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Pharmacokinetics and Pharmacodynamics of Intranasal Insulin Spray (Nasulin™) Administered to Healthy Male Volunteers: Influence of the Nasal Cycle

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Abstract

Background:

The pharmacokinetics and pharmacodynamics of a Bentley Pharmaceuticals proprietary intranasal (IN) insulin formulation (Nasulin™) were studied in healthy volunteers.

Methods:

Thirteen fasting healthy male volunteers received five doses of medication (one dose of 4 international units [IU] subcutaneous (SC) regular insulin and four doses of 25 IU IN insulin) at least 48 h apart. Serum insulin, serum C-peptide, and plasma glucose were measured in the 4 h after dosing. Profiles were compared for IN insulin spray following administration into the dominant nostril (more open at time of dosing) and into the nondominant nostril (less open at time of dosing).

Results:

The formulation was generally well tolerated. A rise in serum insulin levels accompanied by a decrease in plasma glucose was seen following all doses. For IN doses, peak insulin levels were generally attained in 10–20 min and remained elevated for approximately 40–50 min; the resultant effect on glucose peaked at 40 min and waned approximately 2 h postdosing. As reported in other studies, the interindividual response to insulin was variable. The comparative absorption of IN insulin relative to SC insulin was 12.0% (dominant nostril) or 15.4% (nondominant nostril) over 2 h. This increased somewhat if sneezers and volunteers with moderately blocked nostrils were removed from the analysis.

Conclusions:

This IN formulation was generally well tolerated and relatively well absorbed. While both insulin data (maximal plasma concentration and area under the plasma concentration time curve) and glucose data (% fall) support a trend toward better absorption from the nondominant nostril, this did not reach statistical significance. Nasulin can be administered without reference to the nasal cycle.

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Abbreviations: (AUC) area under the plasma concentration time curve, (BMI) body mass index, (Cmax) maximal plasma concentration, (CPE-215) cyclopentadecalactone, (IN) intranasal, (SC) subcutaneous, (IU) international units

Keywords: insulin kinetics, intranasal insulin, nasal cycle, plasma glucose

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Introduction

The control of blood glucose levels is a major determinant of subsequent health complications in individuals with diabetes mellitus, including blindness, kidney failure, and premature death. A key factor in maintaining euglycemia, particularly in type 1 diabetes (no insulin production by pancreas), is the delivery of insulin in doses appropriate to the daily periodic intake and absorption of nutrients, with increases in blood glucose seen after meals and lower levels between meals. Insulin is also increasingly being used in the treatment of patients with type 2 diabetes. The most common regimen of insulin treatment is the subcutaneous (SC) injection of rapid or fast-acting insulin before meals in conjunction with less frequent administration of an insulin formulation with a longer, slower action.

Bentley Pharmaceuticals, Inc. (Exeter, NH) has recently developed a novel nasal spray formulation of insulin. Nasulin™ is composed of regular human recombinant insulin dissolved in sterile water in combination with excipient cyclopentadecalactone (CPE-215), a compound that occurs naturally in plants (*Angelica archangelica*). CPE-215 is a common additive to many foodstuffs, cosmetics, and personal hygiene products (e.g., deodorants) and appears to cause little irritation of the epithelial tissue of the nasal passages.

In a previous study,[1] the Bentley intranasal (IN) insulin formulation was administered to eight healthy volunteers in a fasted state. As had been seen in earlier studies by other investigators with different formulations, plasma insulin levels peaked after approximately 10–20 min.[2–4] Plasma glucose began to fall after 10 min and reached a nadir 40 min after dosing, with a return to baseline levels after approximately 100 min. Mean percentage fall in glucose following an IN dose of 25 international units (IU) was 20.5%, comparable with the fall that might be expected following a SC injection of approximately 4 IU of insulin.[2] A dose response was seen with a greater fall in glucose following higher doses (31.25 and 37.5 IU); however, the number of volunteers given these doses was small. In a subsequent study,[5] the same formulation was administered in various doses to seven patients with type 1 diabetes mellitus in place of their breakfast-time dose of rapid-acting insulin. Plasma profiles of insulin following IN dosing closely resembled those previously seen in healthy volunteers. Comparisons with SC insulin in four patients who used this during one of their study periods suggested that the relative bioavailability of the Bentley Pharmaceuticals formulation was approximately 10–20%. The pharmacodynamic effect of the absorbed insulin was demonstrated by dose-related attenuation in the rise in plasma glucose after breakfast. In both studies, the insulin formulation was generally well tolerated.

