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DISTRIBUTION AND REMOVAL OF HUMAN SERUM ALBUMIN–TECHNETIUM 99m INSTILLED INTRANASALLY

F.Y. AOKI

Division of Communicable Diseases, MRC Clinical Research Centre, Harrow, Middlesex

J.C.W. CRAWLEY

Radioisotopes Division, MRC Clinical Research Centre, Harrow, Middlesex

1 The efficacy of antiviral drugs and vaccines administered intranasally may depend upon the technique of application.

2 The distribution and time-course of removal of human serum albumin-technetium 99m (HSA-Tc 99m)–instilled intranasally were studied in eleven healthy volunteers using a gamma camera and an anterior sodium iodide scintillation detector.

3 In 100 randomized studies material was delivered as drops in the supine position or as a spray to seated subjects.

4 A significantly higher proportion of 'good' distributions (62 in 73 tests) was obtained with drops compared with spray (1 in 27).

5 The volume administered was varied between 0.10 ml and 0.75 ml and the concentration of HSA was changed from 3 to 30% with no significant effect upon the distribution of time-course of removal; pertechnetate in isotonic saline was distributed and removed in a manner comparable to HSA-Tc 99m.

6 Activity recorded by the detector showed an initial rapid 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.

7 A multidose study confirmed that frequent administration by drops is required to maintain a high level of activity in the nasal cavity.

8 Using this technique it should be possible to correlate measurements of antiviral efficacy and vaccines take-rates with certain characteristics of intranasal applicators; such studies may lead to the design of better devices.

Introduction

Some antiviral agents and vaccines used experimentally for the prophylaxis of virus infections of the nose are administered intranasally as drops or by spray. Bucknall (personal communication) has suggested that the intranasal distribution of antiviral agents may be of prime importance in whether or not they show clinical activity. White, Freestone, Bowker, Barnes, Letley & Ferris (1975), working with an attenuated influenza A vaccine, found that different techniques and devices used for intranasal vaccination gave significantly different sero-conversion rates. However, there are no methods at present to demonstrate the distribution after intranasal administration and thus find out whether certain distributions can be correlated with good activity of drugs or higher vaccine take-rates.

Although the transport of isolated particles applied to the mucous layer has been studied in some detail (Ewert, 1965; Proctor & Wagner, 1965; Bang, Mukherjee & Bang, 1967; Quinlan, Salman, Swift, Wagner & Proctor, 1969), little is known of the distribution and removal of multiple particles or solutions instilled intranasally, situations more closely resembling drug or vaccine administration. In order to study directly different methods of administration and to begin to define a rational basis for administration of solutions and vaccines intranasally, we have therefore set up a technique to study the distribution and time-course of removal of human serum albumin (HSA) labelled with technetium 99m (Tc 99m). As well, we studied the effects on these of the volume administered, the concentration of the material and the method of application. This information was used to design a dose schedule aimed at

maintaining intranasal 'drug' content between pre-determined limits.

Methods

Subjects

Eleven healthy subjects aged 19-32 years (mean 25 years) who gave written consent underwent 100 randomized studies (mean 9 studies, range 3-13). The design of the study was approved by the Ethical Committee. None of the volunteers had symptoms of nasal disease at the time of the once-weekly studies; when intercurrent respiratory tract or other illness occurred, at least 14 days were allowed to elapse after disappearance of symptoms before resumption of the studies. No subject had a history of serious trauma to the nose or of nasal surgery; examination was limited to confirming the free passage of air through both nostrils. All were non-smokers.

Preparation of HSA and HSA–Tc 99m

Salt-poor sterile HSA was kindly donated by the Lister Institute of Preventive Medicine, Elstree. It contained not less than 96% albumin of which 80-95% was albumin monomers, the remainder albumin dimer and polymers (Vallett, 1974). The HSA had been prepared from Hepatitis B antigen negative plasma heated to 60° C for 10 h to further reduce the risk of infection. HSA was dissolved in sufficient sterile isotonic saline to yield solutions of 34.0 g/100 ml, hereafter referred to as 30% HSA, and 3.4 g/100 ml, hereafter 3% HSA.

