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Mini-review

Intranasal delivery: Physicochemical and therapeutic aspects

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Abstract

Interest in intranasal (IN) administration as a non-invasive route for drug delivery continues to grow rapidly. The nasal mucosa offers numerous benefits as a target issue for drug delivery, such as a large surface area for delivery, rapid drug onset, potential for central nervous system delivery, and no first-pass metabolism. A wide variety of therapeutic compounds can be delivered IN, including relatively large molecules such as peptides and proteins, particularly in the presence of permeation enhancers. The current review provides an in-depth discussion of therapeutic aspects of IN delivery including consideration of the intended indication, regimen, and patient population, as well as physicochemical properties of the drug itself. Case examples are provided to illustrate the utility of IN dosing. It is anticipated that the present review will prove useful for formulation scientists considering IN delivery as a delivery route.

Keywords: Intranasal drug delivery; Nasal mucosa; Pharmacokinetics; Physicochemical properties

Contents

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1. Introduction

Intranasal (IN) administration represents a viable option for local and systemic delivery of diverse therapeutic compounds (Behl et al., 1998a,b; Costantino et al., 2005; Hussain, 1998; Illum, 2000, 2003, 2004; Pontiroli, 1998; Sayani and Chien, 1996; Song et al., 2004; Wearley, 1991). The large surface area of the nasal mucosa affords a rapid onset of therapeutic effect, potential for direct-to-central nervous system delivery, no first-pass metabolism, and non-invasiveness; all of which may maximize patient convenience, comfort, and compliance. Although the nasal mucosa poses a permeation barrier to high-molecular-weight therapeutics such as peptides and proteins, the tight junctions that form this barrier to paracellular drug delivery can be reversibly and safely opened (Johnson and Quay, 2005). IN delivery is non-invasive, essentially painless, does not require sterile preparation, and is easily and readily administered by the patient or a physician, e.g., in an emergency setting. Furthermore, the nasal route may offer improved delivery for "non-Lipinski" drugs (Johnson and Quay, 2005). Due to such factors, marketed IN formulations exist for a variety of low- and high-molecular-weight drugs (e.g., peptides and proteins), and there are other products under development.

Given these positive attributes, it is logical to consider IN administration when developing new therapeutics, or when extending the life or improving the profile of an existing drug. In order to assess the desirability and viability of such an approach, a series of questions regarding the drug and its use should be addressed. Is the drug intended for local or systemic delivery? Will the drug be delivered chronically or acutely? Is the patient population needle-naïve? Are the physicochemical properties of the drug suitable for intranasal delivery and can clinically relevant bioavailability be achieved (an important aspect for peptides and proteins)? These questions are considered below in light of their impact on a drug's suitability for IN development.

2. Therapeutic considerations

Therapeutic considerations are paramount when selecting the dosing route. Such considerations include the pharmaceutical target (e.g., local versus systemic), the dosing frequency, and the patient population. In some cases, IN delivery may not only be possible, but may also be the preferred mode of administration.

2.1. Local delivery

IN is a logical delivery choice for local (or topical) treatment. Prominent examples are decongestants for nasal cold symptoms, and antihistamines and corticosteroids for allergic rhinitis (Bloebaum, 2002). Examples of nasal products with widespread use in this area include the histamine H_1-antagonist levocabastine (e.g., Janssens and Vanden-Bussche, 1991), the anti-cholinergic agent ipratropium bromide (e.g., Milford et al., 1990), and steroidal anti-inflammatory agents such as budesonide (e.g., Stanaland, 2004), mometasone furoate (e.g., van Drunen et al., 2005), triamcinolone (Lumry et al., 2003), and beclomethasone (Lumry et al., 2003).

