Human factors studies in the development of a new nasal delivery device

This case study illustrates how both device performance and design can improve the reliability of drug delivery

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Opportunities for nasal delivery

The intranasal route of administration is commonly used for treating various diseases, from allergic rhinitis to breakthrough cancer pain. On one hand, nasal delivery is an attractive option for locally-acting medications (e.g., saline solutions, decongestants, corticosteroids or antihistamines), which treat allergic rhinitis and nasal congestion. On the other hand, the nose is the entry for systemic delivery of numerous drugs and therapies for a variety of diseases. In these cases, commonly-used drugs include calcitonin (osteoporosis), fentanyl, sumatriptan and zomitriptan (pain management), estradiol (hormone replacement therapy), nicotine (smoking cessation), desmopressin (enuresis) and metoclopramide (motion sickness).[1]

More drugs targeting other therapeutic fields and diseases may join the increasing list of marketed products for systemic delivery using the nasal route, such as drugs to treat central nervous system disorders like Alzheimer's disease and obesity.[2] The main reason for this trend is the advantage of delivering treatments directly from the olfactory region into the brain, which allows a drug to circumvent the blood-brain barrier.[1]

Furthermore, nasal vaccination is an attractive alternative to injection and causes little discomfort for patients. Mucosal vaccines not only promote good local immune protection, but also a systemic response similar to that of injection.[3] Flu Mist (MedImmune) is a nasal influenza vaccine on the market and a popular alternative to the traditional influenza vaccine injection, particularly for children.

Table 1 summarizes various possibilities that nasal drug delivery offers with respect to medications and therapeutic fields.[1,2,4] The main advantages of nasal delivery over injection and oral delivery are outlined in Table 2.[5]

Device ergonomics to improve compliance

Efficacy of a drug depends upon the spray device's ability to deliver a uniform dose as well as a reproducible droplet size and plume so the delivery system is a critical element for nasal spray performance. The device must be user-friendly and convenient for "on-the-go" use so that a patient can rely on the nasal spray at any time during treatment, for instance, when having a migraine crisis or experiencing allergy symptoms, which can occur outside the convenience of the patient's home.

Not only should therapeutic efficacy and molecule safety be taken into account, but ease of use and comfort of the dispensing system should also be considered. The nasal spray should help the patient accept treatment and, in turn, improve patient compliance. Therefore, ergonomics should be applied to the nasal device design to ensure overall attractiveness and user-friendly features.

Key characteristics to consider are:

- Intuitive handling
- Good grip, which can reduce the risks of injury during use
- Discreet when used in public
- Best delivery accuracy, regardless of actuation profile

Table 1

Potential opportunities for nasal drug delivery[1,2,4]

	Diseases	Medications
Topical	Allergic/Acute rhinitis, Rhinosinusitis, Nasal infection	Saline solutions, Decongestants, Corticosteroids, Antihistamines
Systemic	Pain management, Migraine, Endocrine diseases	Opioids, Triptans, Hormones
Nose-to-brain	Alzheimer's disease, Obesity, Lysosomal storage diseases	Insulin, Melanocortin$_{4\text{-}10}$, Iduronidase
Vaccines	Influenza, Measles, Pertussis, Diphtheria	Antigens, DNA

Table 2

Advantages of the nasal route of delivery

Versus injection	Versus oral delivery
Non-invasive	No first-pass metabolism (elimination of gastric and hepatic drug degradation)
Very accessible, easier than giving an injection	Rapid onset of drug action (high vascularization and nasal mucosa permeability)
Self-administered (may enhance patient compliance and decrease total cost of treatment)	Avoidance of vomiting after taking drug (e.g., during migraine crisis)
Low potential for injuries or disease transmission (hepatitis B, HIV)	Fewer side effects due to potential reduced dosage of drug

- Suitability for a large population (both child- and elderly-friendly)

These attributes should allow the patient to use the device properly and receive the exact dose of medication required.

The importance of human factors

A particular device, by design alone, does not guarantee precise delivery and treatment observance. As with all self-administered drugs, the most critical parameter affecting device performance is the patient himself or herself. To operate the device properly, a patient, who is most of the time untrained, relies on his personal knowledge and the instructions for use.