The degree of congestion of the mucosa of the nasal passages varies such that, at any one time, one nostril is more patent (dominant) while the other is less patent (nondominant). For each individual, the nostril that is dominant varies at different times of the day and night; this is known as the nasal cycle.[6] The nasal cycle may influence the absorption of insulin administered via this route and may contribute to the variability in interindividual responsiveness to IN insulin seen in previous studies. If so, this is of clinical relevance and may have a bearing on dosing instructions to be given to diabetes patients using an IN insulin formulation. The aim of the present study was to assess the pharmacokinetics and pharmacodynamics of a Bentley Pharmaceuticals proprietary insulin formulation designed for IN administration in healthy male volunteers compared to SC regular insulin. Profiles were also compared for IN insulin spray following administration into the dominant nostril (more open at the time of dosing) and into the nondominant nostril (more blocked at the time of dosing).

Methods

This exploratory, open-label, single-dose crossover study examined the pharmacokinetics and pharmacodynamics of a Bentley Pharmaceuticals insulin formulation utilizing CPE-215 technology designed for IN administration. The design was based on previous similar studies performed at Shandon Clinic.[1,5] Prior to study initiation, approval was obtained from the Clinical Research Ethics Committee of the Cork Teaching Hospitals. All subjects provided written informed consent. Twelve healthy male volunteers (body mass index [BMI] 25.49 ± 1.79) received five doses of medication (4 IU SC insulin or 25 IU IN insulin) while in a fasted state. As it was not possible to provide a complete, balanced randomization schedule for 12 subjects and 5 treatment arms, volunteers were dosed in groups of six according to a schedule outlined in the study protocol. Each subject acted as his own control for repeat-dosing days that were at least 48 h apart. A 13th volunteer withdrew after two periods, having

been dosed with 25 IU IN insulin on two occasions. Data from all 13 subjects were analyzed.

In order to gauge the reproducibility of IN insulin administration, each volunteer was dosed twice into dominant and nondominant nostrils, respectively. The decision on which nostril was more patent (dominant) and which was less patent (nondominant) was made by the investigator and the subject together immediately prior to the time of dosing. The subject was asked to make a short, sharp inspiratory effort through each nostril while occluding the opposite nostril and keeping the mouth closed. The investigator and the subject then agreed by consensus which nostril was dominant. Depending on the degree of nasal congestion, the nondominant nostril was graded as being either mildly or moderately blocked. The study medication was presented as 25 IU spray (Nasulin) or 4 IU SC injection (Humulin S, Eli Lilly & Co., Dublin, Ireland). Each subject was given a single dose at approximately 0800h, after a 10 h overnight fast, and remained fasting until lunch, 4 h after dosing.

Previous studies with other IN formulations showed a fall in plasma glucose of 25–30% following doses of 0.8–1.0 IU/kg.[2–4] Two previous studies performed at Shandon Clinic with this IN insulin formulation indicated a bioavailability of between 10% and 20%, relative to SC injection.[1,5] In healthy volunteers, a dose of 25 IU (equivalent to 0.36 IU/kg for a 70 kg volunteer) resulted in a mean fall in plasma glucose of 20.5% (n = 11); this is similar to the fall that would be expected following a SC dose of 4–5 IU insulin and suggests better absorption than has been seen for other IN formulations.[2–4] Healthy volunteers were given doses of up to 37.5 IU; no volunteers experienced symptomatic hypoglycemia. For the 25 IU dose, subjects dropped their blood glucose level from a mean baseline of 86.6 mg/dl to 70.7 mg/dl, with three volunteers falling as low as 59.4 mg/dl. Based on this experience, it was believed that an IN dose of 25 IU would be sufficient to allow valid comparisons to be made between the study periods while remaining low enough to avoid exposing volunteers to any significant risk of hypoglycemia.

During each study period, 16 6.2 ml blood samples were drawn over 4 h, by means of an indwelling catheter, for analysis of plasma glucose and serum insulin and C-peptide levels. Sampling times were as follows: 5 min prior to dosing, 0 h (at dosing), 10, 15 , 20, 30, 40, 50 minutes, 1, 1.25, 1.5, 1.75, 2, 2.5, 3, and 4 hours after dosing (16 samples in each period). Blood glucose levels were also monitored throughout with glucometer readings (Accutrend®, Roche Diagnostics, Burgess Hill, UK). Full resuscitation facilities, including intravenous glucose, were available in the event of severe hypoglycemia. Subjects were given lunch 4 h after dosing; provision was made for a suitable snack (250 ml Lucozade [GlaxoSmithKline Consumer Healthcare, Weybridge, UK] and a digestive biscuit) to be given in the event of mild hypoglycemia.