As reviewed by Salib and Howarth (2003), IN corticosteroids and antihistamines have minimal potential for systemic adverse effects (as opposed to oral therapy), primarily due to the fact that relatively low doses are effective when administered topically. For instance, the recommended therapeutic dosage of IN antihistamines does not cause significant sedation or impairment of psychomotor function, whereas these effects may be seen upon oral dosing (for which a much larger dose is required). Such factors make IN delivery of antihistamines and corticosteroids an attractive and typically preferred route of administration, particularly if rapid symptom relief is required.

2.2. Vaccine delivery

The nasal mucosa has received some attention as a vaccination route. Presentation of a suitable antigen with an appropriate adjuvant to the nasal-associated lymphoid tissue (NALT) has the potential to induce humoral and cellular immune responses (Zuercher et al., 2002). This approach may be a particularly effective approach to achieving rapid mass immunization, for instance in children and/or in developing countries and disaster areas (Roth et al., 2003). IN immunization may lead to development of local, as well as systemic, immunity. Furthermore, vaccination via the IN route does not require a sterile product or a sterile dosing technique (a distinct advantage in developing areas of the world).

An example of an IN vaccine is FluMist®, a cold-adapted live influenza virus (e.g., Kemble and Greenberg, 2003). This product is given as one or two doses over the influenza season via a syringe sprayer. Additional examples of human efficacy testing of IN vaccines includes those tar-

geted against adenovirus-vectored influenza (Van Kampen et al., 2005), proteosome-influenza (Treanor et al., 2006), influenza A (Treanor et al., 1992), influenza B (Obrosova-Serova et al., 1990), meningococcal outer membrane vesicle (Oftung et al., 1999), and a combination respiratory syncytial virus (RSV) and parainfluenza 3 virus (PIV3) live, attenuated intranasal vaccine (Belshe et al., 2004).

Effective nasal immunization requires an effective antigen and/or a potent mucosal adjuvant or carrier. Research in this area includes exploring various IN excipients such as chitosan (Read et al., 2005), chitin (Hasegawa et al., 2005), galactoseramide (Ko et al., 2005), and biodegradable polymers (Koping-Hoggard et al., 2005). It is important to note that even for active antigens, IN delivery may not elicit an immune response in the absence of an effective adjuvant (McCluskie and Davis, 1998). In fact, it has been suggested that IN dosing can be effective for inducing nasal mucosal (Harrison et al., 2004; Mestecky et al., 2005) and oromucosal (e.g., Meritet et al., 2001) tolerance for a variety of molecules, including therapeutic peptides and proteins.

2.3. Systemic delivery

Positive attributes of IN systemic delivery include a relatively large surface area for drug absorption, rapid drug onset, no first-pass metabolism, and non-invasiveness to maximize patient comfort and compliance. Specific pharmacokinetic attributes of IN delivery are reviewed elsewhere (Costantino et al., 2005). As discussed in the various case studies below, IN administration provides an alternative route for systemic delivery of drugs more conventionally delivered by oral or (for poorly orally absorbed compounds such as peptides and proteins) injection routes.

2.4. Chronic versus acute therapeutic use

When deciding on a delivery route, it is important to consider the dosing regimen for the drug. Is the intended use acute or chronic? For an acute indication, the advantage of patient comfort and compliance afforded by IN dosing (as compared with injections) may not be a major factor. Even so, there are advantages to IN dosing in certain acute situations. One example is the case of an emergency room setting, where the avoidance of accidental needle stick potential is desired (Wolfe and Barton, 2003).

Other examples of acutely dosed therapeutics that have been explored for IN administration include epinephrine (Bleske et al., 1996) and cardiovascular agents such as nitroglycerin (Landau et al., 1994). In principal, IN administration is suitable for either acute or chronic use over a wide range of lengths of course and frequency of therapy. Dosing frequencies of current marketed IN products range from those dosed relatively infrequently, e.g., weekly dosing for Nascobal® Spray (for the treatment of vitamin B12 deficiencies), to multiple times daily, e.g., two sprays per nostril two to three times daily for ATROVENT® Nasal Spray (indicated for symptomatic relief of rhinorrhea associated with allergic and nonallergic perennial rhinitis). IN dosing may be particularly suited for the circumstance of a chronic application for a non-orally bioavailable drug to be given to a needle-naïve patient population.

