Tolerability and Absorption Enhancement of Intranasally Administered Octreotide by Sodium Taurodihydrofusidate in Healthy Subjects

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Received March 6, 1991; accepted June 22, 1991

Nasal sprays containing different concentrations of the somatostatin analogue octreotide and sodium tauro-24,25-dihydrofusidate (STDHF) as an absorption promoter were evaluated in two consecutive pharmacokinetic studies in healthy volunteers to characterize their bioavailability and local tolerability. The concentrations of STDHF were selected on the basis of a phase diagram generated by a dynamic laser light-scattering technique to ensure that the mixture was above the critical micellar concentrations. Compared to a 50-μg subcutaneous injection, the nasal spray formulation without STDHF had a mean relative bioavailability of 17.9%. For nasal formulations containing 3 and 1.65% (w/v) of STDHF, the bioavailability increased to 29.0 and 25.7%, respectively. The enhancement of nasal absorption was dependent on the STDHF concentrations as shown by decreasing the amounts to 1.2 and 0.8% (w/v) for tolerability reasons; the bioavailability was reduced to 15.3 and 20.5% in these cases, respectively. The local tolerability of all STDHF-containing sprays was poor, leading to stinging sensations and lacrimation. The poor local tolerability of the octreotide nasal spray containing different concentrations of STDHF required for effective nasal absorption enhancement appears to be impractical for further clinical development. These findings clearly stress the necessity to investigate tolerability and safety issues of new drug delivery systems in early developmental phases.

KEY WORDS: absorption enhancer; octreotide; nasal spray; tolerability; human volunteers.

INTRODUCTION

As a promising alternative to parenteral administration, the nasal route of application has met with considerable interest. This approach is considered to be especially useful for peptides and proteins (1–4). Transport of molecules across the nasal epithelium is inversely proportional to the square of molecular mass (5). Therefore, the bioavailability of nasally administered drugs decreases rapidly with increasing molecular weight. For peptides with more than 20 amino acids relative intranasal bioavailabilities generally are in the area of less than 1%. Another frequent problem is high inter- and intrapatient variability. These shortcomings have stimulated research for molecules that can safety enhance or promote the absorption of intranasally administered drugs.

Sodium tauro-24,25-dihydrofusidate (STDHF)[6] was recognized as a more effective and less irritating enhancer molecule compared to other bile salts. While the enhancer effect on the nasal absorption of insulin in sheep (6) or rabbits and rats (7) was confirmed, large interspecies differences render extrapolations concerning the performance of STDHF-containing nasal preparations in man impossible. Species differences for the effect of STDHF on the nasal absorption of human growth hormone were recently reported (8).

Studies characterizing the influence of STDHF on the morphology of rat nasal tissues (9), the ciliary beat frequency of nasal tissue in guinea pigs (10), and the *in vitro* ciliary movement of human nasal tissue (11) do not lead to a homogeneous picture with respect to the local tolerability. Short-term toxicological studies in rats and dogs for up to 30 days did not reveal changes in the mucosal tissues. Long-term chronic studies have not yet been reported (2). Nasal irritation has been reported in clinical studies with bile salt containing nasal sprays of insulin (3,12). A stinging sensation and lacrimation were seen as local adverse effects of these substances. STDHF was claimed to be devoid of these adverse events.

Octreotide (SMS 201-995, Sandostatin) is an octapeptide analogue of somatostatin, the somatotropin release-inhibiting factor (SRIF). Its clinical utility has been established in a variety of endocrine and gastrointestinal disorders such as acromegaly, gut-related endocrine tumors, carcinoid syndrome, secretory diarrhea, and gastrointestinal fistula (13–15). In contrast to SRIF, which has a biological half-life of 2–3 min, octreotide normally has, due to its metabolic stability, a half-life of 72 or 102 min after intravenous and subcutaneous administration, respectively (16,17). Since octreotide is given as a long-term treatment in daily (multiple) injections, a nonparenteral route of administration would be desirable. Recently a nasal delivery system was suggested for octreotide (18).

