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Distribution and clearance of radioactive aerosol on the nasal mucosa

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SUMMARY

The distribution and clearance of aerosolized radioactive technetium 99m pertechnate in physiologic buffered saline was analyzed in four human adult asymptomatic volunteers following delivery into one nostril in the same manner as for nasal challenge testing (i.e., 0.1 ml via a 251 DeVilbiss atomizer powered by a compressor delivering 0.10 ± 0.01 gm/spray). For comparison, squeeze bottles and spray bottles from commercial sources, a 114 and a 127 DeVilbiss atomizer, and a pipette were employed. Lateral imagery via minicomputer processing was used to determine both distribution and clearance of the radiotracer.

The counts after 1 minute were lower following pipette delivery than with the other devices. None yielded discernable, wide-spread distribution of aerosol throughout the nasal cavity. Following delivery from the 251 atomizer, mean clearance at 17 minutes was 60.0%. Similar clearance rates were obtained with the other spraying methods except for lower values with the squeeze bottle. Analysis of six hour clearance studies by linear regression showed a relatively rapid initial phase, which is probably due largely to mucociliary clearance, and a prolonged late phase related to the very slow disappearance of residual material located far anteriorly in the nose. Achieving good initial retention and rapid clearance of material deposited anteriorly in the nose are desirable attributes of devices employed for administering materials intranasally.

In an effort to better characterize the distribution and clearance of aerosolized solutions delivered to the nose for nasal challenge studies and physiologic investigations, radioactive technetium 99m pertechnetate was utilized as a tracer agent. It is selfevident that the distribution and clearance of materials applied to the nasal mucosa might importantly influence physiology or immunologic responses, and more information about this important potential source of variability is urgently needed to permit development of optimal and standardized methods of nasal testing and intranasal administration of medications and extract for immunotherapy.

PROCEDURE

Four human adult volunteers were tested during periods free from nasal stuffiness and infection at intervals no shorter than three days. Physiologic phosphate-buffered saline (PBS) containing technetium 99m pertechnatate was sprayed into one nostril initially in the same manner as nasal challenge tests are performed, (McLean, 1976); i.e., 0.1 ml was delivered via the 251 DeVilbiss atomizer powered by a compressor delivering 0.10 ± 0.01 gm/spray when the flow rate is held at 11.5 l/min and the duration of atomizer activation is approximately 0.10 sec at 7 psi. The aerosol produced had a mean particle size of 2.0 u with a standard deviation of 1.8 u. Subsequently squeeze bottles and spray bottles from commercial sources, DeVilbiss 114 and 127 atomizers and pipettes were used. The pressure for atomizer activation was adjusted so that the 114 and 127 atomizers also delivered 0.1 ml, and preliminary trials also approximately delineated the conditions required for delivery of 0.1 ml by Rhinilar® sprayer and a squeeze bottle widely used for delivering nasal sprays. The delivery apparatus was held at approximately a 30° angle from horizontal with its tip just outside the external naris except that the squeeze bottle was held vertically with the head tilted forward. For pipette delivery subjects were supine with the head hyperextended. The nose was 8 inches (in.) from the collimator during counting. Preliminary verification of the amount of aerosol delivered was accomplished by aerosolization into a container placed 8 in. away from the collimator, comparing the counts per minute, as displayed by the computer, with counts obtained by pipetting exactly 0.1 ml of the Tc 99m solution into a second container also placed 8 in. from the collimator. Then 0.1 ml of a stock solution containing approximately 600 μCi of Tc99m pertechnetate was aerosolized into the right naris by all the types of delivery techniques to be evaluated. A 10 in. single crystal scintillation camera (PhoGamma IV, Searle, Des Plains, IL) interfaced to a dedicated nuclear medicine minicomputer (Medical Data Systems, Modumed trinary version, Ann Arbor, MI) was used to determine both distribution and clearance of the radiotracer. A pinhole collimator with an aperature size of 4.75 mm was also utilized.

