

Chapter Nine

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ANATOMY AND PHYSIOLOGY

The nose is a prominent structure located on the face between the eyes. The external openings are known as nares or nostrils which open at the back into the nasopharynx and lead to the trachea and oesophagus. The nose is the primary entrance to the respiratory tract, allowing air to enter the body for respiration. It conditions inspired air by filtering, warming, and moistening it. The nose also contains the olfactory organ, essential for the sense of smell.

The nasal cavity is an irregularly-shaped space in the front of the head extending from the bony palate upwards to the cranium (Figure 9.1). The bony framework of the nasal cavity is formed by the fusion of seven bones (Figure 9.2). It produces a chamber approximately 7.5 cm long by 5 cm high, subdivided into the right and left halves by a cartilaginous wall, the nasal septum. The septum consists of the anterior septal cartilage and posteriorly, the vomer and perpendicular plate of the ethmoid bone. It terminates at the nasopharynx.

The floor of the nose and the roof of the mouth are formed by the hard palatine bone and the soft palate, a flap of tissue. The soft palate extends back into the nasopharynx and during swallowing is pressed upward, so that food cannot lodge at the back of the nose, blocking the airway. The ability to breathe through the mouth as well as the nose is extremely beneficial, although the air inspired through the mouth is not humidified, heated and filtered to the same extent as the nose breathed air.

The forward section of the nasal cavity, which is within and above each nostril, is called the vestibule. Behind the vestibule and along each outer wall are three thin, scroll-shaped bony elements forming elevations, the conchae or turbinates, which generally run from front to rear. Each turbinate hangs over an air passage and they serve to increase the surface area of the cavities. The superior, middle and inferior turbinates form flues through which the air flows. The flues are quite narrow, and cause the air to flow in such a way that no part of the airstream is very far from the moist mucous blanket lining the air spaces. The turbulent airflow through this region, and the changes in direction caused by the turbinates, encourage inertial impaction of suspended particles. The width of the air spaces is adjusted by swell bodies in the septum and turbinates. Heating and humidification of inhaled air are important functions of the nose, which are facilitated by the abundant blood flow through

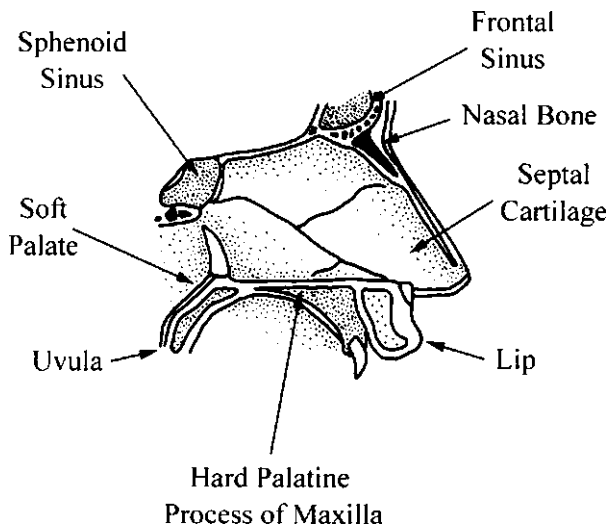


Figure 9.1 Cross section through the nose

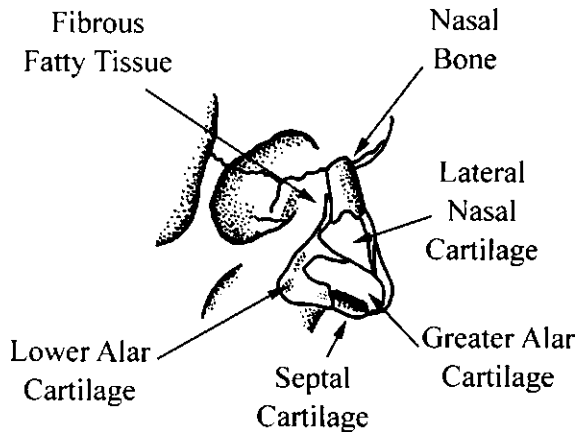


Figure 9.2 Bony structure of the nose

the arteriovenous anastomoses in the turbinates. The rapid blood flow through the *cavernous sinusoids* matches the cross-section of the nasal cavity to meet changing demands. Humidification is produced by an abundant fluid supply from the anterior serous glands, seromucous glands, goblet cells and by transudation¹. Air can be brought to within 97 to 98% saturation, and inspired ambient air between -20°C and $+55^{\circ}\text{C}$ can be brought to within 10 degrees of body temperature. The majority of the airflow from the nose to the pharynx passes through the middle meatus; however, up to 20% is directed vertically by the internal ostium to the olfactory region from where the airstream arches down to the nasopharynx.

Although the nose is considered by most as primarily as an organ of smell, only a relatively small region is involved in this sense, the rest of the cavity being involved in respiration. The respiratory area is lined with a moist mucous membrane with fine hairlike projections known as cilia, which serve to collect debris. Mucus from cells in the membrane wall also helps to trap particles of dust and bacteria. The olfactory region of the nasal cavity is located beside and above the uppermost turbinate. This area is mostly lined with mucous membrane, but a small segment of the lining contains the nerve cells which are the actual sensory organs. Fibres called dendrites project from the nerve cells into the nasal cavity. They are covered only by a thin layer of moisture which dissolves microscopic particles from odour-emitting substances in the air, and these chemically stimulate the olfactory nerve cells. A receptor potential in the cell is generated initiating a nerve impulse in the olfactory nerves to the brain.

The diameter of the nares is controlled by the ciliator and compressor nares muscles and the *levator labii superioris alaeque* muscle. The entrance of the nares is guarded by hairs (vibrissae) which filter particles entering the nose. The average cross-sectional area of each nostril is 0.75 cm^2 . The posterior nasal apertures, the *choanae*, link the nose with the rhinopharynx and are much larger than the nares, measuring approximately 2.5 cm high by 1.2 cm wide. The nasal cavity widens in the middle and is approximately triangular in shape.

Nasal epithelia

Over 60% of the epithelial surface of the nasopharyngeal mucosa is lined by stratified squamous epithelium. In the lateral walls and roof of the nasopharynx there are alternating patches of squamous and ciliated epithelia, separated by islets of transitional epithelium, which are also present in a narrow zone between the oropharynx and the nasopharynx. The

lower area of the pharynx is lined with mucous membrane covered by stratified squamous epithelium. The posterior two-thirds of the nasal cavity is lined by pseudostratified epithelium possessing microvilli. These, along with the cilia, prevent drying of the surface and promote transport of water and other substances between the cells and the nasal secretions. The whole of the respiratory region is covered with goblet cells, which are unicellular mucous glands and supply the surface with viscid mucus.

The mucosal lining of the nasal cavity varies in thickness and vascularity. The respiratory region, which lines the majority of the cavity, is highly vascular and the surface of some of the epithelial cell types are covered in microvilli, increasing the area available for drug absorption.

