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Nasal drug delivery—possibilities, problems and solutions

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Abstract

This paper discusses the problems associated with nasal drug delivery and how it is possible, sometimes by means of quite simple concepts, to improve transport across the nasal membrane. In this way it is feasible to deliver efficiently challenging drugs such as small polar molecules, peptides and proteins and even the large proteins and polysaccharides used in vaccines or DNA plasmids exploited for DNA vaccines. The transport of drugs from the nasal cavity directly to the brain is also described and examples of studies in man, where this has been shown to be feasible, are discussed. Recent results from Phase I/II studies in man with a novel nasal chitosan vaccine delivery system are also described. Finally, the author's thoughts about the future for nasal drug delivery are also depicted.

1. Introduction

Conventionally, the nasal route of delivery has been used for delivery of drugs for treatment of local diseases such as nasal allergy, nasal congestion and nasal infections. Recent years have shown that the nasal route can be exploited for the systemic delivery of drugs such as small molecular weight polar drugs, peptides and proteins that are not easily administered via other routes than by injection, or where a rapid onset of action is required [1]. Marketed products include a range of anti-migraine drugs such as sumatriptan from GlaxoSmithKline, zolmitriptan from AstraZeneca, ergotamine from Novartis and butorphanol from BristolMyersSquibb, as well as a range of peptides, such as calcitonin marketed by Novartis, desmopressin from Ferring and buserelin from Aventis (Table 1). A wide range of nasal products is in development, mostly aimed for exploiting the advantage of a rapid onset of action when administered via this route, for example for the treatment of pain, nasal morphine and ketamine and for the treatment of erectile dysfunction, nasal apomorphine. Lately the use of the nasal route for delivery of vaccines, especially against respiratory infections such as influenza, has also attracted interest from the pharmaceutical companies specialising in vaccine delivery. This is due to the possibility of obtaining not only a systemic but also a local immune response. Hence, the first nasal influenza product from the Swiss company, Berna Biotech reached the European market in 2001 (but is now withdrawn due to potential toxicological problems) and a second product from Aviron is due to be launced in 2003 [2]. The present paper discusses the problems associated with nasal delivery of drugs and how barriers to the nasal absorption of especially

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Table 1
Nasal delivery of peptides and proteins

- Nasal salmon calcitonin
  - Marketed by Novartis
  - Novel nasal formulations under development by other pharmaceutical companies
- Nasal desmopressin
  - Marketed by Ferring and partners
- Nasal buserelin
  - Marketed by Aventis
- Nasal nafarelin
  - Marketed by Searle
- Nasal PTH, nasal leuprolide, nasal insulin, nasal interferon, etc.
  - In clinical trials

challenging drugs can be overcome. It also highlights the possibilities for achieving novel targets (Brain, CSF) using this route of delivery.

2. The nasal cavity

The nasal cavity has an important protective function in that it filters, warms and humidifies the inhaled air before it reaches the lower airways. Any inhaled particles or microorganisms are trapped by the hairs in the nasal vestibule or by the mucus layer covering the respiratory area of the nasal cavity. Due to the mucociliary clearance mechanism, the mucus layer will gradually carry such particulates to the back of the throat, down the oesophagus and further into the gastrointestinal tract. Furthermore, the nasal mucosa has a metabolic capacity that will help convert endogenous materials into compounds that are more easily eliminated.

A midline septum divides the human nasal cavity into two non-connected parts. Each part consists of three regions: Firstly, the vestibule consisting of the region just inside the nostrils with an area of about 0.6 cm^2. Secondly, the olfactory region, which in man is situated in the roof of the nasal cavity and only covers about 10% of the total nasal area of 150 cm^2 as opposed to for example in the dog where the area constitute 77% of the total nasal cavity, and thirdly the respiratory region which constitute the remaining region. The respiratory region contains the three nasal turbinates, the superior, the middle and the inferior which project from the lateral wall of each half of the nasal cavity. The presence of these turbinates creates a turbulent airflow through the nasal passages which ensures a better contact between the inhaled air and the mucosal surface. Similar, more or less complex turbinate structures are present in all animal models normally used for nasal delivery studies.