HSA (0.008 gm) was labelled with Tc 99m by electrolysis in an acid solution with zirconium electrodes using a modification of the technique of Benjamin (1969): Two zirconium wires were inserted through the rubber cap of a sterile 8 ml vial containing 0.21 ml of 1.0 N HCl. Isotonic saline (1.25 ml) containing 10-15 mCi of Tc-99m and 0.1 ml 8% HSA in isotonic saline were added to the HCl and the wires connected to a current source. The vial was inverted and a current of 50,mA passed for 25 s with constant agitation. The solution was allowed to stand for 30 min and then neutralized with 1.0 N NaOH. The proportion of unbound Tc 99m was measured by paper chromatography using methylethylketone. The preparation was rejected if more than 5% of the Tc 99m was unbound. The mean specific activity of 30 preparations of HSA-Tc 99m was 7.4 mCi/ml.

Material for intranasal administration was prepared by adding 100 μCi of HSA-Tc 99m to the appropriate volume of either 3 or 30% HSA, giving a final concentration of 3 ± 0.4% or 30 ± 6% HSA. Nine of the samples were sent to the Northwick Park Hospital pathology laboratory for measurement of HSA concentration and all results agreed with the calculated concentrations.

Doses and administration of HSA-Tc 99m

Subjects were given doses of 0.10, 0.25, 0.50 or 0.75 ml of 3 or 30% HSA solutions in one nostril at each study. Solutions were administered either by drops in the supine position or by spraying in the sitting position. Both solutions were instilled by drops; only the 3% solution could be sprayed.

Initially, 36 randomly allocated studies with these four volumes using 30% HSA were conducted. Thereafter studies with 0.10 ml were discontinued because the results were the same with 0.25 ml, and six new dosage schedules, employing 3% HSA (0.25, 0.50 or 0.75 ml by drops or spray) were introduced into the study and randomly allocated.

Each dose of 100 μCi of HSA-Tc 99m mixed with the appropriate volume of 3 or 30% solutions was administered at 37° C.

Drops were instilled intranasally using a Finn-pipette (Jencons Scientific Equipment, Herts, England) with a disposable sterile plastic tip with its end removed to yield an orifice diameter of 2-3 mm. The volunteer was positioned supine with the neck extended so that the tip of the chin and the external auditory meatus were in the same vertical plane. The Finn-pipette was held vertically with the tip inserted approximately 1 cm into the nasal cavity and the solution was gently ejected into the nose. After instillation of drops, the subject remained in this position breathing through the mouth for one minute before moving to the sitting position for measurement.

Solutions of 3% HSA containing 100 μCi of Tc 99m per dose were also sprayed into the nasal cavity using a Jencon Repette-injector with a disposable tip (Risdon Manufacturing Co., New Jersey, USA) designed to produce a fine spray. The spray was directed towards the apex of the nose by seating the volunteer with the neck extended so that the chin and external auditory meatus were in the same horizontal plane. The barrel of the spray injector was then held horizontally with the tip resting just inside the nasal orifice. The material was sprayed in over 2-3 s by steady pressure on the trigger while the volunteer gently inhaled through the nose. The subject remained still for one minute, breathing through the mouth, before moving to the measurement position.

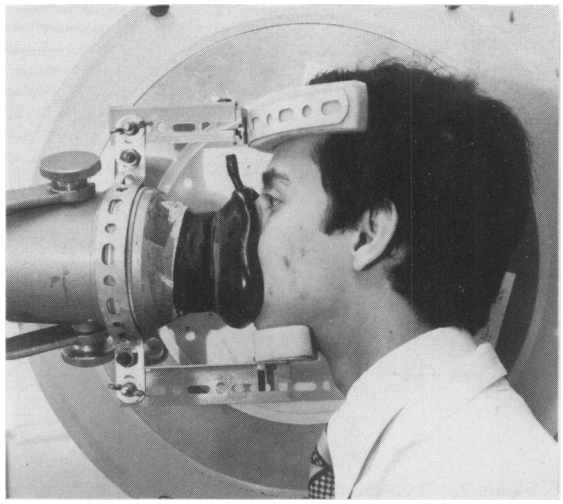

Figure 1 The subject sits in front of the gamma camera with his face in the mask attached to the lead collimeter on the scintillation detector. His head is supported by chin and forehead rests.