Nasal lymphatic system

The nasopharyngeal region possesses a very rich lymphatic plexus, in which the lymph drains into deep cervical (neck) lymphatics. Besides capillary filtrate, some cerebrospinal fluid also drains into the nasal submucosa, which is partly absorbed by the nasal lymphatics. When the nasal mucosa is damaged by an irritant, the resulting oedema results in an increased flow of lymph.

The lymphatics of the nasopharynx play an important part in the absorption of substances which have been deposited on the nasal mucosa. It is believed that these molecules diffuse mainly through the olfactory region of the mucosa to be taken up by both the blood capillaries and lymphatics.

Nasal secretions

The composition of nasal secretion consists of a mixture of secretory materials from the goblet cells, nasal glands, lacrimal glands and a plasma transudate. In a healthy nose, the mucosa is covered by a thin layer of clear mucus which is secreted from the mucous and serous glands in the mucosa and submucosa. It is renewed approximately every 10 minutes. The mucus blanket is produced by the goblet cells, whose numbers increase with age.

Mucus consists of mucopolysaccharides complexed with sialic acid and may be partially sulphated, particularly in diseased conditions. The main component of mucus is water with 2 to 3% mucin and 1 to 2% electrolytes. Normal nasal secretions contain about 150 mEq.L⁻¹ sodium, 40 mEq.L⁻¹ potassium and 8 mEq.L⁻¹ calcium. Nasal mucus also contains lysozymes, enzymes, IgA, IgE, IgG, albumins, a 'kallikrein-like' substance, protease inhibitor, prostaglandins, lactoferrin, and interferon. The antibodies are present to act on bacterial particles which become trapped in the mucus lining. Many enzymes exist in nasal secretions and Table 9.1 lists the best characterized ones.

Table 9.1 Major enzymes found in nasal secretions

cytochrome P-450 dependent monooxygenases,
lactate-dehydrogenase,
oxidoreductases,
hydrolases, acid phosphatase and esterase, NAD ⁺ -dependent formaldehyde dehydrogenase,
aldehyde dehydrogenase,
leucine aminopeptidase,
phosphoglucomutase, glucose-6-phosphate dehydrogenase, aldolase, lactic dehydrogenase,
malic enzymes, glutamic oxaloacetic transaminase, glutamic pyruvic transaminase
NAD ⁺ -dependent 15-hydroxyprostaglandin dehydrogenase
carboxylesterase, lysosomal proteinases and their inhibitors,
β-glucosidase, α-fucosidase and α-galactosidase
succinic dehydrogenase,
lysozyme
steroid hydroxylases

The nasal cycle

The mucosa of each nasal passage has a separate autonomic and sensory innervation. The airflow through each nasal passage is regulated by the tumescence of the venous erectile tissue in the nasal mucosa. Engorgement of the tissue causes a constriction of the nasal passage, thus reducing airflow. This tissue exhibits cycles of constriction causing an alternation of the main airflow from one nasal passage to the other. A nasal cycle is found in about 80% of the population, yet most people are completely unaware of it since the total resistance remains relatively constant. Although the presence of the nasal cycle is well documented, its significance is still only speculated upon. One suggestion for the cycle is that each passage may rest whilst the other takes over conditioning of the inspired air.

As the nasal mucosa shrinks, droplets of secretion appear on the surface, and nasal secretion also follows the nasal cycle. 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 or parasympathomimetic action, release histamine or have antagonistic effects, will influence nasal patency by their action on the nasal vasculature. The amplitude of the nasal cycle is much more pronounced in seated or recumbent subjects compared to subjects who are standing. 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.

Mucociliary clearance of inhaled particles

At the anterior ends of the nasal septum and turbinates, the squamous epithelium is replaced by areas of ciliated epithelium. There are approximately five ciliated to every non-ciliated cell, each ciliated cell having about 200 cilia extending from the anterior surface. Under normal conditions, these cells have a life of four to eight weeks². Ciliary action clears surface fluid into the nasopharynx, where there is a transition to squamous epithelium. From here the mucus can be wiped off by the action of the soft palate and swallowed. There is also a small area in the anterior nose where ciliary action moves particles forward, from where they can then be removed by sneezing, wiping or blowing the nose. The sneeze reflex is similar to the cough reflex except that it applies to the nasal passages rather than the lower respiratory airways. During a sneeze, the uvula is depressed to channel the air through the nose and mouth to help clear the nasal passages of the irritation.

Efficient mucociliary clearance is a function of the physical properties of the mucus coupled to appropriately functioning cilia. Nasal mucus is secreted into the airway from goblet cells and mucus glands as a homogeneous gel. This floats on a 'sol' or periciliary layer that bathes the cilia, in a similar manner to the mucus lining the upper respiratory tract (Chapter 10). The mucus or gel layer acts like a conveyor belt over the 'sol' layer which is produced from serous glands and by transudation.

The cilia are approximately 6 μm long and the tip of each protrudes through the 'sol' layer into the mucus layer to propel it in an antrograde direction. The coordinated beating of the cilia moves the mucus layer along towards the pharynx. The ciliary beat frequency is estimated to be between 12–20 Hz³. Intersubject variations of ciliary beat frequency are small but there is a highly significant correlation between the beat frequency and log of mucus transport time *in vivo*, indicating that this plays an important role in controlling nasal mucociliary clearance^{4 5}.

The filtering and deposition of airborne particles occurs predominantly by inertial impaction. The regions of highest deposition are those where the airstream bends sharply, allowing the momentum of the particles to deviate from the air path⁶. Hence, impaction

points are present at the internal ostium and start of the rhinopharynx. Nearly all particles of 5–10 μm , and a significant proportion of even very small particles, are deposited, although those less than 2 μm can penetrate to the lungs. Virus-containing droplets often coalesce to exceed 5 to 6 μm in diameter and are therefore retained by the nose⁷.

Nasal deposition increases with ventilation flow rate and nasal resistance. Children have much higher nasal resistances than adults but lower normal flow rates. Their nasal deposition percentages are lower than adults under similar conditions, so that despite greater nasal resistances, children have a lower particle filtering efficiency.

The average mucus flow rate is estimated to be approximately 5 mm min^{-1} with a range from 0 to 20 mm min^{-1} . There is some disagreement in the literature concerning the mucus flow in the anterior and posterior halves of the nasal cavity. Earlier studies reported that transit rate tended to increase in the posterior portion, possibly due to less drying of the posterior mucosal surface by the stream of inspired air⁸, but others report no difference⁹. 'Slow' and 'fast' movers have been reported and there is a wide variation in mucociliary clearance rate between subjects, but within one person it is fairly consistent over moderate time spans¹⁰. The inter-individual and intra-individual changes in nasal clearance with time strongly suggest the important role of environmental factors. This view is supported by studies in monozygotic twins¹¹.