The nasal vestibule is covered with stratified squamous epithelium which gradually changes posteriorly into a pseudostratified columnar epithelium that covers the respiratory epithelium. The respiratory epithelial cells are covered by microvilli and the major part of these cells is also covered with cilia. These cilia, which are long (4–6 μm) thin projections, are mobile and beat with a frequency of 1000 strokes per min. The beat of each cilium consists of a rapid forward movement, where the cilium is stretched and the tip of the cilium reaches into the mucus layer and carries this forward followed by a slow return beat, where the cilium is bent and moves in the sol layer that lies beneath the mucus layer. In this way the mucus layer is propelled in a direction from the anterior towards the posterior part of the nasal cavity. The mucus flow rate is in the order of 5 mm per min and hence the mucus layer is renewed every 15–20 min.

3. Barriers to nasal absorption

Lipophilic drugs are generally well absorbed from the nasal cavity with the pharmacokinetic profiles often identical to those obtained after an intravenous injection and bioavailabilities approaching 100%. A good examples of this is the nasal administration of fentanyl where the T_{max} for both intravenous and nasal administration have been shown to be very

rapid (7 min or less) and the bioavailability for nasal administration was near 80% [3]. However, despite the large surface area of the nasal cavity and the extensive blood supply, the permeability of the nasal mucosa is normally low for polar molecules, to include low molecular weight drugs and especially large molecular weight peptides and proteins. For small polar drugs the bioavailabilities are generally in the region of 10% and for peptides such as calcitonin and insulin normally not above 1%. It is interesting to note that the nasal sumatriptan product on the market has a pharmacokinetic profile not dissimilar to that obtained after oral administration and a bioavailability of 15.8% as compared to 14.3% after oral administration [4]. It is evident from the published results that only a minor part of the absorption is due to absorption from the nasal cavity (small peak at 30 min) and that a C_{max} obtained after 2 h is due to oral absorption.

The most important factor limiting the nasal absorption of polar drugs and especially large molecular weight polar drugs such as peptides and proteins is the low membrane permeability. Drugs can cross the epithelial cell membrane either by the transcellular route, exploiting simple concentration gradients, receptor mediated transport or vesicular transport mechanisms or by the paracellular route through the tight junctions between the cells. Polar drugs with molecular weights below 1000 Da will generally pass the membrane using the latter route, since, although tight junctions are dynamic structures and can open and close to a certain degree, when needed, the mean size of the channels is in the order of less than 10 Å and the transport of larger molecules is considerably more limited [5,6]. Larger peptides and proteins have been shown to be able to pass the nasal membrane using an endocytotic transport process but only in low amounts [7,8].

Another factor of importance for low membrane transport is the general rapid clearance of the administered formulation from the nasal cavity due to the mucociliary clearance mechanism. This is especially the case for drugs that are not easily absorbed across the nasal membrane. It has been shown that for both liquid and powder formulations, that are not mucoadhesive, the half life of clearance is in the order of 15–20 min [9,10]. It has further been suggested that the deposition of a formulation in the anterior part of the nasal cavity can decrease clearance and promote absorption as compared to deposition further back in the nasal cavity [11]. Most nasal sprays of various makes have been shown to deliver the formulation to a limited area in the anterior part of the nasal cavity as opposed to nasal drops which will be delivered to a larger area further back in the nasal cavity.

The nasal absorption of such polar drugs can be greatly improved if administered in combination with absorption promoting agents. Agents described in the literature for nasal drug delivery have included surfactants such as laureth-9, bile salts and bile salt derivatives such as sodium taurodihydrofusidate, fatty acids or fatty acid derivatives, phospholipids as well as various cyclodextrins [1]. These enhancer systems work by a variety of mechanisms but generally change the permeability of the epithelial cell layer by modifying the phospholipid bilayer, leaching out protein from the membrane or even stripping off the outer layer of the mucosa. Some of these enhancers also have an effect on the tight junctions and/or work as enzymatic inhibitors. For such enhancing agents greatly enhanced bioavailabilities have been obtained, even for larger peptides such as insulin at least in animal models. Less sucess has been achieved in Phase 1 clinical trials, very often due to a lesser effect in humans or to the irritancy of the enhancer material in the nasal cavity. In animal studies it has been shown for a range of enhancing agent that there is a direct correlation between absorption enhancing effect (bioavailability) obtained and the damage caused to the nasal membrane [1]. This is particularly true for surfactant materials and bile salts. For other enhancers, such as some of the cyclodextrins, chitosan and selected phospholipids the absorption enhancing effect outweighs any damage caused to the mucosa. Hence, it is of great importance that one considers carefully the choice of an absorption enhancer for a nasally delivered drug that is not readily absorbed especially in terms of potential nasal and systemic toxicity.