We report here formulation aspects of STDHF-containing octreotide-nasal preparations and their influence on the absorption and local tolerability in healthy volunteers. Most of the available information on STDHF as an enhancer for transnasal absorption of peptides was generated studying insulin (19). The molar ratio of STDHF:insulin must exceed a threshold level to ca. 1 for an enhancing effect. A plateau is reached at a ratio of 5:1, above which only modest increases in nasal bioavailability occur. Animal and human pharmacokinetic studies used mainly insulin doses of 0.35 to

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[6] Abbreviations used: ANOVA, analysis of variance; AUC, area under the plasma concentration/time curve; C_{max}, maximum plasma concentrations; CMC, critical micellar concentration; HVD, half-value duration; MRT, mean residence time; STDHF, sodium tauro24,25-dihydrofusidate; SRIF, somatotropin release-inhibiting factor; T_{max}, time of maximum plasma concentration.

0724-8741/92/0100-0052$06.50/0

ca. 1 IU/kg in formulations containing 0.5 to 1% (w/v) STDHF in a sodium phosphate buffer (20 m*M*, pH 7.4). The solution can be applied with a mechanical pump spray delivering a volume of ca. 100 μl. In sheep absorption from this nasal spray formulation was equivalent to that from a nasal aerosol containing an insulin-STDHF powder formulation (19). For human growth hormone, similar formulations were used (8). Possible insight into the mechanism of STDHF enhanced nasal peptide absorption might be suggested by the observation that concentrations of STDHF slightly in excess of the critical micellar concentration (CMC) are required for optimal peptide delivery. To minimize local adverse reactions, however, excesses of STDHF should be avoided.

MATERIALS AND METHODS

Materials

Octreotide (Sandostatin) acetate salt was provided by Sandoz Pharma Production and was used as received. STDHF was kindly supplied by California Biotechnology Inc. Ampoules of Sandostatin for subcutaneous injection and matching placebo ampoules were obtained from Sandoz Pharma Production.

Nasal Formulations

For octreotide, the conditions employed for insulin/STDHF formulations are not applicable, because the dose of octreotide is substantially higher than that used for insulin, and octreotide and STDHF can form precipitates presumably by salt formation. Therefore, a phase diagram of octreotide and STDHF was established to define suitable compositions of a nasal delivery system. Only nonprecipitating compositions of nasal formulations were investigated in this study. It is not possible to formulate nasal systems of octreotide with a fixed concentration of STDHF, e.g., 1% (15.5 m*M*), since at this concentration, octreotide already precipitates at 0.4 mg/ml. The composition of the nasal spray was defined by the phase diagram and STDHF concentrations ranging from 0.8 to 3.0% (w/v) were selected in this study, with octreotide doses within the range of 25 to 250 μg/push (90 μl) of the nasal spray. Due to the precipitation problem, both octreotide and STDHF concentrations had to be adapted simultaneously. Nasal application forms were formulated under aseptic conditions. The pH was adjusted to 4.5 for stability reasons. The solutions were not buffered but adjusted to physiological osmolarity. The nasal spray solution was filled into 3.5-ml containers (St. Gobain, Mers les Bains, France) under carbon dioxide and sealed with crimped on rubber stoppers. For nasal administrations, a metered-dose pump (Pfeiffer, Radolfszell, FRG) delivering a fixed volume of 90 μl/push was used. Clinical trial supplies were stored at 5°C.

Light-Scattering Measurements

Static and dynamic light-scattering measurements were performed at 20°C using the Malvern Submicron Particle Analyser equipped with an argon ion laser (Spectra Physics) operating at a wavelength of 488 nm, a goniometer for an angular range from 20 to 150°, and the Lin-Log correlator K7027 (Malvern). Mixtures with different concentrations of octreotide and STDHF were prepared from stock solutions of 20 mg/ml octreotide and 80 mg/ml STDHF in 0.15 *M* NaCl. In some of these solutions, a white precipitate was formed; in the clear unprecipitated mixtures, the interaction of octreotide and STDHF in terms of molecular weight and hydrodynamic radius of the formed aggregates was determined.