From childhood, the nose is continually challenged by pollution and upper respiratory tract infections. No effects of aging (<60 years old) on mucus flow rate are apparent and even in a group of elderly subjects (age > 60 years), 70% of subjects studied showed no significant change in flow rate. For those who did show change, age could not be proven to be the causative factor¹². It therefore seems that the division of 'normal' healthy people into 'slow' and 'fast' movers occurs before adulthood.

Measurement of clearance

Many methods have been used to investigate nasal mucociliary clearance. Initially markers such as sky blue dye¹³ and saccharin have been used to measure clearance rates^{14 15}. Small amounts of powdered saccharin are placed in the nose and the time between application and detection of the taste is taken as the clearance time. Another method described is the use of aluminium discs of different colours placed on the floor and septum of the right and left nostril, used to measure transit rates in smokers and non-smokers¹⁶. A more quantitative method of measuring mucus flow rates is to use gamma scintigraphy to follow the distribution and clearance of radiolabelled formulations^{8 14 15}.

Pathological effects on mucociliary function

Environmental factors are not the sole causes responsible for changes in the efficacy of mucociliary function. There are many pathological disorders which may disrupt the nasal defence mechanism by obstruction, lesions or effects on the nasal mucus or cilia. The most usual are the common cold, closely followed by others such as hayfever, asthma and sinusitis.

Rhinitis

Rhinitis is defined as inflammation of the mucus membranes of the nasal cavity. Acute rhinitis is commonly caused by viral infections and allergic reactions. The commonest and perhaps most inconvenient are the rhinoviruses which cause the 'common cold'. It seems that bacterial infection has remarkably little capacity to disrupt ciliary clearance unless the mucosa is actually destroyed. There is a normal commensal respiratory flora in the nose. Normally, potential pathogens are phagocytosed and cleared by mucus and cilia. If organisms penetrate into the 'sol' layer, however, there is increased opportunity for further

penetration and infection of host cells. Viruses are able to disrupt clearance by penetrating the mucosa and cause degeneration and shedding of epithelial cells. Once this damage has occurred, the nasal mucosa is open to bacterial infection by normal commensals.

Cold sufferers exhibit both markedly increased and decreased mucociliary clearance rates. During the hypersecretory phase (rhinorrhea) the clearance is increased and usually during recovery from a cold there is congestion which slows clearance¹⁷. The susceptibility to rhinoviruses in women is significantly related to the menstrual cycle, possibly due to changes in mucociliary function during the cycle¹⁸.

Allergic rhinitis may be acute and seasonal (hayfever) or chronic (perennial rhinitis). In an allergic person, substances such as pollen or dust may more readily penetrate in and through the surface epithelium. Hayfever is the most common of all allergic diseases, affecting an estimated 10% of the population. The allergy to pollen produces rhinoconjunctivitis, for which the main symptoms are an itchy nose, sneezing and watery rhinorrhea. Mucus clearance time is decreased because nasal secretions become alkaline (pH 8) leading to increased ciliary activity¹⁹. There is an increase in water transport towards the epithelial surface and an altered transepithelial potential difference²⁰. The same mechanisms are true for the increase in clearance seen in perennial allergic rhinitis where dust and fumes or some other allergen can provoke sneezing, rhinorrhea and nasal blockage. The physiological reaction to aerial contamination is of such a degree that it exceeds the selfcleaning capacity of the nose, impairing the nasal filter function.

Asthma

Asthmatics and bronchiectasis sufferers, both with and without allergic rhinitis, have an increased nasal mucociliary clearance time. It is therefore thought that there is some sort of mucus abnormality and ciliary malfunction working in concert²¹. Observations in asthmatics of tracheal mucus transport rates suggest that the mucociliary dysfunction observed after antigen challenge is related to airway anaphylaxis (a hypersensitivity reaction) and its chemical mediators. Pretreatment with sodium cromoglycate, a mast cell stabiliser, prevents the expected antigen induced increase in clearance time, but histamine alone is probably not the main mediator, since it stimulates mucociliary clearance. An alternative possible mediator is known as slow-reacting substance of anaphylaxis (SRS-A).

Sinusitis

Chronic sinusitis is the sequela to acute inflammation. Any condition that interferes with drainage or aeration of a paranasal sinus renders it liable to infection. If the ostium of a sinus is blocked, mucus is accumulated and pressure builds up. The nasal clearance time is increased in this condition due to the increase in quantity of mucus, which is usually highly viscous and adhesive¹². However the inflammatory response is associated with changes in the H⁺ concentration of the nasal mucus, and nasal secretions tend to be alkaline in reaction, therefore increasing ciliary activity¹⁹.

Kartegener's syndrome

Kartegener's syndrome is an inherited disorder which comprises transposition of some or all of the major organs, bronchiectasis and sinusitis. The syndrome may also be associated with a variety of structural and functional abnormalities of cilia (the immotile cilia or ciliary dyskinesia syndrome), common due to a deficiency of the dynein arms which normally generate microtubule movement²². Mucociliary flow rate is therefore decreased due to ciliostasis. As well as the defects in nasal cilia associated with genetic disorders, evaluation of cilia from patients with chronic sinusitis, nasal polyposis, rhinitis and cystic fibrosis has demonstrated multiple membrane, microtubular and radial spoke alterations, although the importance of these in the pathologies is not known².

Sjögrens syndrome

Sjögrens syndrome is an autoimmune disorder predominantly affecting middle-aged or elderly women. The problem is a lymphocytic infiltration into the external secretory glands, which results in atrophy of the acini and consequent reduction of their secretory capacity. There is an increase in mucus transport time. Stasis in the mucus layer is due to the decreased amount of secretion. Normally, particles can become entangled in the mucus, but it seems that in Sjögrens syndrome there is insufficient mucus for this to happen^{12 23}.

Structural dysfunction

Nasal polyps are round, soft, semi-translucent, yellow or pale glistening benign tumours usually attached to the nasal or sinus mucosa by a relatively narrow stalk or pedicle. Their presence prevents efficient humidification, temperature control and particle infiltration of inspired air. The nasal clearance is slowed down due to blockage of the nose and defects in ciliary action or mucus secretion²⁴. There are two types of polyps, neutrophil and eosinophil. Eosinophil or allergic polyps are characterized by eosinophilia, seromucous secretion and steroid responsiveness, whereas neutrophil or infectious polyps demonstrate neutrophilia, purulent secretion and lack of response to steroid treatment¹.

Deviation of the nasal septum or rhinoscleroma causes obstruction which decreases clearance. People with deviated septa have longer clearance times (25–35 minutes) compared to normal subjects (9–15 minutes). Inspired air is directed onto a restricted area of mucosa and the flow rate exceeds its capacity to saturate air. This leads to an increased viscosity of the nasal mucus due to dehydration, making it unsuitable for effective ciliary action¹⁹. Congenital malformations such as cleft palate can also impair the function of the nose.

