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The Distribution of an Intranasal Insulin Formulation in Healthy Volunteers: Effect of Different Administration Techniques

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Abstract—The initial deposition pattern in the nasal passages and subsequent clearance of an insulin formulation labelled with ^{99m}Tc-human serum albumin have been determined in 12 healthy male volunteers. Four different administration modes from a novel aqueous spray device were compared, involving delivered volumes of 80–160 μL, and with either gentle or vigorous inhalation while firing the device. The entire dose was deposited in the nasal cavity, and no significant radioactivity was deposited in the lungs. A mean 25–33% of the radiolabel remained in the nose after 4 h. A significantly smaller area of the nasal mucosa was covered by the smallest (80 μL) bolus, but subsequent clearance rates did not vary significantly with mode of administration. Blood glucose levels fell after administration of the insulin formulation, but no serious episodes of hypoglycaemia occurred.

Drugs may be administered to the nasal passages not only for topical treatment (Mygind & Weeke 1985), but also for delivery to the systemic circulation (Harris 1993). The nasal route is potentially valuable for drugs which are normally given parenterally, including a range of peptides and proteins such as insulin, calcitonin and desmopressin (Pontiroli et al 1982; Harris et al 1986; Chien 1985; Su 1991). The nasal cavity is a useful site for drug absorption because it is highly accessible to sprays and drops, there is a large surface area (ca 150 cm^2) through which absorption can occur, the nasal mucosa is highly vascularized, and venous blood passes directly into the systemic circulation, thereby avoiding first-pass metabolism in the liver.

The conventional treatment of diabetic patients with insulin requires that they are given daily parenteral injections. This is not an ideal situation, since these injections may cause local discomfort and local fat loss, and may adversely affect the patient's quality of life (Flier et al 1985). Attempts to develop alternative non-parenteral routes have been made over many decades; insulin was given by inhalation when Heubner & Laquer (1924) reported a lowering of blood glucose levels in diabetics following inhalation of insulin. When delivered intranasally, insulin is rapidly acting, but the formulation may require the presence of an appropriate absorption enhancer in order to produce clinically therapeutic insulin levels and hence a reduced blood glucose content (Hirai et al 1981; Moses et al 1983; Kennedy 1991). A novel insulin formulation for nasal inhalation has been developed recently, and has been shown in early clinical trials (Drejer et al 1992) to attain a maximum effect after 45 min, with a duration of action of 120–140 min. This formulation is delivered via a pump spray device with an adjustable dose volume. The objective of the present study was to examine the initial distribution and subsequent clearance of the components of an insulin formulation from the nasal cavity following delivery by four different administration techniques, and also to determine whether any of the preparation was delivered directly to the lungs.

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Materials and Methods

Formulation

The nasal insulin formulation (Novo Nordisk A/S, Denmark) was dispensed in a nasal spray, containing 3 mL solution, and incorporating a dial-a-dose mechanism which could be adjusted to deliver between 40 and 140 μL solution containing 20–70 int. units of insulin. The solution concentration was 500 int. units mL^{-1} biosynthetic human insulin (Novo Nordisk A/S, Denmark). The formulation also contained glycerol, didecanoyl-L-α-phosphatidylcholine, cholesterol and fractionated coconut oil (Drejer et al 1992). ^{99m}Tc-Labelled human serum albumin (HSA, Solco) was added to the formulation in a concentration of 0·5 mg mL^{-1}, and inhalers were prepared for individual subjects on each study day, such that the total volume due to be delivered into the nose (80–160 μL) contained approximately 1 MBq ^{99m}Tc at the time of dosing.

Study design

The scintigraphic study was an open randomized cross-over trial, with dosing carried out on four occasions each separated by a minimum of six days. Twelve healthy male subjects (age range 19–30 years, heights 1·68–1·86 m, weights 58–82 kg) took part in the study. Each subject underwent a medical examination, which included haematology, clinical chemistry and urinalysis within 14 days of entering the trial. Subjects were excluded from the study if medical screening revealed the presence of any nasal abnormality (such as deviated nasal septum or nasal polyps) or of nasal disease (such as allergic rhinitis). Subjects with any known allergy to insulin, or who had had a

recent upper or lower respiratory tract infection, were also excluded. Blood screening and urinalysis were repeated within 14 days of the last study day. The study was approved by the Quorn Research Review Committee, Leicestershire, UK, and permission to administer the radiolabelled preparation intranasally was obtained from the Department of Health, London. Subjects were given an information sheet describing the procedures before being asked for their written consent in the presence of a witness.