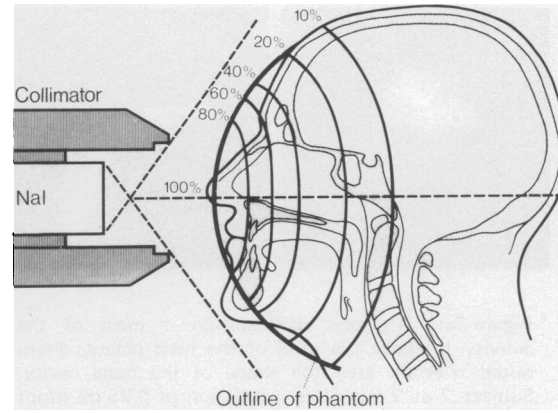

Figure 2 Isosensitivity curves obtained from a circular water phantom are superimposed upon a drawing of a near mid-line sagittal section of the head and the field monitored by the Na I crystal. Material leaving the nasal cavity is in the region between the 10% and 20% profiles. ▥ lead; ▨ bone.

Distribution and time-course of removal of HSA-Tc 99m

In the measurement position (Figure 1) the subject sat in front of a gamma camera (Nuclear Chicago Pho Gamma III) so that the sagittal plane through the midline was approximately 10 cm from the face of a converging collimator ('Div-Con' collimator). The field of view included the upper airway to the level of the glottis, below which all activity was removed by swallowing. Lateral view scintigrams were recorded on polaroid film when rapid sequences were required, or on 14 inch x 11 inch X-ray film at about 1.3 times full size when fewer pictures were required. Exposures of 30,000 to 50,000 counts were obtained in 0.8 to 6 minutes. The median time for the first scintigram was 1.8 min (range 0.8 to 6 min) for 50,000 counts.

Radioactivity was measured by a 2 inch thick x 2 inch diameter sodium iodide (NaI) crystal with a lead collimator (E.R.D. Engineering Ltd, Mk II Universal Scintillation Counter) situated about 7 cm in front of the nose. A rubber face mask, chin rest and forehead rest were fitted to the collimator in order to minimize movement (Figure 1). Isosensitivity profiles of this detector were obtained using a water phantom which consisted of a circular plastic dish with approximate dimensions of a human head; these profiles are superimposed on a diagram of the anatomy of the head as seen in a sagittal plane close to the midline (Figure 2) and the field monitored by the NaI crystal. The sensitivity pattern can only be an approximation because the head contains tissues with different densities. However, the main contribution was from the region above the hard palate–the region of most interest. A scaler/ratemeter (J & P Engineering, M.S. 310) was used to record 10 s digital counts at 1 min intervals and to plot count rate using a chart recorder (Rikadenki Kassette). The measurements started 1.5-2 min after administration of the HSA and continued for 15 min with the volunteer mouth breathing. Thereafter the volunteers resumed their normal work, returning in 15 min and then at 30 min intervals for 1.5 h. Further measurements were made at 1 h intervals up to 6 hours. No limitations were placed on eating and other activities, but volunteers were asked to refrain from blowing their noses.

Analysis of distribution of HSA-Tc 99m

The distribution of HSA-Tc 99m seen in lateral scintigrams taken 1.5-2 min after instillation was analyzed by a radiologist who was unaware of the identity of the volunteer, the volume administered, the concentration or mode of administration. The distributions were classified as 'good', 'equivocal' or 'poor', as follows: A 'good' distribution was characterized by radioactivity over an area the shape of the nasal cavity with most of the activity above the horizontal plane

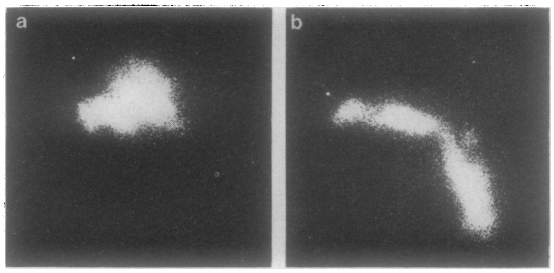

Figure 3a: A 'good' distribution : most of the activity is above the level of the hard palate, distributed over an area the shape of the nasal cavity. Subject 2 at 2 min after instillation of 0.25 ml drops 30% HSA-Tc 99m; exposure 50,000 counts in 1.8 min.

b: A 'poor' distribution : most of the activity distributed below the plane of the hard palate. Subject 10 at 2 min after instillation of 0.25 ml 30% HSA-Tc 99m by spray; exposure 50,000 counts in 1.8 min.

