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Influence of degradable starch microspheres on the human nasal mucosa*†

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SUMMARY

The effect of the nasal administration of degradable starch microspheres (DSM) on the mucociliary system and the geometry of the nasal cavities were evaluated in 15 healthy volunteers. The baseline values for mucociliary clearance of the right nasal cavity were determined on two separate days for each subject using the saccharine-dye test. Acoustic rhinometry was performed before and during the saccharine-dye test. The patients then started the treatment period and inhaled 10 mg of DSM intranasally once daily in each nostril for 8 days. The saccharine-dye test was performed 5 min after the deposition of the DSM on day 1 and day 8. The geometry of the nasal cavities was determined before, 7 min after deposition, and after the end of the saccharine test. Both tests were also performed two days after the end of the treatment period. Each subject was examined by means of rhinoscopy on every visit during the investigation. No changes in mucociliary clearance or in the geometry of the nasal cavities were found after repeated administration of starch microspheres. Thus, intranasally-administered degradable starch microspheres did not have an adverse effect on human nasal mucociliary clearance, and the DSM did not cause any congestion or decongestion of the mucosa.

Key words: mucociliary clearance, saccharine-dye test, microspheres, nasal geometry, acoustic rhinometry

INTRODUCTION

The nasal administration of drugs has several advantages, such as rapid systemic absorption, the avoidance of hepatic first-pass metabolism and good patient compliance. However, hydrophilic peptides and larger peptides, such as insulin, have a somewhat low bio-availability due to difficulties in crossing the nasal mucosa effectively. Absorption promoters (enhancers) are often necessary to increase the absorption rate of peptides. Degradable starch microspheres (DSM) have been shown to enhance the absorption of insulin across the nasal epithelium in animals (Björk and Edman, 1988). As the spheres are administered as a dry powder and swell when they reach the mucosa, it is reasonable to assume that an interaction with the mucociliary transport in the nose could occur because of their retention in the nasal cavity (Illum et al., 1987). The aim of the present investigation was to study the effect of intranasally-administered starch microspheres on mucociliary clearance of the human nasal mucosa. Furthermore, any possible congestive or decongestive effects by the spheres on the mucosa were also investigated.

PATIENTS AND METHODS

An open study design was used. The results after treatment were compared with those before treatment on two different days. The subjects were selected from the students at the University of Göteborg. A total of 15 healthy volunteers (7 males and 8 females) with a mean age of 24.2 years, ranging from 21 to 31 years participated in the study. The subjects lacked any history of allergic or non-allergic rhinitis. They were non-smokers and displayed no signs of pathological nasal conditions such as septal deviation, nasal polyps or acute upper respiratory infection.

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Degradable starch microspheres (DSM) with a mean diameter of 40 μm were produced by Kabi Pharmacia Therapeutics AB (Uppsala, Sweden). The spheres were dispensed in capsules administered intranasally with the aid of a commercial insufflator (Nasalet®). Each subject was treated with 10 mg of the spheres in each nostril once daily for 8 days.

A method previously defined by Andersen et al. (1974) and Proctor (1982) was used for the determination of nasal mucociliary clearance. The length of the nasal cavity from the vestibulum nasi to the pharyngeal wall was determined with a cotton-wool swab. A blue-stained particle of saccharine (diameter 0.5–1 mm) was placed on the antero-medial portion of the right inferior turbinate, 4 cm from the nasal tip. The time between application of saccharine and the sensation of sweet taste in the mouth was defined as the transport time. Mucocilialy clearance (mm/min) was calculated. The geometry of the nasal cavities in terms of cross-sectional areas (CA; in cm^2) and volume (V; 3.0–8.8 cm^3) was calculated separately for the right and left nasal cavities with the aid of acoustic rhinometry (Hilberg et al., 1989). In short they describe this method as: "an audible sound pulse (150–10,000 Hz) generated by a spark propagating in a sound tube and is reflected by local changes in acoustic impedance due to changing of the cross-sectional area with distance. If the signals of the incident and the reflected waves are measured in a time domain, it is possible to determine the distance to the local impedance change and by comparing incident and reflected waves it is also possible to determine the size of change in the cross-sectional area. This provides an estimate of the cross-sectional area as a function of the distance from the nostril." The cross-sectional area in the nasal cavity reflects the congestion of the nasal mucosa. The minimal cross-sectional area (MCA; in cm^2), the cross-sectional area at a distance of 4.3 cm from the nostrils (CA4.3; in cm^2) and one volume (V; in cm^3) located 3.0–8.8 cm from the nostrils, were calculated.

The procedure started with an investigation of each individual by means of rhinoscopy, saccharine-dye testing, and acoustic rhinometry on two different days. A baseline mean value for the mucociliary clearance for each subject was calculated from the results of the saccharine-dye test. Acoustic rhinometry was performed for the right and left nasal cavities separately, before and 2 min after the start of the saccharine test. On the first and eighth treatment day, the DSM was administered intranasally by the investigator. The saccharine-dye test was carried out 5 min after the deposition of the DSM. Acoustic rhinometry was performed for both nasal cavitites immediately before, 2 min after the start of the saccharine test (i.e., 7 min after the administration of starch microspheres), and finally after the end of the saccharine test, approximately 15 min later. All tests including rhinoscopy were then repeated two days after the end of the last treatment day.