2.5. CNS delivery

IN delivery of drugs targeting the central nervous system (CNS) is currently an area of great interest, as reviewed elsewhere (Illum, 2004; Vyas et al., 2005). Improved delivery to the brain via the IN route has been reported for some low-molecular-weight drugs (Sakane et al., 1991, 1994, 1995; Kao et al., 2000; Chow et al., 2001; Al-Ghananeem et al., 2002; Costantino et al., 2005; Barakat et al., 2006), as well as therapeutic peptides and proteins (Frey et al., 1997; Dufes et al., 2003; Banks et al., 2004; Thorne et al., 2004; Ross et al., 2004; Lerner et al., 2004).

However, it should be noted that there are also cases for which there was no evidence found for preferential delivery to the brain via IN dosing (van den Berg, 2005; van den Berg et al., 2004a,b; Yang et al., 2005). Therefore, the potential for preferential brain delivery for IN dosing may be drug-specific, or may depend on the study methods employed (van den Berg, 2005). In addition to the potential for "nose to brain" delivery, IN drugs can enter via a "nose to systemic circulation to brain" pathway (see Fig. 1). In this case, it is necessary for the drug to readily permeate the blood–brain barrier (BBB) from the circulation. In order for this to be achieved, the drug (or prodrug) must exhibit satisfactory passive or active transport across the tight junction barriers of the BBB. For example, an insulin transporter across the BBB has been described (Banks, 2004).

2.6. Factors related to patient population

Yet another factor in considering IN delivery for a therapeutic indication is the patient population. For example, if IN delivery is being considered as an alternative to injections, what is the patient population's experience with injections, and what is their

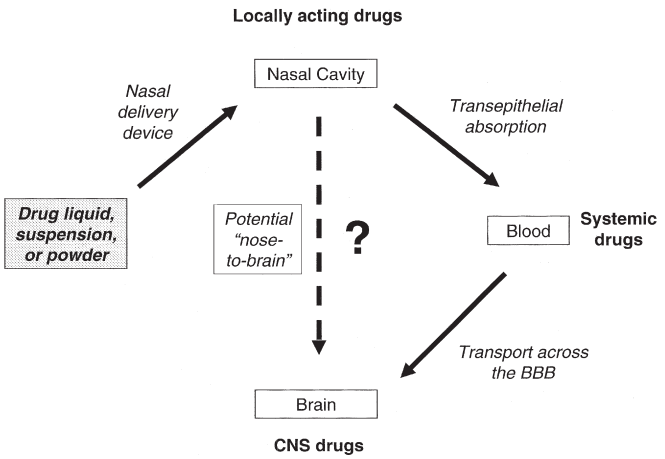

Fig. 1. Schematic of nasal drug delivery. IN drugs formulated as solutions, suspensions, or powders can be administered to the nasal cavity (local action), can transport across the epithelial tissue to enter the blood (systemic drugs), and for drugs that cross the blood–brain barrier (BBB), can subsequently enter the brain (CNS applications). Direct delivery of IN drugs to the brain has been proposed, but is not universally established in the literature.

preferred route of administration? It is believed that IN delivery is favored over injections, e.g., for insulin where a 67% patient preference was reported compared to injections (Frauman et al., 1987), although this may not always be the case, e.g., for a new intranasal fentanyl formulation where a 29% patient preference was reported (Paech et al., 2003). It is interesting to note in this context that calcitonin was first introduced as a subcutaneously delivered product, but intranasal formulations are now more widely used because of improved tolerability compared to injections (Munoz-Torres et al., 2004). As noted above, IN dosing may be particularly suited for chronic dosing to a needle-naïve patient population, as well as when oral dosing is problematic.

