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The influence of solution viscosity on nasal spray deposition and clearance

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Summary

Three hydroxypropyl methylcellulose solutions, having kinematic viscosities 36, 120 and 430 $mm^2 \cdot s^{-1}$, were administered as nasal sprays to 8 healthy subjects. The solutions were radiolabelled with ^{99m}Tc-labelled diethylenetriaminepentaacetic acid and the sites of deposition and the rates of clearance from the nasal cavity monitored using a gamma camera. The areas of deposition were the same for all the solutions. The clearance rates decreased with increasing solution viscosity, the half-times being 1.0, 1.7 and 2.2 h. Thus increasing the solution viscosity may provide a means of prolonging the therapeutic effect of nasal spray preparations.

Introduction

Drug delivery to the nasal mucosa, for either topical or systemic action, will be influenced by the duration of the contact with the preparation. Nasal spray preparations administered using pumps or pressurised metered dose inhalers deposit mainly in the anterior part of the nasal cavity (Aoki and Crawley, 1976; Hardy et al., 1985; Newman et al., 1987). Since this region is largely non-ciliated, clearance is relatively slow and arises from the preparation being dragged posteriorly into the ciliated areas. The path of the resulting spread is mainly along the inferior meatus and into the pharynx. Typically the mucus flow rate in the posterior two-thirds of the nasal cavity is about 6–10 $mm \cdot min^{-1}$ (Hilding, 1963; Yergin et al., 1978), giving a clearance time of 10–15 min (Proctor et al., 1973).

The anatomy of the human nose favours inertial impaction of spray preparations in the anterior third of the nasal cavity. Thus changing the cone angle of the spray (Bond et al., 1984), the solution volume (Aoki and Crawley, 1976) or varying the angle of insertion of the insufflator (Newman et al., 1987) has little effect on the site of deposition and subsequent spreading within the nasal cavity. Modification of the dosing procedure, therefore, is unlikely to have a significant effect on the bioavailability of drugs from nasal sprays. The present study has been undertaken to investigate the influence of solution viscosity on the deposition and clearance of nasal sprays.

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Materials and Methods

Materials

Hydroxypropyl methylcellulose (HPMC) was used to increase the viscosities of the nasal spray solutions. Each solution was prepared by the addition of 50 ml water at 90 °C to HPMC powder (Metolose type 65SH, Shin-Etsu Chemicals, Tokyo, Japan) with vigorous mixing, whilst maintaining the temperature above 80 °C. The required HPMC concentration was achieved by the gradual addition of cold water. After further vigorous mixing the solution was allowed to stand overnight at room temperature. HPMC solution (26 ml) contained in a nasal spray bottle was radiolabelled by the addition of 0.1 ml ^{99m}Tc-labelled diethylenetriaminepentaacetic acid (^{99m}Tc-DTPA) solution (Amerscan Pentetate II, Amersham International, Amersham). The preparation was administered using a nasal spray pump (Fisons, Loughborough).

Subjects

Three male and 5 female volunteers, aged 19–22 years, participated in the study. All were healthy, with no history of nasal problems and free from colds. The study was approved by Nottingham University Medical School Ethical Committee and each subject gave written informed consent before taking part.

In vitro experiments

Solutions were prepared containing 0.1, 0.2, 0.4, 0.6, 0.8, 1.0 and 1.25% w/w HPMC and their viscosities measured at 20 °C using U-tube viscometers calibrated using water and 19, 38 and 56% w/w sucrose solutions.

The HPMC solutions were gently rotated on a roller-mixer to avoid the formation of air bubbles during the mixing with the ^{99m}Tc-DTPA tracer. The time taken to achieve uniform mixing of each solution was determined by withdrawing 0.5 ml samples from four different sites in the nasal spray bottle at 15 min intervals. During each experiment 500 kBq ^{99m}Tc-DTPA was added and the specimens were taken until the assays indicated that the mixing was complete.

The volume of solution ejected from the pumps was measured with water and the HPMC solutions. To 26 ml of each solution in a nasal spray bottle was added 500 kBq ^{99m}Tc-DTPA and the solutions mixed on a roller-mixer. The pump was actuated once into each of 12 sample tubes, care being taken to ensure that the dip tube remained submerged. The solution was washed from the walls of the sample tube with 2 ml of water. Additionally, 0.5 ml of solution was pipetted from the nasal spray bottle into a sample tube and 1.5 ml of water added. The specimens were assayed for radioactivity and the volume of solution ejected per actuation determined.