Blood samples of 6.2 ml were aseptically aspirated, of which 1.2 ml was collected in a fluoride oxalate tube for the determination of plasma glucose. These samples were sent in batches to the Biochemistry Department of the Mercy Hospital in Cork, Ireland, for glucose determination using a hexokinase enzymatic method (Olympus Diagnostics GmbH, Hamburg, Germany). An additional 5 ml was collected into plain tubes (no anti-coagulant) and allowed to clot on the bench at room temperature for 30 min. The serum was separated and divided into duplicate labeled polypropylene tubes and stored upright at -70 °C before being sent to HFL, Fordham, Cambridgeshire, UK, for analysis of serum insulin and C-peptide. Serum samples were analyzed for insulin on an Abbott Axsym system using standard Abbott settings for this assay and using the Abbott Insulin kit. Serum samples were analyzed for C-peptide on a DPC Immulite system using standard DPC settings for this assay and using the DPC C-Peptide kit and calibrator. These assays were conducted according to Good Laboratory Practice procedures.

The comparative absorption of nasally administered insulin relative to SC insulin and at different stages of the nasal cycle was assessed by measuring serum insulin levels at predose and for 4 h postdose. Variables considered for insulin were the maximum measured concentration (C_{max}) during the selected sampling interval as a measure of absorption rate and the area under the plasma concentration time curve (AUC_{0-t}) to estimate the extent of absorption. The pharmacodynamic effect of insulin was assessed by measuring the fall in plasma glucose (%) and AUC_{0-t} during the sampling interval. Pharmacokinetic parameter calculations were conducted using Kinetica 2000® (version 4.4, Thermo Electron Corp., Waltham, MA). The AUC was calculated using a mixed-log linear rule. Statistical analyses were performed using SAS® version 9.1.3 (SAS Institute, Cary, NC).

Safety data were collected by regular nondirectional questioning of the study subjects and by direct reporting of adverse symptoms. In addition, volunteers were encouraged to make a spontaneous comment on the

IN dose at the time of dosing, and adverse experiences related to dosing were formally elicited at the 30 min time point by direct questioning. The study was conducted in accordance with the International Conference of Harmonisation Guideline for Good Clinical Practice (GCP), the recommendations of the World Health Organization, and the Declaration of Helsinki.

Results

Twenty-one volunteers were screened and 13 were included in the study. All were healthy Caucasian males aged 22.7 ± 2.8 years, with a BMI of 25.4 ± 1.7 kg/m^2. Twelve volunteers completed all five study periods; one volunteer withdrew for personal reasons after completing two periods of the study. Samples from all 13 subjects were analyzed. The lower limit of quantification for insulin was set at 1.0 μU/ml. The lowest reported concentration of insulin was 2.1 μU/ml, and the highest was 71 μU/ml. The lowest reported concentration of plasma glucose was 1.8 mmol/liter, and the highest was 5.3 mmol/liter.

There was marked variability in baseline plasma glucose and serum insulin both between subjects and between periods for the same individual. In order to facilitate comparisons between individuals and doses, all glucose and insulin results were adjusted for baseline before kinetic calculations were made. In each case, the mean of the -5 and 0 min results was considered to represent baseline; this value was subtracted from all subsequent results for that individual in that study period.

Serum insulin levels indicate that this IN formulation is well absorbed. Comparative pharmacokinetic data for single IN and SC doses of insulin are shown in **Table 1**. Absorption was rapid via the IN route, with peak serum levels reached after approximately 15 min; levels had returned to baseline after approximately 90 min. Insulin was absorbed more slowly after SC administration, with peak levels achieved after approximately 70 min and serum insulin remaining above baseline levels out to 4 h postdose. The extent of absorption in the 2 h period after dosing (AUC_{0-2}) was similar for both routes of delivery at the doses used in this study (**Table 1**; **Figure 1**). While both C_{max} and AUC were higher following administration via the nondominant nostril compared to the dominant nostril, this difference was not significant. On seven occasions, the IN formulation was administered into a nostril judged to be moderately blocked due to the presence of a mild upper respiratory tract infection; these cases resulted in lower C_{max} levels (14.33 ± 10.47 μU/ml).