2.6.1. *Effect of nasal inflammation*

A common question regarding IN dosing and the intended patient population is whether inflammation of the nasal mucosa (e.g., patients with rhinitis) affects drug bioavailability. Various studies suggest that intranasal drug pharmacokinetics and/or pharmacodynamics are not affected by the presence of rhinitis. These studies include the examination of intranasal formulations of low-molecular-weight compunds (e.g., dihydroergotamine (Humbert et al., 1996), zolmitriptan (Dowson et al., 2005), and butorphanol (Shyu et al., 1993)), as well as peptide drugs (e.g., buserelin (Larsen et al., 1987) and desmopressin (Greiff et al., 2002)).

2.6.2. *Nasal physiology*

Various aspects of nasal physiology and their workings, such as nasal anatomy, airflow, resistance, and the nasal cycle (wherein the turbinates (see below) alternatively swell and congest from side to side) may have a potential impact on IN delivery. Reviews of this subject can be found elsewhere (e.g., Mygind and Dahl, 1998; Jones, 2001). Briefly, the nasal cavity is divided by the nasal septum (comprised of bone and cartilage), with each half opening at the face (via the nostrils). There is also a connection to the oral cavity provided by the nasopharynx. The anterior and posterior vestibules, the respiratory region, and the olfactory region are the three main areas of the nasal cavity. The lateral walls comprise a folded structure (refered to as the nasal labial folds or conchae). This folded structure further comprises the superior, median, and inferior turbinates, providing a total surface area of about 150 cm^2 in humans.

The epithelial tissue within the nasal cavity is relatively highly vascularized, and thus provides a potential conduit for drug delivery. The cellular makeup of the nasal epithelial tissue consists mainly of ciliated columnar cells, non-ciliated columnar cells, goblet cells and basal cells, with the proportions varying in different regions of the nasal cavity. Ciliated cells facilitate the transport of mucus towards the nasopharynx. Basal cells, which are poorly differentiated, act as stem cells to replace other epithelial cells. Goblet cells, which contain numerous secretory granules filled with mucin, produce the secretions that form the mucus layer.

2.6.3. *Variability of IN dosing*

Inter- and intra-subject variability in pharmacokinetics and/or pharmacodynamics is an important consideration when choosing the delivery route. Different administration routes should be compared (e.g., IN, oral, injection), and viable options are those with variability commensurate with the expected therapeutic window. Variability can be affected by numerous factors, including those arising from the patient, delivery device, formulation, and the drug itself. For low-molecular-weight drugs, IN dosing can provide pharmacokinetics with relatively high bioavailability and relatively low variability, which in many cases is similar to or lower than oral or even injection administration (e.g., Coda et al., 2003). However, for high-molecular-weight drugs such as peptides and proteins, IN pharmacokinetics exhibit relatively low bioavailability and relatively high variability compared to injections (Adjei et al., 1992). This can be ameliorated by the use of permeation enhancers (*vide infra*) which can enhance bioavailability and reduce variability (Hinchcliffe et al., 2005).

2.7. *Case examples of therapeutic areas sutiable for intranasal delivery*

The following sections provide case examples of therapeutic areas suitable for IN delivery. While the therapeutic areas are diverse, the common theme among them is an advantage for IN dosing, such as patient convenience and preference, rapid drug onset, avoidance of GI-related side-effects, and more consistent delivery for disease states associated with gastric dysmotility. These case examples range from products in exploratory development to marketed therapeutic products.

