı takiben yapıldı. 20 gönüllü 2'ye ayrıldıktan sonra bir gruba 100 μg SMS 201-995, diğer gruba plasebo (serum fizyolojik) verildi ve safra kesesi volümleri 1 saat süre ile 15 dakika aralarla ölçüldü. Aynı işlemler standart test yemeğinden sonra da tekrarlandı. Açlık döneminde bir saat süreyle izlenen kontrol ve SMS 201-995 gruplarının safra kesesi volümleri sırasıyla 19.9±5.2; 19±68; 20.3±5.4; 18.4±6.2 cm3 ve 19.8±4; 23.2±4.7; 23.2±5.7 cm3 idi. SMS 201-995 grubunun safra kesesi volümleri kontrol grubuna göre anlamlı ölçüde (%17-21.6) büyüktü (p<0.05). Post-prandial dönemde heriki 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 201-995 grubunun safra kesesi volümleri kontrol grubuna göre anlamlı ölçüde (%60-155) büyüktü (p<0.001). Diğer taraftan kontrol grubunun post-prandial period volümleri bazal değerlere göre anlamlı ölçüde (%28-57) azalmıştı (p<0.001). Ancak tokluk dönemi SMS 201-995 grubunun 75 dakikadaki safra kesesi volümü %16 oranında bazal değerlere göre hala büyükken 90, 105 ve 120 dakikalarda safra kesesi volümleri bazal ile aynı düzeye geldiği saptandı. Bu sonuçlar safra kesesi kontraksiyonunun 100 μg SMS 201-995 injeksiyonu ile tamamen azaldığını göstermektedir.*

Anahtar kelimeler: **Somatostatin, safra kesesi, motilite, insan**

ABSTRACT: *The action of the long-acting somatostatin analogue (octreotide SMS 201-995) on human gallbladder contraction, was measured by ultrasound, in normal subjects. Scans were performed in the morning after a 12 hours of fasting. Then, the volunteers received subcutaneous injections of either 100 μg SMS 201-995 or placebo (saline) and the gallbladder was rescanned at 15 minute intervals for 60 minutes. At the end of this period, the volunteers received a standard-liquid test meal, and scans were performed again. During the fasting period, the mean fasting gallbladder volumes in the control and SMS 201-995 groups were followed for a one hour period. The results were 19.9±5.2, 19±68, 20.3±5.4, 18.9±6.2 and 19.8±4, 23.3±4.7, 23.2±5.7 cm3 respectively. The gallbladder volumes of SMS 201-995 group were significantly greater (17-21.6%) than those of the control group, except baseline value (p<0.05). In the postprandial period, the mean gallbladder volumes of the control and SMS 201-995 group were followed for a one hour period and 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 recpectively. Gallbladder volumes of the 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, compared to that of the baseline, were 28-57% lower. (p<0.001). However postprandial gallbladder volume of the SMS 201-995 group was still 16% greater than that of the baseline group at the 75th minute. Gallbladder volumes were insignificantly greater than that of baseline at the 90th, 105th and 120th minutes. These results suggest gallbladder contraction is completely abolished after the injection of 100 μg of SMS 201-995.*

Key words: **Somatostatin, gallbladder, motility, human**

SOMATOSTATIN analogue (SMS 201-995) significantly suppresses postprandial release of gastrin, secretin, gastric inhibitory peptide, cholecystokinin (CCK), neurotensin, motilin, pancreatic polypeptide, glucagon and insulin in man (1-3) SMS 201-995 has been shown to inhibit bile secretion, gallbladder contraction (3,4), and inhibition of CCK release from the gut (3,5).

A single injection of 25 μg of SMS 201-995 in a shortlasting study of normal volunteers caused almost complete abolition of gallbladder contraction, CCK release, and pancreatic polypeptide (PP) secretion in response to a lunch meal (3). Such data could be of importance because of the supposedly high incidence of cholelithiasis in patients with somatostatin-producing tumors (6) and the role of bile stasis in the development of gallstones (3,7-10).

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

MATERIALS AND METHODS

Twenty healthy volunteers agreed to participate

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in the study after the protocol and the subjects compared the protocol. Gallbladder volumes were measured using ultrasonography.

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

Gallbladder volume and emptying were measured using ultrasonography (11). Using a 3.5 or 5MHz transducer, real time ultrasound scans were obtained with Siemens Sonoline SL-2. 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 measurement 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 x length x width x heighth) (12). The results are expressed as mean ± SEM unless otherwise stated. For statistical analysis, the Wilcoxon sihned-rank test or the Mann Whitney U test (13) was used where appropriate.