Table 1.
Pharmacokinetic Parameters for Insulin in the Two Hours after Dosing (25 IU Intranasal Spray or 4 IU Subcutaneous Injection)[a]

Insulin administration	*n*	Pharmacokinetic parameters 0–2 h		
		C_{max} (μU/ml)	t_{max} (h)	AUC_{0-2} (μU/ml.h)
Dominant nostril (25 IU)	25	24.3 (12.4)	0.27 (0.11)	10.2 (6.2)
Nondominant nostril (25 IU)	24	30.3 (17.2)	0.25 (0.08)	14.3 (9.9)
SC injection (4 IU)	12	9.1 (2.4)	1.15 (0.44)	12.0 (3.5)

[a] Values are expressed as mean ± standard deviation

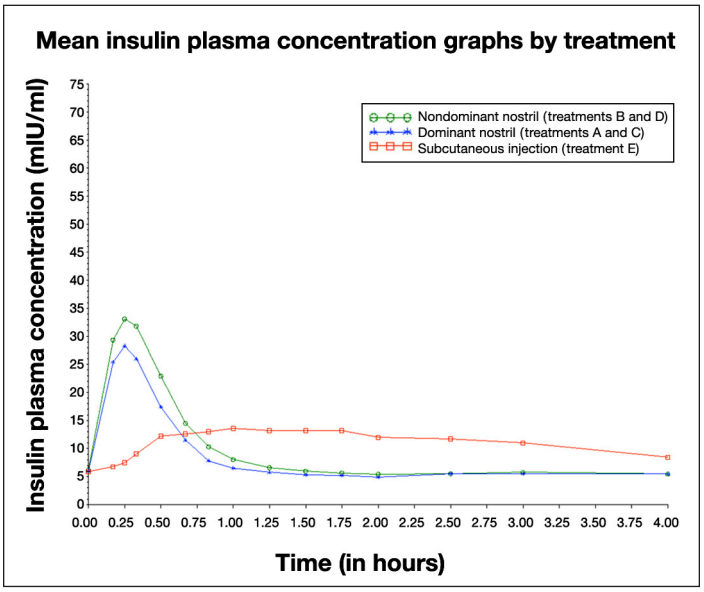

Figure 1. Mean concentration of serum insulin in 4 h following a single dose of 25 IU nasal spray in the dominant nostril (treatments A and C), 25 IU nasal spray in the nondominant nostril (treatments B and D), or 4 IU Humulin S by subcutaneous injection (treatment E).

As expected, the rise in serum insulin seen after dosing was associated with a fall in endogenous insulin production, seen as a decline in serum C-peptide levels. After both IN and SC delivery of insulin, C-peptide levels fell by approximately 50%; following IN insulin, the nadir was reached earlier, and levels returned to baseline sooner.

The pharmacodynamic effect of the absorbed insulin was demonstrated by a fall in plasma glucose levels (**Figure 2**). Blood glucose fell more rapidly following IN dosing; glucose nadir was reached at 50 min compared to 2.25 h following SC injection. Mean maximum percentage fall in glucose was similar for the nondominant nostril,

the dominant nostril, and SC injection at 21, 19, and 17%, respectively. Absolute values fell from a mean baseline of 84.1 mg/dl to a mean nadir of 69.0 mg/dl (nondominant nostril); on two occasions following IN dosing, subjects reached blood glucose levels below 40 mg/dl (the minimum value seen was 32.4 mg/dl). Data from the period in which subjects received SC insulin were compared to data from the four periods in which they received the IN formulation in order to calculate comparative absorption of the insulin spray. Average comparative absorption of Nasulin is shown in **Table 2**.

The IN insulin formulation was generally well tolerated. Two volunteers each had two adverse events that were considered to be possibly or probably related to the study medication. Volunteer 1 complained of tiredness on one occasion and felt "spaced out" (disorientated) on another. Volunteer 4 felt light-headed and, later the same morning, was found to be hypoglycemic. On direct questioning, the volunteers reported a number of IN symptoms in the 30 min period following dosing, in particular, sneezing, a running nose, watering eyes, and a stinging or burning sensation. While one or more of these symptoms were reported for approximately 25–40% of all IN doses given, they were transient (5–20 min) and mild in nature. Other symptoms reported less frequently by the subjects included tickling or tingling, irritation, and an unpleasant taste or smell. All of these symptoms were mild and resolved quickly. Adverse symptoms reported spontaneously at the time of dosing included slight stinging, tickling, or burning and an unpleasant smell. These symptoms diminished with continued administration through the course of the study so that only two of the eight volunteers given an IN dose in Period 5 complained of any ill effects at the time of dosing. No volunteer complained of discomfort at the SC injection site.