2.7.1. *Morphine for breakthrough cancer pain*

Patients with chronic cancer pain often manifest both incident and continuous pain. Incident pain, also described as "breakthrough pain", is typical of rapid onset, is severe in intensity, and has an average duration of 30 min. Various researchers have reported on the investigation of IN morphine to treat this debilitating condition (Illum et al., 2002; Pavis et al., 2002; Fitzgibbon et al., 2003). Morphine has relatively low oral bioavailability due to extensive first-pass metabolism. Therefore, IN delivery provides an attractive option due to the avoidance of first-pass metabolism, non-invasiveness, and rapid onset of action. An example of human PK for IN, oral, and injection (IM) dosing of morphine is presented in Fig. 2. The data illustrate that IN dosing achieves a similarly fast drug onset ($T_{max} \sim 15$ min) compared with IM dosing, and is much faster than oral delivery ($T_{max} \sim 50$ min). As for any analgesic, speed of onset for IN morphine is highly desired for breakthrough cancer pain, since rapid onset of significant pain relief is critical.

2.7.2. *Treatments for migraine and cluster headaches*

Patients with recurrent migraine or cluster headaches may have difficulty managing their disease, and in extreme situations may require emergency room visits to control the pain. When compared with oral delivery, IN dosing provides very rapid drug onset, which is a critical factor for controlling headaches, as well as providing improved bioavailability. Similar to morphine for breakthrough cancer pain, IN analgesics for headache are most effective when the onset of action is rapid, and IN dosing provides a distinct advantage over oral dosing in this

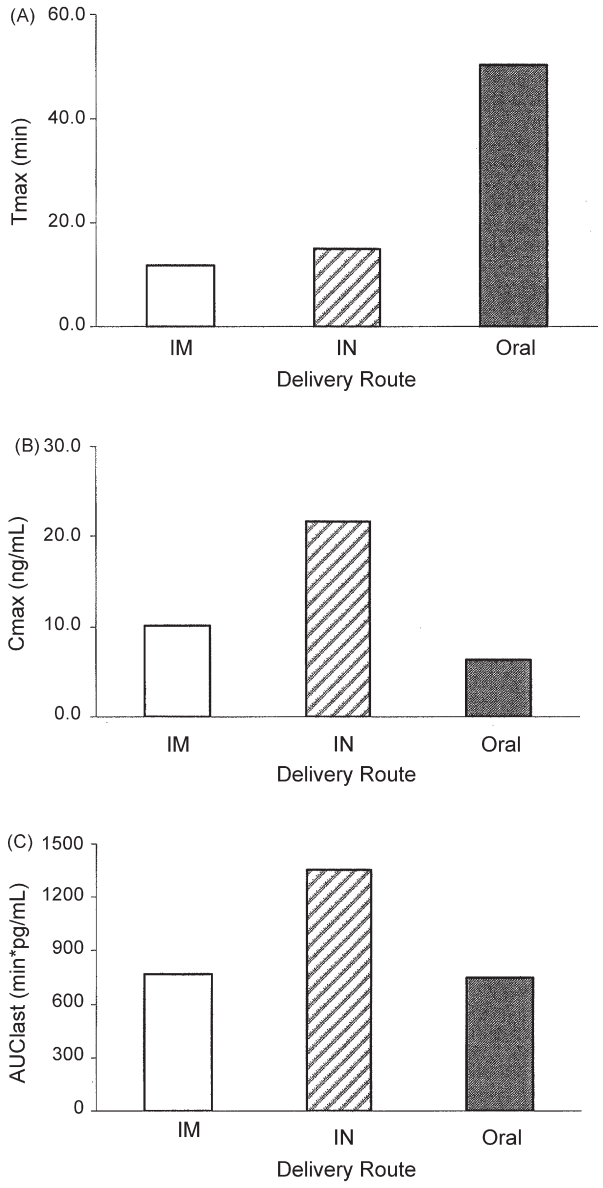

Fig. 2. PK parameters for morphine in humans: (A) T_{max} (min), (B) C_{max} (ng/mL) and (C) AUClast (min pg/mL). Data are shown for intramuscular (IM) dosing at 2.5 mg (white), intranasal (IN) dosing at 2.5 mg (striped) and oral dosing at 10 mg (grey). Data from Costantino et al. (2005).