Human Studies

The nasal preparations were studied in two successive human studies in healthy volunteers. The studies were performed in accordance with the guidelines of the Declaration of Helsinki as revised in Tokyo (1975) and in Venice (1983). The study protocols and informed consent forms were approved by the ethics committee of the University Hospital, University of Basel. Written, informed consent was obtained from all subjects.

The subjects were healthy at the time of the study. Physical examinations, including blood pressure and pulse rate, ECG, and laboratory investigations, revealed no clinically significant abnormalities.

Studies I and II were performed in different populations of six and eight healthy volunteers, respectively. All subjects received the test preparation (8 AM) after an overnight fast of at least 10 hr. Only mineral water was allowed during the night before administration. The subcutaneous (s.c.) injection was given in a thigh. Sprays were administered as one push into the left nostril using the applicator described above. For both studies, there was a washout period of at least 3 days between two successive treatments.

For both studies the following dietary restrictions were observed on the administration days: a standardized breakfast was given 2 hr after administrations. Lunch and dinner were taken 5 and 12 hr after drug administration. During the first 12 hr after administrations, no intake of xanthine or alcohol containing beverages was allowed. The subjects were not permitted to smoke during the study.

The local tolerability of the nasal sprays was assessed at different time intervals (0, 0.5, 6, and 12 hr) through inspection of both nostrils and the pharyngeal wall by an otolaryngologist not involved in the study. Special emphasis was put on the comparison of both nostrils. Based on the results in study I, this inspection was omitted in study II.

Any adverse events reported by subjects or observed by the attending physician were recorded. Records included time of onset, duration, severity (graded as 1 = mild, 2 = moderate, and 3 = severe), attribution of adverse events to the treatment, reasons for attribution, and any treatment required.

Study I. In the first study, all six subjects first received a s.c. injection of 50 μg octreotide (Lot Y208 K4). This was followed by three nasal applications according to a randomized, double-blind, three-periods Latin-squares design: (i) nasal spray containing 250 μg octreotide and 3% (w/v) STDHF per push (Lot W088 1186), (ii) nasal spray containing 100 μg octreotide and 1.65% (w/v) STDHF per push (Lot W089 1186), and (iii) nasal spray containing 250 μg octreotide per push (Lot Y050 C5).

After analysis of this study, a second human study was

performed with nasal spray formulations containing lower STDHF concentrations than the formulations investigated in study I.

Study II. Eight subjects received the following four administrations according to a randomized, double-blind, double-dummy, four-periods Latin-squares design: (i) two pushes of a nasal spray (one in each nostril) containing 50 μg octreotide and 1.2% (w/v) STDHF per push (Lot W023 0487) and a placebo s.c. injection (Lot Y145 G4), (ii) two pushes of a nasal spray containing 25 μg octreotide and 0.8% (w/v) STDHF per push (Lot W022 0487) and a placebo s.c. injection (Lot Y145 G4), (iii) two pushes of a placebo nasal spray containing only vehicle (Lot W024 0487) and a placebo s.c. injection (Lot Y145 G4), and (iv) two pushes of a placebo nasal spray containing only vehicle (Lot W024 0487) and a s.c. injection of 50 μg octreotide (Lot Y208 K4). The randomization code was kept under separate cover.

Plasma Octreotide Determinations

Octreotide plasma concentrations were determined by radioimmunoassay using polyclonal rabbit antibodies and ^{125}I-labeled octreotide as a tracer (21). For separation of free and bound peptides, activated charcoal was used. The antiserum reacted specifically with the intact peptide, whereas binding to peptide fragments was negligible. The detection limit of the assay was 10 pg/ml.

Blood samples for octreotide determination were taken up to 12 hr after administration. Blood (3 ml) was drawn through a cannula placed in an arm vein. Samples were immediately centrifuged in lithium heparin tubes at 4°C and the plasma was stored at −20°C prior to analysis.

Comparison of Tolerability Data

Local tolerability of the different nasal spray formulations was quantitatively compared by incidence and tolerability score. Incidence was calculated as the percentage of subjects who reported stinging in the nose after administration. Tolerability score was defined on the basis of severity of stinging times its duration in minutes. The total score was calculated as the sum of all individual scores for each formulation divided by the number of subjects enrolled in the study.