Table 2.
Comparative Absorption of Intranasal Insulin (25 U) over Time Relative to Subcutaneous Injection (4 U)

Insulin administration	Comparative absorption (mean %)	
	0–2 h	0–4 h
Dominant nostril	12.0%	7.5%
Nondominant nostril	15.4%	9.6%
Dominant nostril (adjusted)[a]	12.7%	7.9%
Nondominant nostril (adjusted)[a]	20.5%	11.9%

[a] Sneezers and volunteers with moderately blocked nostrils were removed from the data set. Analysis of variance model included blocked as a factor.

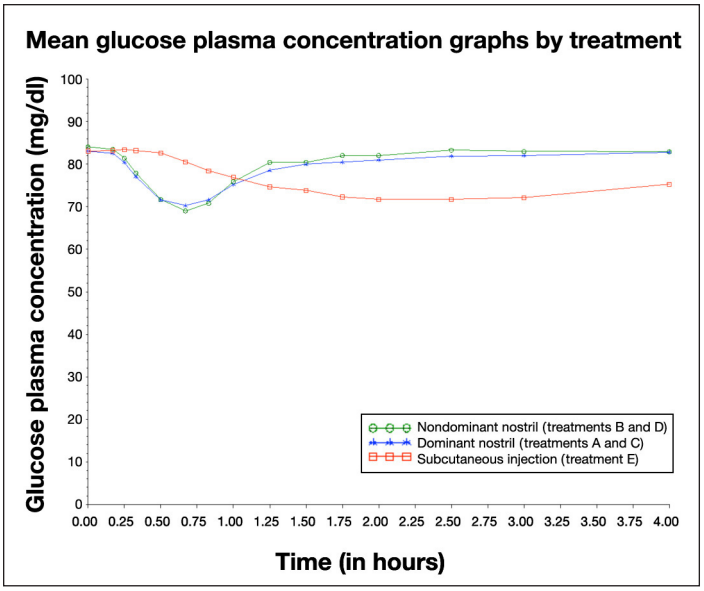

Figure 2. Mean concentration of glucose in plasma over 4 h following a single dose of 25 U nasal spray in the dominant nostril (treatments A and C), 25 U nasal spray in the nondominant nostril (treatments B and D), or 4 U Humulin S by subcutaneous injection (treatment E).

Discussion

For more than two decades, consideration has been given to the prospect of administering insulin via the nasal mucosa. The recent difficulties seen with inhaled insulin have served only to heighten the interest in this route of delivery. Advantages include convenience, potential for improving compliance, and needle avoidance for patients who require multiple doses of insulin but do not want to be provided with an implanted insulin pump. If the nasal mode of insulin delivery proves effective, it could serve as a reliable method for reducing postprandial blood glucose increases. A number of previous studies have been performed using IN formulations both in healthy volunteers[2–4,7–9] and in patients with type 1 and type 2 diabetes mellitus.[10–13] The development of a marketable formulation has been hampered by the poor bioavailability generally seen with this route of delivery and by local irritation caused by these formulations.

The bioavailability of intranasaly administered insulin without absorption-enhancing agents is only 1–2%. Even following the addition of absorption enhancers to the formulation, absolute bioavailability still remains low with most studies, indicating systemic absorption of no more than 10–15%.[14] A number of agents have been used as absorption enhancers in the development

of IN formulations over the past 20 years, including bile salts and derivatives, surfactants, fatty acids and derivatives, and various bioadhesive excipients. The nasal spray used in this study was composed of regular human recombinant insulin dissolved in sterile water in combination with Bentley Pharmaceuticals' proprietary excipient CPE-215. Previous exploratory studies in healthy volunteers and in patients with type 1 diabetes mellitus suggested that the Bentley Pharmaceuticals formulation exhibited an estimated relative bioavailability compared to SC insulin of approximately 15–20%.[1,5] The results of this study are consistent with previous studies with this formulation and confirm that the Bentley Pharmaceuticals formulation of insulin for IN administration is relatively well absorbed. This is illustrated by a rise in serum insulin levels and concomitant suppression of plasma glucose levels. The mean plasma glucose fall of 20% following an IN dose of 25 IU replicates what has previously been seen in healthy volunteers.[1] Absorption was rapid in comparison to SC insulin, with a concomitantly greater suppression of glucose seen in the first hour after dosing. Similarly, there was greater suppression of endogenous insulin production seen in the first hour after dosing (greater fall in C-peptide levels).