regard. As an example, IN zolmitriptan for migraine treatment has been reported to provide significantly more rapid onset of therapeutic drug levels (Yates et al., 2002) and headache relief (Charlesworth et al., 2003) compared with oral dosing. Another important advantage of intranasal administration of drugs for treating migraines is that the therapeutic condition slows gastric emptying and hence oral drug absorption is compromised (Dahlof, 2002). Both oral and IN zolmitriptan are available commercially (under the trade name ZOMIG®). However, for this and other related applications, IN delivery provides a convenient and potentially more effective mode of dosing (Rapoport et al., 2004).

Butorphanol tartrate is another analgesic agent suitable for IN delivery. Butorphanol is extensively metabolized upon first-pass through the GI tract, and as a result, has very poor oral bioavailability (Gillis et al., 1995). The intravenous (IV) and intramuscular (IM) routes provide improved bioavailability and rapid drug onset, but at the cost of invasiveness, pain, and inconvenience. IN butorphanol offers a convenient alternative to IV and IM delivery and has been successfully developed commercially (marketed as STADOL NS®).

Other IN drugs have been explored for migraine and headache treatment (see Rapoport et al., 2004). Examples of drugs tested in humans include IN capsaicin for cluster headache treatment (Fusco et al., 1994), and migraine treatment using IN dihydroergotamine (Treves et al., 1998) and IN lidocaine (Maizels et al., 1996).

2.7.3. *Acetylcholinesterase inhibitors for Alzheimer's disease*

Kays Leonard et al. (2005) have reported on the development of IN galantamine, an acetylcholinesterase inhibitor indicated for the treatment of Alzheimer's disease. Pharmacokinetic testing revealed rapid drug onset for IN administration compared with conventional oral dosing. As with other drugs in its class, galantamine dosed orally has a clinically significant level of mechanism-based gastrointestinal (GI) side-effects such as nausea and vomiting. IN dosing dramatically reduced the emetic response, presumably as a result of avoidance of drug contact in the GI tract. Specifically, there was an order of magnitude reduction in emetic events (Fig. 3).

Patani et al. (2005) have explored an IN formulation of a heptylene-linked *bis*-tacrine analog (*bis*-THA). A series of investigations were conducted to examine various physicochemical properties (e.g., partition coefficient) of *bis*-THA compared with the parent molecule (tacrine). Permeation studies conducted using excised pig nasal mucosa revealed that the nasal mucosa was amenable for systemic delivery of *bis*-THA, and delipidization studies suggested that lipophilic components in the absorptive mucosa played a role in drug permeation.

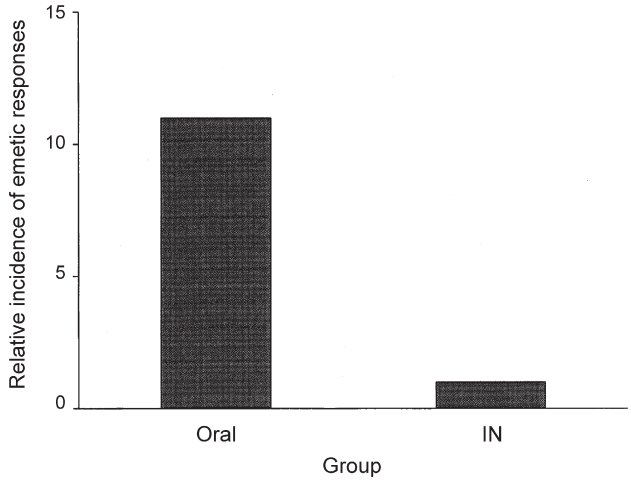

Fig. 3. Relative emetic response (in ferrets) for oral vs. IN dosing of galantamine. Oral dosing results in over a 10-fold increase in emetic responses. Data from Costantino et al. (2005).

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