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Expert Opinion

Delivery

Nasal Drug Delivery

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The Nasal Drug Delivery Conference was held at the Institute of Directors in London, England. The meeting was organised by the Management Forum Ltd and chaired by P Seeney (PA Consulting, UK) and Professor F Merkus (Leiden University, The Netherlands; Innoscience Technology, Belgium). The conference covered a wide range of topics including aspects of nasal physiology, formulation, new nasal products, nasal vaccines, nose to brain transport and pain management via nasal sprays.

Keywords: animal models, brain delivery, FDA guidance, *in vitro* tests, nasal drug delivery, nasal sprays, neuropeptide, olfactory region, preservative-free, toxicology, vaccine

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1. Overview of nasal drug delivery

1.1 Important considerations in nasal drug delivery

Professor L Illum (IDentity, UK) presented a comprehensive overview using a case study approach to highlight developments and challenges for nasal administration. Lipophilic drugs such as the opioid fentanyl are well absorbed from the nasal cavity and can achieve bioavailabilities that approach 70 – 100%. Absorption of polar drugs, on the other hand, is more challenging because transport across the epithelium occurs more slowly, allowing the drug to be cleared from the nose by mucociliary clearance. Polar molecules, therefore, may require utilisation of absorption enhancers or bioadhesive agents to increase the rate and extent of absorption.

In addition, peptides and proteins like insulin may necessitate use of absorption promoters. Historically, nasally administered insulin has been a challenge, due to low bioavailability. Formulations containing bile salts (INSERM, France) and chitosan (West Pharmaceutical Services) achieve plasma insulin levels that rival subcutaneous injection. However, one should keep in mind that some absorption promoters can damage the nasal epithelium, leading to undesirable outcomes.

Dr Illum also illustrated developments in nasal vaccines. Because the nasal passage contains nasal associated lymphoid tissue (NALT), the nose represents a low cost, non-invasive avenue for achieving mucosal and systemic immunity. The market potential for a nasal influenza vaccine alone is projected at US$1 billion (Med Ad News, January 2003).

1.2 Nasal drug delivery: a surgeon's view

Dr T Woolford (Royal Hallamshire Hospital, University of Sheffield, UK) provided the audience with images of nasal cavity using a nasendoscope. The pictures revealed the complexity and narrowness of the passageways. In addition, Dr Woolford presented feedback from patients with reasons why they did not use their nasal spray. Poor patient compliance could be attributed to an inconvenient dosing regimen, a perception that the drug had a slow onset of action and an unpleasant taste. Other patients stated that they were unable to use their nasal spray during an upper respiratory infection. One reason for this 'can't use it' statement, according to an image provided by Dr Woolford, was due to a physical blockage of the passage resulting from swelling and inflammation. Additional reasons for under-utilisation

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of nasal medications were discomfort, rhinitis/crusting and minor nose bleeds.

1.3 Toxicology in relation to studies for nasal products

Dr R Forster (CIT, France) covered issues surrounding safety evaluations using animal models. Commonly used species in nasal toxicology include rats, rabbits, beagle dogs and cynomolgus monkeys. Of these, monkeys appear to be most similar to humans in terms of turbinate structure, scarcity of olfactory epithelium and the cellular components of respiratory epithelium. In terms of volume, dogs (20 ml) were most similar to humans (30 ml).

A typical regulatory study, according to Dr Forster, would include clinical observations of factors such as body weight, food consumption and physiological measurements. In addition, laboratory investigations, such as haematology and immune system toxicity, and post mortem examinations on a wide range of tissues should be conducted. In evaluating the results, one should consider the study design, including how the device was used and reliability of dosing, the number of sprays per session and the number of sessions per day. Investigators should also consider functional changes in mucociliary clearance and other specific tissues, such as the olfactory bulb. Histological exams should involve assessment of serial sections of the turbinates and evaluation of the squamous, transitional, respiratory and olfactory epithelia within the nasal cavity.

2. Nasal drug delivery challenges

2.1 Nose models in animals – is there an animal model we can trust?

Dr S Gizurarson (University of Iceland and Lyfjathróun Biopharmaceuticals, Iceland) addressed the use of animal models in terms of selection of the right species, based on anatomical and physiological factors complimentary to the study objectives. For example, small rodents such as rats are amenable to histological examination of the NALT because inspired air passes over the area of interest in both rats and man. Since cats and sheep contain a large amount of fluid in the nose, drugs can precipitate in the nasal cavity and interfere with measuring irritation. Pharmacokinetics with frequent sampling may be easier in larger animals such as rabbits, dogs and sheep. On the other hand, rats and guinea-pigs are suitable for determining flux across the nasal mucosa. For evaluating new devices, Dr Gizurarson suggests using dogs, minipigs, sheep and primates. However, primates are best for assessing regional distribution of the spray, as the flow of air and mucus is most similar (due to anatomical and cellular structure).

