The Effect of Somatostatin Analogue SMS 201-995 on Complications of Small Bowel Obstruction in Rats

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Özet: İNCE BARSAK TIKANMALARINA BAĞLI KOMPLİKASYONLARDA SOMATOSTATİN ANALOGUNUN (SMS 201-995) ETKİSİ

Somatostatin analogunun (SMS 201-995) etkisi kapalı olup ileal obstrıcksiyonlu sıçan modelinde incelendi. Sıçanlar 24 saat süreyle aç bırakıldı, fakat serbestçe su içmelerine izin verildi. Daha sonra pentobarbital (50 mg / kg) ile intraperitoneal olarak anestetize edildilir. Terminal ileumda 10 cm. lik kapalı lup oluşturmak için laparatomi yapıldı. Sıçanlar subkütan olarak SMS 201-995 100 µg / kg (n : 10) ve serum fizyolojik (SF) (n : 10) olmak üzere randomize edildiler Tedavinin başlangıcından 24 saat sonra sıçanlar öldürüldü, barsaklar çıkarıldı. Lüminal volümü ölçüldü, elektrolit (Na, K, Cl, HCO3) analizleri yapıldı., Lup ağırlığı ölçüldü ve lup histolojik olarak incelendi. Kontrollarla karşılaştırıldığında SMS 201-995 tedavisi lle ince barsakta luminal volüm, sodyum ve potasyum outputunda önemli bir azalma görülmedi. Ek olrak, kontrol sıçan grubunda görülen intestinal distansiyon ve nekroz gibi gross ve mikroskopik belirtiler SMS 201-995 ile tedavi edilen sıçanlarda da mevcuttu. İntestinal obstruksiyonlu bu sıçan modelinde SMS 201-995 ' in koruyucu, etkisin belirlemek için daha fazla çalışmalar yapılmalıdır. Sonuç olarak SMS 201-995 tedavisi intestinal obstruksiyon oluşturulan segmentte elektrolit ve histolojik inceleme bakımından kontrol hayvanlara göre önemli bir fark gözlenmedi.

Anahtar Kelimeler: Somatostatin analogu, ince barsak tıkanması, sıçan .

Summary: The effect of somatostatin analogue (SMS 201-995) was tested in rat model of closed - loop ileal obstruction. Animals were fasted for 24 h. but were allowed freee access to water. They were than intraperitoneally (IP) anesthetized with pentobarbital (50 mg/kg). The laparotomy were made for construction of a 10 cm closed loop of terminal ileum. The rats were randomised to receive SMS 201-995 100 mikrogr / kg (N : 10) subcutaneously or saline (N : 10) twenty four hours after the start of the treatment the rats were killed, the bowel removed, the wolume of the luminal contents measured and analysed for electrolytes (Na, K, HCO 3 , Cl) , the loop weighed and a portion of the loops examined histologically. No significanty decreased intestinal luminal volume and sodium and potassium output was observed with SMS 201-995 treatment when compared to control. Additionally, the gross and microscopic pathologic features of intestinal distension and necrosis seen in control rats were present in rats treated with SMS 201-995 on gastrointestinal tract didnot appeared beneficial in this rat model of intestinal obstruction. There were many possible reason why such a results are surprising in view of further evaluate preventive effect of SMS 201-995 are recommended.

Key words: Somastatin analogue, Small bowel obstruction, rat.

Somatostatin-immunoreactive material has been found in endocrinelike, so called D-cells of the stomach, small intestine, and pancreas (1-6) and is in addition present in vagal nerve fibres and in neurons of th emyenteric and submucosal plexus of the intestinal tract(7-9). Within the gastrointestinal tract an pancreas an accumulation of D-cells has been demonstrated in the fundic and antral area of the stomach and in the islets of Langerhans, where-

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as a more scattered distribution has been shown in the small and large intestine (10-12). This localization of somatostatin in organs that are exclucively responsible for the adequate digestion, absorbtion and disposal of ingested nutrients raises the possibility that somatostatin might have a modulatory role at all stages of nutrient assimilation.

