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Deposition pattern of nasal sprays in man

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SUMMARY

The intranasal distribution from an aqueous pump spray has been assessed in 13 normal subjects, using insoluble Teflon particles labelled with $^{99}Tc^{m}$ which were intended to simulate a suspension of drug particles. Three different combinations of metered volume and spray cone angle were compared. The main deposition of particles was in the anterior, non-ciliated, part of the nose, but some particles also penetrated more posteriorly into the main nasal passages and were cleared subsequently to the nasopharynx. No particles were detected in the lungs. With a single puff of 100 µl volume, 46.5±4.4 (mean±SEM)% of the spray was retained in the anterior part of the nose after 30 minutes, but this was increased to 57.1±4.5% ($P<0.05$) with two puffs of 50 µl. The latter were deposited over a significantly ($P<0.05$) smaller area in the nasal cavity. There was a trend towards lower particle retention and a greater area of deposition when the spray cone angle was decreased from 60° to 35°. These results indicate that the drug particles released from nasal pump sprays are distributed both to ciliated and non-ciliated zones, and that the choice of metered volume and possibly spray cone angle may play a role in determining the amount which penetrates to the main nasal passages.

INTRODUCTION

Several types of therapeutic agent including corticosteroids, vasoconstrictors, sodium cromoglycate and antihistamines may be delivered to the nasal passages using hand-operated pump sprays which release a metered quantity of drug solution or suspension (Mygind and Weeke, 1985). These drugs are intended to produce a local effect within the nose, although pump sprays may also be appropriate for the delivery to the systemic circulation of other drugs which are readily absorbed through the nasal mucosa, but which may be poorly absorbed or inactivated when given orally (Freestone and Weinberg, 1976; Chien and Chang, 1985). The efficacy of drugs delivered by the intranasal route, whether for local or for systemic use, will depend upon several factors including the nature of the drug and the pathology of the nasal passages, but also upon the amount of drug deposited and the intranasal distribution of drug particles or droplets (Freestone and Weinberg, 1976).

The distribution of nasal sprays has been assessed using models of the human nose (Mygind and Vesterhauge, 1978; Hallworth and Padfield, 1986), although the distribution patterns thus observed may not be the same as those occurring in-vivo. In this study, the deposition in both nose and lungs of insoluble radioactive particles released from a nasal pump spray has been determined in a group of normal subjects. Three different combinations of metered volume and spray cone angle have been compared.

METHODS

Insoluble particles of Teflon were made using a spinning disc generator (Newman et al., 1981); these particles had a mean diameter of 2 µm, equivalent to a mass median aerodynamic diameter of 3.2 µm, which is similar to that of the drug particles found in a budesonide aqueous nasal spray (Rhinocort® Aqua, Astra Pharmaceuticals). The radionuclide $^{99}Tc^{m}$ (Eγ 140 KeV; $T_{½}$ 6 hours) was used to label the particles, which were suspended subsequently inside placebo nasal sprays containing 3 ml aqueous vehicle. The sprays were equipped with either 50 µl or 100 µl metering valves (Morén, 1985; Petri et al., 1985) and with nasal adaptors having spray cone angles of either 35° or 60°, in such a manner that three different combinations of metered volume and spray cone angle A, B and C, Table 1) were studied. Droplet size data (Malvern Instruments 2600 HSD analyser), measured 3 cm from the spray nozzle, are also shown in Table 1. The mass median diameter of the spray droplets exceeded 60 µm for each combination and no more than 5% of the droplet mass was contained in droplets smaller than 10 µm diameter.

Table 1. Combinations of metered volume and spray cone angle studied.

code	metered volume (µl)	spray cone angle (deg)	number of puffs	% of aerosol mass < 10 µm diameter	mass median diameter (µm)
A	50	35	2	3	66
B	50	60	2	5	70
C	100	60	1	5	61

Thirteen normal volunteers (8 male, 5 female, age range 22–50 yr) were studied on three randomised occasions, once with each of combinations A, B and C. All subjects were free of upper respiratory tract infections, and gave informed consent in writing before commencing the studies. The Ethical Practices Committee of the Royal Free Hospital and the Administration of Radioactive Substances Advisory Committee (ARSAC) approved the project.

Before administering the spray, the valve was primed by actuating 10 times into a closed vessel. Each puff of aerosol was administered into the right nostril with the

left nostril held closed. The inhaler was held in the sagittal plane in order to minimise deposition on the nasal septum, and was held parallel to the dorsal ridge of the nose. The actuator tip was inserted approximately 1 cm into the right nasal vestibule, and the spray was actuated by an investigator. Subjects gave a rapid sniff-like inhalation through the nose and then exhaled through the mouth via a filter (Inspiron 002290) intended to trap any exhaled particles. A single puff of aerosol was given for combination C, but two puffs for each of combinations A and B. Each study commenced at approximately the same time of day (4 p.m.). Inhalers delivered approximately 370 KBq $^{99}Tc^{m}$ per metered dose; we estimate the dose to the nasal cavity as 560 μGy per study.