Toxicology involving the nasal mucosa should include both short-term and long-term studies, as the surface can regenerate in some species. Dr Gizurarson also suggested that some species are capable of building resistance to nasal irritants. In addition, Dr Gizurarson's presented an irritation model using anaesthetised animals to eliminate confounding results due to stress associated with dosing.

2.2 The challenges of bringing an established European product to the US market

Dr H Nilsson (AstraZeneca R&D, Sweden) shared the lessons learned from bringing Rhinocort® Aqua (budesonide) into the US Market. Three guidances were highlighted in Dr Nilsson's presentation: Q1A Stability Testing of New Drug Substances and Products, ICH August 2001; Container Closure Systems and Packaging of Human Drugs and Biologics July 1999; and Nasal Spray and Inhalation Solution, Suspension and Spray Drug Products Chemistry, Manufacturing and Controls July 2002.

Based on his interactions with the FDA, Dr Nilsson recommended a pre-New Drug Application (NDA) meeting with the Agency. In defining the product, one should allow for batch variability to create space for setting of specifications. In addition, the specification limits should be reasonable and data-driven. The methods used to characterise the product should, if possible, be standard and known to the FDA. One should be prepared to work closely with suppliers and utilise all consulting opportunities during development and/or before NDA submission. Finally, Dr Nilsson suggested that the product should not change after Phase II clinical trials.

2.3 Difficulties in the development of an intranasal flu vaccine

Dr R Glück (Berna Biotech Ltd, Switzerland) presented clinical experiences with a heat-labile enterotoxin (LT)-adjuvanted intranasal vaccine. Nasalflu® (Berna Biotech Ltd) is an inactivated influenza vaccine, composed of influenza antigens in a virosomal formulation with *Escherichia coli*-derived LT adjuvant. Vaccination required two doses separated by 1 week. Clinical evaluation determined that Nasalflu generated immunogenicity. Safety evaluations indicated that Nasalflu was locally well-tolerated and had systemic side effects that were comparable to the licensed intramuscular vaccines. Uncommon adverse reactions associated with the nasal vaccine included a temporal association with Bell's palsy. Bell's palsy is a one-sided paralysis of facial muscles of sudden and unknown cause.

The vaccine was registered in Europe in 2000/2001 and ~ 100,000 doses were administered. Between October 2000 and March 2001, 56 transient cases of Bell's palsy were reported in patients vaccinated with Nasalflu. The pathogenesis of Bell's palsy is not well-defined and may be associated with viral infection, trauma, metabolic disorders and toxins. Retrospective case-controlled studies indicated that the incidence of the adverse reaction were in line with the normal rate of incidence as reported in the literature. Nevertheless, Berna and the Swiss Medic Agency decided to withdraw Nasalflu from the market. Additional prospective studies are ongoing to compare Nasalflu with a parenteral vaccine.

3. New therapies in nasal drug delivery

3.1 PT-141: a melonacortin agonist for the treatment of male and female dysfunction

Dr A Shadiack (Palatin Technologies, US) presented an overview of the development of PT-141 from animal studies through Phase II clinical studies. Melanocortins are associated with a variety of functions including grooming, yawning, inflammation, feeding and sexual function. PT-141, which binds to receptors in the hypothalamus, is a seven amino acid analogue of the peptide α-melanocyte-stimulating hormone (α-MSH). Biological activity studies indicated that PT-141 induces penile erection in male rats and monkeys and increases proceptive sexual behaviour in female rats. Phase I safety studies revealed that the intranasal dose is proportional to onset and duration of action. No serious adverse effects were found during dose escalation studies. The nasal bioavailability of PT-141 is ~ 14%. Phase II studies demonstrated an increase in erectile function in men compared with placebo (> 60%), and an increase in vaginal blood flow to women compared with the placebo (> 63%). No increases in systemic blood pressure were found. Clinical trials are ongoing.