Changes in mucociliary clearance and changes in the geometry of the nasal cavity were analysed by means of a one-way ANOVA utilizing a statistical software package (StatView 512+; Abacus Concept Inc., Calabas, U.S.A.) on a Macintosh microcomputer. A two-tailed test was used, and a p-value of <0.05 was regarded as significant.

RESULTS

All 15 subjects completed the investigation. The starch microspheres were well tolerated and no side effects were registered. Immediately after administration a few of the subjects felt a transient tickling sensation. Most subjects did not feel anything at all. Only a few isolated sneezing events were reported. One subject felt a faint sweet taste after the administration of the starch spheres. Some subjects felt a dry sensation which was probably due to deposition of inhaled spheres in the pharynx. On rhinoscopy it was observered that the majority of the microspheres were well spread on the nasal mucosa, primarily at the surface of the turbinates and on the septum. The mean of the two baseline values for mucociliary clearance was 6.9 mm/min (range 3.6–15 mm/min). There was no change in mucociliary clearance after one dose and after 8 days of treatment with 10 mg of starch microspheres daily or two days after the end of treatment (Figure 1). The geometry of the nasal

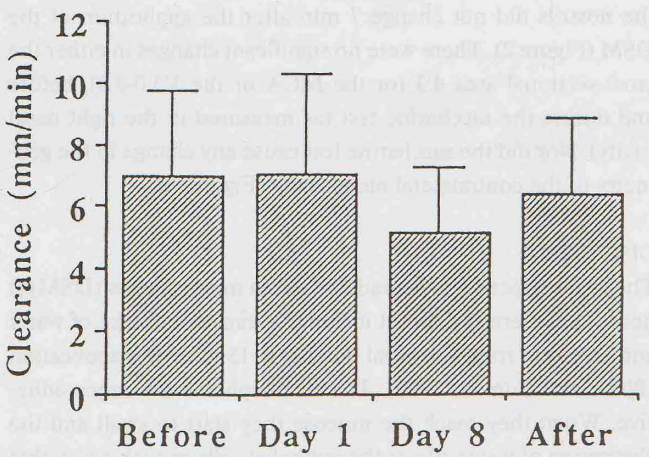

Figure 1. Change in mucociliary clearance (mm/min) before (baseline), after one dose and after 8-day administration of 10 mg of DSM in each nasal cavity daily and 2 days after the end of the treatment. The data are expressed as the mean ± SD (n=15).

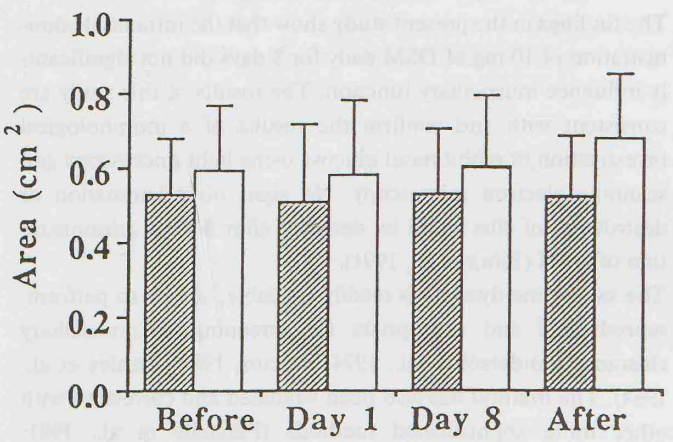

Figure 2. The effect of degradable starch microspheres on the minimal cross-sectional area (closed bars: right nasal cavity; open bars: left nasal cavity). The data are expressed as the mean ± SD (n=15).

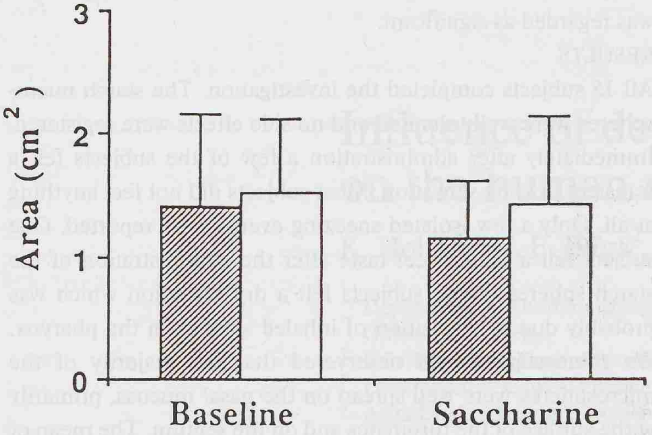

Figure 3. The effect of the saccharine-dye test, performed in the right nasal cavity, on cross-sectional area 4.3 cm from the nostrils (closed bars: right nasal cavity; open bars: left nasal cavity). The data are expressed as the mean ± SD (n=30).

cavities in terms of the minimal cross-sectional area and the cross-sectional area at 4.3 cm and the volume at 3-8.8 cm from the nostrils did not change 7 min after the application of the DSM (Figure 2). There were no significant changes in either the cross-sectional area 4.3 (or the MCA or the V3.0-8.8), before and during the saccharine test (as measured in the right nasal cavity). Nor did the saccharine test cause any change in the geometry of the contralateral nasal cavity (Figure 3).