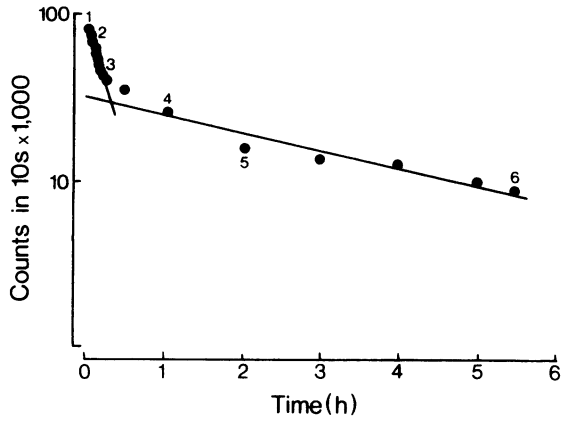

Figure 4, Typical curve of activity on a logarithm scale plotted against time on a linear scale. Subject 1 given 0.50 ml 3% HSA-Tc 99m as drops. Scintigrams were taken at the following times : (1) 1.5 min; (2) 4.5 min; (3) 8.5 min; (4) 1 h; (5) 2 h; (6) 5.5 h. Each exposure was for 2 min.

through the hard palate (Figure 3a). A 'poor' distribution was one in which the activity was not distributed across the area of the nasal cavity with most of the activity seen below the plane of the hard palate (Figure 3b). 'Equivocal' distributions were those which fit neither of these categories.

Analysis of the time-course or removal of HSA-Tc 99m

Each 10 s count was corrected for the decay of Tc 99m (6.05 h half-life) and plotted on semi-logarithmic paper with time on the abscissa. Straight lines were drawn to give the best fit, judged by eye, through the initial and final parts of the curve (Figure 4). Using these lines to estimate the length of the initial straight portion of the curve a line of best fit was then calculated using the method of least squares between $\log_{10}$ (10 s counts) and time on a programmable desk-top computer (Wang 500). The half period ($T\frac{1}{2}$) of the initial slope (Bassingthwaighte, Strandell & Donald, 1968) was then calculated from the equation $y = mx + c$ given by the computer using the expression

$$T_{\frac{1}{2}} = \frac{\log_{10} 2}{m} .$$

Stability of HSA-Tc 99m binding in the nasal cavity

The stability of the Tc 99m labelling was studied by instilling HSA-Tc 99m in 3% HSA by drops in the usual manner, taking a scintigram at 1.5 min and then washing out the nose with 15 ml of 37°C Hanks balanced salt solution according to a standard technique (Tyrrell, 1965). A parallel control solution was prepared by adding the same dose to 10 ml of nasal wash solution. Material obtained by nasal washout, the original labelled HSA-Tc 99m and the control solution, were tested for unbound Tc 99m.

Studies with Tc 99m pertechnetate

Studies were undertaken using 100 μCi of Tc 99m pertechnetate column eluate mixed with isotonic saline and instilled as drops or by spraying.

Multiple dose studies

We used $T\frac{1}{2}$ of the initial slope to design a multiple-dose schedule aimed at maintaining the counts between 50% and 100% of the value at the $t = 0$ intercept of the initial slope. Since the total radioactivity we were authorized to instil per week was 100 μCi, three doses were administered; 50 μCi followed by two doses of 25 μCi at intervals of $T\frac{1}{2}$ after the initial dose.

Relative humidity (RH)

This was measured in the study room using a wet-and-dry bulb whirling hygrometer (Negretti and Zambra Ltd) or with a conventional wet-and-dry bulb apparatus and conversion table (Childs,