Pharmacokinetics and Statistics

The following pharmacokinetic parameters of octreotide were determined: the maximum plasma concentration (C_{max}) and its time of occurrence (T_{max}). Areas under the plasma concentration/time curves (AUC) were calculated using the trapezoidal rule. Concentrations below the detection limit of the assay were set to zero for calculation purposes. The degree of retardation of the plasma profiles was assessed by the half-value duration (HVD) and mean residence time (MRT). HVD was defined as the total time period that plasma concentrations of octreotide were above one-half of C_{max}. If necessary, the end points of that interval were determined by linear interpolation (22). MRT, the first moment of the plasma concentration/time curve, was calculated as described by Gibaldi and Perrier (23).

For statistical comparisons of pharmacokinetic parameters, only dose-corrected data obtained from the nasal administrations results were used. Samples were first tested for normal distribution using the Wilk–Shapiro test and for homogeneity of variances by the test of Levene (24). If normal distribution of the data could not be rejected, samples were tested by two-way analysis of variance (ANOVA) using the GLM procedure of the SAS software package (25). The level of significance was alpha = 0.05. In the event of significant differences, ANOVA was followed by Newman–Keuls multicomparison test for pairwise comparisons (25). For samples not normally distributed or samples with nonhomogeneous variances, ANOVA was applied on rank transformed data [Friedman test (26)].

RESULTS

Laser Light-Scattering Results

The octreotide solutions were clear in all tested concentrations up to 20 mg/ml. The STDHF solutions were also clear, displaying micellar properties with a CMC of 4.6 m*M*, a molecular weight of 18,900, and a hydrodynamic radius of 2.19 nm. From the dilution series, a phase boundary of solubility could be established with a parabolic dependence of octreotide vs STDHF concentrations (Fig. 1). This phase boundary intercepted the STDHF axis at a STDHF concentration close to the CMC of the pure STDHF micellar system. Above the phase boundary, precipitates were formed, while below, clear solutions were obtained. The phase boundary was sensitive to temperature effects: lower temperatures shifted it to higher STDHF concentrations. Therefore, to ensure the stability of octreotide, the compositions of the nasal spray formulations were chosen with a safety margin from the phase boundary to prevent precipitations of the solutions during storage at lower temperatures (5°C).

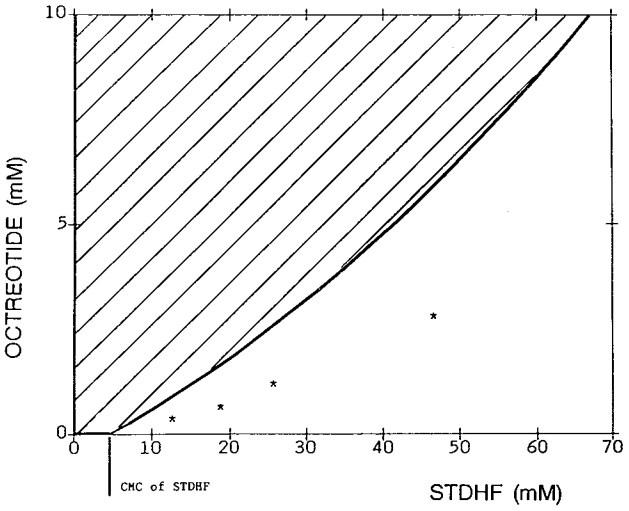

Fig. 1. Phase diagram of octreotide/STDHF. Phase diagram of solutions of octreotide and STDHF in 0.15 *M* NaCl at 20°C. The shaded area represents the region of precipitations, whereas the other region is free of precipitations. Along the axes of the pure components, the solutions are clear. Precipitations consist of octreotide and STDHF in a composition range of 1:2 to 1:2.5. The samples for the human studies lie within the clear region and are marked with an asterisk.

