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Insulin inhalation with absorption enhancer at meal-times results in almost normal postprandial insulin profiles
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Summary
Background: Conventional insulin therapy with subcutaneous injections of regular insulin at meal-times result in plasma insulin peaks that are lower and appear later than meal related insulin peaks in healthy individuals. The present study was designed in order to evaluate the resulting insulin concentrations in peripheral blood after inhalation of microcrystalline human insulin together with an absorption enhancer [dioctyl sodium sulphosuccinate (DOSS)] via a powder inhaler.

Methods: Ten insulin dependent middle-aged non-obese diabetic patients (mean diabetes duration 21 years) were included. Blood samples for glucose and insulin were taken immediately before and 13 times, up to 300 min, after insulin inhalation. The mass median aerodynamic diameter of the particles was 3–2 μm. The inhaled insulin dose was 39 U.

Results: Within 5 min after the end of the 2 min inhalation procedure the mean increase of insulin was 7–0 μU ml⁻¹, and the mean maximum concentration, 12–1 μU ml⁻¹, was reached between 20 and 30 min. There was then a slow decline until base-line was reached after around 210 min and there were no adverse events.

Conclusions: Inhalation of a mixture of 39 U of insulin and enhancer resulted in a rapid plasma insulin peak with a slow decline, similar to the normal postprandial insulin profile.

Introduction
Although subcutaneous insulin therapy has been used for almost 80 years, it is well known that the resulting insulin concentration profiles are far from those seen postprandially in normal individuals. In healthy persons, breakfast, lunch or dinner will induce a marked 5–10 fold increase of the plasma insulin concentration from base-line within 30 min. Within 1 h, insulin will drop to considerably lower levels, and within 2 h it is rather close to base-line again (Olsson et al., 1986) (Fig. 1).

Subcutaneously administered regular insulin, on the other hand, results in considerably slower and lower peaks, usually after more than 1 h (Galloway et al., 1981). New insulin analogues try to overcome this, but still the resulting insulin profiles are not close to those seen normally. This means that conventional insulin therapy never will be quite adequate when given just before meals, causing a relative hypoinsulinaemia immediately after the meal and a relative hyperinsulinaemia some hours later. Thus, even when multiple mealtime insulin injections are given, only rarely the patient may reach a normal blood-glucose profile and HbA1C.

To overcome this, a variety of other methods of administration have been used. Among those are nasal and oral inhalations of insulin. In addition, both ways avoid the pain and discomfort of skin penetration by the insulin injection needle, which is feared by some diabetic patients. At the same time the absorbing capillary surface area is increased, compared with the very small surface area that a conventional subcutaneous insulin injection dose faces.

The nasal mucosa offers a large surface area for the insulin molecules to reach the systemic circulation. Even greater surface area is found in the lungs, where some 300 millions of alveoli constitute a capillarized area of around 100 m². Pulmonary administration of insulin (Gaenssler, 1925) thus has been tried in dogs already shortly after the introduction of insulin injections in 1922, and later several, often small studies in humans have been reported (Wigley et al., 1971; Elliot et al., 1987; Almér et al., 1988; Laube et al., 1993, 1998; Jendle & Karlberg, 1996; Heinemann et al., 1997, 2000; Skyler et al., 2001; Cefalu et al., 2001). Although the feasibility of pulmonary administration of insulin has been well proven, all studies so far show very limited bioavailability of the inhaled insulin.

As insulin is expensive, it is important to increase the efficacy of the inhaled insulin dose in order to reduce the costs. To attain
this an absorption enhancer may be added. Reports on absorption enhancers (Creasia et al., 1988; Heinemann et al., 2000) have been published. These enhancers, facilitating the absorption of the inhaled insulin from the alveoli membranes to the pulmonary capillaries, may also further improve the plasma insulin profiles, causing even more physiological levels compared with inhaled insulin without enhancer.

Administration of the detergent dioctyl sodium sulphosuccinate (DOSS) in aerosol form has been shown to increase the absorption of solutes from the peripheral parts of the lung to the blood in experimental systems (Evander et al., 1988, 1994). The rate of absorption of small, hydrophilic solutes, such as $^{99m}$Tc-DTPA (diethylene triamine pentaacetate, mw 490 dalton) increases dramatically by administration of the detergent, and the rate of absorption of albumin (mw 69 kilodalton) is affected in a qualitatively similar way, but to a smaller extent (John et al., 1997). Increased absorption of inhaled insulin by the addition of surface active agents has recently been demonstrated in experimental animals (Dahlbäck et al., in press).

Administration of DOSS to experimental animals increases the rate of solute absorption without adversely affecting lung function as measured by the compliance of the respiratory system or gas exchange (Evander et al., 1994; John et al., 1997).

The present study was designed in order to evaluate the resulting insulin concentrations in peripheral blood after inhalation of microcrystalline human insulin together with the absorption enhancer DOSS via a powder inhaler, in insulin dependent diabetic patients.