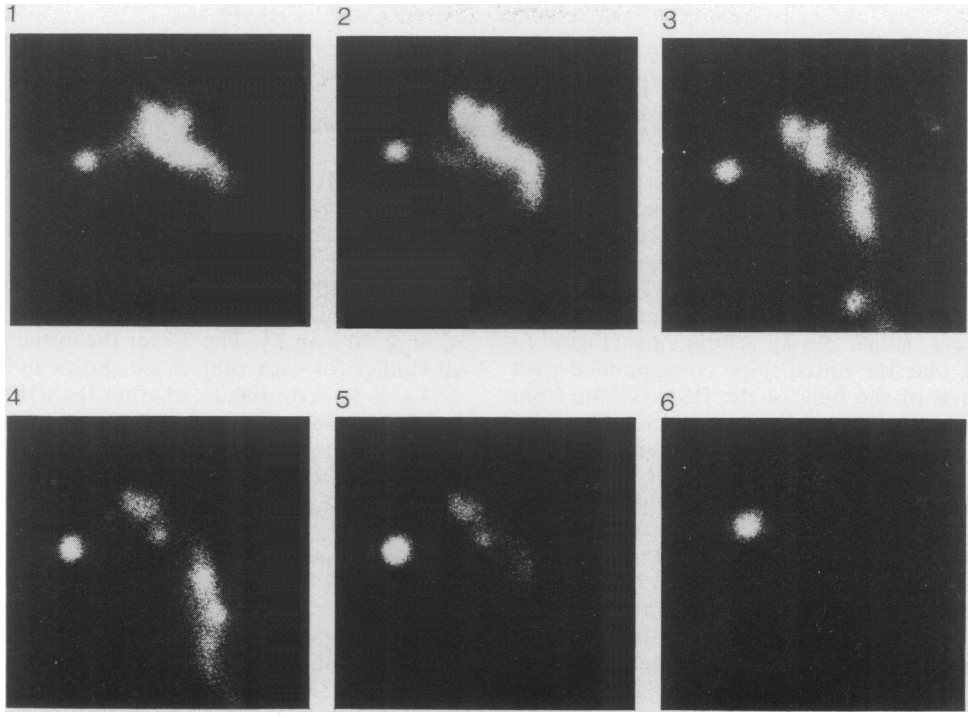

Figure 5 Scintigram 1 shows a 'good' distribution. 1, 2 and 3 show that the initial slope corresponds to the removal of material mainly from the nasal cavity; 4, 5 and 6 correspond to the second component and show that this is mainly due to a small amount of material retained in the anterior part of the nose.

1939). No attempt was made to alter the relative humidity during the studies.

Statistical analysis

Data were analyzed by paired and unpaired *t*-tests and chi squared tests. $P \leqslant 0.05$ was considered significant.

Results

Distribution

The independent observer's classification of distributions on scintigrams taken at 1.5 to 2 min after instillation are shown in Table 1. Chi squared tests showed a significantly higher ($P<0.001$) proportion of 'good' distributions (62 in 73) after drop administration than after spraying (1 in 27). No significant effect of concentration on the proportions of 'good', 'equivocal' and 'poor' distributions was found. In order to analyze the effect of volume on distribution by paired *t*-tests, it was necessary to combine the 'equivocal' and 'poor' classes as 'not good'. This was possible because the proportion of 'good' distributions for 30% HSA drops did not differ significantly from that for 3% drops. No significant effect of volume on the proportion of 'good' and 'not good' distributions was demonstrated, after drop administration. Data were too few to permit similar analyses with the spraying mode. RH $<$ or $\geqslant$ 40% did not significantly affect the proportion of 'good' and 'not good' distributions.

Table 1 The independent observer's classification of distributions on 100 scintigrams in eleven subjects

	Volume (ml)	*'Good'*	*'Equivocal'*	*'Poor'*
3% HSA drops	0.25	10	2	1
	0.50	5	3	1
	0.75	9	0	0
	Total	24	5	2
30% HSA drops	0.10	6	1	1
	0.15	11	0	1
	0.50	12	0	1
	0.75	9	0	0
	Total	38	1	3
3% HSA spray	0.25	0	0	7
	0.50	0	2	7
	0.75	1	1	9
	Total	1	3	23

Analysis of time-course of removal of HSA-Tc 99m from the nasal cavity

A typical plot of the $\log_{10}$ (10-s counts) of activity plotted against time on the abscissa is shown in Figures 4 and 5 together with serial polaroid lateral scintigrams taken at the times indicated. The time-course of the $\log_{10}$ (10-s counts) consistently described such a biphasic curve with a steep initial portion (initial slope) followed by another straight line (the second component), with a shallower slope. Serial scintigrams (Figure 5) indicated that the initial slope corresponded with the removal of the bulk of the HSA-Tc 99m from the nasal cavity. The second component comprised activity arising from sites of less rapid HSA-Tc 99m removal, such as the vibrissae of the nares to which HSA-Tc 99m sometimes adhered, the anterior septal area where others have observed anterograde mucociliary transport (Anderson, Lundqvist & Proctor, 1971; Hilding, 1932) and the eustachian tube orifice (Proctor & Wagner, 1965). We have used the initial slope rather than the first component obtained by subtracting the extrapolated slow component from the initial slope because this represents a weighted mean of the two components (Bassingthwaighte *et al.*, 1968) and is probably more representative of the entire nasal cavity.

