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Influence of acute upper respiratory tract infection on the absorption of inhaled insulin using the AERx® insulin Diabetes Management System

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Aims
To assess the effects due to an uncomplicated acute upper respiratory tract infection (URTI) on the pharmacokinetics and glucose response of insulin when delivered by oral pulmonary absorption.

Methods
Normally healthy adult men (n = 11) and women (n = 9) received a single dose of inhaled human insulin, equivalent to ~6 IU subcutaneous, using the AERx® insulin Diabetes Management System (iDMS), during and following recovery from an URTI. The first dose was administered with ongoing symptoms of <3 days' duration, the second dose following recovery, and within 3 weeks of the first. Blood sampling for determination of insulin pharmacokinetics (serum $AUC_{(0–6\ h)}$, $AUC_{(0–8)}$, C_{max},t_{max}, $t_{1/2}$, MRT) and glucose response (plasma $AOC_{(0–6\ h)}$) was performed from 15 min predose to 6 h postdose.

Results
Insulin pharmacokinetics were not different for subjects during and following recovery from URTI [e.g. URTI: no URTI ratio in serum $AUC_{(0–6\ h)}$ = 0.92 (95% confidence interval 0.81, 1.05)]; this was reflected by a similar glucose response. Inhaled insulin delivered by AERx® iDMS was well tolerated by all subjects; no significant changes were observed in pulmonary function tests. No safety concerns arising from the mode of insulin administration were raised by either dose.

Conclusions
The results suggest that insulin can be administered via AERx® iDMS to nondiabetic subjects experiencing a URTI without any statistically significant changes in insulin pharmacokinetics or pharmacodynamics, and that the necessity for dose adjustments will not differ from subjects with an acute URTI who are receiving subcutaneous insulin.

Introduction

Maintenance of tight glycaemic control, which often involves intensive insulin therapy, has been shown to reduce the risk of a number of long-term complications associated with Type 1 and Type 2 diabetes mellitus [1, 2].

At present, subcutaneous (s.c.) administration of insulin is the only route of delivery for daily use in clinical practice. Although considerable advances have been made with insulin injection systems, the inconveniences of injections, and for many people, injection-related anxiety, often lead to poor compliance and suboptimal glycaemic control [3–5]. As a consequence, alternative, non-invasive routes of insulin administration (transnasal, oral, buccal, pulmonary) are currently being developed [6, 7] with pulmonary delivery systems being closest to reaching the market [7, 8]. The AERx® insulin Diabetes Management System (iDMS; hand-held device and disposable insulin strips, currently under codevelopment by Novo Nordisk A/S, Bagsværd, Denmark and Aradigm Corporation, Hayward, CA, USA) is one such system delivering orally inhaled insulin to the deep peripheral regions of the lungs. This consists of a microprocessor-controlled inhaler that releases a fine particle aerosol of aqueous insulin solution from a single-use insulin strip when the inspiratory flow rate and inhaled volume of the patient correspond to preset values that are optimal for deep lung delivery [9]. The date, time, breathing parameters during delivery and amount of insulin delivered are recorded electronically, allowing an assessment of dosage, breathing manoeuvres, and patient compliance.

A clear dose–response relationship between inhaled insulin doses and pharmacokinetic–pharmacodynamic parameters has been demonstrated for AERx® iDMS in patients with Type 1 diabetes [10]. Moreover, pharmacokinetic and pharmacodynamic profiles are similar to those seen with subcutaneously injected human insulin. Thus, from dose–response studies it is possible to equate a certain dose of inhaled insulin with that injected subcutaneously [11]. Certain situations, however, may alter insulin pulmonary absorption, thereby affecting its pharmacokinetics and pharmacodynamic response, as well as the correlation between inhaled and injected insulin doses. For example, insulin pulmonary absorption from AERx® iDMS is greater in smokers than in nonsmokers [12], but is lesser in nonsmoking nondiabetic subjects with mild to moderate asthma than in those without asthma [13]. In such diabetic patient populations therefore the dose of inhaled insulin would need to be adjusted accordingly.