A gamma camera (General Electric Maxi) connected on line to a Varian V-77-600 data processing system was used to obtain static views of the nose and chest, which were stored as matrices of 64 × 64 (4096) cells. Lateral views of the nose were taken immediately after inhalation, and then 10, 20 and 30 minutes later; further lateral views up to 120 minutes were obtained in several subjects. No blowing or wiping of the nose was permitted throughout this period. An anterior-posterior view of the nose was also obtained immediately after inhalation. In order to determine whether any particles had penetrated the nose and entered the lungs, an anterior-posterior view of the chest was obtained within the first 10 minutes of inhaling the spray. For anatomical reference purposes, subjects wore ^{57}Co marker sources (Eγ 122 KeV; $T_{½}$ 270 days) on the bridge of the nose, chin and nape of the neck during the scans, the marker on the nape of the neck being removed for the anterior-posterior view of the nose.

A region of interest was drawn round the initial site of deposition on each of the lateral scans of the nose, and the number of $^{99}Tc^{m}$ counts, corrected for background and radioactive decay, were determined. The initial lateral and anterior-posterior views of the nose were assessed in order to determine the size of the initial area of deposition, the number of matrix cells within the 5% contour (i.e. within the line which gave a count rate equal to 5% of peak $^{99}Tc^{m}$ activity) being determined. Radioactivity measured over the chest was compared with background levels.

RESULTS

Typical initial particle distributions in the nose and the changes in distribution after 30 minutes are shown in Figure 1 for each of combinations A, B and C. The three ^{57}Co marker sources are also shown. Initially, particles were concentrated chiefly in the anterior part of the nose, but some were located more posteriorly in the main nasal passages. The latter particles had cleared to the nasopharynx after 30 minutes, but there was little change with time in particles located anteriorly. The initial anterior-posterior view of the nose showed a single concentration of particles just to the right of the midline (Figure 2 (i)). No significant radioactivity