No significant systemic effect of distribution, concentration of HSA, mode of administration or volume on $T\frac{1}{2}$ was demonstrated, although paired *t*-tests were not possible on all subgroups due to the limited data. Up to three-fold intrapersonal differences were observed in the $T\frac{1}{2}$ during five duplicate studies in four subjects. Mean $T\frac{1}{2}$ for all 100 studies was 24.3 min (21.5 min s.d.). The range was 5.1 to 90 min; 89% of the half-periods were between 5.0 and 39.9 min.

Relative humidity

Although RH was measured only in the laboratory it may well have reflected general trends throughout the building in which the volunteers were working. Because Ewert (1965) concluded that below RH 40%, mucociliary transport is slowed or even stopped, we have analysed the effect of RH $<$ or $\geqslant$ 40% on $T\frac{1}{2}$. The $T\frac{1}{2}$ for the initial slopes of all studies for each subject are shown in Tables 2, 3, 4 and 5, according to whether the RH was $<$ or $\geqslant$ 40%, or not measured at the time of the study. A statistically significant difference ($P<0.001$) was found between mean $T\frac{1}{2}$ (17.3 min) for RH $<$40% and the mean $T\frac{1}{2}$ (28.8 min) at RH $\geqslant$ 40% (ratio 1:1.6); however, one may ask whether this is clinically important. It should be noted that the ratios of $T\frac{1}{2}$ in duplicate studies at RH $\geqslant$ 40% were 1:1.7, 2.2 and 3.1; at RH $<$40%, 1:1.8. Therefore this statistically significant difference in mean $T\frac{1}{2}$ is unlikely to be clinically important.

Stability of HSA-Tc 99m binding intranasally

Nasal washout retrieved only 5.3% of instilled radioactivity after instillation of 93 μCi although 92% of the volume of Hanks solution was recovered. The % of unbound Tc 99m recovered was 5%; in the initial preparation 0.7% of the Tc 99m was unbound; of control material in Hanks salt solution 1.8% became dissociated over the same period of time. Thus, 3.2% more of the HSA recovered was dissociated than control material.

Table 2 $T_{½}$ (min) after spray administration of 3% HSA at relative humidity $<$ or $\geqslant$ 40%

Relative humidity		*< 40%*					*≥ 40%*		
:Distribution	*'Good'*		*'Poor'*		*'Equivocal'*			*'Poor'*	
Volume (ml)	0.75	0.25	0.50	0.75	0.50	0.75	0.25	0.50	0.75
Subject									
1	–	–	23.6	38.5	–	–	32.6	–	–
2	–	–	41.1	–	–	–	9.8	–	14.6
3	–	–	41.7	21.6	–	–	–	–	8.7
4	–	–	–	27.5	13.6	–	–	–	–
5	19.1	12.9	–	–	14.1	–	–	–	7.5
6	–	17.5	–	–	–	16.7	–	9.1	–
7	–	–	10.1	–	–	–	13.3	–	–
8	–	–	–	–	–	–	–	–	–
9	–	–	18.6	–	–	–	–	–	7.9
10	–	71.4	–	–	–	–	–	–	12.2
11	–	–	14.1	–	–	–	16.0	–	32.2
Totals	1	3	6	3	2	1	4	1	6

Table 3 $T_{½}$ (min) after administration of 3% HSA as drops at relative humidity < or ⩾ 40%

Relative humidity	*<40%*					*⩾40%*						
Distribution	*'Good'*			*'Equivocal'*		*'Good'*			*'Equivocal'*		*'Poor'*	
Volume (ml)	0.25	0.50	0.75	0.25	0.50	0.25	0.50	0.75	0.25	0.50	0.25	0.50
Subject												
1	–	–	90.0	–	–	–	–	–	–	–	30.0	16.5
2	–	13.5	30.6	–	–	34.9	–	–	–	–	–	–
3	–	–	–	–	–	–	–	25.0	–	–	–	–
4	–	–	–	–	–	11.5	9.0	26.1	8.0	–	–	–
5	–	–	–	–	–	{35.3, 20.8}	–	–	–	31.2	–	–
6	–	–	20.5	–	–	10.1	{11.9, 36.6}	–	–	–	–	–
7	–	–	–	–	–	{5.1, 11.2}	–	–	–	–	–	–
8	–	–	–	–	–	–	–	–	–	–	–	–
9	–	–	–	30.6	–	–	–	25.6	–	–	–	–
10	{56.6, 30.6}	–	–	–	6.2	14.5	–	16.7	–	–	–	–
11	–	–	–	–	–	24.4	11.1	22.6	–	7.0	–	–
Totals	2	1	3	1	1	9	4	5	1	2	1	1

