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Intranasal drug delivery by spray and drops

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A solution of ^{99m}Tc-labelled human serum albumin was administered into the nose as a spray and as one or three drops. The patterns of deposition and the rates of clearance in normal subjects were monitored by gamma scintigraphy. The spray was deposited mainly in the atrium, and cleared slowly into the pharynx. The single drop spread more extensively than the spray, while the three drops were sufficient to cover most of the walls of the nasal cavity. Clearance was faster following administration of the drops. These factors have implications when designing dosage regimens for drugs administered by the intranasal route.

Preparations are administered into the nasal cavity for their local action. Additionally, the intranasal route may provide a convenient means of administration for certain systemically acting drugs which would otherwise need to be given by injection (Parr 1983). Controlled volumes of solutions can be applied into the nasal cavity in the form of sprays or drops. The site of deposition and the rate of clearance of the drug will influence the efficacy of the dose received by the patient.

The movement of materials deposited on to the walls of the nasal cavity, and their rates of clearance into the pharynx, have been studied extensively. The techniques employed have included the direct observation of particles (Ewert 1965), and the imaging of radiopaque (Yergin et al 1978) and radiolabelled materials (Proctor & Wagner 1965).

Mucociliary function clears materials from the turbinates into the nasopharynx on average at a rate of 6 mm min^{-1} (Yergin et al 1978; Sakakura et al 1983), with the flow rate increasing posteriorly (Quinlan et al 1969). Clearance from the non-ciliated anterior region of the nasal cavity is slow and results from the mucus layer being dragged into the ciliated region (Hilding 1963; Proctor et al 1973).

In patients with pathological conditions affecting mucociliary function, for example Kartagener's syndrome, Sjögren's syndrome and cystic fibrosis, the clearance rates of materials from the nasal cavity are slow (Sakakura et al 1983). Slow clearance is also associated with nasal polyposis (Lee et al 1984). The common cold can cause either rapid or slow clearance, depending on whether the subject has a 'runny nose' or nasal congestion (Proctor et al 1973; Bond et al 1984). Environmental conditions, such as the relative humidity and temperature, may also influence nasal clearance. Ewert (1965) and Quinlan et al (1969) reported reductions in clearance rates at low relative humidities. Proctor (1983), however, observed little effect on mucociliary transport resulting from changes in relative humidity and ambient temperature.

The site of deposition of preparations within the nasal cavity depends on the delivery system and the technique of administration (Mygind 1979). A study by Aoki & Crawley (1976) compared the deposition and clearance of relatively large volumes of solutions applied as nasal sprays and drops. Greater coverage of the walls of the nasal cavity was achieved following administration of the drops, and this was independent of the volume administered over the range 0·1–0·75 ml. The clearance rates were similar following both methods of administration and for all the dosing volumes.

In the present study small volumes of less than 0·1 ml of ^{99m}Tc-labelled albumin solutions have been administered into the noses of normal subjects, and monitored using gamma scintigraphy. The preparation was applied as either a single drop or as a spray. Additionally, the effect of increasing the number of drops has been investigated.

METHODS

Materials

The preparation was typical of solutions used for nasal drug delivery, and comprised an aqueous solution of 2·0% propylene glycol containing 0·005% w/v thiomersal. Radiolabelling was by the addition of 0·1 ml ^{99m}Tc-labelled human serum albumin solution containing 1 mg albumin (CIS (UK) Limited, London) to 5 ml of the preparation. For the in-vitro experiments 0·1 MBq technetium-99m was used, and 0·1 GBq for the in-vivo studies.

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The spray was administered using a Mistette Mark II nasal spray applicator (Calmer-Albert GmbH, Reigate) having a 60° cone angle and a nominal ejection volume of 100 µl. The drops were applied from a disposable TFL Clinic Dropper (Thomas Fazio Laboratories, Berkley, Massachusetts).

In-vitro experiments

The variation in the quantity of solution dispensed per ejection from the nasal spray applicator was investigated. To each of four 15 ml spray bottles was added 5 ml radiolabelled solution and the pump attached. Each of 20 consecutive ejections from each device was collected into an individual tube, the end of the dip tube remaining continuously immersed throughout the procedure. The droplets were washed from the sides of each sample tube with 2 ml water, and the technetium-99m content assayed using a gamma counter.

In a separate experiment, four spray applicators were primed by dispensing 15 doses from each. Subsequently 10 doses from each device were collected in individual tubes. The droplets were washed from the walls of each tube using 2 ml water before being assayed for technetium-99m. A standard was prepared by pipetting 1·00 ml of the same solution into a counting tube with the addition of 1 ml of water. The count rates were corrected for radioactive decay and background counts, and the volume of each dose calculated. The volume of solution dispensed from the dropper was measured by collecting 10 drops of radiolabelled solution into individual tubes. To each tube was added 2 ml water, and the count rate was compared with that of a standard prepared as described previously.