3.2 Nasal drug delivery opportunities in pain management therapeutics

Dr D Wermeling (Intranasal Technology, Inc., USA) provided a comprehensive overview of opiate analgesics for intranasal administration. Agents to treat acute pain should be potent and possess good aqueous solubility, especially at higher concentrations. The pH of the formulation should be between 4 and 6. In addition, opiates used for acute pain should be lipophilic to rapidly cross the nasal mucosa and achieve an onset of action within 5 – 20 min.

The devices used to deliver the dose should be appropriate for the clinical setting. For example, a hospital pharmacy is more likely to administer unit dose medications. On the other hand, an ambulatory patient is likely to require a multi-dose device. Potent analgesics, such as fentanyl, necessitate accurate and precise dosing to prevent adverse drug reactions. Formulations should be sterile to guard against infection in immunocompromised individuals such as cancer patients. Finally, the device should prevent diversion and limit abuse potential.

3.3 Pain management – migraine

Dr B Charlesworth (AstraZeneca, UK) presented results from studies that investigated the pharmacokinetic and biological response to zolmitriptan (Zomig®, AstraZeneca) nasal spray. A positron emission tomography study was conducted in six human subjects to study the distribution of zolmitriptan in the nasopharynx, gut, lung and brain following nasal administration. Plasma levels of zolmitriptan and its active metabolite were also measured. Nearly 100% of the dose deposited within the nasal cavity. At 5 min postdose, zolmitriptan appeared in the plasma due to rapid absorption from the nose. No drug was present in the gut at 5 min.

Because zolmitriptan is absorbed orally, a four-way cross over study (tablet, tablet + charcoal block, nasal spray and nasal spray + charcoal block) was conducted to determine the percentage of the dose absorbed from the nasal cavity. The results indicated that the area under the curve (AUC) for the nasal spray + charcoal was 29% of that for the nasal spray alone.

A randomised, double-dummy study involving ~ 1500 patients indicated that the biological response in terms of pain relief postdose may be attributed to rapid absorption of zolmitriptan from the nasal cavity. In addition, the headache response over time may be attributed to delayed plasma concentrations of the active metabolite from the nasal spray compared with the oral tablet.

3.4 Nasal penetration of particles and their use for delivery of drugs

Professor O Alpar (University of London, UK) presented strategies for improving nasal delivery of peptides, proteins and vaccines through the use of particles such as bioadhesive starch microspheres, poly(lactide-co-gycolide) microparticles and liposomes. Particle uptake was investigated by radiolabelled microspheres, confocal laser scanning microscopy, modified Ussing chamber and cell culture.

4. New device concepts and *in vitro* spray characterisation

4.1 An update on bidirectional nasal delivery: flow modelling and clinical results

Dr P Djupesland (OptiNose AS, Norway) described a new concept for targeting the nasal cavity. The device (OptiMist) contains two nozzles, one that is inserted into the mouth and one nozzle that is inserted into a nostril. As a patient exhales through the device, the soft palate closes and seals off the nasal cavity. Exhaled air mixes with the formulation in the device and exits through the nosepiece into the nasal cavity. Because the nasal cavity is closed, inhaled air flows along one side of the nasal cavity and exits through the opposing nasal passage. This mechanism allows OptiNose to minimise lung deposition (< 1% of the total dose deposited in the lungs after bidirectional delivery compared to a nasal nebuliser which deposited 23% of the total dose in the lungs) and maximise distribution of aerosolised droplets in the nose.

Clinical results were shown from a nasal vaccination trial in humans that compared serum titres in volunteers that received a) diphtheria antigen (Ag) from a nasal spray pump, b) diphtheria Ag plus adjuvant from a nasal spray pump, or c) diphtheria Ag plus adjuvant using OptiNose's technology. Preliminary results indicated that the bidirectional device significantly increased serum titre levels compared to the spray pump (diphtheria Ag alone). Additional clinical studies are ongoing.

4.2 Preservative-free nasal sprays: what technology should be selected and how should it be evaluated?

Guillaume Brouet (Valois Pharm, France) highlighted the challenges associated with formulating a preservative-free, multi-dose, nasal spray suspension. Eliminating preservatives can reduce nasal irritation and allergies, and reduce any potential effects on mucociliary clearance. In Germany, the use of benzalkonium chloride (BKC) was banned in nasal products. BKC is the most commonly used preservative, especially in the US market. While this may make formulation development easier, removing preservatives may make registration of European products into the US much more challenging.

