Evolution of nasal aerosol products for pain management

Administrating aerosols nasally has produced innovative drug delivery devices

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Introduction

Although nasal aerosol products to treat pain have been available for a number of years, recent developments have brought renewed interest to this market. In addition, estimated at over two billion dollars in 2009, the world market for nasally administered systemic drugs has seen strong growth in the last few years. The nasal pain market within the systemic nasal market has increased by more than 5% in the last few years. This article will look at the past, present and future of this particular aerosol application with a focus on some of the devices used to deliver the aerosolized drug.

Potential advantages of the nasal route of administration compared with parenteral or oral administration include a non-invasive approach that removes any associated pain or anxiety related to injection, rapid onset of action and good bioavailability compared to oral administration. Therefore, high levels of acceptability result in improved comfort and compliance for patients. Compared to oral pain management treatments, intranasal delivery also benefits from the avoidance of first pass metabolism. From a managed care perspective, reduced medical staff supervision or intervention is needed to administer the medication as compared to injection. Patients can also self-administer or self-titrate the medication, leading to potentially significant cost savings, which is a very strong driver for over-burdened healthcare systems worldwide.

The applications for nasally administered treatment and management of severe pain, as opposed to over the counter pain killers are numerous. They include in-hospital treatments, such as post-operative pain management, treatment of burns and management of breakthrough pain associated with cancer and multiple sclerosis as well as other pain episodes. Out of hospital applications include palliative care, paramedic retrieval medical services and anti-migraine treatments, among others. Some of these treatments will use potent drugs and may be managed under controlled substances regulations.

A review[1,2] of the pharmacokinetic (PK) properties of intranasal, intravenous and oral treatments in three classes of drugs (opioids, benzodiazapines and anti-migraine agents) that are potentially suitable for intranasal delivery reveals the attractive PK benefits for this mode of delivery (Table 1).

Taking Methadone as a typical example of opioid bioavailability, we find approximately 100%, 84% and 43% bioavailability by the intravenous, nasal and oral

routes respectively.[1] The PK properties of intra-nasally administered drugs lie between those of intravenous and orally administered drugs. A typical PK profile for a nasally administered drug compared to an intravenous formulation clearly demonstrates the potential of this drug delivery mode. This is because the onset of action for a nasally administered drug can be just as rapid as the intravenous formulation. In a study of the pharmacokintetics and pharmacodynamics of intranasal versus intravenous Fentanyl, in patients with pain after oral surgery,[7] there was 89% bioavailability of the nasally administered dose compared to the intravenous dose.

Table 1

Select pharmacokinetic properties of nasally administered drug classes

	T_{max}, min.	Bioavailability, %
Opioids	<25	>50*
Benzodiazapines	10 to 25	38 to 98
Anti-migraine agents	25 to 90	5 to 40

*Compared to intravenous

Figure 1

Early generation anti-migraine nasal spray devices Migranal and Imigran

(a) Migranal

(a) Imigran

Nasal spray device evolution

Among the first generation of devices used to deliver pain medication via a specifically designed nasal spray system were the anti-migraine products Diergospray/Migranal and Imigran (Imitrex) of the early 1990s. The device for the Diergospray/Migranal was an adaptation of a standard nasal spray pump coupled to a glass ampule containing the product. The glass ampule was opened just before use, the nasal spray pump dip tube was inserted in the drug solution, the product was primed several times and the dose was then delivered into the nasal cavity (Figure 1). The Imigran device used a specifically developed, ready to use, unidose system which did not need priming before use (Figure 1). These kinds of devices are very effective for acute treatments such as migraine attacks. Other devices that followed later, such as Zomig, had more customized and patient oriented designs.

Evolving needs for drug delivery systems used for chronic pain management, where numerous doses have to be taken over a prolonged period of time, has given rise to the development of nasal multi-dose delivery systems for pain management. One of the first to reach the marketplace was Stadol NS, where the active ingredient is Butorphanol, which can deliver up to 15 doses per container. Two recent examples to reach the marketplace in Europe are PecFent from Archimedes Pharma and Instanyl from Nycomed, where the active ingredient is Fentanyl (Figure 2). Here the devices can deliver multiple doses and can be self-administered by patients thus meeting two of the requirements for

Figure 2

Recent multi-dose nasal treatments include PecFent and Instanyl, which is shown below.

improved delivery devices: a reduced cost per dose compared to unit dose systems and the opportunity for self-administration, thus reducing healthcare professional supervision costs. These recent additions to the market have improved external packaging that incorporate child-proof and tamper evident features. Diversion is made more difficult because the containers are secured onto onto the delivery system using a crimp or locking screw closure, thus making them more difficult to access. In addition, the PecFent product has an integrated mechanical counting system. Currently, some of the evolutions in these devices are external but, in future, these functions will be integrated into the devices themselves.

