

The Effect of Nasal Patency on the Clearance of Radiolabeled Saline in Healthy Volunteers

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Purpose. The objective of this study was to investigate the effect of nasal cavity patency on the penetration, deposition, and clearance of an aqueous isotonic saline solution.

Methods. The study was carried out as a single center, open, randomized, 2-way cross-over in healthy volunteers. Nasal patency was assessed using misting patterns on a cold metal surface at the beginning and end of study. 100 μ l of technetium-99m radiolabeled saline solution was introduced into either the most or least patent nasal cavity using a purpose designed spray device. The distribution and residence time of the radiolabel was followed for 2 hours using gamma scintigraphy. **Results.** The mean times to 50% clearance were 34 ± 7 and 28 ± 12 minutes (\pm s.d.) for the side view of the least and most patent nasal cavity respectively. Total clearance of the radiolabelled saline from the nose was not affected by patency. Between 7 and 35% of the radiolabelled saline solution remained in the nasal cavity at the end of imaging. Using endoscopy to track the clearance of an aqueous solution of food dye using the same delivery procedure, identified this region as hair in the nasal vestibule. The dye was seen to dry in this region along with the mucus.

Conclusions. Nasal patency affects the initial, but not total clearance of solutions, however, the remaining solution may not be available for drug delivery.

KEY WORDS: nasal drug delivery; nasal patency; gamma scintigraphy.

INTRODUCTION

The nose is divided into two passages by the nasal septum and the mucosa of each passage has separate autonomic and sensory innervation. The nasal mucosa contains abundant venous sinusoids (capacitance vessels) whose variable blood volume largely determines the lumen diameter of the nasal airway. This pseudoerectile tissue in turn controls the nasal airflow and resistance. It is known that the airflow or "patency" varies in an individual and there is a cycle of alternating nasal congestion between the two passages. The cycles usually last between 3 to 4 hours, but can be between 2 to 7 hours and is relatively constant for an individual (1).

A "nasal cycle" is found in about 80% of the population. Kayser first described it in the scientific literature in 1895 (2), although the first mention appears in ancient Indian literature about yoga (3,4). Most people are unaware of the cyclical change in patency, as the total resistance remains relatively constant in spite of the relative imbalance in the resistance from side to side. A synchronous activity has also been described in the blood vessels of the conjunctiva and the promontory of the middle ear, and also altering of the diameter of the pupil (5).

The nasal cycle can be modified or overcome by a variety of endogenous and exogenous factors. Endogenous effects result from stimulation of the autonomic nervous system from fear, exercise and emotions or hormones as in pregnancy. Exogenous influences include ambient temperature, hypercapnia, allergy and infection. In addition drugs which have sympathomimetic, parasympathomimetic, release histamine or have antagonistic effects will influence nasal patency by their action on nasal vasculature (6). The amplitude of the nasal cycle is much more pronounced in seated or recumbent subjects compared to subjects who are standing (5). The nasal cycle can be overridden when recumbent. Lying on the left side will cause the right nostril to become more patent and vice versa (7).

The effect of nasal patency on drug delivery has not previously been studied. The hypothesis for this study is that nasal patency does not affect the clearance of a solution from the nose.

METHODS

The primary objective of this study was to determine the effect of nostril patency on penetration, deposition and clearance of a solution with a view to examining its relevance as a factor affecting drug delivery.

This was a single-centre, open, randomised, four-period, crossover study conducted in volunteers.

The study was performed in accordance with the Declaration of Helsinki and according to the EEC Note for Guidance on Good Clinical Practice. Ethics Committee approval was granted by Nottingham University Medical School Ethics Committee before the study started.

Twelve healthy volunteers, males and females aged between 18 and 60 years inclusive were recruited to the study. At the pre-study assessment, the volunteer was given a verbal explanation of the study and a copy of the volunteer information leaflet. Written informed consent was then obtained from the volunteer. The suitability of each volunteer was evaluated using a medical questionnaire. The inclusion criteria included no medication which could influence the results of the study (oral contraceptives were permitted), weight within $\pm 15\%$ of the limits defined in the Metropolitan Height and Mass tables (1983), all physical examination, clinical chemistry and haematological parameters within the normal range. Heavy smokers (more than 10 cigarettes a day), excessive drinkers and drug abusers were excluded from the study. Also people with a history of nasal disorders were excluded from the study. Pregnancy testing was carried out on each morning of each study day.