Table 4 $T_{½}$ (min) after administration of 30% HSA as drops at relative humidity < or ⩾ 40%

Relative humidity	*<40%*					*⩾40%*				
Distribution	*'Good'*			*'Good'*			*'Equivocal'*		*'Poor'*	
Volume (ml)	0.25	0.50	0.10	0.25	0.50	0.75	0.10	0.10	0.25	0.50
Subject										
1	–	–	–	16.6	13.1	–	–	–	–	–
2	–	–	–	–	8.2	–	–	–	–	–
3	–	19.2	18.7	–	–	–	–	–	–	–
4	–	–	–	–	10.6	–	–	–	–	6.7
5	–	–	20.0	–	–	–	–	–	–	–
6	–	–	–	16.5	–	–	32.6	–	–	–
7	21.0	–	–	–	–	17.3	–	–	–	–
8	–	–	–	21.6	–	–	–	–	–	–
9	–	–	–	–	–	15.5	–	–	9.4	–
10	–	–	20.0	–	–	–	–	–	–	–
11	–	14.7	–	–	–	20.4	–	18.1	–	–
Totals	1	2	3	3	3	3	1	1	1	1

Table 5 $T_{½}$ (min) after administration of 30% HSA as drops; relative humidity not measured

Relative humidity not measured				
Distribution		*'Good'*		
Volume (ml)	0.10	0.25	0.50	0.75
Subject				
1	–	61.2	19.9	10.9
2	12.4	13.3	–	17.6
3	–	20.7	–	–
4	25.9	16.6	–	10.2
5	21.9	13.5	{25.4, 24.0}	21.1
6	–	–	41.0	30.3
7	–	–	–	–
8	–	15.7	24.0	–
9	–	–	57.7	–
10	–	21.3	11.5	14.1
11	–	–	–	–
Totals	3	7	7	6

Studies with Tc 99m pertechnetate

The distributions and $T_{½}$s of removal of Tc 99m pertechnetate were within the range of $T_{½}$ obtained in duplicate studies using HSA-Tc 99m mixed with 3% or 30% HSA : subject 2 was given 0.75 ml Tc 99m pertechnetate as drops; distribution was 'good'. $T_{½}$ was 20.8 min compared with 30.6 and 17.6 min for duplicate studies showing 'good' distributions and using 3 and 30% HSA respectively. Subject 6 was given 0.75 ml Tc 99m pertechnetate by spray yielding an 'equivocal' distribution. $T_{½}$ was 25.6 min. In a duplicate study using 3% HSA, the distribution was also 'equivocal'; $T_{½}$ was 16.7 min.

Multiple dose studies

The best of four multiple dose studies is shown in Figure 6. Subject 4 was given 50 μCi HSA-Tc 99m in 0.75 ml of 3% HSA. Second and third doses of 25 μCi (0.375 ml) were administered at 13.5 and 26.0 min after the first. All the distributions were 'good' nd the $T_{½}$ of the three curves were 15.7, 13.4 and 14.6 min. The 10-s counts after the second and third doses extrapolated to the times of administration represented 100% and 108% of the calculated count at the time of instillation (initial count). The extrapolated minimum counts were 58% and 54% of the initial count.

The other three studies were less successful because variations up to two-fold in $T_{½}$ occurred during individual studies.

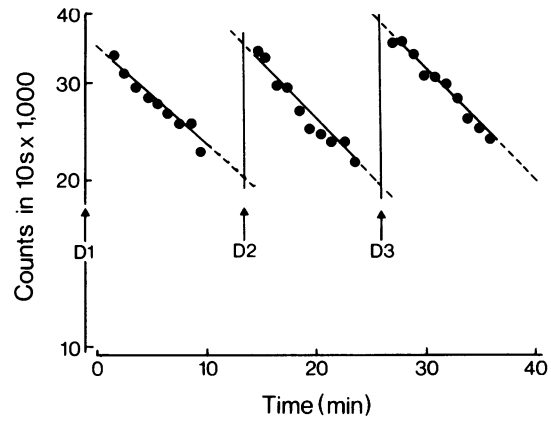

Figure 6 A multidose experiment in which doses of 50 μCi, 25 μCi and 25 μCi 3% HSA-Tc 99m were given to subject 4 at times D1 (0.75 ml), D2 (0.375 ml) and D3 (0.375 ml). If the first initial slope, extrapolated to time zero, is taken as 100%, the extrapolated counts after the second and third instillations are 100% and 108% respectively. The extrapolated minimum counts are 58% and 54%. The $T_{½}$ of the initial slopes were 15.7 min, 13.4 min and 14.6 min.