New developments, challenges and future opportunities

An evolving regulatory landscape has brought its own challenges and opportunities. Regulatory authorities in the EU[3], US[4] and further afield[5] (e.g. Brazil) are increasing their requirements for nasal aerosols products through the issuance of several guidance documents. Some of these focus on usability and avoidance of misuse as well as chemistry, manufacturing and control (CMC) activities that require increased understanding of product performance, such as dosing, droplet size distribution, spray pattern and plume geometry.

Due to increasing regulatory requirements, devices have been obliged to evolve to meet the more stringent demands put on the CMC aspects of drug delivery systems. As a result, there has been considerable activity in these areas over the last few years, for example, the development of sophisticated techniques for controlling extractables and leachables from nasal spray devices. Device manufacturers have reacted by improving the quality, robustness and their understanding of key quality attributes that impact aerosol spray performance. This has resulted in a quality by design approach being applied systematically to the development of new generation of nasal spray delivery devices.

More frequent use of potent molecules, as well as controlled substances, in nasally administered products means that more scrutiny is being placed on issues such as potential overdosing. New innovations in devices to tackle these challenges could either be mechanically based or electronically based and many ideas are emerging in these areas. Dose counters and lockout systems will become common features on future nasal devices to deliver pain treatments (Figure 3). They can aid in the prevention of overdosing, provided the patient or medical staff can monitor the number of doses the patient is taking in any given time period and the device can lock-out automatically to prevent overdosing or diversion.

Another consequence of using potent molecules or controlled substances will be increased attention paid to any potential risk of aerosol particles inadvertently passing through the nasal cavity into the lungs and causing toxicity or irritation in the lungs. Particles greater than 10 µm will be deposited in the nasal cavity, however, particles less than 10 µm could potentially be inhaled into the lungs. Therefore, product developers need to monitor and minimize the number of particles less than 10 µm in such products by using suitable aerodynamic particle sizing methods.

Other innovations in the device area include the novel Optinose device currently in development for anti-migraine treatments,[6] among others, where the patient delivers the dose using a unit or multi-dose device (containing either a liquid or powder dose). This device uses the novel approach of blowing from the mouth into the nasal cavity. This technology claims to provide more efficient coverage of the nasal cavity surfaces.

Other challenges for device manufacturers related to the use of powerful pain management treatments are potential misuse, diversion and overdosing. These issues can largely be negated by using tamper- or child-resistant packaging solutions and using lock-out mechanisms on the delivery devices. These features can be electronically or mechanically based.

Patient compliance is another factor to consider during product development. With increased pressure on healthcare costs, more focus is being placed on getting patients to use devices properly, according to the correct dosing regimen and in the prescribed way. Electronic (E-device) add-ons, such as dose counters, can increase convenience and patient compliance. They assist patients in identifying when products are about to run out and prescriptions need to be renewed. Yet the ultimate advantage

Figure 3

An e-solution for future nasal aerosol devices

of electronic solutions is that they could be integrated, in future, into a telemedicine approach where healthcare professionals can virtually monitor how patients are using devices and make necessary adjustments for maximum efficacy and efficiency on a patient by patient basis. This approach could also significantly reduce healthcare costs.

Summary

Managing pain using nasally administered treatments has many benefits that will surely be exploited in the coming years. Administrating aerosols nasally provides numerous opportunities to introduce innovative drug delivery devices that can meet the increasing pressure on healthcare costs coupled with improved patient compliance and comfort. Nasal drug delivery devices have advanced over the years to accompany evolving regulatory requirements and meet the needs of current products, either already marketed or in development. Many opportunities lie ahead in this aerosol application and the best may be yet to come with a new generation of electronically or mechanically based devices meeting the needs of the evolving market for pain management.

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