Conversations with... Dr Julie Suman, on Nasal Drug Delivery

Current trends, technical challenges and opportunities for therapeutic innovation

Dr Julie Suman, Vice President, Scientific Affairs, Aptar Pharma

Nasal drug delivery seems to be receiving a lot of attention at the moment, could you explain why? What are its unique attractions/features?

A primary driver is recent success with the delivery of emergency medicines via the nasal route, as exemplified by naloxone (Narcan®, Emergent Biosolutions), a treatment for opioid overdose. Naloxone is not new but was previously admininstered intravenously. The nasal spray version delivers similarly rapid onset but can be given by those without the training required to use an injectable device. Narcan® saved lives and sold well, stimulating interest in reformulating other emergency medications in this way. Nasally delivered midazolam (Nayzilam®, UCB Inc.), a rescue medication for seizure sufferers, and glucagon (Baqsimi®, Eli Lilly), for the treatment of severe hypoglycemia, have already reached the market. The attractions are rapid onset and avoidance of first pass metabolism in the gut, as with intravenous delivery, but with easy, portable, non-needle-based delivery, for convenient administration by a caregiver or third party.

COVID-19 is also a factor because of the potential for nasal vaccines to limit viral shedding and for prophylactic nasal treatments. Virus loadings are particularly high in the nasal cavity and nasopharynx even in those who are asymptomatic, so effective nasal vaccines could significantly reduce spread of the disease. Nasal vaccines induce mucosal as well as systemic immunity and may therefore confer protection that cannot be accessed via the intramuscular vaccines we are currently using. Work in both these areas is still at an early stage but may prove pivotal to our long term ability to live easily with the disease.

Finally, it is becoming increasingly clear that nasal drug

delivery holds promise for bypassing the Brain Blood Barrier (BBB) and, by extension, for the treatment of illnesses associated with the CNS that are poorly served by current therapeutics.

What are the current areas of activity with respect to local treatments?

Generally speaking things are quieter with respect to locally acting therapies, though there is a fair amount of generic actvity. Corticosteroids, which are used to treat conditions such as hay fever, sinusitis, non-allergic rhinitis and nasal polyps, are largely now over the counter (OTC) so the goal is product differentiation in a fairly tight marketplace. A notable innovation in this area is dual active products, as exemplified by Dymista® (Mylan) and Ryaltris® (Glenmark), both of which combine a corticosteroid and an antihistamine in a single dose. Both are prescribed for the treatment of allergic rhinitis, providing options

where monotreatments have proven ineffective. Other dual active products are in the pipeline.

The other drug worth mentioning here is dupilimab, a monoclonal anitobody, which has been approved for the treatment of nasal polyps by intravenous delivery (Dupixent®, Sanofi and Regeneron Pharmaceuticals, Inc.). While this is delivered as an injection, it presents as a possible opportunity to convert this to a nasal application. Biologics are still in their infancy with respect to therapeutics for nasal and respiratory illness, and it will be interesting to see whether drugs such as this eventually transition to nasal delivery.

And systemics? Nasal drug delivery is highlighted as having potential to bypass the Blood-Brain-Barrier (BBB). Could you explain the significance of that?

I focused on systemic delivery in my first answer but the potential to bypass the BBB is particularly interesting. The BBB is a unique network of tissue and blood vessels that is highly effective in protecting the CNS from the ingress of harmful substances, including microorganisms and many drugs. As a result would-be therapeutics for conditions associated with the CNS, including Alzheimer's, Parkinson's, depression, anxiety, epilepsy and glioblastoma, often exhibit poor CNS bioavailability. By bypassing the BBB, nasal drug products enable delivery of more of the drug to its intended site of action while simultaneously lowering systemic levels and the associated risk of side effects.

This area of research is still in its infancy but interesting results have already been observed. For example, trials with intranasal insulin have shown a positive effect on memory in patients with moderate to mild Alzheimer's disease[1]. Peptides delivered in this way travel rapidly to the hippocampus and cerebral cortex via the olfactory and trigeminal nerves with minimal amounts passing into peripheral circulation, presenting opportunities for rapid onset with minimal side effects.

How does the development of nasal drug products compare with alternative dosage forms?

Nasal drug products are combination products, consisting of a delivery device and a formulation which, in combination, deliver the intended dose. This is a clear differentiator from other dosage forms, notably tablets. Dependence on a device brings human factors into play since the dose received is influenced by the technique of the patient. As a result, nasal drug product development necessarily includes human factor studies, rigorous assessment of the impact of the device and repeat administration trials to assess patient-to-patient reproducibility. Inter-subject variability, including differences in the physiology of the nasal cavity, is a significant factor in clinical trials, which may need to be larger as a result.