This perspective constitutes the fundamentals of Human Factors Engineering (HFE),[6,7] an inclusive design process that aims at identifying and mitigating all user-induced risks. The HFE process is based on user studies to identify risks and improve the device design accordingly. HFE also considers competence and user satisfaction to be equally important in ensuring patients' adherence to their treatment. Verifying both a safe and user-friendly device eventually relies on a combination of very different factors, ranging from functional to more perceptive parameters such as overall ergonomics or daily-use adaptability.

In response, Rexam developed the Advancia nasal spray device platform to meet both performance and design requirements for nasal drug delivery. Performance requirements included close examination of user independence, dose consistency and other factors. Design requirements included improved ergonomics to increase compliance with treatment. A comparative user study was performed with Advancia to benchmark the device with four other nasal delivery systems available on the market.

The Advancia human factors study

During the last quarter of 2013, a study was conducted with 18 nasal spray users, ages 7 to 80 years old. Per HFE recommendations,[6,7] the panel was assembled to represent the variety of nasal spray users, with respect to age and pathologies addressed by those treatments, from frequent users with allergic rhinitis to occasional users with cough and cold.

Objectives of the study were:

- Benchmarking Advancia Preservative-Free versus four marketed preservative-free systems with respect to dose accuracy
- Evaluating the user-independent feature of Advancia with different patient profiles
- Collecting users' general feedback about use of nasal sprays and, in particular, for the five systems

The study participants were recruited in order to test four nasal spray devices sourced from the market (all preservative-free), as well as the Advancia nasal spray, in a single blind study. To compare the devices and remove all commercial references to the marketed products, the marketed nasal spray devices, including their pumps and actuators/caps, were removed from their respective bottles. All of

the components in contact with the respective formulations were rinsed with distilled water. Then the devices were assembled onto identical, 10 ml bottles filled with distilled water.

Two workshops were conducted: one for measuring performance of the systems (to test dose consistency while capturing actuation speed) and another for collecting user feedback via a questionnaire.

In total, each patient performed seventy-five actuations, fifteen actuations for each of the five pumps. The order of actuation for the pumps was randomized between each user to suppress a test-method bias. The user studies were conducted within simulated testing conditions as defined by the HFE process.[6,7] No intranasal delivery of active ingredient was performed. Pumps were primed prior to being tested. Patients wore goggles and sprayed water in the air in a position close to reality.

Another potentially biasing factor was scrutinized because some pumps featured different dose levels, which changed the stroke distance and could have influenced users' perceptions, giving a relative impression of a "hard" or "soft" actuation force. The potential effect of these influencing elements was considered and mitigated via both the test protocol and the questionnaire and was carefully monitored throughout the test.

While it is possible to nullify the impact of simulated conditions on physical measurements, such as actuation speed or dose accuracy, these factors can exert a much greater influence on user perception, either positively or negatively. For instance, spraying in the air lets the user see the visual aspect of the spray—something one would not usually observe in a real-use scenario, possibly influencing the patient when asked to provide his or her impressions on the perceived precision of a pump. Both the questionnaire design and the moderator played key roles in controlling and neutralizing those biases.

The questionnaire was carefully constructed to allow user opinions to be crosschecked, addressing a point several times and from different perspectives. During the study, the moderator continuously checked the interviewee answers to be sure they were expressed as accurately as possible. This approach, referred to as "member checks," is a qualitative test methodology that aims to minimize the influence test conditions exert on the patient's judgment. By following this methodology, the moderator engaged each subject to double check their impressions and put their opinions in perspective with the actual use of a nasal spray, thus enabling the test to provide an objective output.

Additional testing

Prior to the benchmark device comparison tests, additional device tests were conducted. The protocols are briefly described here. Each test was performed on each device.

Dose accuracy measurements

Between each actuation, the nasal delivery pump weights were determined. Measurements were made on a Mettler-Toledo XS 204 Delta Range analytical precision balance, with precision of 0.1 mg between 0 to 80 g and 1 mg up to 220 g. Each shot weight was then automatically calculated by Excel spreadsheet using the difference of two consecutive measured weights. This data provided the single actuation weight of each spray.

Actuation speed measurements

For this test, a portable, high-speed, digital, video camera (Fastec TroubleShooter) was used, with a high resolution of 320 x 240 pixels. During measurements, study participants were asked to hold the pumps in a specific area for proper video capture and actuation speed collection. All actuations were captured by video. The actuation movement was tracked with Blender, an open source three-dimensional software. Speed of actuation was calculated by an Excel spreadsheet. Actuation speed measurements corresponded to the mean value for each user over the actuations they performed. Then the mean values were graphed, with minimum and maximum mean values for the 18 users.