The radiation dosimetry for this study was 0.15 mSv which is below the dosage limits for the general public of 0.5 to 5 mSv per year. The study had ARSAC approval.

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Preparation and Composition of the Radiolabeled Dosing Solution

Delivery System

A purpose designed unit-dose nasal spray pump (Merck/Pfeiffer) was used to administer 100 microlitres of radiolabelled saline to the nasal mucosa. The solution was contained in a glass vial and rubber stopper assembly within the main body of the spray pump until the device was actuated. The device has previously been fully evaluated to show minimal variability in terms of dose volume (100 μ l, RSD \leq 3%) and spray distribution pattern (mean droplet size and cone angle) (Merck, in house data). In addition, an in-built pre-compression feature of this device ensured that there was no significant user variability.

The glass vials were filled with the dosing solution using a Gilson pipette (P1000) and assembled into the spray devices at the test centre immediately prior to dosing. The study nurse administered the dosing solution to each subject. The spray nozzle was placed 1 cm into the nostril before the unit was actuated.

Visualisation of Nasal Clearance Using Nasal Endoscope

A dilute aqueous solution of blue food dye (100 μ l) was sprayed into the most patent nostril of a subject using the same procedure as for the scintigraphy study. The deposition and clearance was monitored over time using a 4 mm 0⁰ rigid nasal endoscope (Smith and Nephew, UK). The images were recorded on an SVHS Panasonic (AG-4700) video recorder by an Olympus OTV-S5 camera attached to the eyepiece of the endoscope by a zoom lens coupler. Visualisation intervals were minimised to avoid causing excessive inflammation to the nasal cavity due to irritation caused by insertion of the endoscope.

A nasal spray device was modified, by removing internal components, to accommodate the rigid endoscope so that the lens was in-line with the spray nozzle. This was inserted 1 cm into the right nasal cavity of a single subject to identify the potential site of deposition of solution during the scintigraphy study and the images captured on the videotape.

Study Procedure

For each of the two dosing days the volunteer presented at the study centre, at the allotted time. Any adverse events experienced or medications taken since the last visit were recorded and the continued eligibility of the volunteer was confirmed. If the volunteer was not eligible to continue in the study, no further study procedures were undertaken. Female volunteers underwent a pregnancy test on each dosing day before any procedures were performed.

On the first dosing day and prior to each administration of the nasal spray, the medical investigator visually inspected the nasal cavities for any signs of pathology that would preclude further continuation with the study and also to determine the most and least patent side. This was determined subjectively by observing the difference in size of the misting pattern on a cold metal surface. On the second dosing day the medical investigator was blind to the results of the first day.

A sealed marker containing a small (<0.2 MBq) quantity of ^{99m}Tc was taped to the temple of the volunteer to ensure registration of images. The subject was then seated in front of

the gamma camera and the nasal spray containing 100 microlitres of saline radiolabelled with 2 MBq ^{99m}Tc-DTPA was administered to either the most or least patent nasal cavity according to the randomisation code. All administrations of the nasal spray were performed by one individual to maintain consistency of dosing.

Front and side scintigraphic images of 30 seconds duration were taken every 2 minutes after the dose for the first fifteen minutes, after which time imaging was performed at 5 minute intervals until 2 hours post dose. Imaging was carried out using a pinhole collimator to enlarge the image. Once imaging was completed patency of the nose was again assessed to ensure that a changeover had not occurred during the experiment.

Assessment Methods

The data was analysed on a Sun™ workstation by creating regions of interest (ROI) around the whole nose, body of the nose and nasopharynx. A further ROI was also drawn to obtain a background count. Numeric files were transferred to the Apple Macintosh™ via ethernet. These files were opened directly into Microsoft Excel™.