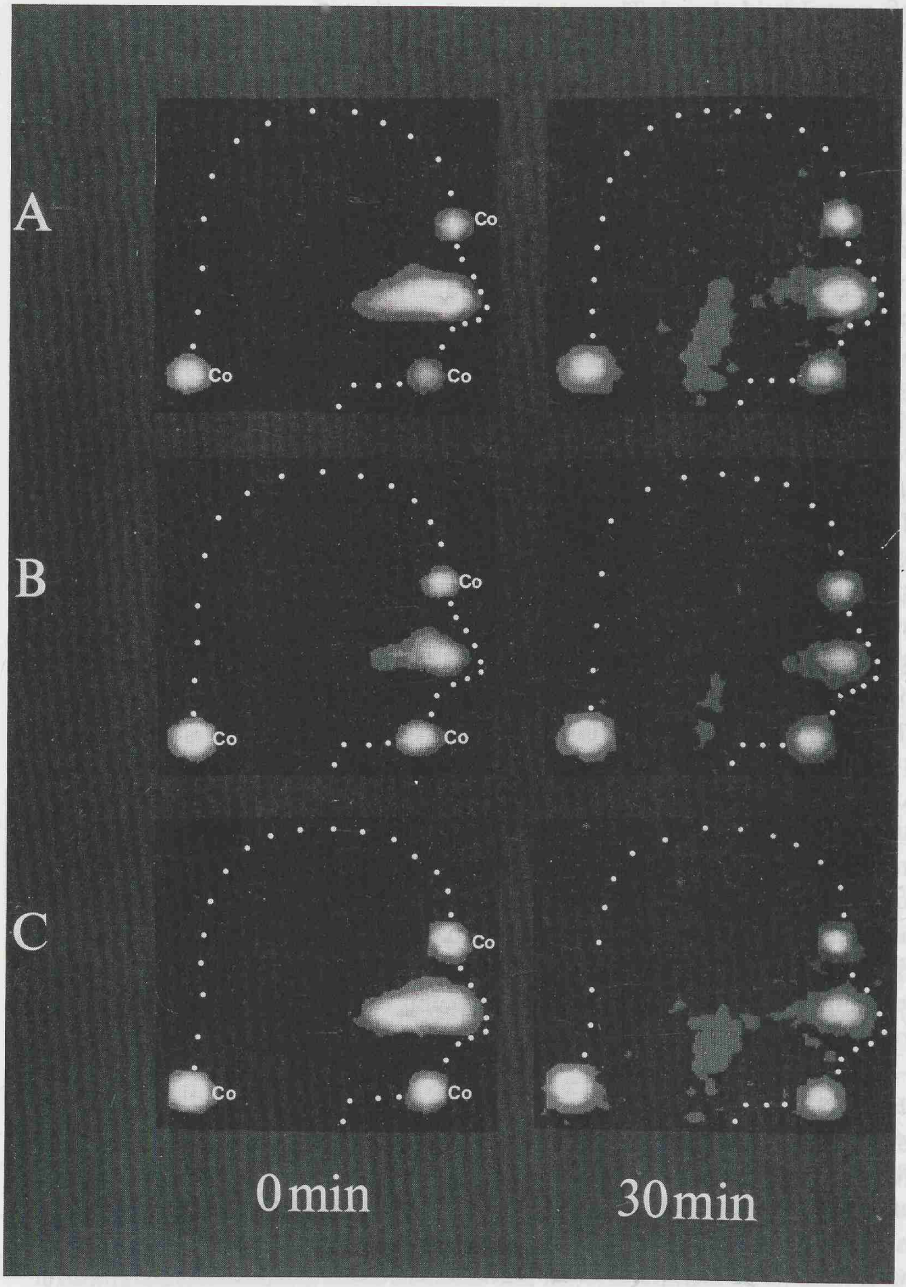

Figure 1. Initial particle distribution in the nose and change in distribution after 30 minutes for one subject with spray combinations A, B and C. The ^{57}Co marker sources on bridge of nose, chin and nape of neck are also shown, denoted by the symbol "Co".

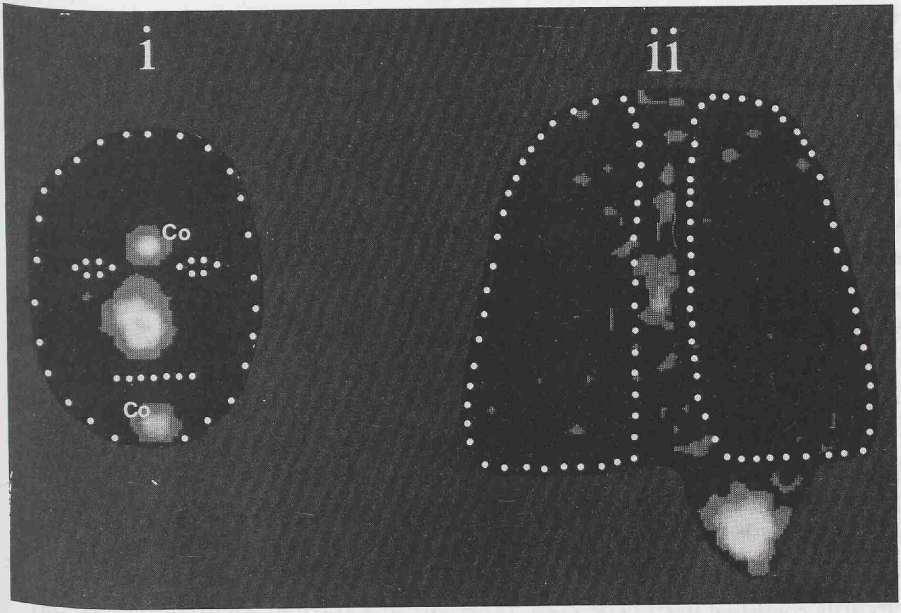

Figure 2. (i) Initial anterior-posterior view of particle distribution in the nose, with marker sources (symbol "Co") also shown on bridge of nose and chin. (ii) Scan of the chest after about 10 minutes. Radioactivity in the lungs was not significantly greater than background, but particles were located in both oesophagus and stomach following clearance via the nasopharynx.

was detected in the lungs (Figure 2 (ii)); the counts emanating from the lungs did not exceed the background count plus three standard deviations of the background. However, some particles were present in the oesophagus and stomach following clearance to the nasopharynx. No significant radioactivity was detected on the exhalation filter.