In vivo studies

On the basis of the results of the in vitro experiments, 0.6, 0.9 and 1.25% w/w HPMC solutions were selected for the deposition and clearance studies. The three solutions were administered to each volunteer on separate occasions; with no more than two of the doses being given into the same nostril.

Each nasal spray bottle contained 26 ml of HPMC solution to which was added 0.1 ml of DTPA solution radiolabelled with 350 MBq technetium-99m. The preparation was mixed on a roller-mixer for 1 h and the pump primed by actuation 10 times into a plastic bag.

With the subject in an upright posture, the tip of the applicator was inserted about 1 cm into the nostril with the nozzle parallel with the ridge of the nose. The pump was actuated during normal inspiration with the mouth closed and the contralateral nostril open. Immediately after dosing, a lateral image of the head was recorded for 60 s using a gamma camera. The nostril containing the dose was positioned to be the nearer to the collimator. The gamma camera had a 40 cm field of view, was fitted with a low energy (160 keV maximum) parallel hole collimator and was turned to detect the 140 keV radiation with a 20% energy window. Images were recorded over a 4 h period, at 10 min intervals during the first hour, 15 min intervals during the second hour and subsequently every 20 min. The data were recorded by computer in a 128×128 matrix.

The first image of each study was displayed on a television monitor and a contour defined through the pixels containing 20% of the maximum pixel

count. The number of pixels within the contour was taken as a measure of the area of deposition. A region of interest was then defined in each image, around the whole nasal cavity. The count rate from each region was corrected for background counts and for radioactive decay, and expressed as a proportion of the count rate from the image recorded immediately after dosing.

Results

The change in the viscosity of the HPMC solutions with increasing concentration is illustrated in Fig. 1. The concentrations, 0.6, 0.9 and 1.25% w/w HPMC, selected for the nasal spray deposition and clearance studies had kinematic viscosities at 20 °C of 36, 120 and 430 $mm^2 \cdot s^{-1}$, respectively.

The mixing time for the incorporation of the radioactive tracer ranged from less than 15 min for the solution of lowest viscosity to 60 min for the 1.25% w/w HPMC solution. All the solutions for in vivo administration were mixed on a roller-mixer for at least 1 h to ensure complete dispersion of the ^{99m}Tc-DTPA.

Priming of the insufflator required 6 actuations to achieve a constant ejection volume with water (Fig. 2). Once primed, the volume ejected per actuation was 0.13 ± 0.01 ml. For the HPMC solutions 7 actuations were required to prime the pumps. The volume dispensed, 0.13 ml, was the same for each solution within the range 0.2–1.25% w/w HPMC.

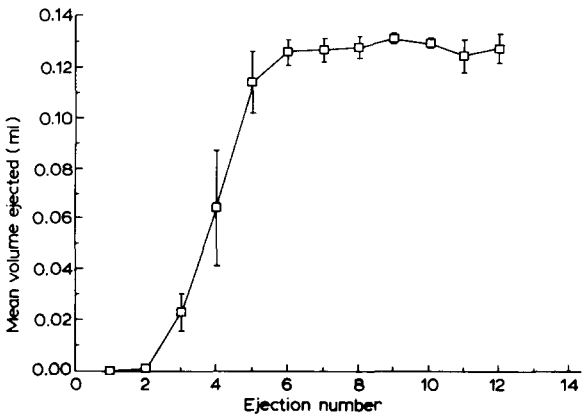

Fig. 2. Priming of the nasal spray pump with water (mean ± 1 S.E.M., $n = 5$).

The nasal spray deposited anteriorly in the nasal cavity, mainly in the atrium. No differences were detected in the deposition patterns of the 3 solutions. The areas of the deposition sites for the 0.6, 0.9 and 1.25% w/w HPMC solutions were 59 ± 23, 48 ± 27 and 49 ± 9 pixels, respectively, and were not statistically different.

