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Could inhaled drug formulations be the future of acute migraine treatment?

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“The current challenge facing inhalation formulations is that the aerosolized drug needs to be increasingly deposited into deep airways and alveoli rather than the oral cavity, the oropharyngeal region and the upper airways.”

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Migraine treatment

A migraine is the most popular neurological vascular headache. It causes a throbbing and pulsating pain around the head as a result of brain and scalp arteries dilating, the matter which results in an aggressive pain.

It is described as an extraordinarily common, chronic, intermittently disabling and inherited from neurovascular disorders. A migraine is also associated with aura, which is a transient neurological symptom [1].

Different approaches can be utilized for migraine treatment either separately or combined. These approaches include: avoidance of triggers, acute attack treatment for aborting attacks and preventive therapy for reducing the number of attacks and severity. Among these approaches, acute attack treatment is the one that seeks rapid, complete pain relief and a fast onset of action with minimum medication side effects [2]. To achieve this, different critical steps are required, such as taking the medication at the correct time (when pain is mild) and administering the correct dose with a suitable route, which allows rapid drug circulation to target tissue in the brain.

Oral administration of anti-migraine drugs are usually associated with many disadvantages, such as delayed onset of action, first-pass effect and incomplete and erratic drug absorption from the gastrointestinal tract. Many migraine patients exhibit gastric irritability with severe nausea and vomiting during migraine attacks and for these reasons, there is an obligatory need for the development of different dosage forms to be administered via different routes.

The nasal delivery of anti-migraine drugs can represent an attractive alternative to the oral route via fast absorption from the nasal mucosa, avoidance of the first-pass effect and rapid onset of action compared with the oral route, especially if the drug is formulated into a dosage suitable for nasal administration which can target the brain [3]. However, disadvantages of nasal delivery of anti-migraine drugs include rapid clearance of the formulation by mucociliary clearance, difficulty in utilizing intra-nasal delivery devices and difficulty of nasal administration, especially if the migraine is accompanied by symptoms such as nausea or vomiting [4].

Inhaled drug delivery

Over the last few years, inhaled formulations for systemic treatment of nonrespiratory diseases have increased in popularity, although inhaled drug formulations have been justified only for treatment of respiratory diseases.

The inhalation route of administration represents a featured alternative drug delivery route as it is characterized by enhanced and rapid drug absorption via an air–blood barrier, a large surface area available for drug deposition and high vascularization. The inhalation route requires a lower drug dose compared with the oral route and it can protect the drug from degradation into the gastrointestinal tract or by the liver via avoidance of the first-pass effect. These advantages of the pulmonary route for administration makes this route better suited for systemic drug delivery, not only a localized one, with treatment efficiency depending mainly on drug volume to the site of action.

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Delivery of systemic drugs, other than those for respiratory diseases via inhalation, started with protein delivery therapeutics such as insulin (Exubera[®]), inhaled growth hormone, IFN- α , erythropoietin and oxyntomodulin in addition to many small lipophilic molecules. The delivered drugs were formulated into different pharmaceutical systems utilizing nanotechnology techniques, such as polymer-based nanoparticles, lipid-based nanoparticles, liposomes, lipid-polymer hybrid nanoparticles, nanostructured lipid carriers and nanospheres [5].

Inhaled delivery of anti-migraines

Dihydroergotamine, a 5-HT_{1B/1D} receptor agonist that has been utilized effectively to treat migraines, was introduced and formulated as an inhalation formulation. Dihydroergotamine is known commercially as Levadex[®] or MAP0004 (MAP Pharmaceuticals, CA, USA) and is being formulated utilizing the mesylate salt in a modified, breath-actuated, metered dose inhaler device (Tempo[®]), which delivers 0.6 mg per each emitted dose. Administration of dihydroergotamine via inhalation was demonstrated to be superior to a placebo in relieving migraine symptoms, with or without aura in adults, and sustaining relief in patients who experience nausea or vomiting, photophobia and phonophobia. Pharmacokinetic studies demonstrated that inhaled dihydroerhotamine demonstrated rapid absorption ($t_{\max}$ of 10 min), high bioavailability (77%) and long $t_{1/2}$ (15 h), thus succeeding low oral bioavailability and absorption, in addition to avoiding patient suffering from being repeatedly injected intravenously [6].

Zolmitriptan, a second generation triptan with selective action on serotonin (5HT_{1B/1D}), is an effective, well-tolerated drug in treatment of acute migraine associated with menses migraine with aura in addition to treatment of acute cluster headaches. Zolmitriptan is being investigated for inhalation delivery, CVT-427 (Phase I completed) by Acorda Therapeutics (NY, USA) in the form of a dry powder inhaler. It was demonstrated that zolmitriptan delivery by inhalation can result in higher $C_{\max}$ (ranged from 6.0 ng/ml [0.825-mg dose] to 35.0 ng/ml [6.0-mg dose]) and improved bioavailability, compared with oral and nasal delivery formulations, with consistent plasma concentrations and faster onset of action ($t_{\max}$ of 0.17 h) [7]. In a recently published study [8], the authors formulated micronized zolmitriptan powder as a pressurized metered dose inhaler via suspending it into different propellants (HFA 134a and HFA 227). One of the developed formulations demonstrated higher drug deposition in the deep respiratory airways either *in vitro* or *in vivo* in rats, resulting in bioavailability of 72.7%, which was 1.25-times higher than the commercial oral tablet's relative bioavailability.

Challenges for migraine treatment via inhalation

For migraine treatment via inhalation, it is important that the formulation can deliver the drug to the brain in a short period of time and in large volumes to allow effective drug action. This can be achieved through direct drug transport, once absorbed from alveoli into systemic circulation to the brain. This explains how inhalation formulations of anti-migraine drugs could be utilized to enhance bioavailability.

The current challenge facing inhalation formulations is that the aerosolized drug needs to be increasingly deposited into deep airways and alveoli rather than the oral cavity, the oropharyngeal region and the upper airways. This can be controlled through adjusting different physicochemical and physiological parameters. The physicochemical parameters of the formulation include the particle size, aerodynamic particle size distribution, mass distribution, mass median aerodynamic diameter, shape, density, velocity and electrostatic charge of the particles and droplets as well as suitable inhalation device engineering. Also, the pharmacokinetic parameters of the drug can be affected by the drug solubility and dissolution of particles. The physiological parameters include geometry of respiratory tree, influence of disease state, breathing pattern and coordination between inhalation and device activation [9,10].

An important factor that controls the drug deposition in the respiratory airway is the inhalation delivery device design. Inhaler devices may be classified into breath-actuated devices including dry powder inhalers, nonbreath-actuated inhaler, including nebulizer (jet and ultrasonic), and pressured metered dose inhaler, with a newly developed pressured metered dose inhaler classified as breath-actuated, which was developed to solve the problem of the miscoordination between inspiration and dosage discharge. Selection of the right device depends on different factors concerning both the drug formulation and the patient.

Conclusion

In conclusion, we can assume that inhaled drug formulations with their own advantages such as rapid absorption and direct transportation to the brain can be considered a promising delivery route for anti-migraine drugs. However, there are many challenges that should be taken into consideration, such as correct selection of the drug delivery

system, correct selection of the inhalation device and correct selection of the patient concerning their clinical status and training of the device.

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