Laryngectomies can significantly accelerate peak transport rate in patients especially during the first sixty days after the operation, but the effect lessens with time. This could be partly due to a change in the nasal secretion¹².

Flow rates in twenty-four lepers who had differing degrees of nasal pathology indicated that, even with distortion, scarring or erosion of intranasal structures, any remaining intact mucosa which was protected from the direct impact of unmodified air, functioned normally. However heavy crusting of mucous membranes was found to inhibit or prevent mucus flow¹³.

External factors affecting mucociliary clearance

There is a very wide normal range of mucociliary clearance which can be observed when particulates are introduced into the nose. Some people display the expected rapid, uninterrupted particle movement, whereas others have a slowing or even a halt in particle movement after an initial fast flow, or constantly slow movement or stasis¹⁰. A constitutional element in the overall control of nasal mucociliary flow may exist, but the mucus flow rate may also be influenced by many environmental factors²⁵.

Clearance may be altered by substances affecting, or those causing an alteration of, the physical (viscoelastic or rheological) properties of the mucus layer. Without the mucociliary and other nasal defence mechanisms, conditions such as chronic bronchitis, pneumonia and squamous metaplasia of large airways would result.

Cigarette smokers unfortunately do not inhale the smoke through their nostrils, and thus the nasal defence mechanisms are bypassed and the relatively unprotected small airways of the lung are directly accessed. Tobacco smoking is known to affect the bronchial tree but has also been shown to significantly prolong the nasal clearance. However, it does not appear to affect the ciliary beat frequency, suggesting that the defective clearance seen in smokers is due to a reduction in the number of cilia or to a

change in the viscoelastic properties of mucus²⁶. The effect of smoking on mucociliary transport of materials in the nose is under controversy. Some workers report that there are no differences in transit rates for smokers and non-smokers^{8 16}, whilst others report significantly longer nasal mucociliary clearance times in smokers (20 ± 10 minutes) compared to non-smokers (11 ± 4 minutes)^{26 27}. However, the difference between the studies diminishes at relative humidities greater than 45%.

The nasal humidification system seems to be so efficient that even the driest air on entering the nasal passages is sufficiently moistened to prevent mucosal injury. However, the state of the ambient air is known to affect the mucociliary transport rate. Moderate decreases in mucus flow rate in the anterior and middle parts of the nose are observed with ambient temperatures above or below 23°C. The nasal resistance also decreases with warm air and increases with cold, as one would expect. However, none of these functional changes are sufficiently great so as to be physiologically important. There are differing opinions as to the effect of relative humidity on nasal mucociliary clearance. Some workers suggest that flow rate is correlated with relative humidity and that it increases from 6 to 9 mm min⁻¹ when the relative humidity rises above 30%^{8 27 28}. However, other studies have failed to find differences in either mucus flow or in nasal airway resistance, at relative humidities ranging from 10 to 70%, even though temperatures were similar to the previous studies, at around 23°C^{9 25 29}.

Other factors such as increased temperature, smog, clouds of dust and mild dehydration do not appreciably affect mucociliary clearance¹³. However nasal flushing or drinking very hot tea doubled the flow rate. The effect of irritants is greatest on the mucociliary transport in the anterior part of the nose, and for subjects with an initially slow mucus flow rate^{25 29}.

Chemical-induced changes

Many chemicals including nickel, chromium and aromatic hydrocarbons, have been implicated in the causation of cancer of the nose and sinuses³⁰. These materials poison the nasal cilia. Occupational settings that carry an increased risk of cancer of the nose are wood-working in the furniture industry, the use of cutting oils, and employment in the shoe and leather industry. The wood dust impedes the normal mucociliary function allowing accumulation and retention of inhaled substances in the nasal cavity. The mucus transport rate decreases to less than 1 mm.min⁻¹ (mucostasis). This increases the risk of developing adenocarcinoma of the nasal cavity and sinuses, especially the ethmoid^{31 32}. Formaldehyde vapour also causes a slowing of clearance in the anterior nose, and exposure has been shown to precede nasal cancer in rodents²⁹.

Studies in rats have shown that inhalation of sulphur dioxide (SO₂) increases the thickness of the mucus blanket, and exposure to ammonia, formaldehyde and sulphur dioxide results in the cessation of ciliary movement to varying degrees³³. Volunteers subjected to 1 ppm, 5 ppm and 25 ppm SO₂ concentrations in inspired air showed a significant decrease in mucus flow rate with the higher concentrations, the effect being greatest in the anterior part of the nose. The subjects reported discomfort proportional to the SO₂ concentration. There was also a marked decrease in cross section of the nasal airways, even at 1 ppm²⁵. However, these levels are significantly higher than those normally present in the air.

Other factors which affect mucociliary clearance

An increase of mucociliary transport rate has been shown during the periovulatory phase of the menstrual cycle¹⁸. The mucociliary transport rate shows a diurnal cyclic pattern which is out of phase with the levels of serum IgA concentrations. The phase shift is such that the

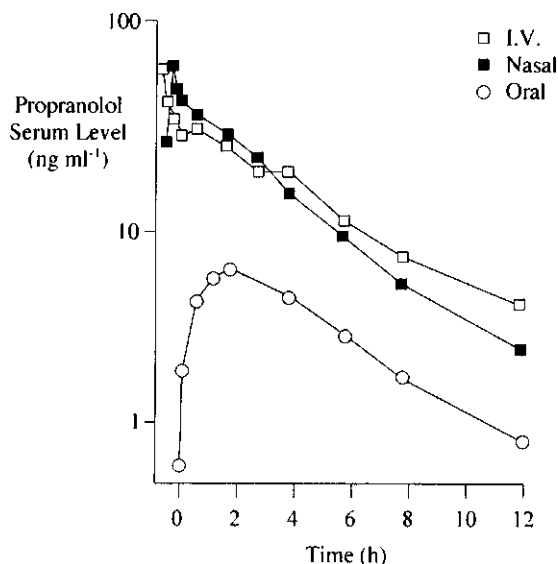


Figure 9.3 Absorption of propranolol from nasal, intravenous and oral formulations

cyclic impairments of one activity will be compensated for by an improvement in the other, thus helping to preserve the nasal defence mechanism.

INTRANASAL ADMINISTRATION OF DRUGS

Currently, intranasal drug delivery is primarily employed to treat allergies and infections which cause nasal irritation, sneezing and congestion by the topical action of drugs. The observation that nasally-administered sympathomimetics and antihistamines, used for their local action, produced quite significant systemic effects, suggested that the nasal route could be used effectively to deliver drugs systemically. Much recent research has focused on delivery of large molecules via this route, particularly peptides and proteins.

The intranasal route is very useful for avoiding injections in the young and is a good way of administering drugs to the elderly. Small drugs are absorbed rapidly, at rates comparable to intravenously administered drugs (Figure 9.3). However, the physiological conditions of the nose (vascularity, speed of mucus flow, retention and atmospheric conditions) will affect the efficacy of drugs or vaccines, as will the nature of the formulations, e.g. volume, concentration, density, viscosity, pH, tonicity, and pharmacological and immunological activity. The slower the clearance of the drug, the longer the time available for drug action or absorption.