The area initially covered by the particles tended to be less for combination B compared to both combinations A and C (Table 2). This difference was statistically significant compared to combination C for both lateral ($P<0.05$) and ante-

Table 2. Numbers of matrix cells (Mean ± SEM) within the 5% contour for initial lateral and anterior-posterior views of the nose.

	combination		
view	A	B	C
lateral	53.2 ± 6.9	43.7 ± 3.7*	57.5 ± 7.3
anterior-posterior	18.9 ± 2.2	15.5 ± 0.8**	19.1 ± 1.9

* $P<0.05$ compared to C
** $P<0.02$ compared to C

rior-posterior ($P<0.02$) views, but did not reach statistical significance compared to combination A, (Wilcoxon rank sum test for paired data, Siegel, 1956).
The retention of particles at the initial site of deposition after 10, 20 and 30 minutes, expressed as a percentage of the amount initially deposited, is shown in Table 3. There was a trend for retention with combination B to be greater than that for combination A and C, although this only reached significance ($P<0.05$) when combinations B and C were compared after 10 and 30 minutes. The mean retentions of particles in the nose after 30 minutes were 49, 57 and 46% respectively for combinations A, B and C, indicating that a mean 51, 43 and 54% of particles had cleared.

Table 3. Mean ± SEM percentage retention of particles at the initial site of deposition.

	combination		
time	A	B	C
10 min	60.8 ± 5.2	71.3 ± 4.9*	58.3 ± 5.1
20 min	50.8 ± 5.0	61.8 ± 4.9	51.2 ± 4.8
30 min	48.7 ± 5.0	57.1 ± 4.5*	46.5 ± 4.4

* $P<0.05$ compared to C

Particle retention for one subject who was monitored up to 120 minutes after inhalation is shown in Figure 3. There was virtually no change in the counts from the nose (after correction for radioactive decay) between 30 and 120 minutes, although blowing the nose and then wiping the nasal vestibule with a paper handkerchief reduced the count-rate after 120 minutes by one-third. Similar results were observed in several other subjects monitored for 120 minutes after inhalation.

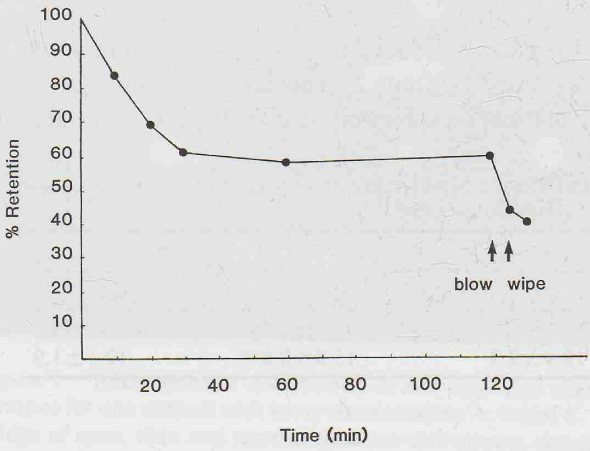

Figure 3.
Particle retention at the initial site of deposition in one subject recorded up to 120 minutes. After this time, the nose was blown and the vestibule of the nose wiped.

DISCUSSION

The radioactive particles used in this study were insoluble in body fluids, and their removal from the nose posteriorly towards the nasopharynx is presumed to have occurred by mucociliary clearance. While the main clearance pathway of drugs delivered to the nasal mucosa is by absorption (Chien and Chang, 1985), the use of a non-absorbable radiotracer permitted the relative amounts of spray deposited in ciliated and non-ciliated zones to be determined.

According to Proctor (1982), the anterior part of the nose, comprising the nasal valve and the most anterior regions of the inferior and middle turbinates, is free of ciliary activity. Insoluble particles deposited in this region may be cleared only very slowly by traction from contiguous mucus (Proctor et al., 1973), although there is also a zone in which the mucociliary stream moves deposited particles in an anterior direction to a point from which they may be removed by blowing or wiping the nose (Hounam, 1975; Proctor, 1982). The non-ciliated zone corresponds approximately to the area of the nasal valve where the airway cross-section is very small, the airstream is turbulent, and deposition by impaction is likely (Heyder and Rudolf, 1977). In these studies, approximately 50% of the radioactive particles delivered in the spray were deposited in the non-ciliated zone and remained static in the nose, even up to two hours, while about 50% had penetrated to the ciliated region in the main nasal passages and were cleared. Bi-phasic nasal clearance curves have been noted in other studies (Aoki and Crawley, 1976; Hardy et al., 1985; McLean et al., 1984). A relatively anterior distribution of droplets from nasal sprays has been observed not only in vivo but also in vitro using models of the human nasal cavity (Mygind and Vesterhauge, 1978; Hallworth and Padfield, 1986).

