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Absorption of an Aqueous Solution of a New Synthetic Somatostatin Analogue Administered to Man by Gavage

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Summary. To determine the local gastrointestinal absorption of a new synthetic somatostatin analogue (SMS 201-995 = Sandostatin), an intestinal tube was passed in eight healthy volunteers and on different days an aqueous solution was administered at four different locations: stomach, proximal duodenum, ligament of Treitz and jejunum. In a follow-up study, an oro-ileal tube was passed in six of the original volunteers and the drug solution was administered in to the terminal ileum.

The aqueous solution of SMS was rapidly absorbed from the gastrointestinal tract after local application, and it was well tolerated. Absorption of the drug from the different sites was comparable, although there was a tendency to decreased peptide absorption after ileal administration. Absorption of the drug was quite variable between the subjects and the different locations. The dose-corrected systemic availability relative to subcutaneous administration in another study was 0.28%.

However, significant plasma SMS concentrations were achieved, suggesting that oral delivery of the polypeptide may eventually be possible for long-term treatment of a variety of disorders.

Key words: somatostatin analogue; oral formulation, gastrointestinal absorption, SMS 201-995, healthy volunteers

Because of its potent inhibitory effects on different endocrine and gastrointestinal functions, the use of somatostatin, a tetradecapeptide originally isolated from bovine and porcine hypothalami [1, 2], has been advocated in the treatment of acromegaly [3], gastrointestinal endocrine tumours [4–6], peptic ulcer haemorrhage [7, 8], and pancreatic fistulae [9]. Its very short half-life of about 2 min prevents administration other than by intravenous infusion [7, 10], and so makes its long-term clinical application impossible.

The new synthetic somatostatin analogue SMS 201-995 possesses many of the pharmacological properties of the natural peptide. Due to its much longer half-life, the analogue has been useful in treating patients with acromegaly and gastrointestinal endocrine tumours by giving 2–3 daily subcutaneous injections [3, 6].

Since many of the indications for SMS treatment require long-term usage, oral administration would greatly facilitate therapy and might aid patient compliance. Therefore, an aqueous solution of SMS 201-995 was developed for initial oral experiments. Pilot experiments in man and in the rat suggested that there was sufficient absorption of the compound, but that it might be restricted to the upper small intestine, which led to the hypothesis of a proximal absorption window (unpublished data).

The present study was designed to test whether the compound was absorbed in such amounts as to produce therapeutic plasma concentrations, and whether the "window hypothesis" was correct. At the same time the ability of SMS to produce the same effects on meal-stimulated insulin and glucose release was also examined. To achieve these aims, plasma SMS and insulin and glucose concentrations were measured after local oral administration of the peptide at various defined locations in the upper gastrointestinal tract.

Materials and Methods

Eight healthy male volunteers, aged 23 to 32 years (median 26 years) participated in the study. Their median weight was 74 kg (range 63–93 kg). All sub-

jects had normal renal and hepatic function. The study was conducted according to the Declaration of Tokyo/Helsinki. The study design was approved by the University Hospital Ethical Committee for Human Research and an informed consent form was read and signed by each individual.

Experimental Procedure

Subjects were always studied at 7.30 a.m. after an overnight fast. Each of them swallowed a rubber tube, which was positioned under fluoroscopy so that the tip was located 30 cm distal to the ligament of Treitz. Four identical tubes were used, which differed only in the opening of the port used to deliver the drug solution at four different locations: location S was in the stomach, P was opposite the papilla of Vater, L at the ligament of Treitz, and J was 50 cm distal to that ligament. Only one location was tested on each study day. The interval between administrations was at least 72 h.