Discussion

If the inhibition of viral replication in nasal epithelium requires that the mucosa is constantly bathed in inhibitory concentrations of the antiviral agent, then our results indicate that a rational dose schedule to achieve this requires repeated intranasal administration of 0.10 to 0.75 ml as drops to the supine subject at frequent intervals.

Although studies of the transport of particle(s) on the nasal mucous blanket indicate regional intranasal differences in the direction and rate of mucociliary transport (Hilding, 1932), it has not been possible to translate this information into recommendations for intranasal dosing. In addition, while intranasal distribution of drugs may affect efficacy, there have not been methods available for directly assessing the distribution produced by drops or different spray devices or of deciding whether variations in volume, viscosity and so on had a large or small effect on the fate of the solutions given.

Our studies using labelled molecules were aimed at obtaining information that might be useful in the design of more rational dose schedules for administering drugs intranasally.

We found that the proportion of 'good' distributions of HSA-Tc 99m in 3 or 30% HSA was significantly higher after instillation as drops to

supine subjects than after spraying to seated volunteers. Neither the concentration of HSA, changes in volume nor relative humidity affected the distribution after drop administration.

A 'good' distribution on the scintigram may represent actual distribution over the entire nasal mucosa but we are mindful of the limitations of scintigrams in this respect. Mucociliary transport during the time of exposure may have had a significant effect upon some scintigrams but in general 'good' distributions were observed with short exposures.

The time-course of removal of HSA-Tc 99m was not significantly altered by differences in distribution, volume, mode of administration as drugs or spray, or the concentration of HSA. One interpretation of the decline in activity monitored by the scintillation detector (Figure 4) is a two compartment system. Serial scintigrams (Figure 5) showed that the initial slope corresponded to the removal of the bulk of the material from the nasal cavity whereas the slower component mainly represented material retained in the anterior area of the nose. This interpretation is supported by the isosensitivity profiles (Figure 2) showing that material that has left the nasal cavity contributes little to the count rate. Proctor (1966) found a similar slow removal of particles which he called a plateau (his figure 22), corresponding to material retained mainly in the anterior area of the nose.

Knowing that $T\frac{1}{2}$ represented the mean rate of removal of intranasal material and that 'good' distributions were obtainable with drops, we successfully designed a dose schedule which maintained the level of activity within desired limits. To obtain this result we had to monitor the decline in activity during repeated administrations of the HSA-Tc 99m.

The question therefore arises whether our results are relevant to the use of prophylactic antiviral solutions in the general population. We feel our data are relevant to this problem : since pertechnetate was distributed and removed in a manner comparable to that of HSA-Tc 99m, our findings may apply to a wide range of solutions. While other spray devices and solutions may yield different distributions than the systems we have studied, our technique of drop administration can be expected to produce a very high proportion of 'good' distributions. Our results give limited information for dosing intervals. $T\frac{1}{2}$ was 5-40 minutes in our subjects; intrapersonal variations up to 1:3.1 were found. This is consistent with intrapersonal differences in mucociliary transport observed by Bang *et al.* (1967) and Anderson *et al.* (1971). This range of $T\frac{1}{2}$ suggests that only frequent doses of solution can be expected to maintain intranasal content at a level sufficient to treat most of the mucosal cells most of the time.

In addition, different methods of administering intranasal prophylactic drug solutions and vaccines can be compared by this technique. This can complement measurements of drug effects and vaccine take-rates, making it possible to define the distributions that best correlate with efficacy of antivirals and sero-conversion rates so that the specifications of those applicators which give the best results can be established.

Studies correlating antiviral efficacy and vaccine take-rates with techniques of application should prove whether schedules for intranasal administration based on our methods will enhance the results.

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Reprint requests to J.C.W.C.

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