Insulin absorption is similar from either dominant or nondominant nostrils. Both insulin data (C_{max} and AUC) and glucose data (% fall and AUC) support a trend toward better absorption from the nondominant nostril, and it is possible that increased vascularity of the mucosa during the more blocked phase of the nasal cycle facilitates absorption of insulin administered via this route. The difference between dominant and nondominant nostrils did not reach statistical significance, however, and this study is too small to allow any firm conclusions to be drawn. Comparisons with SC insulin suggest that the relative absorption of the Bentley Pharmaceuticals formulation varies from 12 to 20% in 2 h after dosing. Once again, this is consistent with previous data from this formulation and compares well with data from other IN formulations.[5,14]

These data also suggest that moderate blockage of the nostril (e.g., due to an upper respiratory tract infection) or sneezing within 15 min of dosing result in somewhat diminished absorption. In each case, the numbers of volunteers tested was small, however, and the differences did not reach statistical significance. The study results do not support patients being instructed to increase the dose under these circumstances; a possible clinical implication would be to suggest that a patient should try to open a moderately blocked nostril by gently blowing the nose prior to dosing.

As reported by other authors and as was the case for previous studies with this formulation, the absorption of insulin following IN administration was variable. This was true both between individuals and within individuals using the same dose in the same nostril. Intersubject variability for IN dosing varied from 41 to 94%, depending on pharmacokinetic parameter and phase of the nasal cycle studied. Intrasubject variability was lower at 33–47%; whether this variability is likely to have a bearing on the performance of Nasulin in therapeutic use is unclear in the context of a product that is designed to be used a number of times each day, possibly for years.

It is acknowledged that this study has important weaknesses. First, as has been seen in previous studies with this (and other) formulation(s), the inter- and intrasubject variability of insulin pharmacokinetics following IN dosing is high. This means that a much larger study would be required in order to have statistical power to detect a true difference between dominant and nondominant nostrils. Even more subjects would be needed in order to confirm that no significant difference exists. The statistical power of this study was increased by the replicate dosing (twice in each nostril); nevertheless, the power of the study remains low. Second, the doses of insulin used in this study are lower than those that would generally be used by diabetes patients. It is uncertain whether higher doses given while applying the euglycemic clamp technique would have shown different results. Nevertheless, the relative absorption of insulin via the IN route shown here is consistent with the results of previous studies with the same formulation, which employed higher doses.[1,5] Two volunteers each dropped their blood glucose to below 40 mg/dl during one study period. While these volunteers remained asymptomatic, it is clear that choosing a higher dose might have compromised the safety of the volunteers.

Having said all this, it must be remembered that this study was designed from the outset to be no more than an exploratory pharmacokinetic investigation, and the data here provide ample information with which to design a subsequent pivotal study. These data are a significant addition to the body of scientific knowledge about Nasulin and about IN dosing of insulin in general. Finally, the main concern should remain whether or not any difference in choice of nostril is of clinical significance rather than statistical significance. Future studies aiming to answer this question should preferably include diabetes patients rather than healthy volunteers.

A number of volunteers experienced transient, mild, adverse nasal symptoms following dosing. These findings, which were in keeping with previous studies with this formulation and previously published studies with other IN formulations, were not consistently present with each dose and had generally resolved within 5–20 min. In general, however, the Bentley Pharmaceuticals IN insulin formulation appears to be well tolerated. Volunteers were not formally questioned about whether or not they would prefer the IN formulation to a SC injection; anecdotally, the majority expressed an opinion that the adverse symptoms experienced by some subjects at the time of dosing were not sufficiently troublesome to prevent them from using this therapy. This is consistent with the findings of a separate investigation in type 2 diabetes patients in which 62 of 69 subjects receiving Nasulin three times daily for three months completed the study (Clinigene, Bangalore, India; data on file at Bentley Pharmaceuticals). Examinations performed before and after that study showed no evidence of any inflammatory reaction in the nasal mucosa of patients. Furthermore, three-month toxicology studies performed in both rats and dogs at maximal doses did not reveal any inflammatory changes (Covance, Madison, WI; data on file at Bentley Pharmaceuticals). Only one subject developed symptomatic hypoglycemia during the course of this study. This subject's symptoms were mild and settled rapidly following the administration of oral glucose.