Study Design

Four types of administration were done in each of the eight volunteers on different days according to a randomized four-way cross-over design. On Day 1, 15 ml aqueous solution containing 8 mg synthetic somatostatin analogue (SMS 201-995) was instilled through the stomach lumen as a rapid bolus followed by 50 ml isotonic NaCl solution (0.9%). The tube was removed after 2 h and a standard commercial liquid breakfast was swallowed (Fresubin: 500 ml liquid with 500 kcal, containing 19 g protein, 17 g fat, and 69 g carbohydrate). Blood samples were taken at the beginning and at regular intervals thereafter for 10 h after drug administration. Blood from a forearm vein was collected in EDTA tubes to which was added aprotinine (Trasylol, Bayer) 5000 U/5 ml blood. The samples were centrifuged at 4 °C (10 min, 3000 rpm) and the plasma separated and frozen for SMS, insulin, and glucose determinations. Whenever blood was sampled the heart rate and blood pressure were measured. Subjects had to refrain from smoking and were not allowed to take xanthine-containing beverages.

On Day 2, the drug solution was given as described above at location P, on Day 3 at location L, and on Day 4 at location J. The study design and blood sampling schedule were identical.

In a follow-up phase, six of the original eight volunteers participated in an additional study to assess absorption from the ileum. The subjects entered hospital at 22.00 h and swallowed the intestinal tube as described before. After an overnight fast, on the morning of the following day the correct position of the tube was checked by fluoroscopy, the tip of the tube being positioned in the ileum 3 m distal from the teeth. After the tube had reached its correct position, 15 ml drug solution (8 mg somatostatin analogue) was instilled as a bolus followed by 50 ml isotonic saline. The same protocol was used as described above.

Assays

Plasma SMS was measured by a specific RIA [11] with a detection limit of 10 $pg \cdot ml^{-1}$. The intra- and inter-assay variability were below 3% and 10%, respectively. Plasma insulin levels were measured as previously described [12]; the sensitivity was 2 $U \cdot ml^{-1}$ plasma. Plasma glucose levels were measured colorimetrically [13].

Data Analysis

For evaluation of the plasma concentrations of SMS, the following parameters were calculated: 1) area under the curve (AUC) to assess the relative systemic availability of the substance, 2) the maximal plasma concentration (C_{max}), and 3) the time of the maximal plasma concentration (t_{max}). All the above parameters were tested for their normal distribution by the Kolmogoroff-Smirnoff test [14] and for the homogeneity of variances according to Levene's test [14]. Data were analyzed for the significance of differences by analysis of variance and subsequently either a parametric multi-comparison test (Newman-Keuls) or a non-parametric test (Friedman), as appropriate [14]. The significance level was set at $p = 0.05$.

Results

Plasma SMS Concentrations

The plasma concentration/time curves of SMS 201-995 after local administration at different levels of the upper gastrointestinal tract are depicted in Fig. 1. The various pharmacokinetic variables are listed in Table 1.

SMS was rapidly absorbed following the different applications, peak concentrations being reached within 60 min. No difference was observed between the 5 application sites with respect to AUC, peak plasma concentration (C_{max}) or the time of the maximal plasma concentration (t_{max}). The time course of plasma SMS and the AUC after ileal application suggest that less peptide was absorbed from that site

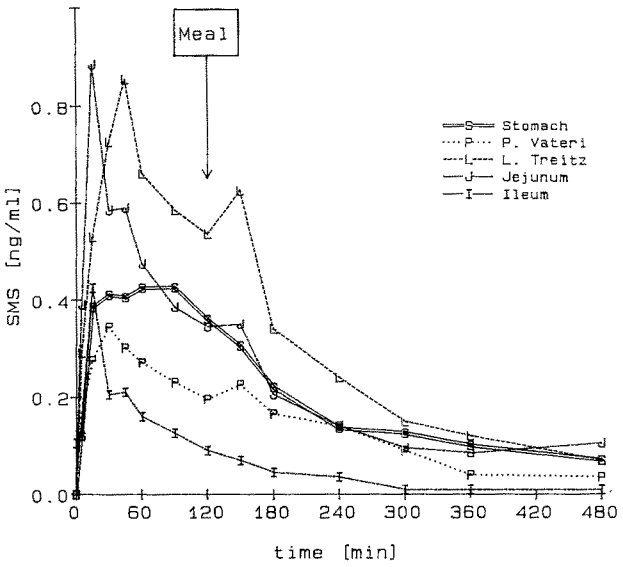

Fig. 1. Plasma SMS concentrations after oral administration of 8 mg SMS at different sites in the upper gastrointestinal tract. Data are median, $n=8$ with the exception of the ileal application where $n=6$

