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Nasal distribution of budesonide inhaled via a powder inhaler*

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SUMMARY

The distribution pattern of budesonide in the nasal passages and lungs was investigated in 10 healthy subjects after nasal inhalation. The subjects inhaled drug powder, radiolabelled with ^{99m}Tc, at maximum flow rate (46.3±6.8 l/min) and at 29.9±2.5 l/min via Turbuhaler®. At both flows, the majority of the dose was deposited in the anterior part of the nasal cavity on a single, rather localized area, but some particles also penetrated more posteriorly into the main nasal passages and to the lungs. At maximum flow rate, the nasal deposition was 65.2% (range 39.5–84.1%) and the lung deposition 4.7% (range 1.4–9.3%) of the metered dose, and at 30 l/min, the nasal deposition was 67.6% (range 49.7–81.6%) and the lung deposition was 4.2% (range 1.7–7.9%). A large fraction of the metered dose was deposited in the nasal adaptor of the inhaler during the administration (mean values 29 and 28%, for the two inhalation flows). Of the dose actually reaching the subject, 91 and 93% (mean values) was deposited in the nose. There were no statistically significant differences in distribution pattern between the two inhalation flows.

Key words: nasal drug delivery, budesonide, allergic rhinitis

INTRODUCTION

Administration by means of pressurized metered-dose inhalers (MDI) and aqueous pump sprays are hitherto common ways of nasal drug delivery. Previous studies using radiolabelled particles delivered intranasally from MDI's (Newman et al., 1987a) and aqueous pump sprays (Newman et al., 1987b) have shown that the major portion of the dose from these two devices is deposited in the anterior part of the nasal cavity, with some penetration to the more distal parts but with no detectable deposition in the lungs. However, some deposition of drug in the lungs was seen when the inhalation was made from an MDI via Nebuhaler®, a pear-shaped spacer (Morén and Newman, 1990).

A new device, Turbuhaler® (Astra Draco, Sweden), has been developed for topical application of dry powder budesonide. Budesonide, delivered as pure powder from this multi-dose dispenser, has been shown to be effective and safe for the treatment of seasonal allergic rhinitis (Pedersen et al., 1991). The aim of the present study was to elucidate the distribution pattern of ^{99m}Tc-labelled budesonide after nasal inhalation with this device at different flow rates.

METHODS

Ten healthy, non-smoking subjects participated in the study (two males, eight females, age range 21–38 year). The study was approved by the Local Ethics Committee and the Administration of Radioactive Substances Advisory Committee. The trial was performed in accordance with the Declaration of Helsinki. All subjects were healthy as judged by routine medical examination, including blood chemistry tests and haematology, and all were free of upper respiratory tract infections. The subjects gave their informed consent in writing before commencing the study. No medication apart from the study drug was taken during any study day. The subjects were asked to adhere to their normal prandial and everyday habits, but they were not allowed to drink alcoholic beverages for 24 h preceding or during each experimental day.

The radiotracer method for labelling of budesonide involved extraction of the radionuclide ^{99m}Tc into methylethylketone (MEK), subsequent evaporation of the MEK and addition of the radiolabel to the budesonide powder in an aqueous medium. The water in which ^{99m}Tc was added to the budesonide powder was then evaporated by freeze-drying. This method is not a chemical labelling of budesonide, but merely an addition of label to powder. Thus, the radiolabel acts as a marker for the presence of drug *in vivo*. Accordingly, 50 mg of micronized budesonide was labelled with ^{99m}Tc and filled into Turbuhaler,

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delivering a nominal dose of 200 μg of budesonide together with approximately 1 MBq ^{99m}Tc. The inhalers were equipped with a nasal adaptor, fitted with an insert with spiral-shaped channels. The metered dose (i.e., the dose leaving the dosing unit), based on radioactivity, was calculated from calibration doses using probe scintillation counters. The metered dose was fractioned into percentages found in adaptor, nasal cavity, lung, and exhaled air. The delivered dose (i.e., the dose actually reaching the subject) was calculated by subtraction of the fraction found in the nasal adaptor from the metered dose. The radioactive measurements were performed with a gamma-camera (Ohio Nuclear 110), connected on-line to a Nuclear Diagnostic data-processing unit. The actual inhalers used in the study were subsequently analyzed by Andersen sampler regarding the distribution of chemical budesonide activity in different particle-size fractions. The deposition data were compared with those of a reference inhaler, containing the original batch of unlabelled budesonide.