Drugs administered for local action

Topical therapy is widely used to treat allergic rhinitis. It is well known that histamine is an important mediator of allergic symptoms causing itching, sneezing and hypersecretion. Research is being directed towards discovering the relative roles of leucotrienes, prostaglandins and other arachidonic acid metabolites in the allergic process. Local eosinophilia is a characteristic feature of allergic rhinitis, some non-allergic rhinitis and nasal polyposis. Rhinitis is commonly treated with topical administration of corticosteroids, sodium cromoglycate or azelastine, an H₁-antagonist which is administered via a nasal spray.

The α -adrenergic agonist decongestant sprays containing phenylephrine, xylometazoline or tetrahydrozoline, often used in the management of allergic rhinitis, significantly increase nasal mucous velocity within ten minutes of administration. This is

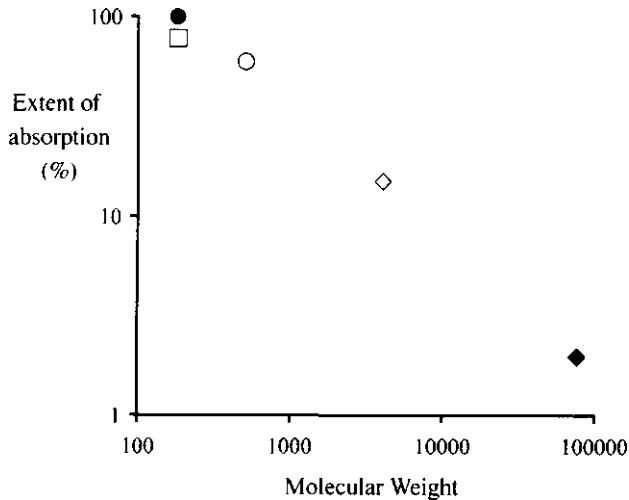


Figure 9.4 Effect of molecular weight on nasal drug absorption. ● 4-oxo-4H-1-benzopyran-2-carboxylic acid; □ p-aminohippuric acid; ○ sodium cromoglycate; ◇ inulin; ◆ dextran.

related to vasoconstriction of nasal mucosal vessels leading to a decrease in the fluid content of the mucosa³⁴.

Amazingly, little is known about the pathohistology and pathophysiology of the common cold. The beneficial effect of ipratropium bromide, which is a cholinceptor antagonist, on the watery rhinorrhea in the first few days of a cold suggests that at least the early symptoms are reflexly mediated³⁵. There is no convincing evidence that kinins and not histamine plays a major role in symptom production³⁶.

Drugs administered for systemic effect

The nasal route is being actively developed as a method of delivering drugs to the systemic circulation. This route is easier and more comfortable for the patient than the parenteral route and it avoids enterohepatic recirculation and gut enzymes. This naturally makes it attractive for the delivery of peptides and recombinant DNA technology. However, absorption rates fall off sharply when the molecular weight exceeds 1000 Daltons³⁷ which probably explains why desmopressin³⁸ is delivered successfully (m. w. 1069 Daltons), whilst insulin (m. w. 6000 Daltons approx.) is not (Figure 9.4)³⁹.

The nasal mucosa demonstrates typical absorption mechanisms. Water soluble drugs enter via passive diffusion through aqueous channels. As the diffusion path through the nasal mucosa is short, intranasally administered drugs demonstrate a rapid rise to peak plasma concentrations, but the rapid clearance from the mucosa limits available time for absorption. Amino acids such as tyrosine and phenylalanine are absorbed by active transport, presumably by similar mechanisms to those observed in the blood brain barrier.

Currently, commercial products which utilise this route for systemic delivery exist for some gonadorelin analogues, which are hypothalamic hormones. These include busarelin for dependent prostatic cancer, oestradiol dependent endometriosis and infertility, and nafarelin also for endometriosis and infertility. A number of other hormones are being investigated at a preliminary stage, including desmopressin for diabetes insipidus and primary nocturnal enuresis and lypressin for diabetes insipidus. Anterior pituitary hormones include LHRH

agonists and analogues which are used as contraceptive agents. Synthetic nasal salmon calcitonin is used in Hong Kong to treat osteoporosis⁴⁰.

A nasally delivered live attenuated influenza vaccine (FluMist™) has been developed to aid annual immunisation for influenza particularly for children and the elderly⁴¹. It consists of egg allantoic fluid, primarily ovalbumin and live attenuated influenza viruses types A and B.

In the US, sufentanil and midazolam are administered intranasally for sedation. Anti-migraine treatments such as ergotamine tartate, sumatriptan and butorphanol are also administered intranasally to relieve the nausea and vomiting which is associated with severe migraine.

Penetration enhancers

The drive to increase the absorption of large molecular weight molecules has led to the use of penetration enhancers. Bile salts, e.g. sodium deoxycholate, sodium glycocholate and sodium taurocholate, decrease the viscosity of mucus and create transient hydrophilic pores in the membrane bilayer. EDTA, and fatty acid salts such as sodium caprate and sodium laurate, increase paracellular transport by removal of luminal calcium, thus increasing permeability of the tight junctions. Non-ionic detergents e.g. Laureth-9 alter membrane structure and permeability. It should be remembered that the penetration enhancers are generally non-specific and there remains the potential that any large molecule can enter the systemic circulation once the epithelial barrier is breached. Some penetration enhancers, e.g. Laureth-9 and bile salts, have been reported to be toxic to the nasal mucosa.

Cyclodextrins have been used as solubilizers and absorption enhancers for nasal drug delivery⁴². Methylated β -cyclodextrins have been used to promote absorption of peptides and proteins, but mainly in animals. Limited studies show that the cyclodextrins are well tolerated in humans^{43 44}.

DRUG DELIVERY SYSTEMS AND DEPOSITION PATTERNS

Inhaled particles are deposited by five mechanisms; interception, electrostatic precipitation, impaction, sedimentation and diffusion. However, it is only the last three which are important in nasal drug delivery. Aerodynamic particle size is a key factor in nasal deposition. Correlation of aerodynamic particle diameter and nasal deposition efficiency at a given flow rate shows that particles of 0.5–1 μm are the least likely to impact. Above this particle size deposition increases due to inertial forces, and below it due to turbulent diffusion. Although the lung filters particles more efficiently during expiration compared to inspiration, expiratory deposition is lower than inspiratory deposition due to the loss of particles deposited in the lung⁴⁵.

There are four basic formulations which are suitable for nasal drug delivery. These are solution, suspension, emulsion and dry powders. The liquid formulations are often water based but may contain alcohol, oils or other organic solvents. Mechanical pumps and pressurised aerosol devices may be used for accurate dosing.