Somatostatin has been shown both to inhibit and to stimulate phenomena associated with the interdigestive motility of the gaastrointestinel tract.

In the dog somatostatin infusion prevented motilin-induced contractile patterns from migrating to the jejunum, and the cycle of natural interdigestive motor complexes was also interrupted by somatostatin (13).

Somatostatin infusion in man has been shown to delay small-bowel transit time (14,15): It is not known whether somatostatin exerts such and effects as a physiological mechanism. Slowing of transit, however, is a pharmacological effect that may contribute to the beneficial effect of somatostatin in patients with large-volume diarrhoea (in addition to antisecretory effect).

And also somatostatin inhibite intestinal and pancreatic secretion stimulated by various secretagagus in animals (16,17) and has been shown to reduce the stool output of patients with the malignant carcinoid syndrome and coeliec disease (18). The very short half-life of somatostatin limits its use, as it must be given as acontinuos intravenous infusion. The new somatostatin analogue SMS 201-995 has much longer half-life and can be administered subcutaneously.

Mechanical bowel obstruction results in distension, strangulation, vascular compromise and necrosis of intestine. Because SMS 201-995 stimulates water and electrolyte absorbtion and inhibits water secretion in the small bowel, we have studied its effects on intestinal secretory disturbances in rats with complete small bowel obstruction.

MATERIAL and METHODS

Albino male rats 150-200 or were used for experiments. Animals were fasted for 24 h but were allowed free access to water. They were than intraperitoneally anesthetized with pentobarbital (50 mg/kg). The laparatomy were made for construction of a 10 cm closed-loop of terminal ileum. The rats were randomised to receive SMS 100 mikrogr/kg (Sandoz Pharm Co) (n:10) subcutaneously or saline (n:10), twenty four hours after the start of the treatment the rats were killed, the bowel removed, the volume of the luminal contents measured and analysed for electrolytes (Na, K, HCO3, Cl), the loop weighed, and a portion of the loops examined histologically.

An observer who did not know to which treatment group the rats belonged calculated a gross pathologic score based on the presence or absence of bowel distention, edema, erythema, cyanosis, adhesions, necrosis, perforation and free peritoneal fluid (0: normal score, 10: maximal score). Luminal contents of the obstructed intestine were measured and aliquots saved for analysis of sodium and potassium by autoanalyser. Samples of obstructed intestine were preserved in formalin, sectioned and stained with hematoxylin and eosin, and examined microscopically for the presence or absence of inflammatory infiltrates, hemorrhage and mucasal necrosis. With this criteria, a microscopic pathology score was assigned (0: normal score, 3: maximal score).

Statistical analysis was performed utilizing student' s t-test for unpaired values . A p value of less then 0.05 was considered significant. Throuqhout, the data is given as mean SEM.

RESULTS

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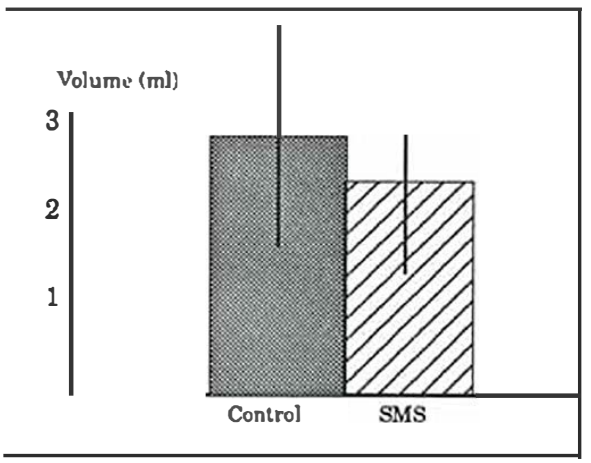

Figure 1 : Effect of SMS 201-995 on intestinal obstruction in closed-loop and proximal segments in intestinal luminal volume