The subjects were instructed and trained to take a "sniff-like" inhalation via the right nostril, according to two different manoeuvres: (1) a maximum peak inspiratory flow rate, reached within 1 s. The duration of inhalation was maximized to 1 s; (2) a peak inspiratory flow rate of 30 l/min reached within 1 s with a maximum duration of inhalation of 2 s.

A Vitalograph® Compact spirometer (modified for inhalation) was used to control and register the inhalation manoeuvre, giving a record of inhaled volume, peak inspiratory flow rate (PIF), and duration of inhalation. After drug inhalation, an immediate slow exhalation through the nose via a filter (Respirgard-II®) was made to collect any exhaled particles. The left nostril was held closed during the entire inhalation/exhalation manoeuvre.

Three different measurements were made immediately after each administration: (1) a lateral view of the head with the right side facing the gamma-camera; (2) an anterior-posterior view of the head; (3) an anterior-posterior view of the chest, to check whether any material had been deposited in the lungs. Another lateral view of the head was taken 15 min after inhalation.

A ^{57}Co marker source was used to mark reference points of the outline of the head on the scans. The size of the initial deposition of radioactivity in nasal cavity and lungs was determined from the number of picture elements within the 5% contour (the line marking 5% of the peak activity) on lateral and anterior-posterior views of the nose.

RESULTS

The particle size distribution of the dose delivered from the Turbuhaler® inhalers used in this study was measured at 28 l/min by Andersen sampler (Table 1). The particle-size distribution is similar to that of a reference, made with the same batch of unlabelled micronized budesonide. The somewhat larger fraction of small particles found for the radiolabelled powder is within the normal range of variation. Particle size distribution data were also recorded with a Multi-stage Liquid Impinger (60 l/min). These data did also show a good match between drug and label, but are not presented for brevity.

Table 1. Distribution of budesonide in different particle-size fractions using the Andersen sampler. Reference distribution of untreated powder (ref.) budesonide and test distribution of ^{99m}Tc-labelled powder (test) budesonide, are given as per cent of delivered dose. Mean values of 20 doses for the reference powder and of 10 doses for the labelled powder, measured from 5 inhalers respectively, are given.

size range (μm)	ref. (mean±SD)	test (mean±SD)
>10.0	57±3	40±8
10.0–9.0	3±1	2±1
9.0–5.8	6±1	6±1
5.8–4.7	6±1	8±1
4.7–3.3	12±1	18±3
3.3–2.1	10±1	18±3
2.1–1.1	6±0	9±2
1.1–0.7	1±0	0±0
0.7–0.4	0±0	0±0

The duration of the inhalation at maximum flow was 0.9±0.1 s (mean±SD), with a PIF of 46.3±6.8 l/min. The corresponding values when an inhalation flow of 30 l/min was aimed at were 1.6±0.2 s and 29.9±2.5 l/min. The inhaled volumes during administration were 0.54±0.12 l and 0.71±0.09 l for the two inhalation manoeuvres, respectively. The durations of the inhalations were at all times less than 1 s and 2 s, respectively, and the standard deviations for the PIF values and the inhaled volumes were small. Thus, the subjects complied well with the study protocol.

The initial site of deposition is exemplified in Figure 1, in which a ^{57}Co marker source has been used to give reference points of the head relative to the deposition area. The major portion of the dose was deposited in the anterior part of the nasal cavity on a single, rather localized area. From Figure 1 the dose appears to be in front of or in the middle nasal meatus. Some radioactivity had been eliminated from the nasal cavity after 15 min. No attempt was made to quantify this portion, since the radiotracer undergoes not only mucociliary clearance but also local absorption into the bloodstream. The area within the 5% contour on the lateral and anterior-posterior views of the head, immediately after dosing, is shown in Table 2.