DISCUSSION

The mode of action of degradable starch microspheres (DSM) is not fully understood, but it includes a transient uptake of water and moisture from the nasal mucosa 0–15 min after application (Björk and Edman, 1990). The microspheres are muco-adhesive. When they reach the mucosa they start to swell and the absorption of water affects the epithelial cells in such a way that the paracellular passages (tight junctions) are opened. The spheres, which must be water-insoluble, form gels which are transported by the cilia but not by drainage. So there are several reasons why the DSM could affect the mucociliary function of the nose, especially when given for a long time.

The findings in the present study show that the intranasal administration of 10 mg of DSM daily for 8 days did not significantly influence mucociliary function. The results of this study are consistent with and confirm the results of a morphological investigation of rabbit nasal mucosa using light microscopy and scanning electron microscopy. No signs of inflammation or destruction of cilia could be detected after 8-week administration of DSM (Björk et al., 1991).

The saccharine-dye test is readily available, simple to perform, reproducible and appropriate for screening of mucociliary clearance (Andersen et al., 1974; Proctor, 1982; Stanley et al., 1984). The method has also been validated and correlated with other more sophisticated methods (Puchelle et al., 1981; Brondel et al., 1983). Our baseline mean value for mucociliary clearance matches previous investigations. In the right nasal cavity where the saccharine-dye test was performed, the blue dye of the saccharine-dye crystal could be observed in each subject. One disadvantage of this method is that the test cannot be repeated on the same day.

The results of the present study do not necessarily conflict with the results from the studies conducted by Illum et al. (1987) who found in a gamma-scintigraphy study in man that DSM (labelled with technetium-99m) given intranasally as a dry powder were eliminated very slowly from the nasal cavity. In that study, the clearance rate of spheres from the nasal cavity was followed, whereas the present study followed the influence of DSM on normal mucociliary function. A plausible explanation of the difference in clearance rate could be that DSM are muco-adhesive and stick to the epithelial lining without affecting the normal mucociliary activity. After the administration of starch microspheres with Nasalet® a thin layer of white powder was observed covering the anterior and the medial surface of the inferior turbinate and the septum. Thus, administration by Nasalet® seemed to hit a wide area of the nasal mucosa as a rule. On some occasions the microspheres had stuck together inside the capsule and were impossible to apply. This was obvious on a couple of occasions and a new capsule then had to be used. It is therefore necessary to store the starch microspheres in an air-tight capsule.

In two determinations in two different subjects, the transport of the saccharine crystal appeared to be blocked by the starch microspheres and the blue colour and the saccharine appeared instead to collect in the vestibulum. In these two subjects no sweet taste was experienced within 30 min of the administration of the DSM. Whether the starch microspheres in these cases caused a transient ciliostasis or only a transient prolonged transport for mechanical reasons can not be concluded from the present study. However, one of these two subjects had a slight septal deviation which probably caused the DSM to concentrate at the front of the inferior turbinate and thus possibly stop the mucociliary clearance at this very point in the mucosa for mechanical reasons. It therefore appears to be necessary to spread the spheres over a large area rather than at one point in the mucosa.

Acoustic rhinometry was used to exclude any congestion or decongestion caused by the DSM. Acoustic rhinometry is more sensitive than anterior rhinomanometry when it comes to identifying a change in nasal patency after allergen challenge (Scadding et al., 1992). Acoustic rhinometry reveals not only the size but also the location of the minimal cross-sectional area (MCA) which is the most resistant place in the upper airway (Hilberg et al., 1989). In the healthy nose, the MCA is situated in the valve area (isthmus nasi) but moves backwards to the head of the inferior turbinate during congestion of the mucosa. In this study, we expected a change in the tonus of the mucosa of the inferior turbinate where a majority of inhaled particles are deposited, and the cross-sectional area at 4.3 cm from the nostrils and the volume between 3.0 and 8.8 cm from the nostrils were therefore calculated. These values (and the MCA) did not change during treatment with DSM.

Acoustic rhinometry of the right nasal cavity, before and during baseline determinations on two different days with the saccharine-dye test, did not reveal any significant congestion or decongestion of the mucosa. Consequently, the saccharine-dye test

per se does not affect the tonus of the nasal mucosa in healthy subjects.

In conclusion, DSM were well tolerated and no significant changes in either mucociliary clearance or the congestion/decongestion of the nasal mucosa were seen. On the basis of these results, it is obvious that DSM can be regarded as a biologically acceptable system with low local irritation. Consequently, DSM have potential as a novel delivery system for nasally administered drugs.

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