Another contributing (but normally considered less important) factor to the low transport of especially peptides and proteins across the nasal membrane is the possibility of an enzymatic degradation of the molecule either within the lumen of the nasal

cavity or during passage across the epithelial barrier. These sites both contain exopeptidases such as mono- and diaminopeptidases that can cleave peptides at their N and C termini and endopeptidases such as serine and cysteine, that can attack internal peptide bonds [12]. A range of studies has been carried out in vitro using tissue homogenates or nasal wash or in vivo in animal models to assess the possible effect of such enzymes on the stability of peptides [13–15]. However, it is often difficult to truly evaluate the relevance of the experimental set up to the real in vivo situation in man. Very often the exposure of the peptide to the enzyme has been overestimated and for some peptides degradation half-lives of less than 30 min have been quoted.

4. Chitosan

In designing effective delivery systems for a range of challenging molecules especially biopharmaceuticals, we have tried to take into account the factors that can effect nasal absorption. Absorption has been improved by using a number of strategies taking into account the drug, the disease and the destination. We have concentrated on overcoming two of the main barriers to effective absorption, namely transport across the epithelial membrane and the rapid mucociliary clearance of the formulation. We have focused upon a strategy employing the use of bioadhesive nasal delivery systems that provide the prolonged contact between the drug formulation and the absorptive sites in the nasal cavity by delaying the mucociliary clearance of the formulation. Such bioadhesive systems can be in the form of powders as well as liquids or liquid gelling systems. The powders can be administered as freeze dried or spray dried particles or microspheres. For such systems we have found starch and chitosan to be preferred materials in terms of their efficiency. Most recently we have focused our work on the use of the bioadhesive polysaccharide chitosan and the development of a range of delivery systems based on this material [1].

Chitosan is a positively charged linear polysaccharide that is bioadhesive and able to interact strongly with the nasal epithelial cells and the overlaying mucus layer thereby providing a longer contact time for drug transport across the nasal

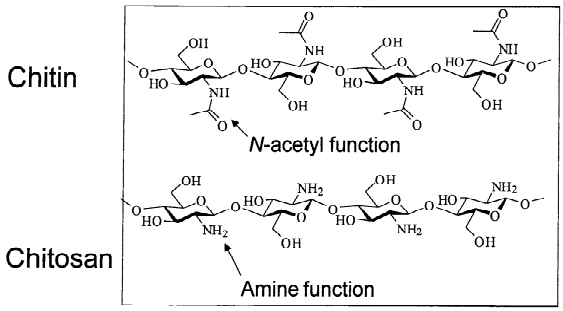

Fig. 1. Chitin and chitosan.

membrane, before the formulation is cleared by the mucociliary clearance mechanism [1,10,16]. In addition, chitosan has been shown (in Caco-2 cell culture studies) to increase the paracellular transport of polar drugs by transiently opening the tight junctions between the epithelial cells [17,18]. Chitosan is produced from chitin present in shells of crustaceans by a process of deacetylation and is available in a range of molecular weights and degrees of deacetylation. The structure of chitosan is shown in Fig. 1. The type of chitosan most often employed for nasal delivery is a chitosan glutamate salt of a mean molecular weight around 250 kDa and a degree of deacetylation of more then 80%. This chitosan salt is soluble in water up to a pH of about 6.5.

5. Nasal delivery of polar drugs

Various pre-clinical and clinical studies have been carried out in animal models and in human volunteers and patients for the development of therapeutically relevant nasal formulations of small polar drugs and a range of peptides and proteins using the chitosan nasal delivery system. Morphine is a good example, since for the management of breakthrough pain it is important to obtain a pharmacokinetic profile where an early peak plasma level is achieved and thereby a rapid onset of action is provided. This is not achieved at present. Breakthrough pain is generally treated with oral morphine solution or similar drugs where the plasma peak level is not achieved before 30–45 min after administration. The morphine opioid is relatively polar (log P=0.89) and when administered nasally in a simple formulation to

human volunteers the pharmacokinetic profile resembles that following an oral administration with a T_{max} about 40 min [19]. Only low amounts are absorbed nasally of the order of 5–10%.