The spreadsheet analysis software corrected the data for background radiation and isotopic decay of the radioisotope over the study period. The corrected counts were expressed as percentage activity of the total radioactive dose administered to the nasal cavity against time. Graphs were drawn for each subject to show the percentage of activity remaining in each region against time. Mean graphs were constructed from interpolated individual subject data. Time to 50% percent remaining (T₅₀) and area under the curve (AUC) were calculated. Statistical comparisons were performed using T-tests.

All adverse events were recorded on safety assessment data sheets. A record of all adverse events, including details of the duration, severity, relationship to study medication and outcome, was made.

RESULTS

Twelve volunteers were recruited to the study of which 11 completed the trial. One volunteer was withdrawn due to the presence of previously unreported nasal pathology. No adverse events were reported during the trial.

Nasal patency was not found to change in any volunteer during the imaging period.

Mean data for clearance from the whole nose, body of the nose is shown in Fig. 1 and 2 for most and least patent nostril respectively. The T₅₀ and AUC values with statistical data are summarised in Table 1.

Visualisation of the clearance of the dye with the endoscope demonstrated that its initial clearance was rapid. The dye was washed down from the sides of the nasal cavity to the floor where it travelled to the nasopharynx as a "stream". However, the residual dye trapped in the nasal hairs and mucus in the front of the nose did not clear, but was seen to dry along with the mucus.

DISCUSSION

The nasal cycle has been well documented and has been shown to be present not only in most adult and infant humans, but also in the rat, rabbit and pig (8). Its functional significance is still not certain, but it is thought to be that one nasal chamber

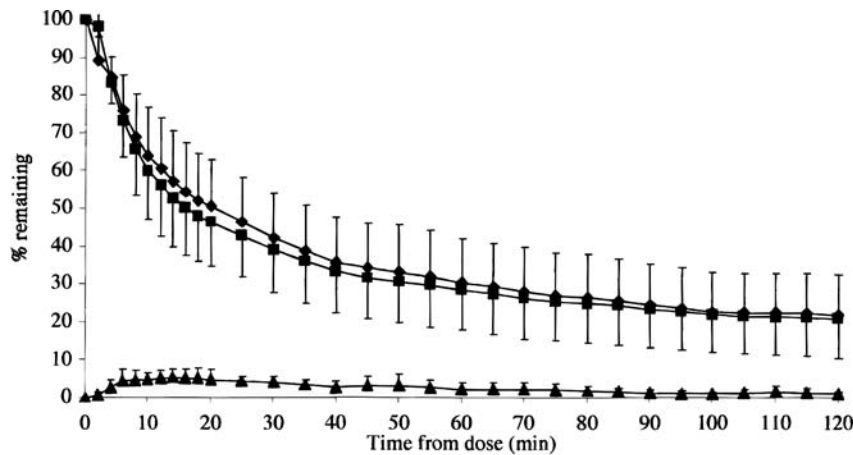


Fig. 1. Clearance curves for the most patent nostril front view (whole nose (○), nasal cavity (■) and pharynx (▲) ± 6 sd).

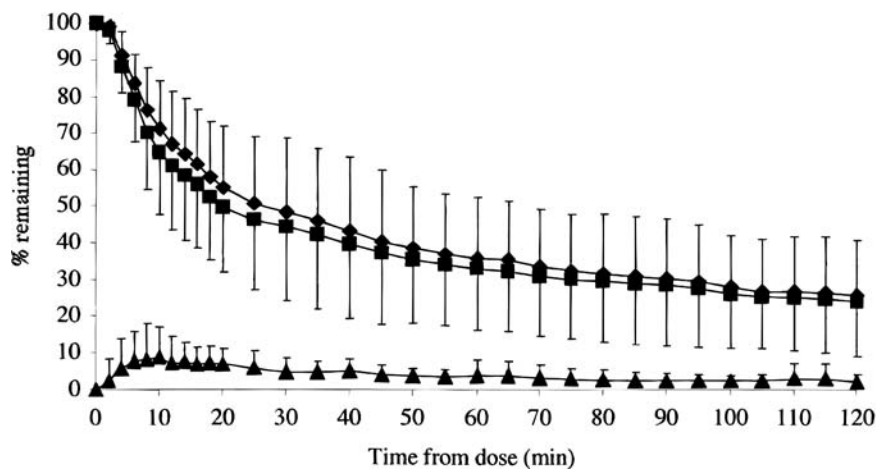


Fig. 2. Clearance curve for the least patent nostril front view (whole nose (◆), nasal cavity (■) and pharynx (▲) ± sd).