Uncomplicated, acute upper respiratory tract infections (URTI – also referred to as a 'common cold') are expected to occur with a similar frequency in patients with diabetes mellitus as in the general population. Since these infections are commonly associated with complications of the upper respiratory airways (i.e. sore throat, cough [14]), it is important to assess whether an acute URTI alters the delivery of inhaled insulin as assessed by the time course of insulin plasma concentrations. This study was therefore conducted to investigate the pharmacokinetic and pharmacodynamic properties of inhaled insulin in otherwise healthy subjects during and following recovery from an URTI.

Subjects and methods

The study was approved by the Human Research Ethics Committee of the Royal North Shore Hospital, St Leonards, NSW, Australia and conducted at this site in accordance with ICH Good Clinical Practice guidelines and the Declaration of Helsinki [15]. Signed informed consent was obtained before any study-related activities.

Subjects

Twenty caucasian subjects (11 men and nine women, age range 18–44 years), with a body mass index (BMI) of 30 kg m^{-2}, body weight >60 kg, normal fasting blood glucose concentrations, no current or previous history of diabetes mellitus, and healthy apart from an ongoing URTI, participated in the study. They were nonsmokers for at least 3 years prior to the study, had a smoking history of no more than 7 pack-years [i.e. one pack (20 cigarettes) per day for 7 years], and had normal pulmonary function. A URTI was defined as the acute production of a significant degree of nasal mucus judged to be caused by a viral infection (excluding hay fever and allergic rhinitis), and was confirmed by one or several of the following criteria: subjective nonwell-being reminiscent of a viral infection (<3 days duration), an acute sore throat suggestive of a viral infection (excluding streptococcal pharyngitis), body temperature ≤38.5 °C, and a cough. Subjects were excluded from the study if they had any active, acute, chronic or history of pulmonary disorder (excluding an acute URTI or acute bronchitis). Five of the female subjects were taking concomitant oral contraceptives, and one female and one male were taking concomitant antipyretic analgesics. Subsequent analysis did not find that their results systematically differed from the remainder of the subjects and this aspect was not examined further.

Study design

The study was of an open-label, two-period crossover design. The study was powered on the primary endpoint,

i.e. area under the serum exogenous insulin profile from 0 to 6 h ($AUC_{(0–6\ h)}$). A sample size of 18 was calculated to detect a treatment difference of 20% with a power of 90%.

Subjects were trained with saline solutions in how to use the device before the study began. After an overnight fast, they received a single dose of inhaled insulin of 45 U (corresponding to ~6 IU of s.c. human insulin [9]) via AERx® iDMS while experiencing an URTI (of <3 days' duration) and a second identical dose upon symptomatic recovery from infection, and within 3 weeks of the first insulin dose. A post-trial safety follow-up visit was performed within 7 days of the last dosing visit. The AERx® iDMS (Novo Nordisk A/S; Aradigm Corporation) used was a representative handheld version prototype. Disposable insulin strips (Novo Nordisk A/S; Aradigm Corporation) contained a fast-acting human insulin inhalation solution (45 U per insulin strip).

Blood sampling and measurements

Blood sampling, for determination of insulin pharmacokinetics and pharmacodynamics, was carried out on both dosing days as follows: 15, 10, and 5 min predose, immediately prior to dosing, and at 5, 10, 15, 20, 25, 30, 40, 50, 60, 70, 80, 90, 100, 120, 140, 160, 180, 210, 240, 300, and 360 min postdose with an assay coefficient of variation ranging from 2.6 to 9.3% (highest to lowest; average 5.6%) over the insulin concentration range encountered. Serum insulin and C-peptide concentrations were measured using standard enzyme-linked immunoabsorbent assays (Dako, Ely, UK) at a central laboratory (Medi-Laboratory A/S, Copenhagen, Denmark). Plasma glucose concentrations were determined using an on-site Beckman Glucose Analyser II (Beckman-Coulter, Fullerton, CA, USA) with an average assay having a coefficient of variation of <1%.