Table 1. Plasma kinetics of SMS after oral administration at different sites in healthy volunteers

Application site	AUC (0–8 h) ($ng \cdot min \cdot ml^{-1}$)	C_{max} (ng/ml)	t_{max} (min)
Location S (stomach)	130 (89%)	0.77 (88%)	60 (72%)
Location P (papilla of Vater)	72 (153%)	0.45 (138%)	53 (89%)
Location L (Treitz)	170 (95%)	1.06 (86%)	45 (75%)
Location J (jejunum)	112 (110%)	0.95 (99%)	23 (107%)
Location I (ileum)	36 (210%)	0.52 (122%)	15 (190%)
Subcutaneous administration (200 µg s.c., $n=6$) [15]	60240 (31%)	–	–

Data are median (CV in %); $n=8$ with the exception of Location I where $n=6$; no significant differences were found

(Fig. 1, Table 1). The inter- and intra-subject variability was quite high, as can be seen from the coefficients of variation (Table 1).

Pharmacodynamic Effects

The median curves of plasma glucose and plasma insulin concentrations are shown in Fig. 2. No difference was found between the different applications although the plasma glucose concentrations

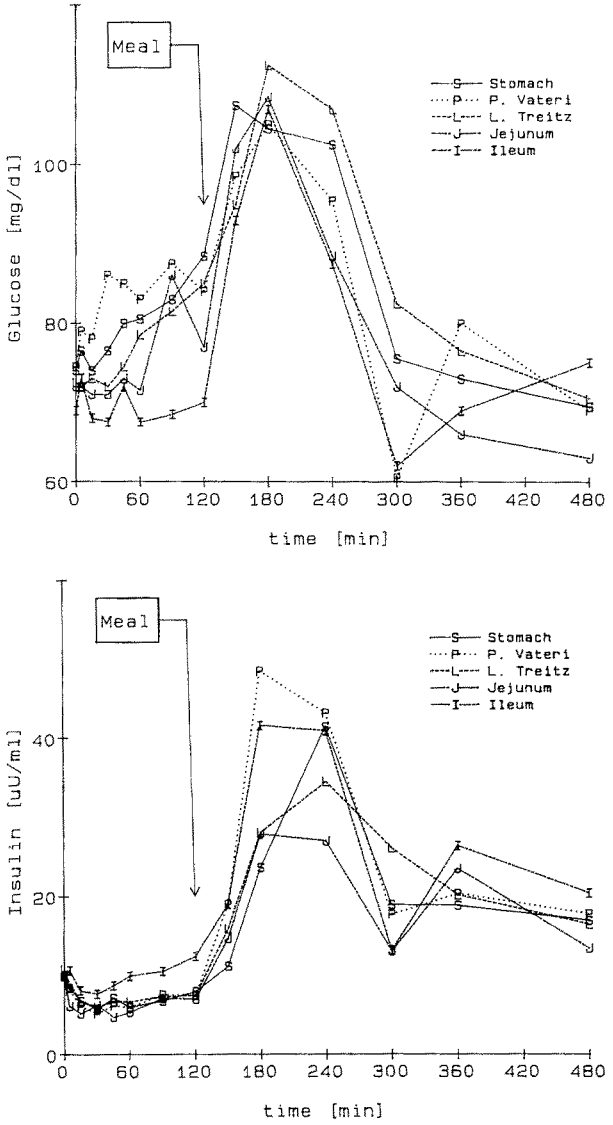

Fig. 2. Plasma glucose *(upper panel)* and plasma insulin *(lower panel)* concentrations following a meal 2 h after 8 mg SMS given at different sites. Data are median, $n=8$ with the exception of the ileal application where $n=6$

appeared to be slightly lower and the plasma insulin concentrations slightly higher after the ileal as compared to the other 4 application sites. This, again, might reflect the slightly lower plasma SMS concentrations.