On each study day, subjects attended the clinic in the non-fasting state. Before dosing, subjects were asked whether they had experienced any recent symptoms that might influence absorption of the drug (e.g. upper respiratory tract infection) and if such symptoms were present, the study was deferred. An intravenous cannula was inserted into a forearm vein for blood sampling, and for administration of glucose should symptoms of hypoglycaemia occur or should the blood glucose fall below 3·0 mM. Thirty minutes before dosing, subjects began a carbohydrate-rich meal, which was consumed within 15 min, to minimize the possibility of any serious hypoglycaemic events occurring. Subjects were allowed to consume as much food as they required, and subsequently took a second meal between 180 and 210 min post dose.

Modes of administration

The administration technique was as follows. With the device at an angle of approximately 45° to the vertical, the nozzle was held at an angle of approximately 5° to the sagittal plane, pointing slightly towards the nasal septum, and was introduced as far as possible into the nostril without causing pain. The insulin was administered by the subject by pulling the trigger device down and forward whilst sniffing either gently or vigorously, as described in Table 1. The device was held in place with the one hand, and was actuated with the other hand.

The subjects had practised on a previous day with a placebo-filled inhaler after watching an instructional video, and also practised with an air-filled placebo immediately before dosing. The devices were weighed before and after dosing in order to check that the required volume had been delivered. The nose was blown gently before administration. The protocols used in the study are shown in Table 1.

Table 1. Mean (s.d.) dose weights, number of pixels on the initial lateral view of the head within the 5% contour, and the percent of the dose within the nose at fixed times after dosing. Data are shown for four administration techniques: A = 70 int. units insulin inhaled by a gentle sniff into the right nostril; B = 70 int. units insulin inhaled by vigorous sniffing into the right nostril; C = 40 int. units insulin inhaled by a gentle sniff into the right nostril; D = 80 int. units insulin inhaled as 40 int. units by a gentle sniff into each nostril.

Administration technique	A	B	C	D
Dose weights (mg)	130 (19)	134 (17)	71 (12)	155 (15)
Pixels	197 (47)	233 (137)	145 (36)*	216 (42)
% in nose immediately after dose	100	100	100	100
% in nose after 35 min	62 (24)	50 (24)	67 (26)	66 (20)
% in nose after 65 min	52 (25)	42 (27)	59 (26)	54 (24)
% in nose after 125 min	40 (25)	34 (26)	47 (32)	45 (25)
% in nose after 245 min	27 (22)	25 (22)	33 (28)	29 (16)

*$P < 0.01$ compared with techniques A and D; $P < 0.05$ compared with technique B.

Scintigraphic measurements

Scintigraphic measurements were taken after dosing, with the subjects placed in a reproducible position in front of an IGE Maxi-camera coupled to a Bartec data processing system to give a background view of the lung fields (image duration 180 s) immediately before dosing; a lateral view of head and neck (image duration 60 s) immediately after dosing; anterior and posterior views of the chest (image duration 180 s) immediately after recording the lateral view of head and neck; and further views of head and neck and further anterior and posterior views of the chest after 35, 65, 125 and 245 min.

The geometric mean of the count rates from the anterior and posterior views was determined. Count rates were corrected for background radiation and for radioactive decay. The percentages of the dose in nasal cavity and lungs were determined immediately after dosing and then 35, 65, 125 and 245 min later. To obtain a measure of the area of the nasal cavity on which the formulation was deposited, the number of picture elements (pixels) within the 5% contour on initial views of nasal cavity, i.e. within a contour denoting 5% of peak activity, was also determined.

Nasal retention data and the number of pixels within the 5% contour in the initial nasal view were compared amongst the four study days using the Friedman two-way analysis of variance by ranks. Where a significant difference was observed, pairs of data were compared using the Wilcoxon matched-pairs, signed-ranks test (Siegel & Castellan 1988).

Blood sampling

Samples containing 3 mL whole blood were withdrawn via the indwelling cannula at 30 and 5 min before the dose, and at 10, 15, 20, 25, 30, 45, 60, 75, 90, 120, 150, 180, 210, and 240 min post dose. From each sample, < 50 μL was taken for an immediate determination of blood glucose using an Exactech meter (MediSense UK). The remainder was centrifuged and the plasma stored at −20°C for subsequent analysis of plasma glucose should any serious hypoglycaemic episodes occur. Subjects were discharged from the study site providing that they felt well and that the blood glucose had been checked at least three times in the previous hour, with its value remaining stable above 4·5 mM. Since the subjects' diets were not controlled, the blood glucose data were obtained for safety purposes only, and no attempt was made to correlate blood glucose with the nasal deposition and clearance.