Human Studies

Study I

The study was performed in six healthy volunteers (one female, five males) with a mean age of 24 years (range, 20 to 29 years), a mean body height of 178 cm (range, 164 to 184 cm), and a mean body weight of 72 kg (range, 55 to 85 kg).

Local Tolerability. The rhinolaryngeal inspection of both nostrils before and after nasal administrations showed no macroscopic changes of the nasal and pharyngeal mucosa with any of the nasal sprays. However, after administration of the STDHF containing nasal sprays, many local side effects were reported by the subjects. After administration of the nasal spray containing only 250 μg of octreotide in 90 μl, three of six subjects reported mild local adverse effects (running nose, nasal congestion, and itching by one subject each). Itching occurred immediately and lasted for 5 min. However, after administration of both STDHF containing nasal sprays, all subjects complained about mild to severe itching immediately following dosing but lasting for 10 to 60 min [3% (w/v) STDHF] and 15 to 30 min [1.65% (w/v) STDHF]. In addition, a stinging throat and a salty and bitter taste were reported. Three subjects had a stinging and tearing eye at the side of spray administration after one or both of the STDHF-containing spray applications (Fig. 3).

Pharmacokinetic Results. Compared with the nasal spray without STDHF, both STDHF containing nasal sprays showed a substantial enhancement of octreotide absorption (Fig. 2, Table I). After administration of the 3 and 1.65% STDHF-containing nasal sprays, the bioavailability had increased on average from 17.3% for the nasal spray without STDHF to 29.0 and 25.7%, respectively. Both STDHF-containing formulations showed clinically significant maximum plasma concentrations; the 3% STDHF-containing formulations exceeded those of the 100-μg s.c. injection. As indicated by T_{max}, HVD, and MRT values, there was a tendency for a more rapid and shorter-lasting absorption of octreotide and a smaller degree of retardation of octreotide plasma profiles for the STDHF containing formulations.

Study II

The study was performed in eight healthy male volunteers with a mean age of 24 years (range, 22 to 25 years), a mean body height of 175 cm (range, 168 to 189 cm), and a mean body weight of 72 kg (range, 51 to 81 kg).

Local Tolerability. After administration of the placebo nasal spray seven of eight subjects did not report any local symptoms. Only one subject reported a short-lasting warm feeling of the nose after dosing. After intranasal administration of the 1.2% (w/v) STDHF-containing spray, all subjects complained about instantaneous stinging of the nose with a mild to severe intensity, lasting for 5 to 60 min. After administration of the 0.8% (w/v) STDHF-containing nasal spray, seven of eight subjects complained about instantaneous stinging of the nose with a mild to severe intensity lasting for 5 to 20 min (Fig. 3).

Pharmacokinetic Results. Compared with the s.c. reference in this study and the reference nasal spray in study I, both STDHF-containing nasal sprays showed no or only a slight enhancement of octreotide absorption (Table II). Compared with the formulations used in study I, the reduction of STDHF and octreotide concentrations in the nasal sprays could not be compensated by the twofold larger volumes of the applied sprays (two pushes instead of one in study I) and by the increased area of possible absorption (both nostrils instead of only one in study I). Despite the same total dose of octreotide applied, the 100-μg nasal spray given in study I [containing 1.65% (w/v) STDHF] showed a greater oc-