Furthermore, there are other complicating factors. For nasal drug products it has proven harder to develop models correlating in vitro data with pharmacokinetic behavior, limiting our ability to use simple lab tests predictively. Stability testing and regulatory requirements are more demanding so I might need as many as 20,000 devices to implement a rigorous assessment of chemical stability, which could take up to 2 years of fairly laborious effort. Finally, for drug repurposing projects, identifying the required dose is a challenge because our understanding of how to scale from small/large animal tests to humans is not secure for nasal drug delivery.

In summary, levels of clinical and analytical testing may both be substantially higher when developing nasal drug products than with alternative dosage forms.

When it comes to choosing a nasal drug delivery device what are the options and what factors influence choice?

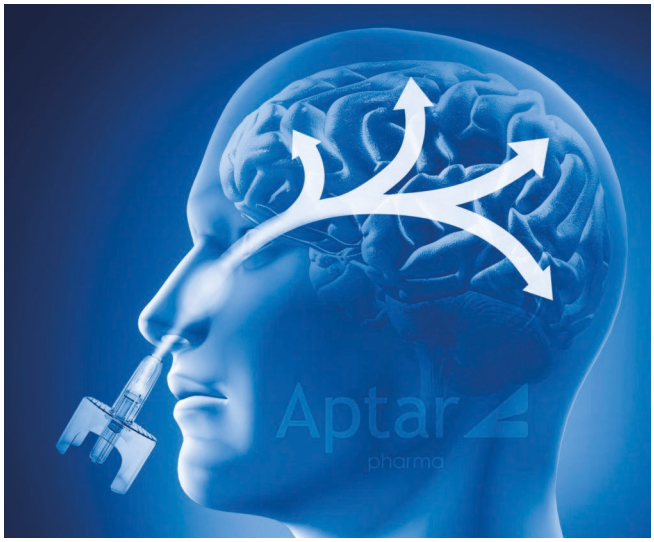
The primary choice is usually between a spray or powder. Droppers can't easily deliver the precision required for prescription drugs and the propellants associated with nasal aerosols make them increasingly unappealing, even though more environmentally benign HFAs (hydrofluoroalkanes) now dominate this market. Large doses and/or poor drug solubility mitigate towards nasal powders.

Beyond that primary choice lies a more detailed assessment of the relative merits of different devices. The use of preservatives is one factor, with preservative-free devices available for formulations that demand them. For example, Aptar Pharma offers the CPS Technology Platform, which has a membrane filter to remove contaminants from the incoming air, an anti-clogging spring-loaded tip seal to prevent bacteria migration during product use and fully validated microbiological integrity. A further factor in device choice is the need in many instances for a single pre-measured dose. Vaccines and emergency medicines exemplify this requirement.

And with respect to the formulation, can you explain how properties are controlled to achieve desirable performance?

For liquid formulations viscosity is a key property since it defines how the formulation responds to the shear applied by the device. Viscosity directly influences defining characteristics such as droplet size, which impacts deposition behavior, and clearance, how quickly the formulation is removed by mechanisms such as ciliary beating. Viscosity modifiers are used to achieve desirable results.

Other excipients used to improve performance include



mucoadhesives and penetration enhancers. Mucoadhesives, as the name suggests, enhance adhesion to the mucosal layer to increase retention times. Penetration enhancers such as Intravail® (Neurelis), on the other hand, boost drug transport across the mucosal layer by, for example, reversibly loosening the tight junctions in epithelial cells and/or by enhancing permeability.

Particle engineering techniques such as spray drying are used to control the size, morphology and surface roughness of powder formulations. Again, a typical goal is to maximize deposition at the target site but dissolution rate is also a common concern. Nanoparticulate systems are also being explored to improve uptake in the CNS or immunocompetent cells.

Does the device-formulation nature of nasal drug products have implications for regulation?

Yes it does, whether you're developing new or generic products; it's one of the primary reaons why nasal drug products are classified as complex generics. Nasal drug products are tested as combination products, i.e. device and formulation together, and I've already highlighted some of the

implications that has for development/testing. For regulatory approval, leachables studies are also important to determine whether trace contaminants from the device migrate into the formulation over time. For emergency medication there is also a need to demonstrate reliability, to ensure that the product will work as required at first use. Some nasal spray pumps require priming but clearly this is not an option for single use vaccines and emergency therapeutics.

The environmental impact of inhalers has recently been in the spotlight. Do nasal drug products suffer from similar issues? And are there any specific issues associated with toxicity?