Results

Analysis of the scintigraphic data showed that the entire dose from the pump spray device was deposited in the nasal cavity. No tracer was detected in the lungs in any of the 48 individual studies. The initial chest views sometimes showed the presence of radioactivity, but this was restricted to the oesophagus and stomach, and represented material deposited in the posterior part of the nasal cavity that had been cleared rapidly to the nasopharynx by the mucociliary

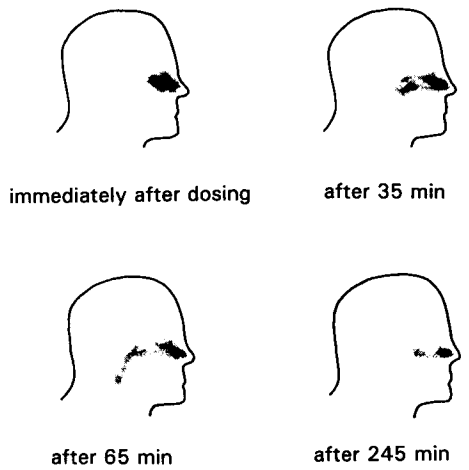

FIG. 1. Scans from one individual showing the initial distribution of the formulation in the nose and subsequent clearance into the nasopharynx for administration technique B.

mechanism. Typical examples of initial deposition and subsequent clearance are shown in Figs 1 and 2 for administration techniques B and C, respectively.

Nasal clearances for the four administration modes were similar. There was a trend towards a greater percentage clearance from the nose at each time point for regimen B, but this was not statistically significant (Fig. 3, Table 1). The number of pixels within the 5% contour on the initial nasal views (Table 1) was significantly smaller for administration technique C (80 μL) compared with the three other administration techniques containing larger bolus volumes (A: $P < 0{\cdot}01$; B: $P < 0{\cdot}05$; D: $P < 0{\cdot}01$). The dose weights (Table 1) were close to the nominal values.

Blood glucose using the Exactech meter (Fig. 4) rose after the subjects took food and fell after insulin administration. The changes in blood glucose were similar for each of the inhalation modes. Three subjects (one each with regimens B, C and D) experienced mild symptoms compatible with hypoglycaemia after dosing with the intranasal insulin

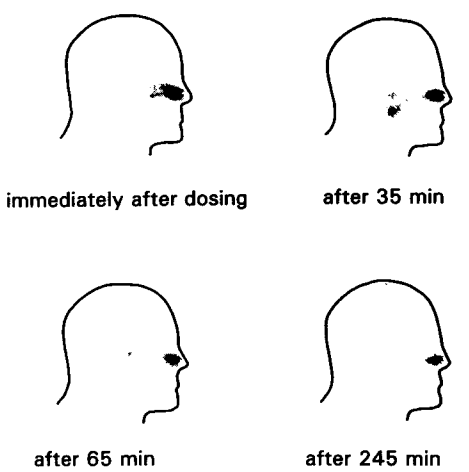

FIG. 2. Scans from one individual showing the initial distribution of the formulation in the nose and subsequent clearance into the nasopharynx for administration technique C.

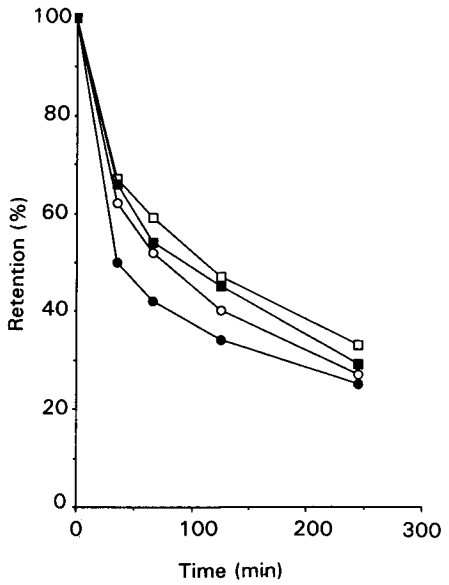

FIG. 3. Mean percentage retention of radiotracer in the nose for the four administration modes. ○ A, ● B, □ C, ■ D.

preparation, but these responded to oral glucose or sugar-containing drinks and confectionery. In none of these individuals did the blood glucose level as measured by the Exactech meter fall below 3·0 mM. There were no instances in which either the fall in blood glucose or the clinical symptoms warranted intravenous glucose infusion.