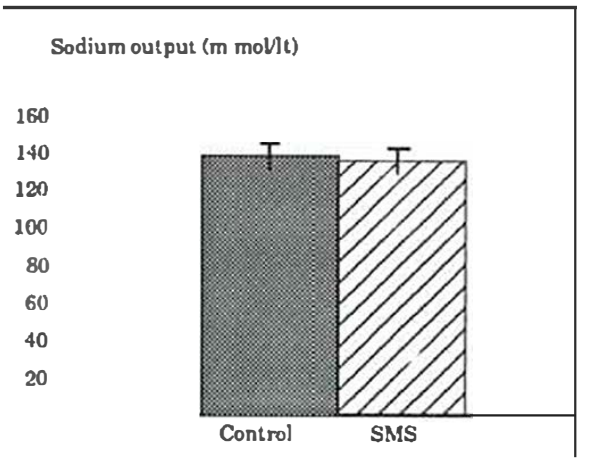

Figure 2: Luminal sodium output in obstructed rat small intestine with and without treatment with SMS 201-995.

luminal volume in the obstructed small intestine . Control and SMS 201-995 treated groups rats had a mean luminal volume of 2.69 ± 1.1 ml and 2.19±0.7 ml. (Figure 1).

Luminal sodium concentration was unchanged in the treated and in the control groups. Mean luminal sodium outpunt in the closed loop segment was 136±2.3 mmol in the control group compared with 135.2±2.9 mmol in the treated group (Figure 2).

SMS 201-995 treatment resulted with no significantly changing luminal potassium output in the proximal obstructed intestine in compared to control. Ther were no significant differences luminal potassium concentration in treated SMS 201-995 and control group rats (Figure 3).

Luminal chlorur concentration was unchanged in the treated and in the control groups. Mean chlorur output in the closed - loop segment was 83.1 ± 5.2 mmol in the control group compared with, 77.3 ± 20.0 mmol in the treated group (Figure 4).

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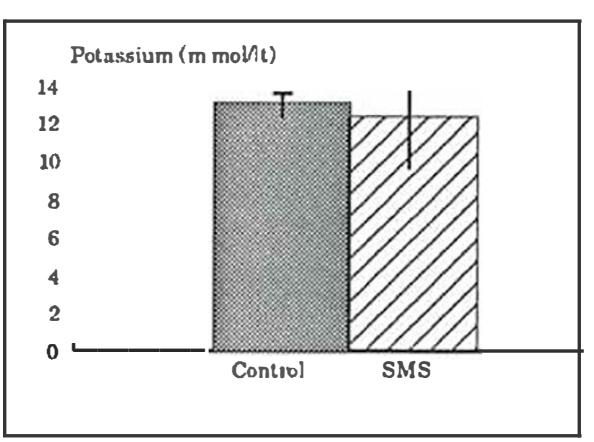

Figure 3: Luminal Potassium output in obstructed rat small intestine with and without treatment with SMS 201-995.

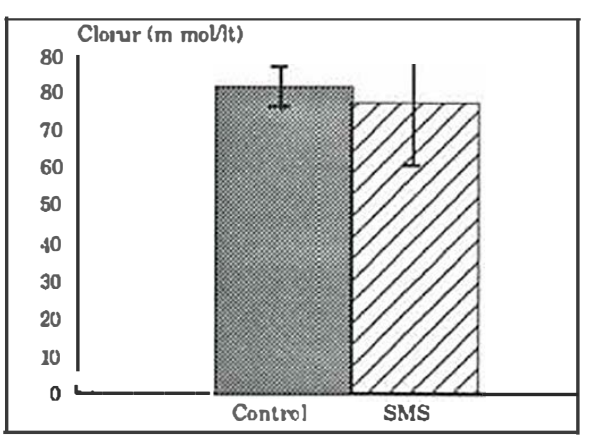

Figure 4: Luminal chlorur output in obstructed rat small intestine with and without treatment with SMS 201-995.