Safety assessments

Adverse events were monitored throughout the study period. Treatment emergent adverse events (TEAEs) were defined as adverse events that occurred from the first dose of insulin to 7 days (inclusive) following the final dosing visit. Chest X-ray was performed at screening. Clinical laboratory assessments (haematology, biochemistry, and urinalysis), 12-lead ECG, physical examinations, pulmonary function tests [physical fitness tests (PFTs): forced vital capacity, forced expiratory volume in 1 s (FEV_1), and FEV%], and vital signs (blood pressure and pulse rate) were performed at screening and at the post-trial examination. Physical examinations, PFTs and vital sign assessments were again performed predosing and 6 h postdosing on the dosing days.

Calculations and statistical analysis

Pharmacokinetic endpoints [area under the serum exogenous insulin profile from 0 to 6 h, and that calculated from 0 h to infinity (respectively, $AUC_{(0–6\ h)}$ and $AUC_{(0–8)}$), serum maximum measured exogenous insulin concentration (C_{max}), time to serum maximum measured exogenous insulin concentration (T_{max}), terminal half-life and mean residence time of the serum exogenous insulin (respectively, $t_{1/2}$ and MRT)] were determined by standard methods [10]. For each subject, treatment, and time point, the exogenous insulin concentration was derived as:

$$\text{insulin}_{\text{exogenous}} = \text{insulin}_{\text{measured}} - (\text{insulin}_{\text{initial}}/\text{C-peptide}_{\text{initial}}) \times \text{C-peptide}_{\text{measured}}$$

where the initial insulin and C-peptide concentrations were calculated as the average of the measured values before dosing. The rate of insulin absorption was estimated by the initial (0–15 min) rate of increase of serum insulin concentration. The pharmacodynamic endpoint [area above the plasma glucose curve, but below the predose level, from 0 to 6 h ($AOC_{(0–6\ h)}$)] was determined from plasma glucose measurements. The trapezoidal method was used to calculate $AUC_{(0–6\ h)}$, $AUC_{(0–8)}$, and $AOC_{(0–6\ h)}$.

$AUC_{(0–6\ h)}$ was log-transformed, adjusted for sex, and analysed in an analysis of variance model with medical condition (URTI; no URTI) as fixed effect and subject as random effect. The difference between medical conditions was estimated and a 95% confidence interval (CI) calculated. The procedures were repeated for the other endpoints. A *post hoc* analysis using the homeostasis model assessment (HOMA) method [16] was used to assess insulin sensitivity during a URTI and following recovery. HOMA indices of insulin resistance were analysed in an ANOVA model with adjustment for sex.

Results

Twenty subjects (mean age 26 ± SD 7.8 years, mean BMI 24.5 ± SD 2.7 kg m^{-2}, mean weight 76.4 ± SD 13 kg) were enrolled and were included in the evaluation of safety. One subject was withdrawn from the study due to inappropriate inclusion. Another was excluded from the pharmacokinetic and pharmacodynamic analysis due to a defective insulin strip during a URTI (i.e. URTI, $n = 18$).

Mean exogenous serum insulin and mean plasma glucose concentration profiles are shown in Figure 1; pharmacokinetic and pharmacodynamic parameters are summarized in Table 1. Mean values for males and females were generally similar (results not shown).