The dose deposited in adaptor, nose, lungs and exhaled air was expressed as percentages of the metered dose which are shown in Table 2. To avoid assumptions regarding the distribution of data, the present study has been analysed non-parametrically (Wilcoxon signed-rank test) for possible differences between the two inhalation manoeuvres. There were no statistically significant differences between the two inhalation manoeuvres concerning the adaptor, nose and lung deposition, or initial deposition area. Although the difference was not statistically significant, there was a trend towards a larger deposition area at

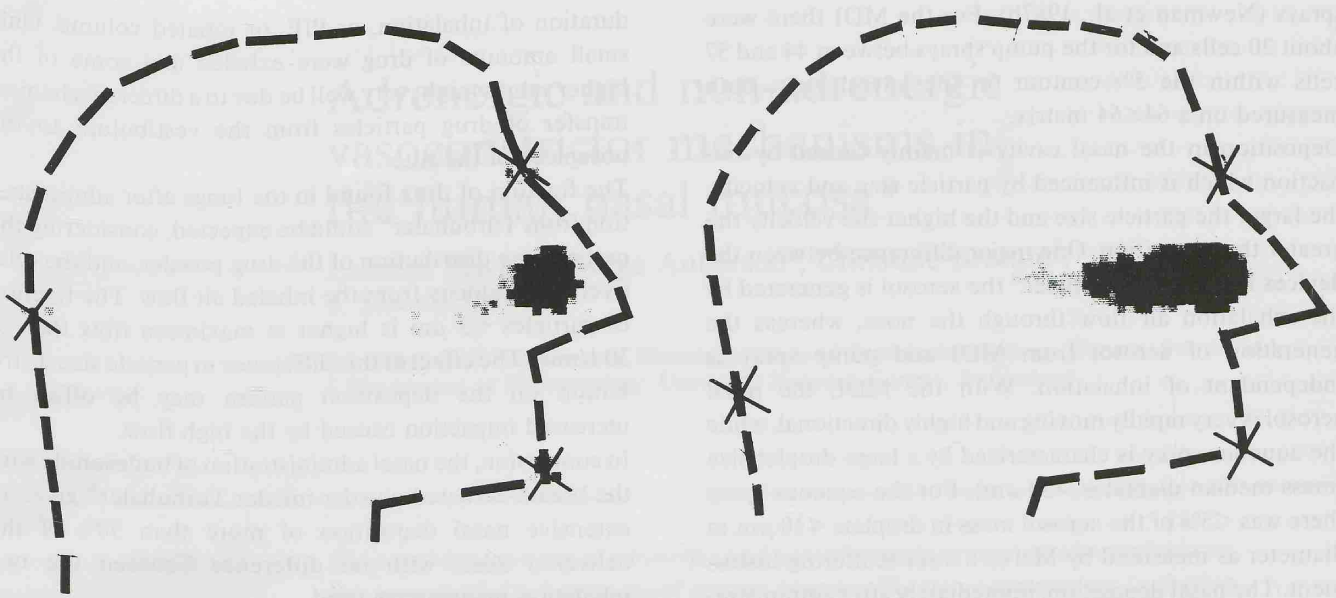

Figure 1. Lateral deposition patterns immediately after nasal inhalation of ^{99m}Tc-labelled budesonide via Turbuhaler®, showing examples in which a small area (1A) of the nasal cavity and a larger area (1B) were covered by the deposited aerosol. The inhalations were made at an air flow of 29.5 l/min (subject No. 9) and 53.0 l/min (subject No. 7) for 1A and 1B, respectively. The crosses indicates the location of a ^{57}Co marker source.

Table 2. Fraction of metered dose (percentages in adaptor, nose, lungs, and exhaled air) and number of cells within 5% contour on anterior-posterior and lateral scans of the nose at maximum flow rate (F_{max}) and at 30 l/min (F_{30}).

deposition (% of metered dose)									number of cells within 5% contour			
	adaptor		nose		lungs		exhaled		anterior-posterior		lateral	
subject	F_{max}	F_{30}	F_{max}	F_{30}	F_{max}	F_{30}	F_{max}	F_{30}	F_{max}	F_{30}	F_{max}	F_{30}
1	27.8	16.5	69.8	78.1	1.4	5.0	1.0	0.4	59	48	107	57
2	12.6	32.3	84.1	64.4	3.0	3.1	0.3	0.2	44	57	75	91
3	53.5	43.3	39.5	54.8	5.2	1.7	1.8	0.2	70	38	115	57
4	27.6	14.9	68.1	81.6	2.7	3.2	1.6	0.3	59	38	107	68
5	15.4	43.5	79.4	49.7	2.7	2.5	2.5	4.3	45	54	99	82
6	23.0	21.0	70.7	74.5	5.5	4.2	0.8	0.3	44	52	67	150
7	23.2	33.6	66.5	60.3	9.3	5.8	1.0	0.3	89	51	232	85
8	27.3	17.1	63.4	76.5	8.7	5.9	0.6	0.5	92	69	185	100
9	50.5	14.5	42.9	77.5	5.1	7.9	1.5	0.1	115	46	129	53
10	28.7	39.2	67.3	58.3	3.3	2.5	0.7	0	39	48	67	66
Mean	29.0	27.6	65.2	67.6	4.7	4.2	1.2	0.7	66	50	118	81
SD	13.3	12.0	14.1	11.4	2.6	1.9	0.7	1.3	26	9	53	29