Liquid spray and drop preparations are most commonly used to deliver drugs intranasally. For the nasal drop to be correctly applied, some complex manoeuvres are required which include lying on a bed with the subject's head at a 90° angle and the nostrils uppermost. The drops are then applied and the head is swirled from side to side! Apart from not being very practical, the volume delivered cannot be easily controlled and contamination of the formulation can easily occur. High concentrations of preservatives cannot be used as they may damage the nasal mucosa and affect mucociliary clearance. Single use preparations may avoid the potential problems of contamination of the containers. The currently available devices are the bottle pack and a device which operates with an actuator and a

chamber with a piston. This can either be a single shot or double shot device, which enables both nasal cavities to be dosed.

Liquid formulations generally clear from the nose within 30 minutes, but the exact figure is very variable and ranges of 5 to 90 minutes have been reported. Radiolabelled nasal sprays exhibit bi-phasic clearance from their initial site of deposition⁴⁶. The first phase lasts 15–20 min in which more than 50% of the administered dose is cleared. The slower clearance is the removal of material from, the non-ciliated vestibule and anterior septal area.

Dry powders are less frequently used in nasal drug delivery, even though they are preservative-free and have greatly improved stability. Powders can be administered from several devices, the most common being the insufflator. Many insufflators work with predosed powder in gelatin capsules. To improve patient compliance a multi-dose powder inhaler has been developed which has been used to deliver budesonide⁴⁷.

Pressurized metered dose inhalers (pMDIs) originally developed for pulmonary delivery have been adapted for nasal use by alteration of the shape of the applicator. These have the advantage that generation of an aerosol is independent of inhalation. They are small, portable, available in a wide range of doses per actuation, provide accurate dosing and protect the contents. The disadvantages include possible irritation of the mucosa produced by the propellants and surfactants, and malfunctioning in cold conditions.

Vitamin B₁₂ in a nasal gel for systemic delivery has recently been introduced into the marketplace. The gel has been used to prolong nasal retention, but the bioavailability may depend upon the mode and site of administration, since its viscosity prevents lateral spreading in the nose.

Care should be taken when studying bioadhesives for drug delivery to the nose. Any fraction of the dose which impacts on nasal hair will remain in the nose for exceptionally long periods, but it is however, not available for drug absorption⁴⁸. Generally during studies, subjects are requested to refrain from blowing their nose, but it is this action which clears material impacted on the hair. Nasal patency will also affect the initial rate of clearance of nasal sprays from the mucosa. As would be expected, the clearance of a formulation is slower from the least patent nostril (T_{50} —least patent 39.3±5.1 minutes vs most patent 24.2±2.9)⁴⁸. Vigorous breathing during inhalation of aqueous sprays does not affect nasal deposition patterns⁴⁹. Few studies have been carried out on the pharmacokinetic inter- and intrasubject variability after nasal administration of drugs⁵⁰. However, there appears to be a non-linear dose-response curve for some formulations⁵¹.

The turbinates, which are covered by respiratory epithelium, are the primary sites for systemic drug absorption. Not surprisingly, drugs which are deposited posteriorly will clear faster than drugs deposited anteriorly. Nasal sprays deposit drugs more anteriorly than nasal drops and hence the type of dosing device used can affect absorption. For instance, the bioavailability of desmopressin is significantly increased when administered in a spray rather than drops. The particle size of the aerosol droplet is also very important since small particles (<10 µm) may be carried in the air into the lung whereas particles between 10 and 20 µm mainly deposit on the nasal mucosa. Aqueous sprays tend to produce droplets which are > 50 µm, with only 10% being less than 10 µm. The intensity of sniffing as the nasal spray is administered does not appear to affect the deposition pattern⁵².

It should be remembered that regardless of the mechanism by which drug is administered to the nose, any drug which is not absorbed will either be blown out of the nose, or will clear to the gastrointestinal tract. When considering administering any drug to the nose, the consequence of gastrointestinal absorption should always be considered.

Mechanisms to increase nasal residence time of formulations

Two basic approaches have been used to increase the nasal residence times of drugs, and correspondingly to decrease intrasubject variation. These are firstly to use viscosity enhancers, and secondly to use a “bioadhesive” formulation to reduce the clearance rate. Two classes of bioadhesives have been used; firstly polymers which interact with the nasal mucus, and secondly microspheres. A large number of such formulations have been studied and many of them increase the residence time of the formulation, and alter the pharmacokinetics of the drug, causing increased bioavailability or duration of action. It is difficult to assess the exact physical mechanism by which these formulations operate. Many of the so-called bioadhesive polymers also act as viscosity modifiers, and many of the microsphere formulations hydrate to form glue-like gels which will adhere to the nasal tissues even in the absence of a specific particle-mucus interaction. As a result it is almost impossible to separate the importance of these effects *in vivo* and the importance of specific ‘bioadhesive’ interactions is questionable.

Viscosity modifiers

Spray preparations containing 0.25% methylcellulose have been reported to exhibit decreased mucociliary clearance resulting in delayed absorption of nasally administered desmopressin⁵³ and hydroxypropylmethylcellulose increased the residence time of spray formulations⁵⁴.

Smart hydrogel (poly (oxyethylene-b-oxypropylene-b-oxyethylene)-g-poly (acrylic acid) (GelMed Inc. USA) demonstrates great potential for nasal drug delivery. It is a thin liquid at room temperature, but it gels at body temperature. When administered as a spray to the nose, 80% cleared within 4 h, but 10% was still detectable at 20 hours post administration (Figure 9.5)⁵⁵.

Bioadhesive polymers

A number of polyelectrolyte polymers are generally considered to show specific interactions with mucus. Polyacrylic acid and polyacrylates such as Carbopol 934 were shown to