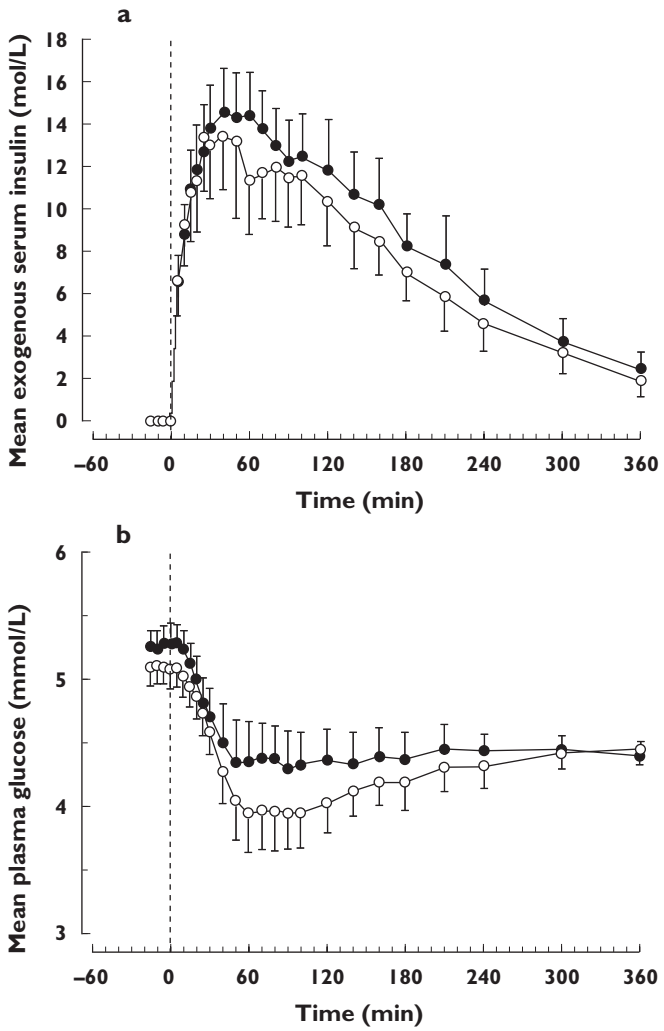

Figure 1

(a) Mean exogenous serum insulin profiles for subjects with an URTI and following recovery (No URTI). (b) Mean plasma glucose profiles for subjects with an URTI and following recovery (No URTI). Normally healthy volunteers received a single dose of inhaled insulin (equivalent to ~6 IU of subcutaneous human insulin) via AERx® iDMS during an URTI (closed circles) and following recovery (open circles). Each *point* represents the mean (± 2 × SEM), of 18 (URTI) or 19 (no URTI) subjects; the *dotted line* indicates the time of dosing (t = 0)

No significant difference in the primary endpoint, $AUC_{(0–6\ h)}$, was observed for the two medical conditions. Similarly, a URTI was also without effect on $AUC_{(0–8)}$, C_{max}, $t_{1/2}$, MRT, and the estimated rate of insulin absorption. Similar mean plasma glucose concentration profiles were observed during a URTI and following recovery, although a URTI was associated with slightly higher mean fasting plasma glucose levels and a partially reduced glucose response to insulin. However, mean plasma glucose $AOC_{(0–6\ h)}$ values did not differ significantly for subjects with or without a URTI. A *post hoc* insulin sensitivity analysis indicated that subjects were more resistant to insulin during a URTI; mean HOMA indices during a URTI and following recovery were 1.64 and 1.24, respectively [mean difference = 0.40 (95% CI 0.08, 0.71), $P = 0.017$].

Twenty-one mild to moderate TEAEs were reported (URTI, 10; no URTI, 11) in similar percentages of subjects (URTI, 30%, no URTI, 42%); fatigue (~15% subjects) was the most commonly reported TEAE. There were no clinically relevant changes in laboratory parameters, vital signs, pulmonary function tests, ECGs or physical examinations (apart from recovery from the URTI) during the trial.

Discussion

Due to the logistical difficulties in recruiting a cohort of patients with Type 1 diabetes mellitus with a URTI in an acceptable period of time, the study was performed in nondiabetic volunteers. With this study design, the subject, drug, and drug delivery methodology are inextricably linked so that generalizations about the same drug under other circumstances may be tenuous. Nevertheless, since patients with diabetes would be expected to be as susceptible to contracting a URTI as the general population, this study tested whether such an infection interferes with the delivery of orally inhaled insulin, and thus, whether a need for dose adjustments might be predicted. It found that a URTI did not significantly affect the delivery of orally inhaled insulin or the resultant glucose response, suggesting that insulin may be administered via AERx® iDMS to subjects experiencing an uncomplicated, acute URTI without additional dose adjustments other than those usually warranted during an infection.