Clearance of the solution from the deposition site was predominantly along the inferior meatus and into the pharynx. The rates of clearance of the 3 solutions from the nasal cavity are shown in Fig. 3. The 0.6% w/w HPMC solution cleared accord-

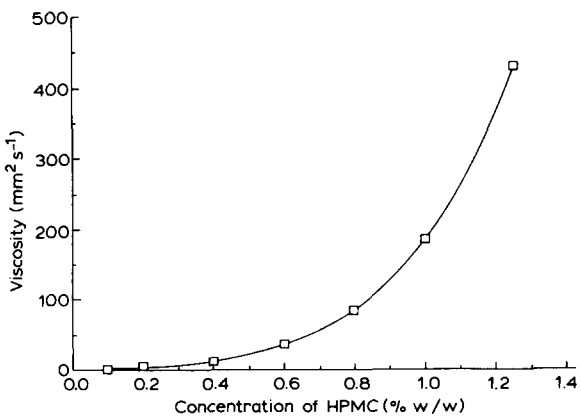

Fig. 1. Variation in the viscosity of the HPMC solutions with concentration.

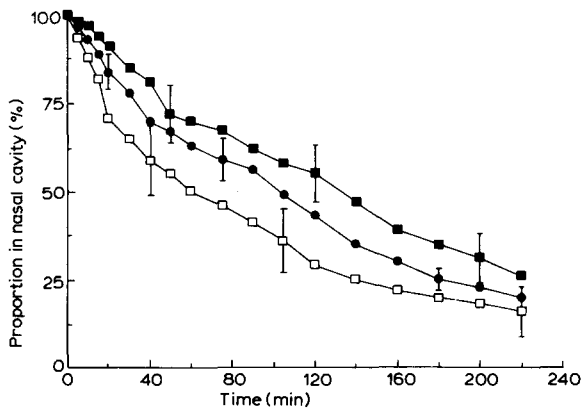

Fig. 3. Clearance of the nasal spray solutions from the nasal cavity: 0.6 (■), 0.9 (●) and 1.25% w/w (□) HPMC concentrations (mean ± 1 S.E.M.).

TABLE 1

Clearance of the HPMC solutions from the nasal cavity

Solution concentration (% w/w HPMC)	Clearance half-time (h)	
0.60	0.47 (45%)	2.1 (55%)
0.90	1.7	
1.25	2.2	

ing to a biphasic pattern, whereas clearance of the more viscous solutions was approximately monoexponential. The clearance half-times are listed in Table 1; the overall value for the 0.6% w/w HPMC solution being 1.0 h. Due to large inter-subject variability, the differences between the times for 50% clearance of the 3 solutions were not statistically significant.

Discussion

Most nasal spray pumps are designed for the delivery of solutions of low viscosity. The pumps used in the present study functioned satisfactorily with all the solutions investigated. It is, however, important to prime the pumps adequately prior to dosing. Any effect of viscosity on the dispersion of the nasal spray following ejection was of little consequence since the distance between the tip of the nozzle and the site of impaction was only a few millimetres.

In previous studies of the clearance of nasal spray solutions from the nasal cavity a biphasic pattern has been observed (Aoki and Crawley, 1976; Hardy et al., 1985). This has been interpreted in terms of relatively fast clearance of the solution deposited more posteriorly, in the ciliated regions, and slow clearance of that deposited anteriorly. In the present study a similar biphasic clearance pattern was observed with the 0.6% w/w HPMC solution. The more viscous preparations, however, exhibited an approximately monoexponential clearance. This may be due to the more viscous solutions forming a continuous film which is dragged from the deposition site at a steady rate. In contrast, the films of the less viscous solutions may tend to break up under traction.

The clearance rate was slowest for the most viscous solution, having a half-time of 2.2 h. In contrast the least viscous solution cleared with an overall half-time of 1.0 h. The clearance half-time of 30 min for a propylene glycol solution with a kinematic viscosity at 20 °C of 1.1 $mm^2 \cdot s^{-1}$ (Hardy et al., 1985) is in keeping with the trend observed for the HPMC solutions. Thus it is apparent that the duration of residence of spray solutions in the nasal cavity can be enhanced by increasing the viscosity.

The rates of clearance of solutions from the nasal cavity can be greatly influenced by pathology (Sakakura et al., 1983; Bond et al., 1984; Lee et al., 1984). It is important, therefore, to consider the patient group to be treated when formulating nasal spray preparations. Additionally, studies need to be performed to assess the effects that changes in solution viscosity may have on drug bioavailability. The results of the present study, however, indicate that increasing solution viscosity may provide a means of prolonging the therapeutic effect of nasal spray preparations.

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