RESULTS

The fasting gallbladder volumes in the control and SMS 201-995 groups were followed up quarter hourly for a one hour period. The results 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±5.7 respectively. The fasting gallbladder volumes of SMS 201-995 group, as compaired to baselines became significantly greater 20%, 20%, 17.6% and 16% respectively after the 15th minute of SMS 201-995 injection. However, control group showed change for a one hour period. Volumes of SMS 201-995 group, as compared to control group, were significantly greater 25%, 17%, 16.5% and 21.6% respectively, except baseline volumes ($p<0.05$).

Post prandial gallbladder volumes in the control and SMS 201-995 group were 14.3±7, 11±6.5, 8.7±5.6, 8.4±5.7 and 23.1±6.7, 22±7.2, 22±4.2 cm3 respectively. In the SMS 201-995 group, the volume of the gallbladder was 16% greater than that of the baseline group at the 75th minute, while gallbladder volumes were significantly greater than that of the baseline group at the 90th, 105th and 120th minutes respectively. Postprandial gallbladder volumes of the SMS 201-995 group, compared to the control group, were significantly greater (60%, 100%, 155% and 140% respectively) between the 75th 120th minutes (Figure 1, Table 1).

Table 1. The mean values of gallbladder volume on pregnant women

Groups	*The Mean Volume (cm^3) in Different Time (X±SEM)* (min)								
	Baseline	15	30	45	60	75	90	105	120
Control	19.9±5.2	19±4.8	20.3±6.6	20±6.6	18.9±6.2	14.3±7	11±6.5	8.7±5.3	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 difference from baseline in control	—	US	US	US	US	<0.05	<0.01	<0.001	<0.001
% difference from cnotrol in verapamil group	—	+20	+20	+17.6	+16	+16	+11	+11	+2
p difference from baseline in SMS group	—	<0.05	<0.05	<0.05	<0.05	<0.05	US	US	US
% difference from control in SMS	-0.5	+25	+17	+16.5	+21.6	+60	+100	+153	+140
p difference from control in SMS group	US	<0.05	<0.05	<0.05	<0.05	<0.001	<0.0001	<0.0001	<0.0001

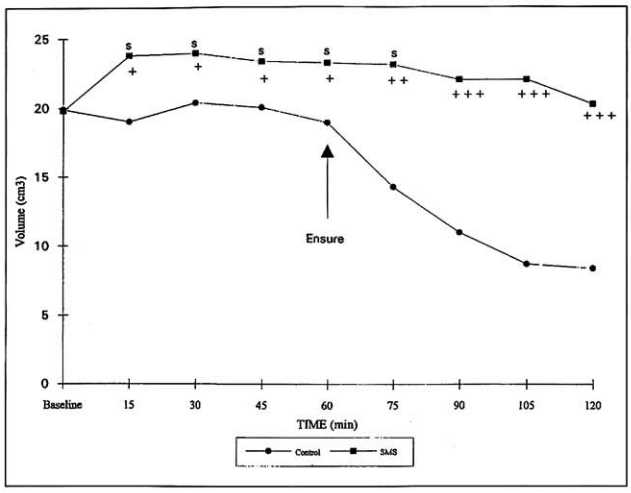

Figure 1. Effect of SMS 201-995 on gallbladder volume.

* p<0.05, ** p<0.01, *** p<0.001 difference from baseline in control group.
s p<0.05 difference frome baseline in SMS 201-995 group.
\+ p<0.05, ++ p<0.001, +++ p<0.0001 difference from control in SMS 201-995 group.

DISCUSSION

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

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 (13,14) SMS 201-995 almost completely suppressed meal-stimulated plasma CCK release in healthy volunteers after six days of pretreatment with 25 μg twice daily (13,15,16). On the other hand, this study reveals that integrated postprendial 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 respnse to exogenous CCK did exceed the threshold of 1.3 pmol/1 previously determined in healthy volunteers (17).

Absence of a statistically significant direct correlation between plasma CCK levels and corresponding gallbladder volumes in the SMS, was not found in the placebo study. A direct effect of SMS at the gallbladder 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 (19). 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 to that of CCK (18,19).

In conclusion, this study demonsrated that gallbladder contraction is completely abolished after an injection of 100 μg of SMS 201-995.

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