Delivery system technology for unit dose nasal sprays is readily available. However, multi-dose, preservative-free systems are still being evaluated. The attributes of a preservative-free system include protection of the product during storage, no need to protect the nosepiece between uses and avoiding contamination through air uptake into the device. Strategies for designing a preservative-free aqueous spray pump include use of mechanical seals (obturation), bacteriostatic agents such as silver ions, filtering systems within the device to extract contaminants, and negative pressure within the container. Mr Brouet presented the results from an assessment of a Valois multi-dose spray with a self sealing nozzle (obturation) controlled by hydraulic pressure. The device contained a preservative-free beclomethasone suspension stored at room temperature. Elimination of BKC had a negative influence on suspension stability. However, the self sealing actuator maintained sterility after microbial challenge tests.

4.3 *In vitro* tests on nasal delivery systems – a practical guide

Dr J Suman (Next Breath, LLC, USA) presented an overview of the FDA Guidance: Nasal Spray and Inhalation Solution, Suspension and Spray Drug Products Chemistry, Manufacturing and Controls July 2002. The talk focused on practical applications for measuring *in vitro* spray characteristics such as spray pattern, plume geometry, droplet sizing by laser diffraction and cascade impaction and pump delivery.

5. Nose to brain transport – fact or fiction

Conventional drug uptake into the brain and cerebrospinal fluid (CSF) occurs via transport from the systemic circulation across the blood–brain barrier (BBB). A few recent publications [1-5] have introduced and debated the concept that direct transport into the CSF may occur via the olfactory region located in the superior regions of the nasal cavity. Transport can occur either along the olfactory neuron (intraneuronal) or between junctions in the olfactory epithelium (extraneuronal). This topic, bypassing the BBB through the nose, sparked a rather heated debate at the Nasal Drug Delivery Conference. The following sections summarise the research that was presented during this session. A summary of the discussion, as well as the opinion of the author, appears in section 6.

5.1 Sniffing neuropeptides: a transnasal approach to the human brain

Dr W Kern (Medical University of Luebeck, Germany) described three studies that were performed in human subjects that indicate, in his opinion, drug transport is occurring directly from the nose into CSF. In those studies, volunteers were dosed using a traditional nasal spray pump. Plasma and CSF samples were drawn during each study visit. The nasal spray was administered while the volunteers were sitting upright.

Three neuropeptides were administered: melanocortin, insulin and vasopressin, which effect learning, memory and body weight regulation through receptor interactions in the brain. Of interest, are the profiles for intranasal insulin. Within 10 min after dosing, insulin concentrations increase from baseline levels in the CSF to an average value of ~ 22 pmol/l, whereas insulin blood levels are no different from the placebo and do not increase after intranasal delivery. Vasopressin levels also rapidly increased in both the CSF and serum after intranasal administration. A 10 mg dose of melanocortin (α-MSH 4-10) produced an AUC of 515 ng.min/ml in the CSF compared to an AUC of 11 ng.min/ml in serum [1]. Like insulin, MSH levels rapidly increased in the CSF within 10 min, while serum levels remain near baseline.

5.2 Transport of non-peptide drugs from the nose to CSF

Dr P Merkus (Academic Hospital of Vrije University, Netherlands) presented the results from a patient study where patients received intranasal and intravenous administration of hydroxocobalamin or melatonin. The study population consisted of postoperative patients with no history of anatomical disorders in the nose. The formulations were administered to supine patients using traditional spray pumps. CSF and plasma levels were measured on each study day.

The results for hydroxocobalamin, a hydrophilic drug, indicated a similar increase in AUC in the plasma and CSF following both modes of administration (nasal and intravenous). The difference in AUC was ~ 2-fold at 180 min postdose. For melatonin, which is a lipophilic drug, both the AUC in the CSF for the two routes of administration were nearly superimposable. Dr Merkus indicated that the results from these studies provided no evidence for a nose to brain pathway in humans.

5.3 Nose to brain transport – fact or fiction

Dr F Merkus (Leiden University, The Netherlands and Innoscience Technology, Belgium) provided a historical perspective regarding the potential nose to brain pathway. Among the studies presented, Dr Merkus discussed a study by Tenk *et al.* [6] in which patients inhaled nasal midazolam. There was an attempt to correlate time to maximum concentration (t_{max}) with sleep onset. The t_{max} for the 5 mg dose was 8 ± 1 min, whereas the t_{max} for the 10 mg dose was 10 ± 5 min. At 8 min, two of five patients had fallen asleep

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