A single puff of 100 µl (C) was deposited over a greater area than two puffs of 50 µl (B); consequently more particles were delivered to the ciliated zones and were cleared, while fewer particles were retained in the anterior part of the nose. This observation is at variance with those of Aoki and Crawley (1976) and Bond et al. (1984) who observed no dependence of deposition and clearance of $^{99}Tc^{m}$ labelled human serum albumin on the metered volume of a nasal spray. However, the size of the deposition area was quantified in neither of these studies, and the numbers of subjects studied by Bond et al. (1984) may have been insufficient to enable relatively small differences between clearance curves to be detected. When the spray cone angle was raised from 35° (A) to 60° (B), there was a tendency for the deposition area to be reduced in size and for particle retention to be increased, perhaps because less of the spray was able to penetrate the narrow nasal valve onto the ciliated airways with the larger spray cone angle. Bond et al. (1984) noted similar clearance curves for sprays with cone angles of 30° and 60°.

Our results thus suggest that choice of metered volume and possibly choice of

spray cone angle may play a role in determining the quantity of drug able to penetrate to the main nasal passages. It may be desirable to maximise drug delivery to this region not only for effective topical therapy, but also to permit efficient absorption of compounds into the systemic circulation. The sites of action of drugs in the nose are not fully understood however, and it may be appropriate for some drugs for topical therapy to be deposited relatively anteriorly, since this is where inhaled allergenic particles might also deposit. The transport of some of the drug posteriorly might then counteract the effects of allergens being transported in the same direction.

Therapeutic agents may be delivered to the nose as drops, from pump sprays or from pressurised metered dose inhalers. The distribution of drops in the nasal cavity is more uniform than that of pump sprays (Aoki and Crawley, 1976; Hardy et al., 1985), although rather complex manoeuvres may be required on the patients' part in order to achieve this (Mygind, 1985). By contrast, the deposition from a pressurised inhaler is restricted to the anterior one-third part of the nose, with only 20% of deposited particles being cleared to the nasopharynx (Newman et al., 1987). This suggests that pump sprays might be superior to pressurised inhalers, although the corticosteroid budesonide, given as 400 µg daily, was equally effective by each device (Irander et al., 1984). It is possible that the amounts of drug used conventionally are more than sufficient to give a full therapeutic effect, despite no more than a small percentage of the dose reaching directly the area to be treated. Alternatively, there may be local absorption and redistribution of drug within the very vascular nasal mucosa, thus augmenting the topical effects of deposited corticosteroids.

These studies were performed in normal subjects, and the variability observed between individuals may reflect not only variation in nasal anatomy, but also variation with time in the airway resistance of each nostril. The deposition patterns observed in patients and the subsequent nasal clearance curves might differ from those observed here, especially if the nasal passages are congested or are obstructed by nasal polyps. Abnormalities in nasal clearance curves have been noted in subjects suffering from common cold (Bond et al., 1984), clearance being either speeded up or retarded according to whether the nose is runny or blocked. The present study forms a basis for a detailed analysis of the factors affecting the intranasal delivery of drugs, including the pathology of the nasal passages and whether or not the patient inhales while firing the spray.

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ZUSAMMENFASSUNG

Die intranasale Verteilung eines Pumpensprays wurde bei 13 gesunden Probanden untersucht. Benutzt wurden dabei nichtlösische Teflonteilchen, die mit $^{99}Tc^{m}$ markiert wurden, um die Verteilung von Medikamentenpartikeln zu simulieren. Drei unterschiedliche Kombinationen von Volumen und Sprühwinkeln wurden verglichen.

Die überwiegende Ablagerung der Teilchen wurde im vorderen, nicht zilientragenden Teil der Nase gefunden, aber einige Teilchen drangen auch tiefer in die Nasenhöhle ein und wurden von dort in den Nasopharynx transportiert. In der Lunge wurden keine Teilchen gefunden. Bei einer einzigen Vernebelung von 100 µl Volumen, wurden $46{,}5 \pm 4{,}4\%$ (mean $\pm$ SEM) des Sprays nach 30 Minuten im vorderen Teil der Nase nachgewiesen, bei zwei Sprühstoßen von je 50 µl stieg dieser Anteil auf $57{,}1 \pm 4{,}5\%$ an. Die zweite Vernebelung wurde über eine signifikant kleinere Fläche ($p < 0{,}05$) in der Nasenhöhle verteilt. Eine niedrige Teilchendichte bei grösserer Flächenverteilung trat bei Reduktion des Winkels des Sprüh-Konus von 60° auf 35° auf. Die Ergebnisse zeigen, daß Medikamente, die über ein Pumpen-Spray nasal verabreicht werden sowohl auf zilien-besetzte als auch auf zilienfrei Areale verteilt werden und die Wahl des Dosiervolumens und des Sprühwinkels einen Einfluß auf die Menge der intranasal vorgefunden Partikel hat.

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