Lateral imaging of the nose and nasopharynx for a period of 20 minutes (min) was then performed with the subject's head in an upright position. At the conclusion of each setting a profile of the subject's head was obtained by outlining the head with a radioactive point source. This was done to display the distribution of the aerosolized solution in the nose, nasopharynx and oropharynx. The data was processed using the minicomputer mentioned above. Displays of the data for the 1st, 2nd and 20th minutes of the experiment were examined and photographed for comparison. The display was then sampled for the entire 20 min period and superimposed with the profile for another photograph. A curve of radioactive counts present per unit time anteriorly in the nose was then generated using the total number of radioactive counts for each of the 20 one-minute frames as data points.

In additional experiments the distribution of aerosolized material was studied hourly over 6 hours following administration of tracer with a 251 DeVilbiss atomizer employing the same initial 20 min imaging session as previously described.

RESULTS

Figure 1 shows results of preliminary verification measurements of the amount of aerosol delivered by the various devices into a container held in front of the collimator in the same position as the nose. It is seen that delivery by all methods yielded counts which did not differ significantly from pipetting the solution into the container. It is noteworthy that the variance of the "standard" 251 nebulizer method is relatively small (c.v. ± 13.6%). The last column in Figure 1 emphasizes

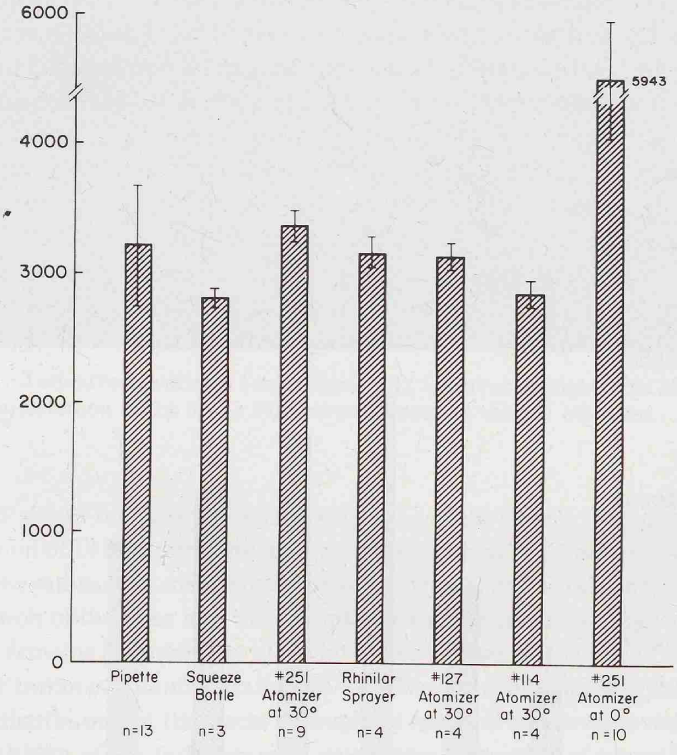

Figure 1. Outputs of the test devices determined just before use in each experiment. Each bar indicates the mean percentages of the cpm values of material sprayed into a container held 8 in. before the collimeter as compared with the cpm of exactly 0.1 ml of the same Tc 99m pertechnetate solution pipetted into a test tube held 8 in. before the collimeter. Also indicated are ± 1 SD of the percentages obtained in different experiments. The atomizers and sprayers were held 30° from horizontal except for the squeeze bottle, held vertically, and the indicated experiments where the 251 atomizer was held horizontally.

the importance of holding the nebulizer at a constant angle, the output increasing very much at a horizontal position.

Figure 2 shows the counts during the first minute of imaging after intranasal delivery of Tc 99m pertechnetate by the various devices. The mean of 2721 cpm following aerosol delivery by the DeVilbiss 251 atomizer constitutes 81% of mean cpm of 3376 obtained after spraying into a container (Figure 1); the other nebulizers and the Rhinilar® sprayer gave fewer counts, but the differences were not significant. However, following pipetting or application by squeeze bottle the nasal counts during the first minute were much lower ($p < 0.05 + p < 0.05$ respectively by Student's t test). This indicates that either the solutions partly passed rapidly through the nose or did not enter the nasal cavity. The former possibility is documented in the pipetting experiments wherein the first minute display shows radioactivity already present in the oropharynx, whereas this did not occur when the Tc 99m pertechnetate was sprayed into the nose. The fact that subjects were supine during the pipetting experiments no doubt contributed to the rapid drainage into the oral pharynx, as well as the lack of physical dispersion of the test material.