In-vivo studies

The solution was administered to healthy volunteers, seven male and one female, aged 20–23 years. None of the subjects had nasal problems and all were free from colds. On separate days four subjects each received a single dose from the insufflator, and a single drop of solution. The other four subjects were each dosed with one drop and three drops of solution, also on separate occasions. The study was approved by the local ethical committee, and each subject gave written informed consent before participating.

The nasal spray device was filled with 5 ml solution and primed by activating the pump 15 times into a closed system. With the subject in an upright position, the applicator tip was introduced 3–5 mm into either nostril keeping the nozzle parallel with the dorsal ridge of the nose. A single dose was dispensed during normal inhalation, with the contralateral nostril open.

The nasal drops were administered with the subject supine, following the procedure recommended by Mygind (1979). The subject's head was tilted back and the solution dispensed into one nostril during normal breathing. The head was then turned to the right and left and then back to the original position before the subject assumed a sitting position with the head tilted forward. Each posture was maintained for 30 s.

The tracer was monitored using a gamma camera having a 40 cm field of view and fitted with a low energy (160 keV maximum) parallel hole collimator. The equipment was tuned to detect the 140 keV radiation with a 20% energy window. Immediately after dosing each subject was seated with the nostril containing the dose nearer the collimator and a lateral view of the head recorded for 60 s. Additional images were recorded at frequent intervals over the following 90 min. Throughout the monitoring periods the subjects continued to breathe normally, and did not blow their noses or sneeze. The data were recorded by computer for subsequent analysis. Each image was displayed on a television monitor and a region of interest defined around the nasal cavity. The count rate from that region was corrected for background counts and for radioactive decay. Each corrected count rate was expressed as a proportion of the count rate from the nasal cavity in the initial image.

RESULTS

In-vitro studies

It was essential to prime the insufflator before dispensing a dose. As is apparent from Fig. 1, approximately 10 activations were required in order to achieve a uniform delivery. The volume ejected,

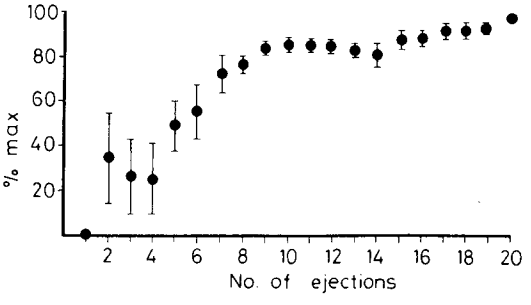

FIG. 1. Volumes ejected during priming of nasal spray applicators (mean ± 1 s.e.m.).

72 ± 9 μl, was less than the nominal dose from the pumps of 100 μl. The volume of a nasal drop was 30 ± 4 μl.

In-vivo studies

The nasal spray deposited anteriorly in the nasal cavity, with little of the dose reaching the turbinates (Fig. 2). In contrast, during dosing with the drops the solution dispersed throughout the length of the nasal cavity, from the atrium to the nasopharynx. In comparison with the administration of a single drop, dosing with three drops resulted in greater coverage of the walls of the nasal cavity (Fig. 2). For each administration, the whole of the dose remained in the nasal cavity at the time of the initial imaging.

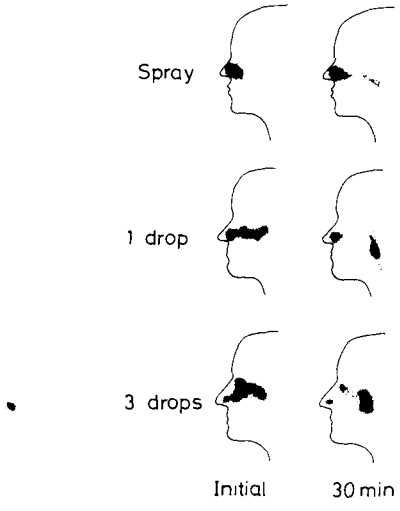

FIG. 2. Sites of deposition and patterns of clearance following administration of nasal spray and drops. Each pair of images is of the same subject, but the three sets are of different subjects.