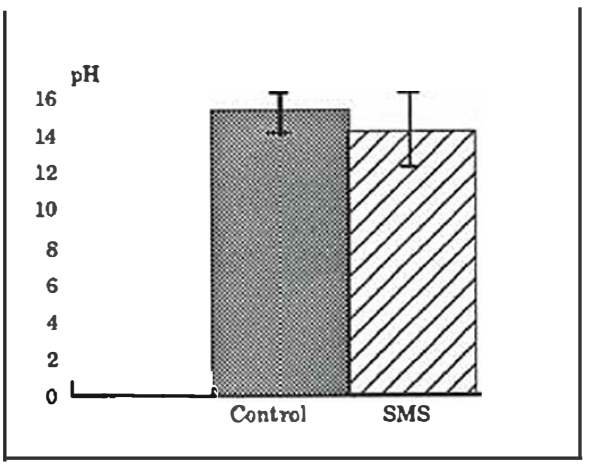

Figure 5 : Luminal pH in obstructed rat small intestine with and without treatment with SMS 201-995.

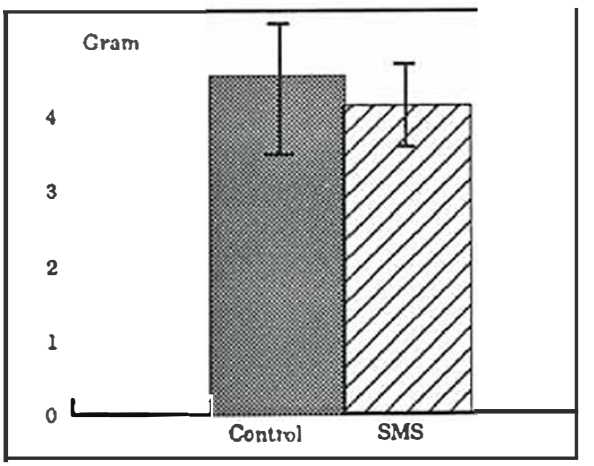

Figure 6: Loop weight of obstructed intestine with an without SMs 201-995 treatment.

luminal pH in the obstructed small intestine. Control and SMS 201-995 treated groups luminal pH of 14.74 ± 0.9 and 13.64 ± 1.85 (Figure 5).

SMS 201-995 treatment also resulted with no diffferences in the loop weight of the obstructed intesting compared to control. In the control rats had a mean the weight of 4.4 ± 0.9 gr, closed - loop segments in rats treated with SMS 201-995 had non of changes with mean of 4.05 ± 0.4 gr (Figure 6).

SMS 201-995 treatment also resulted with no differences in the gross appearance of the obstructed intestine compared to control. In the control rats had a mean gross pathologic score of 2.67 ± 0.58. Closed - loop segments in rats treated with SMS 201-995 had non of changes with mean scores of 2.27 ± 0.93 (Figure 7).

At microscopic examination, microscopic pathologic score was 2.16 ± 0.77 in SMS 201-995 treated group. Extensive mucosal necrosis and intramural hemorrhage and inflammatory infiltrates were seen in closed-loop segments, findings the were seen in the control group. No significant histopathologic changes were seen in the control groups (Figure 8).

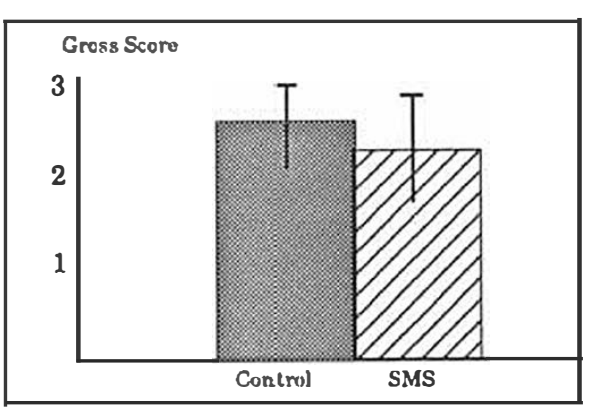

Figure 7: Gross patlologic score of obstructed intestine with and without SMS 201-995 treatment.