However, when morphine is administered in a simple chitosan solution formulation a five to six-fold increase in bioavailability to about 60% is achieved with a T_{max} of 15 min or less [20]. The shape of the plasma curve has been found to be similar to that obtained for the intravenous administration of morphine (Fig. 2). Furthermore, the metabolic profiles obtained after intravenous and nasal administration of the respective formulations were very similar with comparable ratios between the plasma levels of morphine-3-glucuronide and morphine-6-glucuronide and similar low levels of both metabolites as compared to the five times higher levels of both after oral administration. It was also found that the nasal formulation was well tolerated with minimal side effects of less than 30% of total maximal scores. The effect of the nasal chitosan–morphine formulation on the management of breakthrough pain has been investigated in a pilot study in 14 cancer patients. This demonstrated that within 5 min the patients experienced a significant decrease in pain intensity and an associated increase in pain relief [21]. The chitosan–morphine nasal product is now in Phase II clinical trials both in the USA and in the UK and is expected to reach the market within the next 2 years.

Apart from the small molecular weight drugs, the chitosan delivery system, whether in the form of a solution or a powder, has also been shown to be very effective in delivering peptides such as leuprolide (1300 Da), salmon calcitonin (S-CT) (3500 Da) and parathyroid hormone (PTH) (4000 Da) across the nasal membrane. Nasal bioavailabilities of around 20% or more have been obtained in clinical trials for these drugs. Generally, it has been shown that chitosan powder formulations, whether in the form of microspheres or powders, can in many instances be able to provide a better absorption promoting effect than chitosan solutions. Hence, for the LHRH analogue, goserelin it was found in the sheep model that a chitosan microsphere formulation was able to provide bioavailabilities in the order of 40% relative to an intravenous injection [22]. For some drugs, such as PTH, a chitosan powder formulation is also

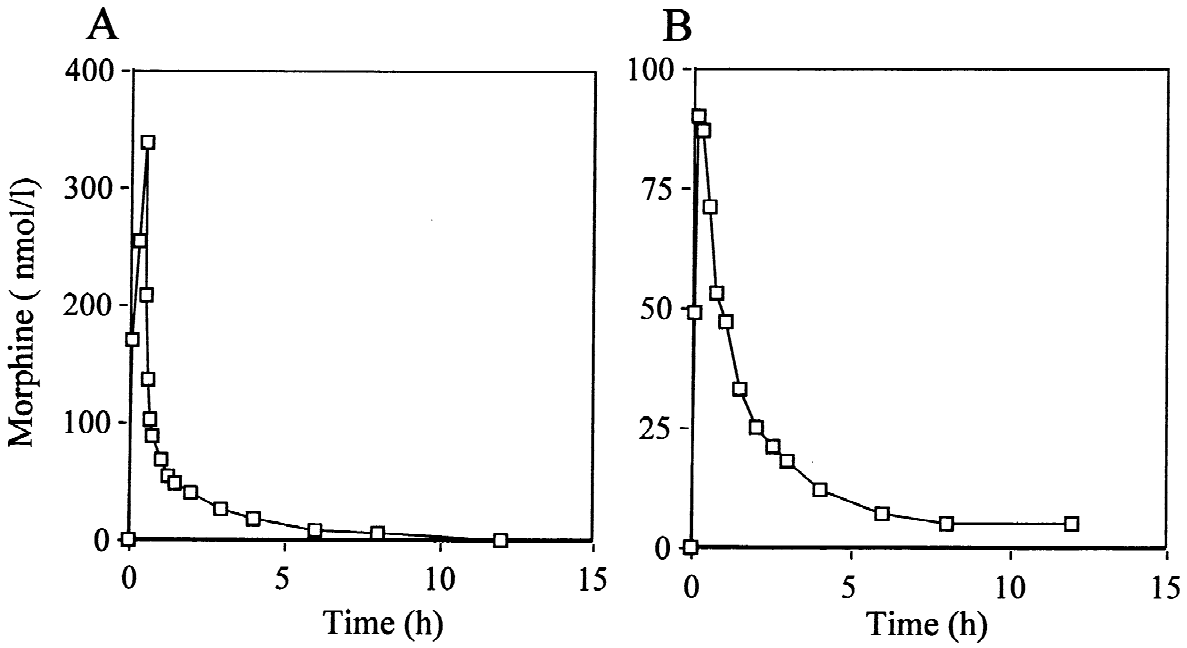

Fig. 2. A comparison between the pharmacokinetic profile of morphine (10 mg) administered as a slow (30 min) infusion (A) and morphine administered nasally in a chitosan solution formulation (B).

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