Discussion

The primary objective of this study was to determine the initial deposition site and subsequent clearance pattern of the insulin formulation. The entire dose from the insulin spray was deposited in the nasal cavity. The finding of no detectable lung deposition is not surprising, since it concurs with the findings of earlier studies for sprays inhaled intranasally from both a pressurized metered dose inhaler (Newman et al 1987a) and an aqueous pump device (Newman et al 1987b). Owing to the mechanical action used to generate the aqueous spray, the droplets produced are likely to be too large for inhalation into the lungs, with a

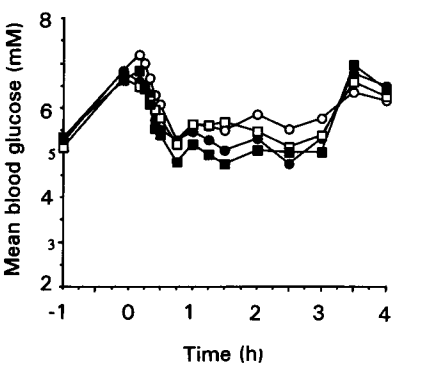

FIG. 4. Whole blood glucose values at various time points for the four administration modes. ○ A, ● B, □ C, ■ D.

mass median diameter > 50 μm, and with less than 5% of the drug mass contained in droplets smaller than 10 μm (Petri et al 1985; Newman et al 1987b). Additionally, the nose is a very efficient aerosol filter, capable of removing both respirable and non-respirable droplets from the inhaled air (Heyder & Rudolf 1975).

It is not common practice in scintigraphic studies to chemically radiolabel the drug substance, since it is difficult to find radionuclides for this purpose with appropriate decay properties. In this study, the formulation was radiolabelled by the addition of ^{99m}Tc-HSA, such that the droplets in the nasal spray contained both drug and radiolabel. This enabled the initial distribution pattern to be determined, although subsequent scans reflected primarily the mucociliary clearance of the poorly absorbed ^{99m}Tc-HSA marker rather than the clearance of the drug substance. The clearance curves give important information about the initial fractionation of the dose between the ciliated and non-ciliated portions of the nasal cavity. Much of the material was deposited posteriorly on the ciliated portion of the nasal cavity and underwent rapid clearance to the nasopharynx, with long-term retention of a small portion of the dose in the anterior part of the nose, which is non-ciliated (Proctor 1982, 1985). This pattern of clearance has been noted before in studies on other nasal spray devices (Hardy et al 1985; Newman et al 1987a,b).

The similarity of the clearance curves on the four study days suggests that the fractionation of the formulation between the ciliated and non-ciliated regions did not vary significantly with the administration technique. However, the smallest bolus volume of 80 μL given into a single nostril was distributed over a significantly smaller area (measured in terms of gamma camera pixels) of the nasal mucosa compared with the larger volumes delivered on other study days. A total delivered volume of 160 μL given as 80 μL into each nostril gave a coverage of the nasal mucosa similar to that of 140 μL in a single nostril. Increased bioavailability of desmopressin was reported when the drug was given as two doses each of 50 μL, compared with a single dose of 100 μL, with consequent improved biological responses (Harris et al 1988). By contrast, Newman et al (1987b) observed that a single puff of 100 μL was deposited over a greater area than two puffs of 50 μL, while Bond et al (1984) could not detect any dependence of the deposition and clearance of ^{99m}Tc-HSA on the metered volume of the nasal spray. No previous data exist regarding the effect of different inhalation techniques on the delivery of a nasal aqueous spray, but the data in this study suggest that the deposition patterns were essentially independent of whether the subjects took a gentle or a vigorous sniff. There were wide differences between individuals in the initial deposition patterns and in subsequent clearance rates, even when the inhalation manoeuvres and bolus volumes were carefully controlled.

In conclusion, the distribution of the formulation of insulin in the nasal passages varied according to the bolus volume, but was not significantly affected by the inhalation manoeuvre. None of the formulation reached the lungs. The future potential for the delivery of insulin by the nasal route depends upon the development of effective and well-tolerated formulations, containing safe absorption enhancers, delivered accurately to the nasal passages (Harris 1993).

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