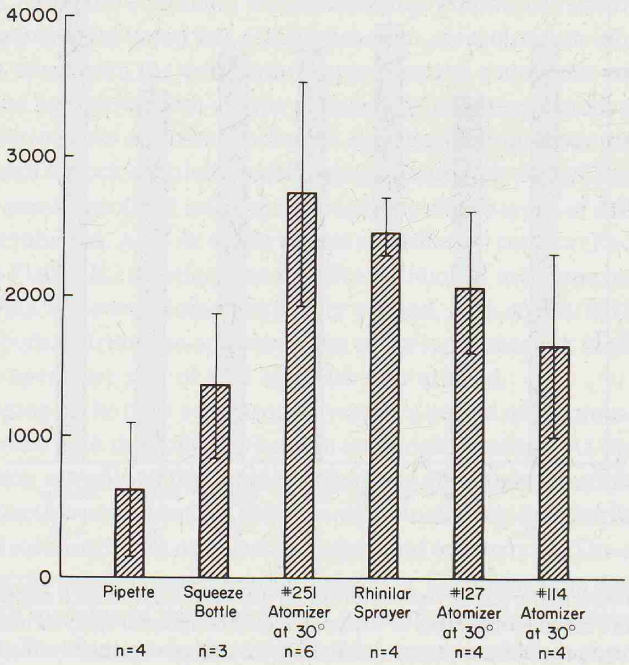

Figure 2. Counts during the first minute after nasal administration of Tc 99m pertechnetate by the various devices. Nose was 8 in. from the collimeter. Vertical bars indicate ± 1 SD.

Figure 3. Lateral image of nose 1 min (upper left), 5 min (upper right), and 20 min (lower) after administration of 0.1 ml Tc 99m pertechnetate by the 251 atomizer.

Figure 3 shows representative lateral images of the nose 1, 5 and 20 min after application of Tc 99m pertechnetate via the DeVilbiss 251 atomizer. A major portion of the radioactive material can be seen to travel posteriorly through the inferior portion of the nose into the nasopharynx and pharynx, though a significant amount remains far anteriorly in the nose (see below). With none of the methods used for intranasal administration of Tc 99m pertechnetate was there a widespread distribution of the tracer throughout much of the nasal cavity. To assess the sensitivity of the test system to detect small amounts of tracer in the nose, tubes containing serial dilutions of Tc 99m pertechnetate were positioned 8 in. away from the collimator. It was found that greater than a 30 fold dilution of the tracer still gave counts well above background (which was only 0–5 cpm). Attempts to achieve better distribution of the tracer through use of a nebulizer, such as is used for bronchial administration of drugs, resulted in insufficient aerosol output to generate a clear image in the nose.

To determine whether the residual radioactivity remaining in the nasal mucosa at 20 min after delivery by the 251 DeVilbiss atomizer was on the mucosal surface or absorbed into the submucosa, clearance of the Tc 99m pertechnetate was determined after nasal washes with saline. After washing at 1 min, clearance was 96.2 ± 2.6% at 20 min; after washing at 18 min, clearance was 92.0 ± 3% at 20 min. This indicates that the Tc 99m pertechnetate remaining at 20 min, largely far anteriorly, is not substantially bound to or in the mucosa at that time.