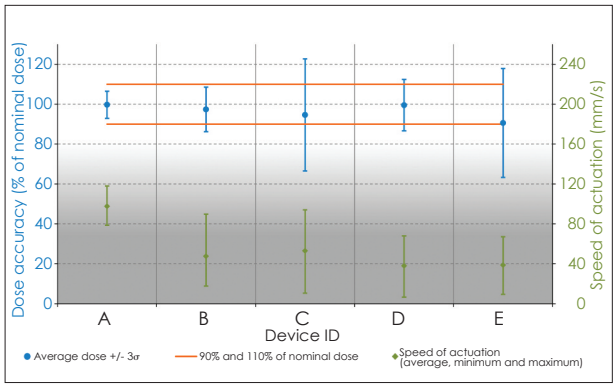
Performance results: Comparison of five preservative-free pumps

Regardless of the device design, reproducibility of the dose is a crucial attribute, as this parameter affects the delivery of the drug to the intended biological target. Pump spray weight delivery acceptance criteria should control the weight of the individual sprays to within 15% of the target weight and their mean weight to within 10% of the target weight.[8] Figure 1 shows that pump A complied with the target mean dose weight and produced the best results for both dose versus nominal value and reproducibility independent of the user.

Due to the user-independent feature, the activation speed is higher for pump A (Advancia) than for

Figure 1

Comparison of dose accuracy and actuation speed of preservative-free pumps (n = 18)



other pumps. This is illustrated by the green diamonds in Figure 1. The design of the Advancia pump allows energy to accumulate at the beginning of the stroke. Consequently, the user cannot stop the pump actuation before the end of the stroke and will therefore receive a full dose.

Patients' feedback

Patients preferred a full cap to a small tip cap, as it was believed to offer several advantages: greater hygiene, prevention of accidental pump activation, better ergonomics (i.e., easier to grab) and less prone to loss. It was also considered more adaptable to patients' way of life, as it was easier to put in or retrieve from a pocket. Figures 2a and 2b illustrate a tip cap and full cap.

Figure 2

Figure 2a shows a nasal delivery device with a tip cap (plus the device actuator without the tip cap). Figure 2b shows a nasal delivery device with a full cap (Advancia).

2a

2b

Regarding the actuator extremity: a dual diameter tip (designed to accommodate adults as well as children) was appreciated, provided that a smooth transition existed between the two diameters. A good finger grip (which incorporated a mix of textures, patterns and a properly-shaped surface for the finger flange) was important as well, in terms of patient comfort during device use. Last but not least, having textures on the finger flange was beneficial for enhancing patient comfort, provided the textures were sufficiently visible and offered a good grip.

Users highlighted the design of pump A considering it to be adaptable to real-life situations where users carry their nasal delivery devices with them. The full cap design was thought to be less prone to accumulating dirt in a bag or a pocket, easier to manipulate and less prone to loss than the classic, small tip caps present on most nasal devices. Moreover, the ergonomic features of actuator designs were more appreciated when the actuator was designed for all users, compliant with newborns' small nostrils and fitting equally effectively in small or large hands.

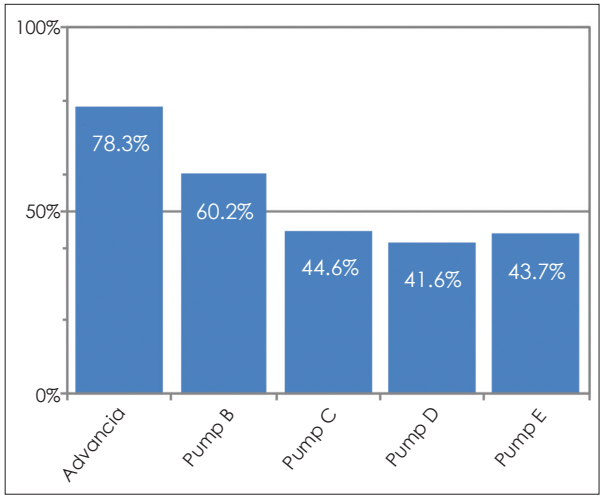
After testing and manipulating the five different systems, users were asked to rate the nasal delivery devices on a scale of 1 to 5 based on a range of criteria, combining convenience, ease of actuation and device design. A score of 1 was "best" and 5 was "worst." Those numbers were then transposed into the following percentages: 1 = 100%; 2 = 75%; 3 = 50%; 4 = 25% and 5 = 1%. Results are shown in Figure 3.