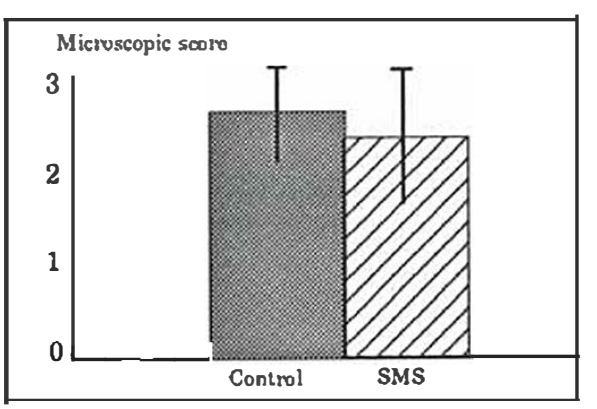

Figure 8: Microscopic pathologic score from ileum with closed-loop obstruction with and without SMS 201-995 treatment.

DISCUSSION

In the face of unremitting mechanical obstruction, progresive intestinal distension lead to vascular compromise, ischemia and necrosis. At least three factors contribute to intestinal distension in this situation : 1- Accumulation of gastric, pancreatic and biliary secretions, 2- Decreased absorption of water and sodium from the intestinal lumen, and 3- Increased secretion of water and sodium into the lumen of the distended segment. Some investigators described an in vivo model of ileal obstruction in dogs and rabbits 19.20. They found decreased absobtion of water and sodium in the obstructed segments followed by increased secretion of water and sodium intraluminally as distension increased. These findings were confirmed who produced temporary ileal obstruction with balloons in humans with ileostomies 21. A vicious cycle of decreased absorbtion and increased occurs in distended, obstructed ileal segments.

Somatostatin - 14 (SMS-14) has been shown in vitro to increase water and electrolyte absorption in rabbit ileum 17.22 and to inhibit water secretion in rat jejunum 16. Additionally, numerous studies have demonstrated inhibiton of gastric, biliary and pancreatic secretion by SMS-1423.

And also it was observed that somatostatin can abolish abnormal small-bowel secretion in humans even when secretion is not due to a circulating secretagogue as in total villous atrophy 18 and since somatostatin delays small-bowel transit 24. It was reasonable to attempt treatment of the obstructed small-bowel segments in rats with this peptide.

These studies as well as several clinical reports 25,26 of control of secretory diarrhea by SMS-14. Because of SMS analogue have much longer half life and can be administered subcutaneously, , we used it in the management of the intestinal secretory disturbances caused by mechanical small - bowel obstruction.

Although the results of literature, in our study, intestinal obstruction in these rats led to marked distension, cyanosis and patchy necrosis, particularly in the closed loop segments. These findings were not prevented by SMS 201-995 treatment, 24 h after obstruction. In addition to the marked decreases in intestinal luminal volume did not seen us in treated rat, significant reductions in sodium and potassium output were not present, implying inhibition of water, sodium and potassium secretion in the obstructed intestine by SMS analogue.

There were many possible reason why such a results are surprising in preventive effect of SMS 201-995.

It is clear that SMS 210-995 treatment can not correct the underlying pathology when complete mechanical small- bowel obstruction exists.

Whereas it was postulated that marked reduction of diarrhea with SMS 210-995. The effect of analogue was due to two factors. First, somatostatin prolongs intestinal transit time. This has been shown for native somatostatin 24 and for the analogue (14.15). However, a delay in transit was not the only mechanism involved and the somatostatin analogue probably had a direct effect on mucosal secretion. Caused by circulating agents by reducing secretagogue release from endocrine tumors (26-31). The ischemia powerful vasoactive intestinal peptide (VIP) are released locally in the qut wall 22. Somatostatin may inhibit release of such agents and protect microcirculation failure and edema and hemorrhage in the bowel wall.

Future studies will be designed to examine the protective effect of somatostatin analogue in small- bowel obstruction.

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