Clearance of the Tc 99m pertechnetate from the nasal cavity during the first 20 min after its introduction was assessed by 2 procedures. First, percent clearance was determined by comparing the cpm at 20 min with the cpm during the first min (Table 1). The large coefficients of variation in Table 1 reflect substantial inter-subject variability in assessing the various devices. Table 2 shows somewhat lower intra-subject variance in repeatedly testing the 251 nebulizer in the same individual. However, all other investigators noted significant inter- and intra-subject variability (Hilding, 1932; Proctor and Wagner, 1965; Bang et al., 1967; Proctor et al., 1973; Proctor, 1969; Quinlan et al., 1969). There were no significant differences among the devices (Table 1) except for the lesser clearance after using the squeeze bottle ($p < 0.05$ compared with the 251 atomizer; $p < 0.05$ compared with the pipette).

Table 3 indicates the effect of sniffing in on Tc 99m pertechnetate clearance following delivery via Rhinilar® sprayer. As noted, this manoeuvre hastened clearance.

Table 1. Variation between devices for % clearance at 20 min.

device	n	mean	standard deviation	coefficient of variation
squeeze bottle	5	17.0	7.3	43%
no. 114 atomizer	4	55.7	22.6	41%
no. 127 atomizer	4	57.0	17.4	30%
Rhinilar sprayer	4	57.1	15.5	27%
pipette	13	42.2	21.9	52%
no. 251 atomizer	9	63.9	18.9	29%

Table 2. Reproducibility of clearance measurements in the same individual on repeated trials with the DeVilbiss 251 atomizer.

subject	mean clearance*	sd	cv**	n
1	60.9	23.4	38.4	5
2	76.4	17.9	23.4	5
3	47.9	4.5	9.3	5
4	63.2	18.3	28.9	4

* at 17 min.
**coefficient of variation.
Mean cv = 25.0

Table 3. Comparison of clearance with and without sniffing in during delivery, by Rhinilar sprayer.

	without sniff		with sniff	
subject	1st min counts	% clearance at 20 min	1st min counts	% clearance at 20 min
1	2710	75%	3648	95%
2	1580	44%	1982	55%
3	2107	49%	2504	59%

Table 4.

spray device	mean slope	standard deviation
no. 251 atomizer	−0.029	.025
no. 127 atomizer	−0.016	.007
no. 114 atomizer	−0.024	.017
pipette	−0.015	.010
Rhinilar sprayer	−0.018	.009
squeeze bottle	−0.005	.002

To take advantage of all the 1 min counts from 1 to 20 min, clearance also was evaluated by calculating the linear regression of nasal cpm against time for each device in each test subject. Figure 4 displays the mean results for each device, and Table 4 indicates the variance of these slopes. There was no significant difference between these slopes by this method of analysis.

Figure 5 shows the mean clearance of Tc 99m pertechnetate over 6 hours from the nasal cavities of 3 normal subjects after spraying with a 251 DeVilbiss atomizer. It

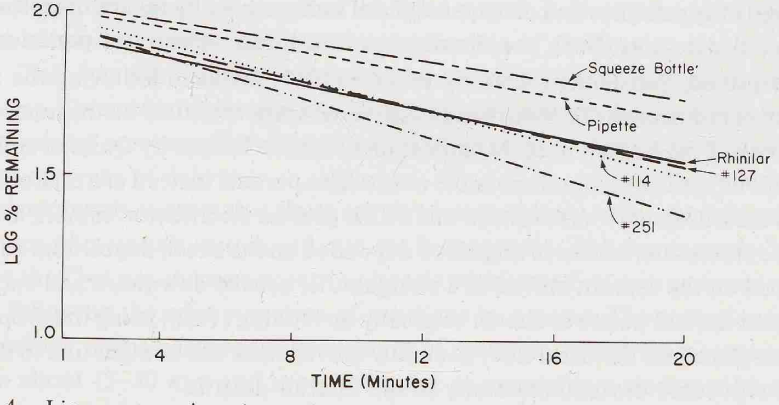

Figure 4. Linear regression slopes depicting man clearance of Tc 99m pertechnetate during the first 20 min after application by pipette -----; squeeze bottle — - — - —; 251 atomizer — .. — .. — ..; 127 atomizer — — — —; 114 atomizer .....; and Rhinilar® sprayer ————.

