THE NASAL SYSTEMIC DRUG DELIVERY

AS AN ALTERNATIVE TO INJECTION

NASAL SPRAY

BLOOD UPTAKE

VASCULARISATION
Back in the 1970s, a scientist and entrepreneur named Alessandro Zaffaroni founded a company specialising in drug delivery technology. One of its main platforms, and most spectacular success stories, was the transdermal patch: a new user-friendly route for administering drugs that would otherwise have to be given by injection.

Now it’s the turn of intranasal delivery, and this route can offer similar prospects of commercial success to those who invest resources in developing it. This is the opinion of Professor Frans Merkus of the University of Leiden, who was one of the participants at a unique workshop convened by Valois, the French Drug Delivery Device expert specialising in nasal delivery systems. The object of the workshop was to invite discussion among experts on the intranasal route for administration of drugs for systemic therapies.

**A wide range of expertise – and an open agenda**

The meeting represented a wide range of expertise in the drug delivery field. The pharmaceutical industry was represented by Greg Anderson and Margot Jones from Glaxo SmithKline; also Eric Chetaille from Servier. The medicoeconomic viewpoint was expressed by a managed care consultant, Gilles Bignolas; attitudes of the medical profession and the public towards nasal delivery were explored by Andy Fry, of Team Consulting. Apart from Prof Merkus, the viewpoint from academia was represented by Professor Paolo Colombo, from the University of Parma.

The agenda for the workshop was intentionally open, to encourage a free exchange of opinions. Three general subject areas were identified for discussion. First, what therapies, now given by injection, are potential candidates for intranasal administration? Second, what are the limitations of the nasal route? And finally, participants were invited to explore the future prospects and opportunities for nasal therapies.

**Opportunities**

The meeting identified several types of drugs that are appropriate for intranasal administration; some are already being exploited, while others are potential opportunities.

**Vaccines**

There was general agreement that vaccines are ideal candidates for the nasal route. They can be self-administered, eliminating the need for injections given by health professionals. For mass campaigns, vaccines could be supplied in cheap, single-use nasal spray devices. A major advantage is that accuracy of dose is not vital, as long as sufficient vaccine is delivered to evoke an immune reaction.

**Rapid route to the CNS**

The workshop heard many examples of drugs which act on the central nervous system and are good candidates for intranasal administration. They included anti-epilepsy agents, drugs for Parkinson’s disease; hypnotics, and drugs used in pain management, including migraine treatments and patient-controlled analgesia for severe and/or chronic pain. An advantage of the nasal route for all of these indications is that drugs given by this route can have a relatively rapid onset of action – usually within 30 minutes. The proximity of the olfactory bulb to the brain, with the possibility of direct diffusion of drug through the Blood Brain Barrier, was discussed.

Prof Merkus gave the example of midazolam, when used as “rescue” treatment in epilepsy. This provides immediate help to ward off an impending attack, but at present it must be given by injection, which requires the presence of a healthcare professional. An intranasal formulation has been developed which could offer an almost equally rapid-acting alternative; the patients could simply carry the device around in pocket or handbag, and a dose could be self-administered at the first signs of an attack.

**Pulsatile delivery**

Eric Chetaille and Prof Colombo drew attention to the suitability of the nasal route for pulsatile delivery of drugs. Sometimes, it is better to deliver a drug in timed pulses, rather than as an uninterrupted flow, as commonly occurs with transdermal patches. HRT was mentioned as a specific instance where pulsed delivery may be more effective and minimise side-effects.

Erectile dysfunction was cited as another condition appropriate for nasal drug administration, possibly offering more rapid action than the oral route, and delivering a relatively short-acting bolus of drug when it is required.

**Limitations and challenges**

The main potential limitation for nasal delivery, identified by several speakers, is the chemical and physical nature of the drug. Delivery of large molecules across the nasal mucosa can be problematical. Eric Chetaille pointed out that for any drug with a molecular weight of more than 500 daltons, some form of active transport is likely to be required. Absorption enhancers (for example, substances which temporarily “open” the mucosal barrier to the passage of large molecules) are one possible answer to this problem. However, those which have already been investigated tend to have
problems such as unacceptable toxicity. There is ample scope here for research into better-tolerated absorption enhancers.

For a drug which is not efficiently absorbed across the nasal mucosa (perhaps because of molecular size), there is likely to be wide variability in the proportion of a dose that reaches the bloodstream. Prof Merkus gave the instance of intranasal calcitonin, where amounts absorbed can range from 1% to 3% of the administered dose. However, for a drug which is efficiently absorbed by this route, there is not likely to be significant inter-individual variation in the dose absorbed.

Margot Jones highlighted two other potential drawbacks related to the nature of the drug: irritancy to the nose, and unpleasant taste. Again, these depend on the characteristics of the individual drug: for some chemicals there is no taste or irritancy problem at all. And in some circumstances, if the patient experiences a taste after a nasal administration, it provides sensory confirmation that the dose has been delivered.

**Image and perception**

Apart from problems which may arise because of the physicochemical nature of the drug, another main challenge identified by the meeting was the perception of nasal delivery among the public and even the medical profession. Greg Anderson pointed out that the tablet is the “ultimate delivery device”; people prefer taking tablets to putting something up their noses. Nasal delivery is commonly associated with administration of (illegal) recreational drugs, such as snorting cocaine. This negative image is particularly important when considering the nasal route for administration of drugs in dry powder form – although a powder may be more effective than a liquid mist for reaching the olfactory bulb, as Prof Colombo suggested.