maximum flow, with eight out of 10 subjects having their largest lateral deposition area at this flow. The nasal deposition, calculated from the delivered dose, was found to be 93.2% at 30 l/min and 91.2% at maximum flow, as a considerable amount of the metered dose was deposited in the nasal adaptor during administration.

DISCUSSION

In this study, nasal administration of budesonide was made with Turbuhaler®, a breath-actuated powder inhaler containing no additives, modified for nasal inhalation. The ability among patients with rhinitis to inhale budesonide from Turbuhaler® has previously been studied. Asymptomatic rhinitis patients reached a mean PIF of 57 l/min (Bertil Andersson, Astra Draco AB; personal communication). A mean PIF of 46 l/min was reached by the healthy subjects in the present study, when a maximum flow was aimed at. A similar mean value, 49 l/min, was reached in another study on 68 healthy subjects (Göran Randvall, Astra Draco AB; personal communication). PIF shows considerable interindividual variation, ranging from 20–85 l/min in these studies. Some patients with symptoms might attain lower flows and may need to take a nasal decongestant before the administration of budesonide powder from Turbuhaler®.

In this study a 128×128 computer matrix was used, while earlier studies (Newman et al., 1987a, b) were performed with a 64×64 matrix. For the lateral views of the nose, there were 118 cells (equivalent to 30 cells in 64×64 matrix) within the 5% contour at 46 l/min, and 81 cells (equivalent to 20 cells in a 64×64 matrix) at 30 l/min. This distribution pattern resembles more closely that observed previously for an MDI (Newman et al., 1987a) than those observed in a study with three different aqueous pump

sprays (Newman et al., 1987b). For the MDI there were about 20 cells and for the pump sprays between 44 and 57 cells within the 5% contour on the lateral view, both measured on a 64×64 matrix.

Deposition in the nasal cavity is mainly caused by impaction which is influenced by particle size and velocity, the larger the particle size and the higher the velocity the greater the deposition. One major difference between the devices is that in Turbuhaler® the aerosol is generated by the inhalation air flow through the nose, whereas the generation of aerosol from MDI and pump spray is independent of inhalation. With the MDI, the nasal aerosol is very rapidly moving and highly directional, while the aqueous spray is characterized by a large droplet size (mass median diameter >50 μm). For the aqueous spray there was <5% of the aerosol mass in droplets <10 μm in diameter as measured by Malvern laser-scattering instrument. The nasal deposition, immediately after administration, has been found to be around 82% with MDI (Newman et al., 1987a), calculated from metered dose. This deposition figure is to be compared with the initial nasal depositions in this study, being 65 and 68% for the two different inhalation manoeuvres, respectively. The inhaled particles from Nebuhaler® attached to an MDI are smaller and have the same velocity as the inhaled air flow. Accordingly, when dosing was made with Nebuhaler®, the deposition in the nasal cavity was less than, and the lung deposition larger than, when no spacer was used (Morén and Newman, 1990).

With Turbuhaler®, only a minor fraction of the delivered dose was deposited in the lungs or exhaled, leaving more than 90% in the nose, after both inhalation manoeuvres. Despite the differences between the two inhalation techniques used in this study, both resulted in an extensive nasal deposition of the drug. There were no statistically significant correlations between lung deposition and duration of inhalation, or PIF, or inhaled volume. Only small amounts of drug were exhaled and some of the higher values might very well be due to a direct mechanical transfer of drug particles from the vestibulum to the nosepiece of the filter.

The fraction of drug found in the lungs after administration from Turbuhaler® could be expected, considering the particle size distribution of the drug powder, and the relatively low velocity from the inhaled air flow. The fraction of particles <3 μm is higher at maximum flow than at 30 l/min. The effect of this difference in particle size distribution on the deposition pattern may be offset by increased impaction caused by the high flow.

In conclusion, the nasal administration of budesonide with the breath-actuated powder inhaler Turbuhaler® gives an extensive nasal deposition of more than 90% of the delivered dose, with no difference between the two inhalation manoeuvres used.

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