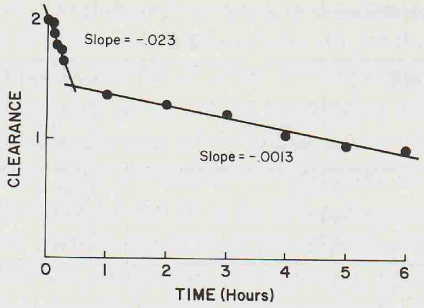

Figure 5. Mean 6 hr clearance of Tc 99m pertechnetate after administration by the 251 atomizer (N = 3). The 2 slopes were calculated by linear regression, the early slope being $-.023 \pm .02$ and the second, slow slope being $-.0013 \pm .00026$.

is apparent that the long-term clearance is a biphasic process with mean slopes of -.023 and -.0013. The slow, second phase is related to the gradual disappearance of the tracer retained far anteriorly in the nose. Since the long interval images fail to show backward movement of this material, it is unknown whether it is slowly cleared posteriorly in concentrations too low to be detected or whether it is slowly absorbed anteriorly over several hours.

DISCUSSION

In 1965 Proctor reported clearance studies on the human nose using a saline solution containing 10–20 uCi of macroaggregated albumin labelled with iodine I^{131} which was delivered via a microsyringe into the nose along selected areas. Radioactivity distribution was followed by serial scanning and recording the time course of appearance and disappearance of radioactivity by means of crystal scintillation detectors. Both the distribution and linear velocity of particles were determined. Subsequent work by Proctor (1969) involved following the movement of radioactive (Tc-99m) beads with serial scans in a study on the mucociliary activity of the human nose. Modification of this technique by Quinlan and Proctor (1969) utilized a nondispersible radioactive particle instead of a microdroplet, and measurements were carried out with a gamma scintillation camera. In these three studies the course of migration depended on the site of deposition. Particles placed on the septum moved in a straight line, usually downward and backward toward the soft palate as shown originally by Hilding (1932) using ink drops. Particles placed on the nasal floor generally moved back in a straight line to the palate with some deviation laterally to the inferior meatus.

Bang et al. (1967) reviewed the mucociliary clearance rates for the human nose published prior to 1967 utilizing powder or dyes. The average rate was 4–5 mm/min with a range of 1–12 mm/min. Results of more recent studies (Proctor et al.,

1973; Yergin et al., 1978) employing radioactive tracers or radioopaque teflon discs showed an average of 4–11 mm/min, with a range of 0–22.5 mm/min. The relevance of this information to our data is uncertain since we were not using macromolecular or particulate radioactive tracers, but the values given are in accord with the hypothesis that the second pase of clearance (see below) is due at least in part to mucociliary activity. However, it is to be emphasized that the focus of this study has been an evaluation of different methods for challenging (or testing) the nasal mucosa, and the methods employed are less suitable for measuring mucociliary activity than some of those employed in the previously cited studies.

More closely related to our work are the studies of Aoki and Crowley (1976) who instilled Tc 99m human serum albumin intranasally in eleven human volunteers and studied the time course of removal using a gamma camera and an anterior scintillation detector. Much like our results, activity recorded by the detector showed an initial fall associated with removal of most of the material from the nasal cavity, followed by a slower decline associated with the removal of material mainly from the anterior region of the nose. Proctor is also reported to show a similar initial rapid and later slow removal of particles, corresponding to material retained in the anterior nonciliated area of the nose (Proctor, 1966).

Utilizing a silastic material to produce a cast of the human nose, Mygind and Vesterhauge (1978) studied aerosol distribution patterns produced by various pressurized aerosols and nebulizers. Toludine blue was used as the tracer material. Freon-propelled, pressurized canisters produced aerosols reaching all parts of the nose, but the main distribution was concentrated to a narrow band especially marked on the septal wall. The amount of distribution from a squeeze type plastic bottle nebulizer was broader and shorter than the pressurized aerosols and highly dependent on the strength of the hand power. A DeVilbiss 15 nebulizer and an automized pump produced the largest area of distribution on the nasal lining. This was significantly influenced by the direction of the orifice of the nebulizer. The automized pump also afforded better delivery because of the constant dose and pressure. Simultaneous inhalation improved the area of distribution for all types of delivery.