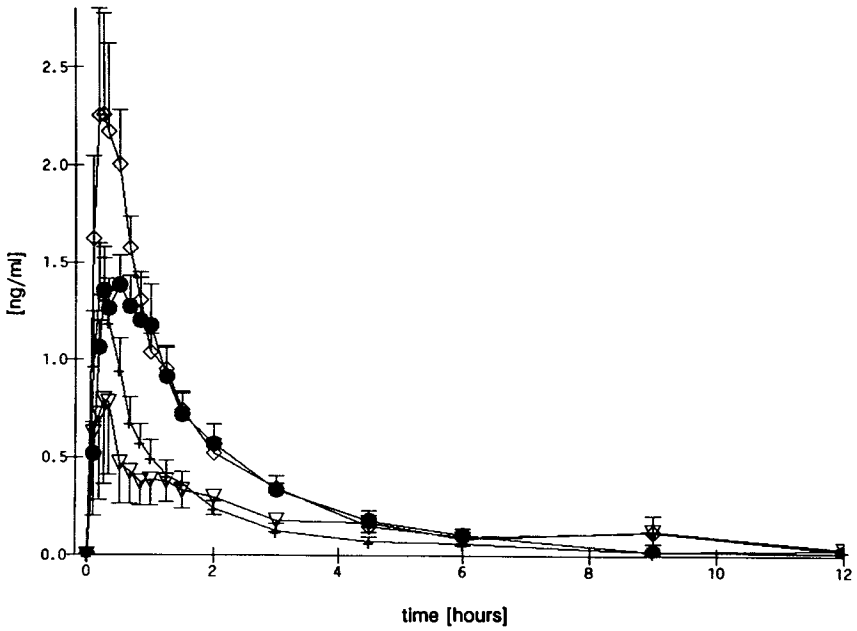

Fig. 2. Octreotide plasma concentrations after administration of (—●—) 50 μg octreotide s.c., (—▽—) 250 μg octreotide i.n., (—◇—) 250 μg octreotide (+3% STDHF) i.n., and (—+—) 100 μg octreotide (+1.65% STDHF) i.n.

Table I. Pharmacokinetic Parameters in Study I (Means ± SD; $n = 6$)

	250 μg i.n.	250 μg i.n. (3% STDHF)	100 μg i.n. (1.65% STDHF)	50 μg s.c.
AUC (0–12 hr) (ng hr/ml)	2.12 ± 1.39	3.71 ± 0.81	1.66 ± 0.84	3.10 ± 1.11
Bioavailability (%)	17.3 ± 15.4	29.0 ± 18.1	25.7 ± 7.7	100 (reference)
C_{max} (ng/ml)	1.12 ± 1.04	2.64 ± 0.90	1.41 ± 0.66	1.57 ± 0.41
T_{max} (hr)	0.73 ± 0.73	0.29 ± 0.12	0.21 ± 0.07	0.47 ± 0.24
HVD (hr)	1.70 ± 1.10	0.75 ± 0.12	0.69 ± 0.25	1.37 ± 0.44
MRT (hr)	2.59 ± 1.72	1.99 ± 1.27	1.51 ± 0.64	0.83 ± 0.83

treotide absorption than the 50-μg nasal spray [containing 0.8% (w/v) STDHF] given as two pushes.

DISCUSSION

STDHF added at concentrations of 0.8 to 3.0% (w/v) to an aqueous nasal spray containing 25 to 250 μg of octreotide in 90 μl enhances the absorption of octreotide after intranasal administration. The enhancing effect is dose dependent, fading off at concentrations at or below 0.8% (w/v). The concentrations of STDHF used in our studies were in the same range as those in other studies (6). The poor local tolerability of all investigated STDHF containing nasal sprays suggests that a further reduction of the STDHF concentrations is necessary to improve tolerability. This would, however, probably lead to a loss of absorption enhancement.

The ratios of octreotide to STDHF concentrations were determined by laser light-scattering investigations. These experiments showed a clear interaction of octreotide and STDHF (development of mixed micelles) in some concentration ranges and sharp limits of the octreotide/STDHF concentration ratio with respect to solubility. Thus, to reduce the STDHF concentrations, octreotide concentration in the formulations had to be decreased. To achieve better tolerability, an additional reduction of the STDHF concentration would also lead to a further reduction of the octreotide concentrations. Consequently, to ensure a clinically sufficient dose, the applied volume would have to be increased, which does not seem to be feasible from a practical point of view.