**Regulatory hurdles**

One of the challenges facing companies developing nasal delivery formulations and devices is the regulatory process. Products for nasal delivery face more stringent regulatory hurdles than, for example, simple injections, and this tends to hold back new developments in the nasal area, because it makes the product development process longer and more expensive.

Also, there is at present a lack of adequate models to test intranasal absorption before a formulation/device is developed for clinical testing. Animal noses are too unlike human noses to be useful as experimental models. There is a need for fundamental research into the development of a “nasal model” that would give a realistic preview of the behaviour of a new nasal formulation in the human nose.

**Profit and cost factors**

Prof. Merkus described his own early experience in attempting to find a pharmaceutical company interested in commercialising an intranasal form of Vitamin B12 which he had developed. A leading multinational company was not interested because the potential market (pernicious anaemia) was not large enough. Smaller companies were unable to afford the costs involved in clinical development and production scale-up. The same problem was encountered when the anti-epileptic “rescue therapy” using midazolam was being developed. This illustrates a fundamental barrier to be overcome: even if the drug is appropriate for nasal delivery, economic factors may deter both large and small companies.

**Future prospects and opportunities**

Throughout the morning’s discussions, workshop participants offered positive recommendations as a counterbalance to the problems and challenges which they identified, and they were positive, in some cases even enthusiastic, about future prospects for the nasal delivery route. These were some of the specific points made:

- There are opportunities for improvement in the design of nasal delivery devices. The device must deliver adequate quantities of drug deep into the nasal passages. Devices should be easy to use correctly.
- Device design should also communicate an image of “serious medicine”. Current devices often resemble those used to deliver locally-acting decongestants for colds and rhinitis. Others are more like cosmetic delivery vehicles – often streamlined and produced in bright or pastel colours. A device which aims to deliver a drug systemically for a serious medical purpose should reflect this in its aesthetic design.
- Planning for the device design should begin at an early stage in product development; it should not be an “afterthought”. The drug, the formulation and the device are
all equally important parts of the whole.

- Formulation development will need to take the physical characteristics of the device into account; factors such as particle size and delivery vehicle will have a profound effect on the way the formulation behaves in the device.

- The physical design of the device itself will need to be adapted to its intended function. This should include such considerations as whether the device is for use in an “on demand” situation, or in a regular dosage schedule – which may be once or more times per day, or once a week, or even once a month.

- Doctors, patients and payers are also important contributors to the process of new product development, and they should have a role in the evolution of new nasal delivery modalities. In fact the customers (doctor and patient) and payers (health service, insurer, managed care provider) should be involved at an early stage of new product design, so that their expectations can be recorded before the drug and formulation scientists and device engineers are briefed on the project.

- There is important educational, even missionary, work to be done towards creating a positive image for nasal delivery. The development of user friendly nasal devices can be seen as a step towards greater patient empowerment, and this is in line with current trends internationally.

- One of the important aspects of nasal delivery, for the user, is nomenclature. The word “device” should be avoided; it is too cold and mechanical. Similarly a phrase such as “dry powder inhaler” gives a negative impression to an asthmatic patient, with its connotation that the medication will irritate his over-sensitive airways. Speakers suggested that the focus should be on the nose, or nasal delivery; or more radically on a new way of giving medical treatment.

- The cost factor must be confronted in communication with payers. A nasal delivery product will cost more than a simple injection or tablet, partly because of the need to develop a specific formulation, and partly because of the development and production of a delivery device. However, the increased cost of the product is usually offset by the saving in professional time and in avoiding the need to provide for safe disposal, as with an injection syringe. Any cost comparison must paint the full picture, not just a part of it.

- Major opportunities for nasal delivery include vaccines, especially influenza vaccine; migraine prophylaxis and treatment; management of severe and/or chronic pain; rescue treatment for epilepsy; on-demand treatment of erectile dysfunction; the management of Parkinson’s disease, and anticoagulation (LMW heparins).

- Companies focusing on nasal delivery should select drugs which are good candidates for this technology; this is the best way to introduce the benefits of intranasal delivery and generate acceptance among payers and customers. At present, molecular size and lipophilicity are limiting factors. A major opportunity is offered by protein and peptide delivery, but this will involve fundamental work towards achieving delivery of large-molecule drugs.

- Here is no “one size fits all” in the field of nasal devices. Individual drugs each have their own physical and chemical characteristics; the needs of therapy are also specific in terms of dosing schedules, speed and duration of effect, and so on. The sophisticated devices that hold the key to the future of systemic delivery by the nasal route will each be individually designed with specific goals in mind.

The right time …

Greg Anderson pointed out that this was absolutely the right time to be having the workshop. Prof Merkus agreed; he said the prospects for nasal delivery were extremely bright, and needed only the kind of commitment that Alessandro Zaffaroni brought to the transdermal field thirty years ago.

Founded in 1947, Valois SAS is a world leader in the design and manufacture of spray and delivery systems for the Pharmaceutical, Perfumery and Cosmetics markets. Since 1993, Valois SAS has been part of the Aptar group, headquartered in Chicago (USA). Aptar is listed on the New York Stock Exchange.

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