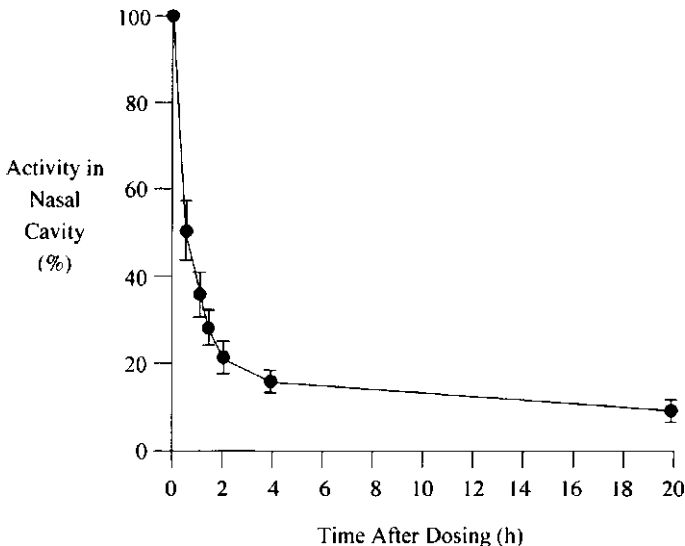


Figure 9.5 Clearance of ^{99m}Tc-labelled ‘Smart Hydrogel’ from the nose,

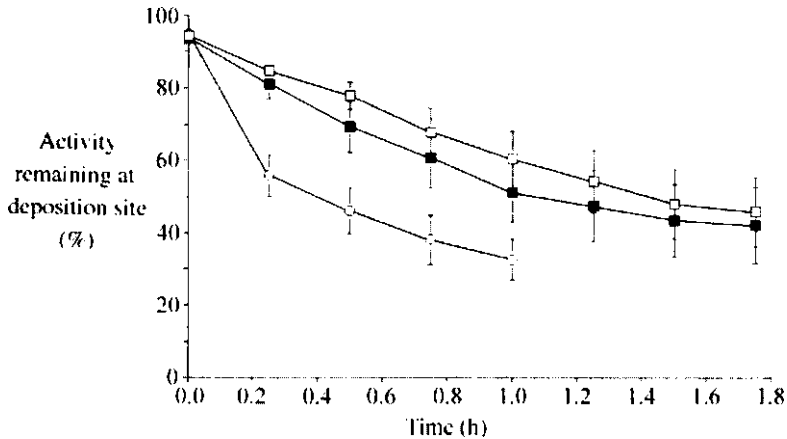


Figure 9.6 Clearance of ^{99m}Tc microspheres from the nose. \square microspheres, subject seated; \blacksquare microspheres, subject supine; \circ DTPA solution control.

increase the nasal absorption and residence of insulin⁵⁶, and solutions thickened with hyaluronan showed an increased residence time⁵⁷.

Bioadhesive microspheres

Microsphere formulations studied include albumin, Sephadex, starch, dextran⁵⁸, hyaluronan⁵⁹, and chitosan⁶⁰. The majority of these studies were intended for the delivery of peptides, particularly insulin, and caused increased absorption. Unfortunately there are conflicting reports concerning their nasal residence, and some workers have suggested that they are rapidly cleared but somehow increase nasal permeability⁵⁸. In some cases, one is led to suspect that the isotope labelling of microspheres used for scintigraphy studies may be at fault.

The studies which demonstrate long nasal retention times for bioadhesive microspheres report that this occurs in the anterior part of the nasal cavity, which is non-ciliated and non-absorptive (Figure 9.6)¹⁵.

Excipient and drug effects on clearance

Much interest has been shown in the ciliotoxicity of formulation excipients included in nasal sprays, although recently a differentiation is being made between ciliotoxicity and cilioinhibition⁶¹.

In the early 1980's, it was recommended that mercury-containing preservatives, e.g. thiomersal, should not be employed in nasal preparations since these materials produced a rapid, irreversible inactivation of cilia in a chick tracheal preparation⁶². However later studies showed that thiomersal at the concentrations used in these experiments had no effect on mucociliary transport in man⁶³. Recently, the combination of topical steroids and benzalkonium chloride has produced areas of squamous cell metaplasia in rat nostrils. This was not observed in any nasal cavities exposed to the topical nasal steroid without the preservative, or to 0.9% NaCl, suggesting that benzalkonium chloride is potentially toxic⁶⁴. It obviously does disrupt the membrane, allowing large molecules to pass through, since it enhances insulin absorption three-fold (6.31% vs 1.96%)⁶⁵. Benzalkonium chloride is also present in many buserelin and nafarelin formulations and has also been shown to reduce ciliary beat frequency by 35% for 20 minutes *in vitro*, but it appears to have little effect *in*

*vivo*⁶⁶. The benzalkonium chloride story is further confused by *in vitro* studies which compared its ciliotoxicity to that of chlorobutol using concentrations of 0.005% for both compounds⁶⁷. In commercial formulations, different concentrations of both are used i.e. 0.01% benzalkonium chloride and 0.5% chlorobutol. Hence, not surprisingly, the data generated using 0.005% chlorobutol demonstrated it to be less ciliotoxic than benzalkonium chloride, whereas studies using representative concentrations of both show that the reverse is true^{68 69}.

Many drugs administered in nasal preparations can also influence ciliary motility. The list of materials which are cilioinhibitory includes anaesthetics⁷⁰ antihistamines, propranolol⁷¹ and bile salts⁷². However, β -adrenergic and cholinergic drugs stimulate ciliary motility. Early *in vitro* studies indicated that penicillin had an inhibitory effect on ciliary function, however this was not found in subsequent studies using orally administered penicillin⁷³.

Dexamethasone nasal drops (used in the treatment of allergic rhinitis) may cause pathological changes leading to Cushing's syndrome⁷⁴. Cushing's syndrome results from hypersecretion of the adrenal cortex leading to symptoms such as protein loss, fatigue, osteoporosis, amenorrhoea, impotence and oedema. The drug acts by absorption through the nasal mucosa and partly through the intestinal mucosa after a portion of the dose is swallowed. This problem does not occur with the newer intranasal steroids (e.g. beclomethasone and flunisolide) which are less readily absorbed through the nasal mucosa, and are inactivated in the liver after gastrointestinal absorption.

Care must be taken when extrapolating cilioinhibitory or toxicity data from *in vitro* to *in vivo* situations. For example, azelastine was claimed to be ciliotoxic, since it reduced *in vitro* ciliary beat frequency⁷⁵, however, this effect was not observed in animals and in long term use in allergic rhinitis patients it actually improved the nasal clearance rate⁷⁶.

Effect of formulation pH

The average baseline nasal pH is 6.4 in the anterior of the nose and 6.27 in the posterior of the nose (Figure 9.7)⁷⁷. The ranges were 5.5–6.5 and 5.0–6.7 in adults and children respectively. Nasal pH varies with air temperature, sleep, emotions and food ingestion³⁷. In acute rhinitis and sinusitis the nasal secretion is alkaline.

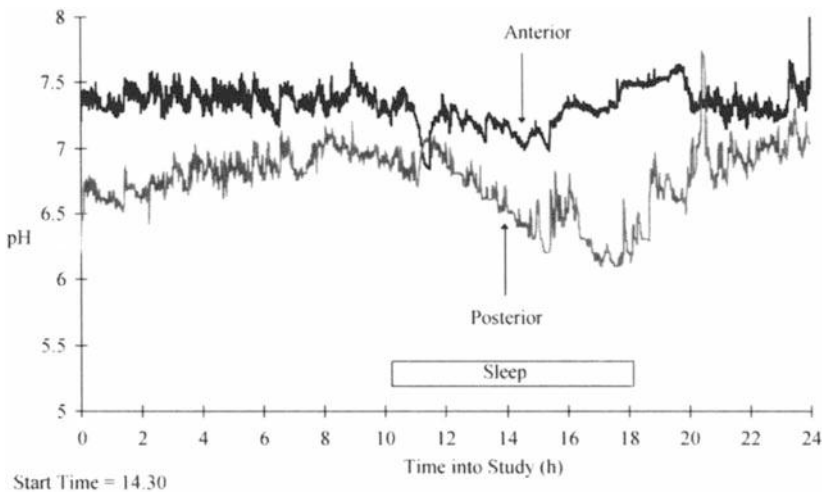


Figure 9.7. Diurnal variation of nasal pH.