Advancia as an innovative device for nasal delivery

A new Advancia nasal spray device platform will be available on the market in 2014 and will respond

Figure 3

Patient ranking of the five nasal pumps, based on a range of criteria including convenience, ease of actuation and device design



to key demands for both convenience and performance (such as spraying formulations that require finer droplets and addressing drug crystallization issues). The new platform is based, in part, on the human factors studies described in this article.

Select features include:

User-independence

Quality and spray consistency are essential in delivering optimal treatment. It has been observed that the force applied by children to nasal spray devices is different from that by adults and this negatively impacts the resultant spray weight reproducibility.[9]

User-independent features and the demonstrated performance level incorporated in Advancia offer a consistent spray and limit the particle size and spray variations that can result from the patient's method of using the device, thereby ensuring the same dose is delivered through product life whomever the patient.

Prime retention

In many nasal spray devices, drug evaporation occurs inside the dispensing head; therefore, the next dose delivered is no longer a full dose. Despite instructions that advise spraying a few times into the air to re-prime a pump, a limited number of patients comply with, or even read, those instructions. Therefore, a risk exists that the patient will not receive the best treatment because a low dose is delivered.

In a study of prime retention, Advancia pumps were actuated 10 times after priming, stored in a vertical position at room temperature for 84 days, then actuated again. As illustrated in Figure 4, the first dose after a period of 84 days of non-use was a full dose.

The Advancia dosing pump function has been improved to be more accurate, even after several weeks of non-use. The new platform offers prime retention for up to 84 days in its standard version. This can be valuable to patients, for instance, during a migraine crisis. In addition, strong prime retention helps avoid wasting drug, and ultimately money, because if a pump requires additional priming, several sprays are wasted.

Device safety

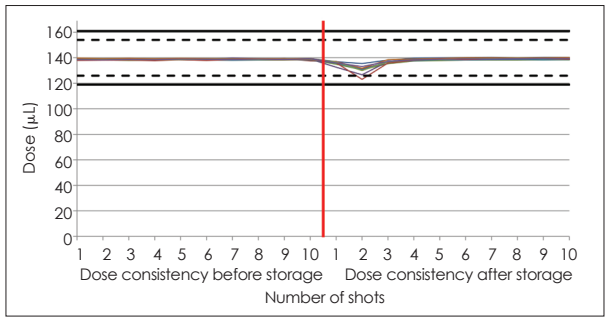
In order to increase device safety, Rexam has removed any potential points of contact between the formulation and the metal parts of Advancia, such as the spring. The risk of introducing alien substances in the delivered dose is therefore minimized.

Preservative-free

Preservatives, such as benzalkonium chloride, are commonly used in nasal drug formulations. However, preservatives can irritate the mucosa, deteriorate ciliary clearance and cause unpleasant adverse effects such as itching, which may negatively impact compliance. The development of preservative-free nasal medications is especially important for chronic treatments which, by their nature, require daily use over several months (e.g., for allergic rhinitis therapies) and require appropriate multi-dose delivery systems that prevent contamination. The new Advancia platform is available in both standard and preservative-free options.

Figure 4

Dose consistency of the Advancia device before and after 84 days of storage at room temperature



Conclusion

Nasal drug delivery offers a non-invasive alternative to injection and avoids first-pass metabolism compared to the oral delivery route, with rapid onset of local and systemic drug action. New medicines are under investigation for nasal drug delivery and there is interest from both clinical and pharmaceutical perspectives for this mode of administration. The nasal spray market is highly demanding with regard to device performance, particularly in the testing required for parameters such as dose consistency, spray characterization and user-independence.[8] In addition, the device design plays a crucial role in fostering patient adherence to treatment. Consequently, the ergonomics of a nasal spray device must encourage a user-friendly experience and provide convenient transportation within a pocket or purse, while remaining clean. New generations of multi-dose nasal delivery systems, such as Advancia, offer solutions that provide technical and ergonomic performance for patients. Both are key factors for treatment efficacy.

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