Methods

Patients

Ten insulin dependent non-obese diabetics, four women and six men, aged 39–70 years, and with a mean diabetes duration of 21 years (range 4–33 years) were included in the study. Two had never smoked, five had stopped smoking several years ago, and three were still smokers. Eight patients were taking regular insulin three times daily at meal times and Neutral Protamine Hagedorn (NPH) insulin at bed-time, while two were on one or two NPH insulin injections daily.

The mean fasting blood glucose level, 16.9 mmol l$^{-1}$, indicates low and insufficient insulin levels from the bedtime NPH insulin injection, taken the night before.

Written informed consent was given by the patients after explanation of the study procedures. The study was approved by the Local Research Ethics Committee and was carried out according to the principles of the Declaration of Helsinki.

Protocol

The patients were asked not to inject insulin in the morning before the inhalation of insulin. The patients were fasting when they arrived at the Clinical Research Unit, Department of Medicine, University Hospital of Malmö. They all had a physical examination, and then venous blood samples for glucose and insulin were taken immediately before the insulin inhalation, and after the inhalation at 5, 7, 10, 15, 20, 25, 30, 45, 60, 120, 180, 240 and 300 min. Free insulin was analysed with RIA method (Pharmacia, Uppsala, Sweden). The insulin preparation was prepared as a dry powder from microcrystalline human regular insulin, mixed with DOSS in weight relation 2:1, based on experience from animal experiments. Lactose was added (insulin 40 mg, DOSS 20 mg, lactose 940 mg) before it was placed in a powder inhaler. Every inhalation from this inhaler gave 100 µg insulin, and all patients took each 15 inhalations, 1500 µg, approximately 39 U of insulin. The mean particle diameter was below 4 µm, in order to avoid impaction in the upper air passages and to increase the amount reaching the peripheral lung units. All patients were able to inhale the insulin dose within 2 min.

Results

All but one of the 10 patients showed a rapid elevation of the insulin concentration already within 5 min after the end of the 2 min inhalation. At this time the mean increase of insulin was 7.0 µU ml$^{-1}$, corresponding to 58% of the mean maximal peak (12.1 µU ml$^{-1}$) (Fig. 2). At 10 min 88% of the mean maximum was achieved, and at 15 min 98%. The mean maximum concentration (12.1 µU ml$^{-1}$) was reached between 20 and 30 min after the end of the inhalation. There was then a slow decline from 45 min onward, until around 210 min after the inhalation, when the concentration was back at baseline level.

The remaining effect of the night time NPH insulin injection given the evening before was assumed not to improve the configuration of the insulin curve after insulin inhalation.

The blood glucose fell from a mean fasting level of 16.9 mmol l$^{-1}$ to 13.1 mmol l$^{-1}$ after 5 h, a mean fall of 3.8 mmol l$^{-1}$. Because of the high fasting blood glucose levels all patients but one did not receive any breakfast. The only patient with a normal fasting blood glucose level (4.2 mmol l$^{-1}$) received a standardized breakfast (170 ml of milk and a crisp bread sandwich) in order to avoid
hypoglycaemia. He had a normal, almost flat glucose profile after insulin inhalation and breakfast, with a peak at 5.7 mmol l\(^{-1}\) at 30 min and 4.6 mmol l\(^{-1}\) after 5 h, exactly as seen in healthy individuals.

There were no adverse reactions to the inhalations, such as cough or hypoglycaemia, during the study.

**Discussion**

In healthy individuals it has been shown that the postprandial insulin peak comes quickly and is initially achieved by the release of prefabricated insulin within the beta cells. Most of the insulin will be released during the first hour, when the food and drinks are being absorbed. The postprandial insulin concentrations in healthy individuals are related to the absorption of nutrients from the small bowel, which in turn is related to the motility of the stomach, and the type of food ingested. Thus, there is a wide variation in the shape of physiological insulin profiles. However, studies have shown (Olsson et al., 1986) that already at the end of a mealtime (breakfast, lunch or dinner) insulin has reached its maximum peak, and the insulin concentration then quickly falls, in relation to the amount and type of nutrients in the food. Both type 1 and type 2 diabetic patients would benefit from an insulin preparation that is quickly absorbed and mimics the physiological insulin profiles with rapid insulin concentration elevation after the onset of a meal and then a rather swift lowering of the insulin concentration down to baseline before next meal as shown by Bruttomesso et al. (1999). So far, insulin therapy has almost exclusively been given by subcutaneous injections. However, because of slow subcutaneous absorption only a small fraction is released to the blood during the first hour and the peak is generally delayed until more than 90 min after injection.

Absorption of solutes from the peripheral lung units varies both physiologically and in disease states. The rate of absorption of \(^{99m}\)Te-DTPA has been studied extensively in a wide variety of conditions. The rate of absorption increases with increased lung volume, e.g. when ventilation increases during exercise.
curves, which is not the case of insulin injections. One advantage of a more physiological plasma profile of insulin may be reduced postprandial hypoglycaemia. Insulin inhalations are also more convenient than injections.

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