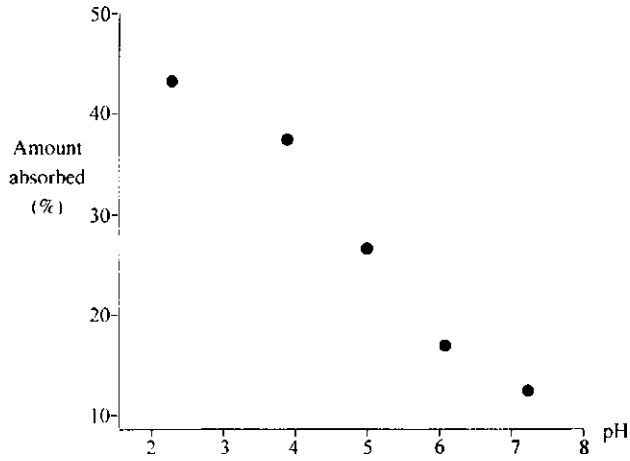


Figure 9.8 Fraction of benzoic acid absorbed in 60 minutes in the rat perfused nasal cavity model

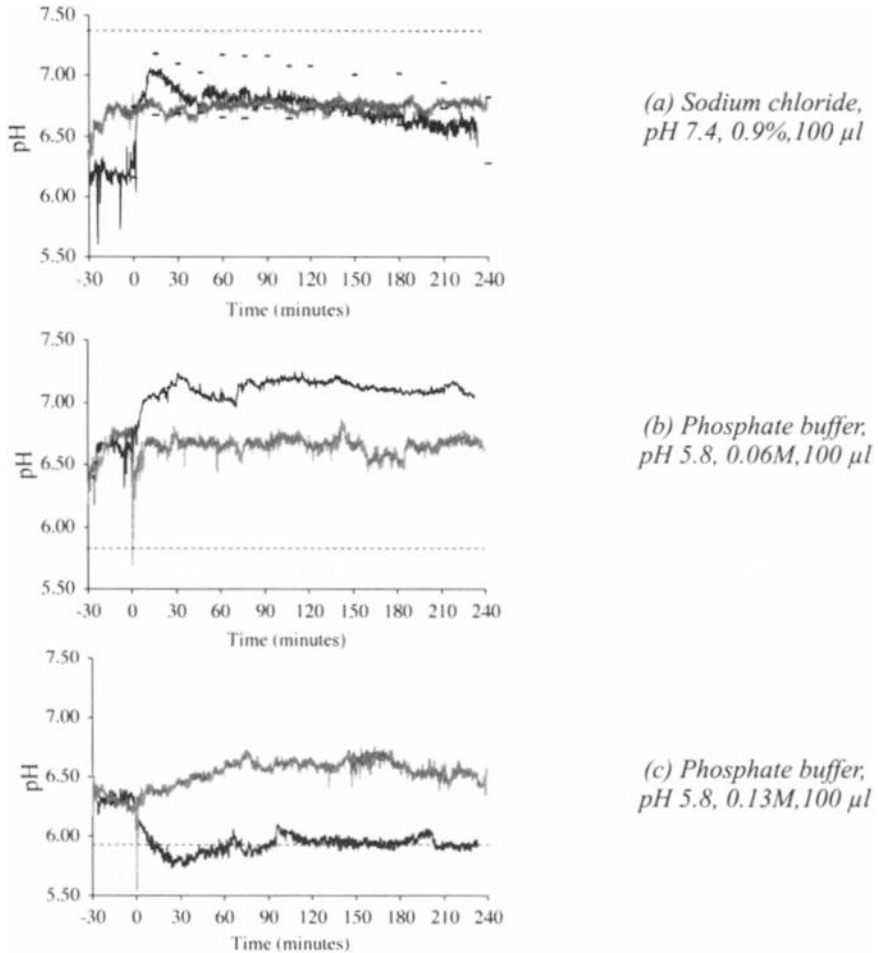


Figure 9.9 Effect of buffers on nasal pH. Anterior pH black line and posterior pH grey line

Local pH has been demonstrated *in vitro* and *ex-vivo* studies to significantly affect the rate and extent of absorption of ionizable compounds (Figure 9.8)⁷⁸. Buffering a solution to a target pH optimised for a particular drug should in theory, improve the absorption across the nasal epithelia. Reducing the pH of the mucosa enhanced the absorption of vasopressin in rats⁷⁹, but the rat tracheal cilia model shows that decreased pH has an adverse effect on ciliary beat frequency⁸⁰. Reduction in nasal pH has also been demonstrated to result in lower blood glucose levels in dogs treated with intranasal insulin⁸¹.

Recently, it has been demonstrated that buffers can be used to modify the pH of the human nasal cavity (Figure 9.9)⁸². Nasal anterior pH can be decreased when buffers of 0.1M and above are used. Mildly acidic solutions produce an increase in pH, presumably due to reflux bicarbonate secretion. It is more difficult to modify the pH in the posterior of the nasal cavity and stronger buffers are required to do this.

INTERSPECIES COMPARISONS

The majority of investigations published demonstrated the immense potential for nasal drug delivery. However, the majority of studies have been carried out in animals. A comparison of interspecies physiology and nasal clearance times is shown in Table 9.2. In humans, nasal drug delivery is only useful for drugs which have a low molecular weight, are active in low doses and have good aqueous solubility. It should also be borne in mind that the level of sedation used with different animals varies depending on ease of handling, and if general anaesthetics are used, these will usually reduce mucociliary transport. As a result the contribution of anaesthetics on published results can be difficult to assess.

Table 9.2 Comparison of interspecies nasal cavity characteristics⁸³

Conchae complexity	Weight (kg)	Nasal volume (cm ³)	Surface area (cm ²)	Volume admin. per nostril (μl)	Clearance half-time (min)
<i>Single scroll</i>					
Man	70	20	160	150	15
Monkey	7	8	62	58	10
<i>Double scroll</i>					
Guinea pig	0.6	0.9	27	25	7
Mouse	0.03	0.03	2.8	3	1
Rat	0.25	0.4	14	13	5
Sheep	60	114	327	307	42
<i>Branching</i>					
Dog	10	20	221	207	20
Rabbit	3	6	61	58	10

CONCLUSIONS

Nasal delivery is receiving a considerable amount of attention, but there is still a lack of much fundamental physiological and biopharmaceutic information. For example, the relationship between pharmacokinetics and deposition patterns is largely unknown. Neither is it a simple route for delivery since gastrointestinal involvement will also be a contributory factor in absorption.

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