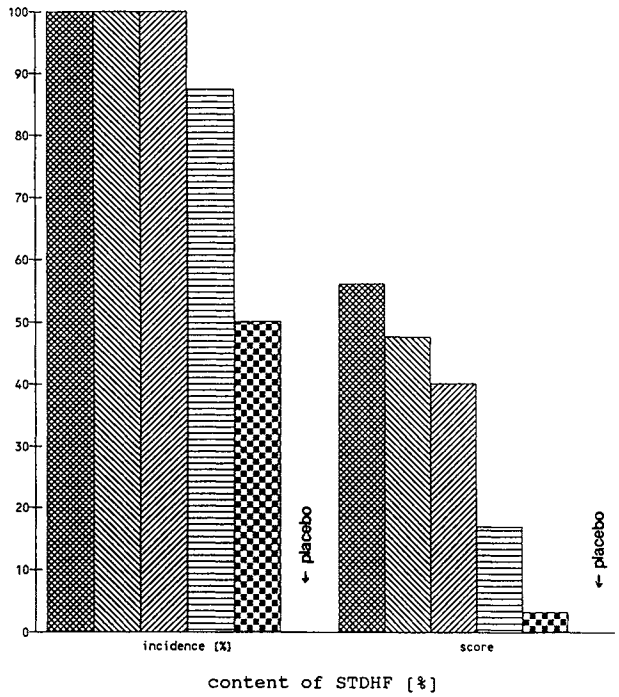

Fig. 3. Local tolerability of nasal sprays: incidence (% subjects with itching) and tolerability score (% subjects with itching × duration of side effects). Cross-hatched: 250 μg octreotide + 3% STDHF; left hatched, 100 μg octreotide + 1.67% STDHF; right hatched, 100 μg octreotide + 1.2% STDHF; horizontal hatched, 50 μg octreotide + 0.8% STDHF; checkered, 250 μg octreotide; open, placebo. After administration of placebo, no itching was observed.

Mechanisms of insulin absorption enhancement by STDHF were discussed on the basis of inhibition of nasal mucosa proteases, improvement of passive paracellular drug transport (2), and solubilization by the formation of micelles above the CMC of 0.15% (w/v) of STDHF (6). The best results were obtained with concentrations of STDHF of 0.5 to 2.0% (w/v). In contrast, other authors proposed that the absorption enhancing effect of bile salts and their derivatives was caused by their damaging effect on the nasal mucosa (27,28). This hypothesis was supported by several findings. It was shown in a red blood-cell hemolysis assay that the increase in the ability to enhance nasal insulin absorption was accompanied by an increase of the membrane lytic properties of STDHF (6). Furthermore, the membrane lytic potential correlated with a dose-dependent increase in the inhibitory effect of STDHF [0.1 to 1.0% (w/v)] on human nasal tissue ciliary movement which was investigated *in vitro*. In this assay a complete inhibition of ciliary movements was observed with doses higher than 0.3% (w/v) (11). Recent confirmation of these findings was provided by the observation that STDHF, at concentrations of 0.5 and 1.0% (w/v), affected the morphological integrity of the nasal mucosa as assessed by scanning electron microscopy (9).

Table II. Pharmacokinetic Parameters in Study II (Means ± SD; $n = 8$)

	100 μg i.n. (1.2% STDHF)	50 μg i.n. (0.8% STDHF)	50 μg s.c.
AUC (0–12 hr) (ng hr/ml)	1.21 ± 0.66	0.73 ± 0.64	3.99 ± 0.87
Bioavailability (%)	15.3 ± 7.7	20.5 ± 21.1	100 (reference)
C_{max} (ng/ml)	1.51 ± 0.49	0.91 ± 0.48	1.66 ± 0.40
T_{max} (hr)	0.17 ± 0.05	0.20 ± 0.06	0.43 ± 0.22
HVD (hr)	0.43 ± 0.11	0.42 ± 0.06	1.37 ± 0.51
MRT (hr)	0.89 ± 0.37	0.75 ± 0.45	2.19 ± 0.94

Our human results confirm and extend these *in vitro* and animal studies by demonstrating clinically significant local side effects after administrations of nasal sprays containing 0.8 to 3% (w/v) STDHF.

Since most of the octreotide indications require life-long treatment, a feasible nasal spray formulation needs to be free of any local irritating effects. The poor local tolerability of this octreotide nasal spray containing different concentrations of STDHF to promote nasal absorption enhancement of the peptide appears, therefore, prohibitive for further clinical development.

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