can rest allowing the nasal mucosa to recover from ambient air related injuries whilst the other carries on conditioning the inspired air (9). Nasal secretion also follows the nasal cycle, thus supporting this theory (10). As the mucosa in one chamber shrinks, droplets of secretion appear on the surface whilst secretion is inhibited in the congested mucosa on the contralateral side. It is highly probable that the increased secretion in the

most patent nostril accounts for the significantly faster clearance of the radiolabel compared to the least patent nostril in virtually all subjects (10/11).

The intrasubject variation of nasal clearance is very high with T_{50} s ranging from 10 to 79 minutes for the side view and 10 to 122 minutes for the front view of the least patent nostril. The most patent nostril demonstrated T_{50} s ranging from 7 to

Table 1. Summary of T_{50} and AUC Values for Clearance from the Most and Least Patent Nostrils (Mean ± Sem) T_{50} in Minutes, AUC in % · Minutes

| T_{50} | Whole Nose | Nasal Cavity | Pharynx |
|--------------------|-------------|--------------|-----------|
| Side—Least patent | 33 ± 7 | 28 ± 12* | 845 ± 337 |
| Front—Least patent | 39 ± 5 | 24 ± 3** | 673 ± 364 |
| Side—Most patent | 4250 ± 1458 | 3446 ± 1384 | 845 ± 337 |
| Side—Least patent | 4235 ± 1416 | 3603 ± 1341 | 673 ± 364 |
| Front—Least patent | 4634 ± 1858 | 4278 ± 1905 | 475 ± 284 |
| Front—Most patent | 4161 ± 1097 | 3909 ± 1031 | 318 ± 122 |

* p = 0.03.
** p = 0.05.

43 minutes for the side view and 7 to 39 minutes for the front view. It appears that slow nasal clearance (less than 3 mm.min⁻¹) is found in approximately 20% of normal subjects and the reason for this has not been identified. It has been postulated that this is due to variations in airway secretions rather than cilia beat frequency (11). This intrasubject variability is almost certainly due to aspects of nasal function and not related to variability from the delivery system or the method of administration. The device had been designed to reproducibly deliver 100 µl with a controlled cone angle (Merck, in house data). The difference in values between side and frontal imaging are likely to arise from differences in tissue attenuation of the isotope.

The AUC data did not reveal a difference in overall clearance of the solution from the nostrils. This appears to result from the biphasic nature of nasal clearance. Initial clearance of solutions is affected by nasal patency, as is shown by the T₅₀ values, however, the slower terminal phase is not. Endoscopic imaging of a blue dye administered to the nostril of a volunteer enabled direct visualisation of the clearance processes. Initially the clearance of the dye was rapid. The dye was washed down from the sides of the nasal cavity to the floor where it travelled to the nasopharynx as a "stream." However, the residual dye trapped in the nasal hairs and mucus in the front of the nose did not clear, but was seen to dry along with the mucus. Clearance of the dried mucus would probably occur when the nose was blown. A study looking at the effect of inhaling vigorously on the deposition of methylene blue administered to healthy volunteers in an aqueous nasal spray, demonstrated that there was approximately 13% coverage of the anterior end of the middle turbinate with dye (12). Vigorous inhalation had no significant effect on the deposition pattern.

The effect of nasal patency on drug delivery would depend on two factors: the rate at which the drug is absorbed from the site of deposition and the initial pattern of deposition of the drug. It appears that between 7 and 35% of the drug, which is

deposited in the anterior portion of the nose, will be lost by blowing the nose to remove the dried mucus.

CONCLUSIONS

Nasal patency affects the initial clearance of drugs from the nose, but it does not affect the total clearance as measured by AUC. A proportion of the solution (7–35%) deposited in the anterior of the nasal cavity may be lost from the body when the nose is blown.

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