A linear correlation was not found between the postprandial insulin response (AUC_{ins}) and plasma SMS absorption (AUC_{SMS} and C_{max}): $r=0.12$ and $r=0.22$, respectively. As no control (placebo) group was used, the extent of inhibition of postprandial insulin concentrations by SMS cannot be assessed.

The drug was well tolerated. Only in two of 38 administrations was there mild gastrointestinal discomfort, and it was not dose-related.

Discussion

The results of the present study can be summarized as follows:

1) A liquid solution of the synthetic somatostatin analogue SMS 201-995 was rapidly absorbed from the gastrointestinal tract after oral application and significant plasma levels were achieved
2) Absorption was comparable from the different application sites, although there was a tendency to decreased peptide absorption after ileal and duodenal (papilla of Vater) administration
3) Absorption showed great variability both between the subjects and the different locations.

SMS 201-995 has a molecular weight of 1019 daltons, and at a physiological pH in the lumen of the small intestine it should be ionised and positively charged. This might be expected to impede absorption. However, significant plasma SMS concentrations were found after local application of 8 mg of a liquid solution of the peptide. These plasma concentrations should suffice to suppress growth hormone secretion (>0.3 ng/ml, [3]). The AUC of SMS after local instillation at the ligamentum of Treitz (location L) was compared to that after a single subcutaneous dose of SMS in another group of volunteers [15]. After dose correction, the relative systemic availability of the drug was estimated to be 0.28%.

The AUCs of SMS after the different applications showed considerable variation, both inter- and intra-subject. This was partly due to Subject 7, who showed a very different absorption pattern which might have masked a possible significant difference between the 5 application sites. Nevertheless, a clear trend was observed for the plasma AUC of SMS with decreasing plasma SMS concentrations after ileal application of the solution. It is noteworthy that the application at the papilla of Vater resulted in somewhat lower absorption of the compound, 7 of the 8 subjects showing a reduced systemic availability of the peptide. A possible explanation of this decrease might be that application site P differed from the stomach or distal duodenum by having a high intraluminal concentrations of pancreatic and bile fluids, which might have caused some ill-defined interaction between the peptide (precipitation?) and elements of the duodenal juice (pH, possibly bile salts).

Analysis of the time to reach the maximal plasma concentration (t_{max}) did not show any significant differences between the different applications, but again, there was a trend to a shorter time to peak from the ileum to the stomach.

The hypothesis of a proximal absorption window was not confirmed by the present experiments, as similar plasma concentrations were obtained after each of the different applications. However, absorption of SMS was reduced in 5 of the 6 volunteers after ileal application. This could be explained by a reduced absorption area. The findings suggest that the absorption of SMS may be confined to the small intestine.

Plasma insulin and glucose concentrations were similar in the different experiments. The standard liquid breakfast induced a prompt increase in both parameters. As there was no control (placebo) group in the study, nothing can be stated about the absolute effect of SMS on postprandial insulin and glucose concentrations.

Thus, the present study has demonstrated that a liquid solution of 8 mg SMS 201-995 (Sandostatin) was rapidly absorbed from the upper gastrointestinal tract to give significant drug plasma concentrations. The drug was well tolerated. The preliminary data should encourage further development of an oral formulation, which would be particularly suitable for patients with acromegaly, gastrointestinal endocrine tumours and possibly even diabetes mellitus, who would require long-term treatment with the compound.

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