Based on a number of pharmacokinetic and pharmacodynamic endpoints, this study demonstrated that a URTI was without a statistically significant effect on the pharmacokinetics of a single dose of inhaled insulin delivered by AERx® iDMS. Although these observations suggest that there is no effect on insulin absorption, dose adjustments may be necessary during a URTI in patients with diabetes. An increased frequency of blood glucose monitoring is recommended as part of routine sick day management [17], irrespective of the route of insulin administration, since the physiological response to a URTI may increase the risk of episodes of hyperglycaemia by inducing or worsening insulin resistance. Consistent with this, the present study showed that subjects with a URTI were more resistant to insulin than when they had recovered from infection. This *post hoc* analysis was used as confirmatory evidence that the subjects were unwell and were generally, rather than

Table 1
Pharmacokinetic and pharmacodynamic parameters following a single inhaled dose of insulin in healthy subjects with an upper respiratory tract infection (URTI) and following recovery

Parameter	URTI	No URTI	URTI/no URTI or difference (URTI – no URTI) (95% CI)	*P*-value
Serum insulin				
n	18	19	–	–
$AUC_{(0–6\ h)}$ (mU l^{-1} h^{-1})[a]	44.0	47.7	0.92 (0.81, 1.05)	0.21
$AUC_{(0–8\ h)}$ (mU l^{-1} h^{-1})[a]	50.7	54.9	0.92 (0.81, 1.05)	0.19
C_{max} (mU l^{-1})[a]	15.4	17.3	0.89 (0.72, 1.09)	0.24
T_{max} (min)[b]	59	80	– 21.5 (– 45.8, 2.87)	0.08
$Increase_{(0–15\ min)}$ (10–2 U l^{-1} min^{-1})[e]	3.6	3.9	0.92 (0.79, 1.08)	0.29
$t_{1/2}$ (min)[c]	94 (57)	104 (42)	–	–
MRT (min)[d]	190 (97)	188 (74)	–	–
Plasma glucose				
$AOC_{(0–6\ h)}$ (mmol l^{-1} h^{-1})[a]	4.71	4.57	1.03 (0.89, 1.20)	0.67

[a]*The estimated treatment means, ratios, confidence intervals (CIs), and* P*-value are based on analysis of variance with logarithmically transformed response and adjustment for sex.* [b]*The estimated treatment means, difference (URTI – no URTI), CIs, and* P*-value are based on analysis of variance with adjustment for sex.* [c]*Geometric mean (CV%).* [d]*Mean (SD).* [e]*Initial rate of increase in exogenous serum insulin levels in the first 15 min following inhalation.*

only locally, affected. The increased resistance observed during the URTI is likely to account for the slightly reduced, but statistically insignificant, glucose response to insulin. In normal subjects, the observed 24% increase in insulin resistance associated with a URTI did not significantly affect the pharmacodynamic response to insulin and was of no clinical significance. However, this may not be the case for subjects with diabetes mellitus, since in another study we observed that the 20% higher insulin resistance associated with women with gestational diabetes (compared with women of normal glucose tolerance) was clinically significant [18]. Obviously, further clinical experience is required in the management of patients with a URTI using AERx® iDMS, but this is expected to be gained from phase 3 clinical studies.

It is acknowledged that the hypoglycaemic response observed for nondiabetic subjects to inhaled insulin was not marked, and this expected response facilitated the study being performed without Biostator control. However, the dose given (corresponding to ~6 IU of s.c. human insulin) was sufficient to produce a significant pharmacokinetic–pharmacodynamic response and does not change the conclusions made for the primary pharmacokinetic endpoint. A s.c. insulin dose of 6 IU is within the normal range of doses given to Type 1 diabetic patients in a basal/bolus regimen. Therefore, it can be assumed that an equivalent inhaled insulin dose given to patients with Type 1 diabetes mellitus is sufficient to maintain near-normal glycaemia.

The AERx® iDMS is currently under development for the pulmonary delivery of insulin to patients with Type 1 and Type 2 diabetes mellitus. This investigation suggests that it is safe to use during a URTI. It is anticipated that patients will be able to continue use of AERx® iDMS during a URTI rather than switching to injected insulin, and without need for additional dose adjustments other than those usually warranted during an infection.

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