Our experiments suggest that there are three components to the deposition and clearance of materials introduced into the human nose. The first is a very rapid "water shed" or run-through occurring largely within the first min and seen especially following the administration of solutions by pipette. The second component relates to the progressive movement of material toward the nasopharynx within about 15–30 min and is probably due to mucociliary clearance. A third phase consists of the very slow disappearance, over a number of hours, of material initially retained far anteriorly in the nose. It is very possible that this material remaining far anteriorly is resting on the squamous, non-ciliated epithelium lo-

cated in that area (Hilding, 1932; Proctor and Wagner, 1965; Quinlan et al., 1969; Proctor et al., 1973; Aoki and Crawley, 1976). The second and third phases of nasal clearance observed by us are in agreement with the observations of Aoki and Crawley (1976) and of Proctor et al (1973), though results of studies in different laboratories are apt to be influenced importantly by aerosol particle size. Intuitively it would seem that delivery systems which maximize the second phase of clearance may be most useful in exposing the nasal mucosa to testing materials or therapeutic agents over a desirable period of time (e.g., when nasal challenge test are being performed every 15 min). The various devices tested showed no significant differences in this respect except for the squeeze bottle. This suggests that clearance following the initial deposition of the technetium 99m pertechnetate generally is rather similar. However, the significantly decreased clearance at 20 min following use of the squeeze bottle most likely is due to increased initial deposition in the far anterior area of the nose where the tracer remains immobile for a prolonged period. It would seem obviously desirable to provide initially a wide-spread distribution of test or therapeutic material throughout the nasal cavity, but none of the methods assessed in this study achieved this goal as far as could be determined within the limits of sensitivity of our monitoring system. It would have been desirable also to have tested freon-propelled nasal sprays, but we lacked equipment to pressurize and seal canisters fast enough to permit experiments employing a tracer with such a short half life as technetium 99m pertechnetate.

ZUSAMMENFASSUNG

Die Verteilung und Aufnahme von aerosolisiertem radioaktivem Technetium 99m Pertechnat in physiologischer Kochsalzlösung wurde an 4 freiwilligen gesunden Versuchspersonen durch Einblasung in ein Nasenlumen ähnlich dem nasalen Provokationstest (d.h. 0,1 ML Nr. 251 De Vilbiss Zerstäuber, angetrieben von einem Kompressor $0{,}10 \pm 0{,}01$ gn/Spray) getestet. Verwendet wurden dabei vergleichsweise sowohl einfache Plastik-, Sprühflaschen kommerzieller Herkunft Nr. 114 und Nr. 127 De Vilbiss Zerstäuber, auch eine Pipette. Dabei fand sich eine Minute nach Applikation des Aerosols bei Pipettengabe eine niedrigere Verteilungsquote als mit den anderen angewendeten Zerstäubern. Bei keiner Anwendungsgabe war das Aerosol in der ganzen Nasenhöhle verteilt. Die durchschnittliche Aufnahmequote betrug bei Verwendung des Zerstäubers Nr. 251 nach 17 Minuten ca. 60%. Gleiche Ergebnisse wurden mit den anderen Spraymethoden erzielt mit Ausnahme der einfachen Plastikflasche, die niedrigere Werte ergab. Die Analysen der Aufnahme des Aerosols innerhalb 6 Stunden bei linearer Regression ergaben eine relativ schnelle Anfangsphase, die weitgehend durch den mucociliaren Abtransport erklärt werden kann und eine verlängerte Spätphase, bedingt durch das sehr langsame Verschwinden von Restmate-

rial in der vorderen Nasenregion. Bei der intranasalen Applikation von Medikamenten sollten deswegen Geräte zur Anwendung kommen, die eine initiale gute Speicherung und nachfolgende schnelle Aufnahme des Aerosols gewährleisten.

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