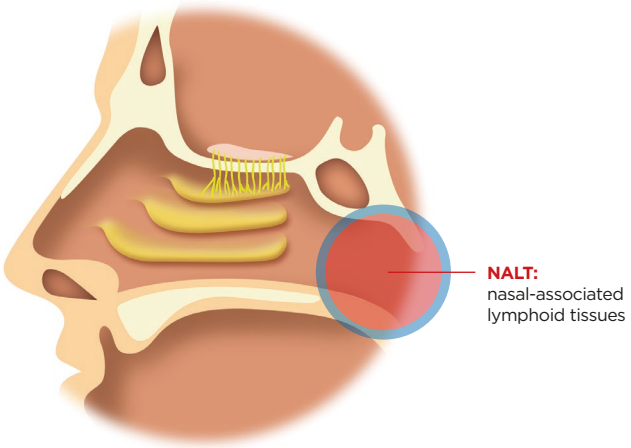
Most nasal drug products do not use a propellant, thereby avoiding the greenhouse gas effects that have recently been highlighted in connection with metered dose inhaler (MDI) use. However, the throwaway nature of nasal spray devices, especially single use products, is problematic. Device manufacture and disposal is therefore a major issue, with initiatives such as the Eco-Pharmaco Stewardship in the EU helping to focus minds on the longer-term impact of product use.

Nerve toxicity is the primary concern with respect to the risks associated with nasal drug product use because of the potential for nose-to-brain drug delivery. The possible dangers are clearly illustrated by the withdrawal of an inactivated influenza virosome vaccine which was found to trigger Bell's Palsy, a problem attributed to the use of E. Coli as an adjuvant[2].

How do you think the industry is going to maximize its use of nasal drug delivery? What challenges do we need to solve to unlock its full potential?

Firstly, we need a better understanding of drug absorption pathways, more specifically how nasally delivered drugs bypass the BBB and reach target areas of the brain. This understanding is vital to maximize intended drug delivery but also to reduce the risk of adverse health effects. This is especially true as we explore the delivery of nanoparticles via the nasal route. There is some evidence that using nanoparticles can help us to improve the uptake of vaccines and the delivery of drugs into the CNS, thereby unlocking new levels of performance. However, the health concerns associated with nanoparticles are well-documented. We need a secure knowledge of drug absorption via the nasal cavity to support their safe use.

Other topics that need more work include how to control regional deposition. The nasal-associated lymphoid tissues (NALTs) are a primary target for vaccines, while the olfactory region may be preferential for drugs for disorders of the CNS. It would be good to have a robust understanding of how to ensure consistently high levels of drug delivery to these regions. Finally, we need to marry expertise in how to formulate biologics with expertise in how to formulate for nasal drug delivery if we are to use the route for biopharmaceuticals. These are not fields of expertise that currently have much overlap.



What sort of therapies do you think will become routinely used nasal drug products over the next decade or so? Do you have a vision for how nasal drug delivery will develop?

I'm confident we'll see more energency/rescue medications because these are such a compelling proposition. These products are good news for patients, because they allow non-experts to administer life-saving therapies, and good news for pharma because they allow companies to repurpose drugs and access new revenue streams. I'm also expecting to see a wider range of nasal vaccines for respiratory illnesses and potentially for cancer too as this is very much an active area of research.

We are just beginning to see biologics being delivered via the nasal route as exemplified by Foralumab (Tiziana)[3] which is being assessed under an Individual Patient Expanded Access Program for the treatment of secondary progressive multiple sclerosis but I'm fairly sure that will become routine. mAbs have proven to be such valuable drugs, particularly for the treatment of cancer and inflammatory diseases such as arthritis, that it's hard to imagine that we won't be able to make some significant breakthroughs by marrying them with nasal drug delivery technology.

In summary, I hope and expect that nasal drug delivery will become more commonplace than it currently is, especially for systemics, and that, as a result, we will have some more effective products for debilitating conditions that are ill-served by existing therapeutics.

[1] S. Craft et al 'Effects of Regular and Long-Acting Insulin on Cognition and Alzheimer's Disease Biomarkers: A Pilot Clinical Trial. Available to view at: https://content.iospress.com/articles/journal-of-alzheimers-disease/jad161256

[2] D. J. M. Lewis et al 'Transient Facial Nerve Paralysis (Bell's Palsy) following Intranasal Delivery of a Genetically Detoxified Mutant of Escherichia coli Heat Labile Toxin' PLoS One 2009, 4(9): e6999 doi: https://dx.doi.org/10.1371%2Fjournal.pone.0006999

[3] News Item 'Tiziana Announces the FDA Has Allowed Treatment for a Secondary Progressive Multiple Sclerosis Patient for the Nasal Administration of Foralumab, a Fully Human Anti-CD3 Monoclonal Antibody, Under an Individual Patient Expanded Access Program' Available to view at: https://www.biospace.com/article/releases/tiziana-announces-the-fda-has-allowed-treatment-for-a-secondary-progressive-multiple-sclerosis-patient-for-the-nasal-administration-of-foralumab-a-fully-human-anti-cd3-monoclonal-antibody-under-an-individual-patient-expanded-access-program/