In every study, the tracer, which was not absorbed from the nasal cavity, was observed to clear into the pharynx. The solution deposited anteriorly in the nasal cavity, however, was slow to clear (Fig. 2). This was particularly evident with the spray administration. The clearance from the atrium was predominantly along the inferior meatus, with no apparent spreading over the turbinates. Clearance of the tracer from the ciliated regions was more rapid as can be seen from the images recorded 30 min after dosing. Figs 3 and 4 show that the solution administered as drops was removed more rapidly than the doses administered as a spray. Analysis of these curves revealed a biphasic pattern of clearance, the initial rates being similar for the three methods of dosing (Table 1). The prolonged second phase following the nasal spray dosing reflects the slow removal of the tracer from the non-ciliated region.

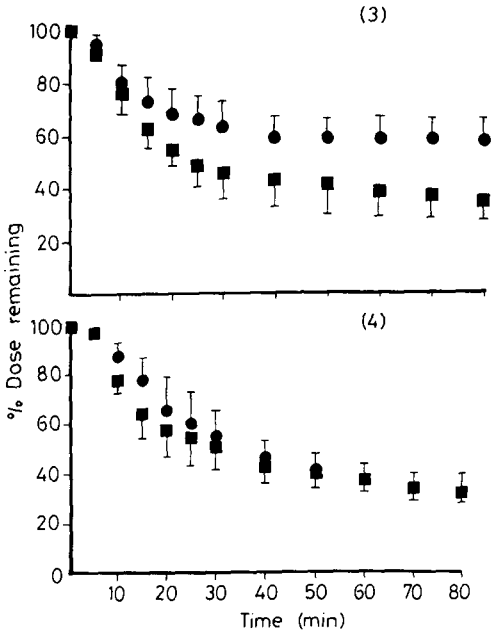

FIG. 3. Clearance of tracer from the nasal cavity after administration of spray (●) and a single drop (■) to four subjects (mean ± 1 s.e.m.).

FIG. 4. Clearance of tracer from the nasal cavity after administration of one drop (●) and three drops (■) to four subjects (mean ± 1 s.e.m.).

DISCUSSION

The extent to which intranasally administered pharmaceutical preparations are dispersed over the walls of the nasal cavity depends on the method of application. The present investigation confirms the findings of Aoki & Crawley (1976) that greater coverage could be obtained with drops than with sprays. The method of administration of the drops recommended by Mygind (1979) would tend to maximize the initial area of distribution. Aoki & Crawley (1976) found that changing the volume over

Table 1. Tracer clearance from the nasal cavity.

Method of administration	Clearance half-times (min) Initial phase	Later phase
Spray	8	580
1 drop	6	108
1 drop	9	75
3 drops	6	84

the range 0·1–0·75 ml had no effect on the extent of the deposition. With three drops (90 μl) the pattern of deposition was similar to that reported for larger volumes, but a single drop was insufficient to provide such extensive coverage. The spray droplets tended to deposit at their impaction sites, and produced a more localized distribution (Lee et al 1984). In a previous study (Bond et al 1984) it has been shown that changing the cone angle of the applicator from 60 to 30°, or the administration of the dose as one or two ejections, had no apparent effect on the distribution.

Clearance of the tracer from the nasal cavity was by movement into the pharynx, and then to the stomach. For all three methods of administration approximately 40% of the dose cleared rapidly with average half-times ranging from 6–9 min. Following this rapid phase, clearance of the spray was much slower than the drops (Table 1). This would be expected since most of the spray deposited on the non-ciliated regions, whilst the solution from the drops spread more extensively over the ciliated areas. The average overall half-times for clearance of the drops was 30 min, which is similar to the value of 24 min reported by Aoki & Crawley (1976).

The clearance rates may be influenced by relative humidity, but this is unlikely to be an important factor (Aoki & Crawley 1976). During the present study the relative humidity was maintained within the range 38–52%. It is well established that pathologies involving mucociliary dysfunction can greatly affect the clearance rates of tracers from the nasal cavity (Sakakura et al 1983). The effect of the common cold is highly variable even within a single subject (Bond et al 1984).

There are two overriding factors to be considered when optimizing dosage regimens for intranasally administered drugs; the method and technique of administration, and the presence of pathologies affecting nasal function. Drugs administered for either their topical or systemic actions must reach their sites of action or absorption. Drop delivery followed by appropriate manoeuvres by the patient can result in extensive coverage of the walls of the nasal cavity. If large volumes are administered, much of the preparation is likely to be swallowed at the time of dosing. Although insufflators can deposit well controlled doses of drug into the nostril, the drug may be localized and little if any may spread to the site of action. Additionally, to obtain an accurate dose the device may need extensive priming as with the pumps used in this study. Even if the drugs are delivered to the required sites in the desired concentrations, relatively trivial conditions such as the common cold can greatly affect the clearance rates and hence the efficacy of the preparations. The intranasal route, therefore, may not be appropriate for the administration of well controlled doses of drugs.

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