In conclusion, this study has shown that a Bentley Pharmaceuticals formulation of insulin designed for IN administration shows preliminary evidence of efficacy and appears to be well tolerated in healthy volunteers. While slight differences were seen with respect to dosing of Nasulin at different phases of the nasal cycle, these were not significant and do not warrant the adoption of any specific dosing instructions. This requires confirmation in a larger study involving diabetes subjects and using therapeutic doses of Nasulin.

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Disclosure:

Robert Stote is employed as a consultant to CPEX Pharmaceuticals, Inc.

References:

1. Leary AC, Stote RM, Breedt HJ, O'Brien J, Buckley B. Pharmacokinetics and pharmacodynamics of intranasal insulin administered to healthy subjects in escalating doses. Diabetes Technol Ther. 2005;7(1):124–30.
2. Drejer K, Vaag A, Bech K, Hansen P, Sørensen AR, Mygind N. Intranasal administration of insulin with phospholipid as absorption enhancer: pharmacokinetics in normal subjects. Diabet Med. 1992;9(4):335–40.
3. Haruta S, Hanafusa T, Fukase H, Miyajima H, Oki T. An effective absorption behavior of insulin for diabetic treatment following intranasal delivery using porous spherical calcium carbonate in monkeys and healthy human volunteers. Diabetes Technol Ther. 2003;5(1):1–9.
4. Paquot N, Scheen AJ, Franchimont P, Lefebvre PJ. The intra-nasal administration of insulin induces significant hypoglycaemia and classical counterregulatory hormonal responses in normal man. Diabete Metab. 1988;14(1):31–6.
5. Leary AC, Stote RM, Cussen K, O'Brien J, Leary WP, Buckley B. Pharmacokinetics and pharmacodynamics of intranasal insulin administered to patients with type 1 diabetes: a preliminary study. Diabetes Technol Ther. 2006;8(1):81–8.
6. Eccles R. A role for the nasal cycle in respiratory defence. Eur Respir J. 1996;9(2):371–6.
7. Newman SP, Steed KP, Hardy JG, Wilding IR, Hooper G, Sparrow RA. The distribution of an intranasal insulin formulation in healthy volunteers: effect of different administration techniques. J Pharm Pharmacol. 1994;46(8):657–60.
8. Nolte MS, Taboga C, Salamon E, Moses A, Longenecker J, Flier J, Karam JH. Biological activity of nasally administered insulin in normal subjects. Horm Metab Res. 1990;22(3):170–4.
9. Jacobs MA, Schreuder RH, Jap-A-Joe K, Nauta JJ, Andersen PM, Heine RJ. The pharmacodynamics and activity of intranasally administered insulin in healthy male volunteers. Diabetes. 1993;42(11):1649–55.
10. Pontiroli AE, Alberetto M, Secchi A, Dossi G, Bosi I, Pozza G. Insulin given intranasally induces hypoglycaemia in normal and diabetic subjects. Br Med J (Clin Res Ed). 1982;284(6312):303–6.
11. Moses AC, Gordon GS, Carey MC, Flier JS. Insulin administered intranasally as an insulin-bile salt aerosol. Effectiveness and reproducibility in normal and diabetic subjects. Diabetes. 1983;32(11):1040–7.
12. Salzman R, Manson JE, Griffing GT, Kimmerle R, Ruderman N, McCall A, Stoltz EI, Mullin C, Small D, Armstrong J, Melba JC. Intranasal aerosolized insulin: mixed meal studies and long-term use in type 1 diabetes. N Engl J Med. 1985;312(17):1078–84.
13. Sinay IR, Schlimovich S, Damilano S, Cagide AL, Faingold MC, Facco EB, Gurfinkiel MS, Arias P. Intranasal insulin administration in insulin dependent diabetes: reproducibility of its absorption and effects. Horm Metab Res. 1990;22(5):307–8.
14. Hinchcliffe M, Illum L. Intranasal insulin delivery and therapy. Adv Drug Deliv Rev. 1999;35(2-3):199–234.