New drug delivery options for migraine

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"Recent developments in drug delivery systems include a novel breath-actuated device for intranasal sumatriptan delivery, an iontophoretic transdermal delivery system of sumatriptan and a new inhaler system for administration of dihydroergotamine through the lung via oral inhalation."

Migraine is characterized by attacks of moderate to severe intensity headache, associated with some combination of severe disability, autonomic dysfunction such as gastric stasis, poor absorption from the small bowel, and associated symptoms such as nausea, vomiting, phonophobia, photophobia and worsening with exertion [1,2]. Oral medications may not be ideally suited for those migraineurs with nausea, vomiting and poor gastrointestinal absorption and an non-oral route of delivery may be optimal in such patients. Injection and nasal delivery systems for migraineurs do exist and they bypass gastrointestinal absorption; however, these approaches may be associated with limiting adverse events and/or lack of efficacy for some patients [3,4].

The recent developments in drug delivery systems presented here are either entering, in the middle of, or have completed Phase III development. Each may offer clinical benefits including a convenient, noninvasive delivery of medication that bypasses the GI tract and hepatic first-pass metabolism, allowing for a rapid and consistent response to treatment with fewer adverse events. These delivery devices may prove to be the route of choice for patients experiencing symptoms consistent with gastrointestinal dysfunction (nausea, vomiting and gastric stasis) associated with migraine.

Intranasal delivery (OptiNose™)

The use of a novel, breath-actuated device for intranasal delivery of a powder formulation of sumatriptan in acute migraine treatment was evaluated in one Phase I and one Phase II trial [5,6]. The use of this bidirectional delivery system named OptiNose™ (Optinose US Inc., PA, USA) has shown improved deposition to the olfactory mucosa, which is essential for rapid systemic absorption [7]. Traditional nasal delivery methods deliver a significant part of the dose anterior to the nasal valve and the fraction that does bypass the nasal valve is largely swallowed. By contrast, the OptiNose device consists of a mouthpiece and a sealing nozzle that fits into one nostril; blowing into the device causes the soft palate to close, isolating the nasal cavity. As the patient continues to blow out, the device is triggered, releasing the drug into the air flow and carrying it deep into the nasal cavity. The air flow carries the drug through a communication between the two nasal passages and forwards in the other nostril towards the entrance. A Phase I study showed a faster and more extensive systemic absorption, probably due to better absorption across the nasal mucosa, than the existing sumatriptan nasal spray device [5]. The Phase II study was designed to evaluate the efficacy and

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safety of a single dose of 10 or 20 mg of a powder formulation of sumatriptan delivered with the novel device in comparison with placebo, in 117 adults with a moderate to severe intensity migraine attack [6]. The most common adverse event was dysgeusia, reported as a bitter or metallic taste in 10% of subjects receiving the 10 mg dose and 13% receiving the 20 mg dose. There were no cases of chest discomfort or pain, paresthesia or asthenia in the active treatment groups. In terms of efficacy, a greater proportion of subjects who received sumatriptan 10/20 mg were pain-free at 120 min compared with those who received placebo (54%/57% vs 25%; number needed to treat [NNT]: 3.1/3.4; $p < 0.05$). Significant benefits were also observed for pain relief at 120 min (84%/80% vs 44%; NNT: 2.5/2.8; $p < 0.001/0.01$). Pain freedom occured as early as 60 min (73%/74% vs 38%; $p < 0.01$) and continued for 48 h as sustained pain freedom (47%/49% vs 27%; NNT: 4.55/5; $p < 0.05$).

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Transdermal delivery (Zelrix™)

Iontophoretic delivery of medication via a skin patch is another noninvasive approach. It uses small amounts of electrical current to promote rapid movement of the ionized drug transdermally and into the systemic circulation. This delivery bypasses hepatic first-pass metabolism and also avoids gastric transit delay and slowing of small intestinal absorption associated with gastrointestinal stasis in migraineurs. A newly developed transdermal drug delivery device uses this technology to deliver sumatriptan (NP1O1, Zelrix™; NuPathe Inc., PA, USA). Two pharmacokinetic studies have demonstrated that iontophoretic transdermal delivery of sumatriptan results in rapid and consistent achievement of therapeutic plasma concentrations [8,9]. In addition, these studies suggest that transdermal delivery using iontophoresis significantly reduces typical triptan-related adverse events, probably by avoiding patient exposure to a rapid rise in and high plasma concentrations of the drug, as seen with injectable sumatriptan.

The results of a randomized, double-blind, placebo-controlled, Phase III study of Zelrix in the treatment of acute migraine have been recently reported, although not yet fully published [10]. In this trial, 530 patients meeting the International Classification of Headache Disorders diagnostic criteria for migraine from 37 sites in the USA were treated for a single, moderate-to-severe migraine attack with either Zelrix or a matching placebo patch. Compared with placebo, significantly more Zelrix patients fulfilled the four co-primary end points. Active treatment was superior to placebo in achieving pain freedom at 2 h post-treatment (18 vs 9%; NNT: 13.8; $p = 0.0092$), freedom from photophobia at 2 h (51 vs 36%; NNT: 6.66; $p = 0.0028$), phonophobia (55 vs 39%; NNT: 6.25; $p = 0.00021$) and nausea (84 vs 63%; NNT: 4.8; $p < 0.0001$). As for secondary end points, active treatment achieved no use of rescue medication (60 vs 40%; NNT: 5; $p = 0.0001$) and sustained headache pain relief for 2–24 h post-patch activation (34 vs 21%; $p = 0.0021$). The sumatriptan transdermal delivery patch was well tolerated. Treatment-emergent adverse events were reported by 51% of the active group and 45% of placebo patients, and were mostly mild or moderate intensity application site events. The discontinuation rate due to adverse events was low (2%) and similar in both treatment groups [11].

Oral inhalers (Levadex™)

Dihydroergotamine (DHE) was synthesized in 1943 and has been used in a variety of formulations. Although it has better tolerability that ergotamine tartrate, the poor bioavailability of oral formulations, the modest improvements with intranasal forms, the inconsistent absorption when administered through routes other than intravenously, and the nausea and vomiting associated with injection therapy has lead to its limited clinical use [4,12]. MAP0004 (Levadex™, MAP Pharmaceuticals, CA, USA) is a novel and proprietary formulation of DHE designed to optimize the delivery of DHE and minimize the side effects associated with older formulations. With MAP0004, DHE is delivered through the lung via oral inhalation. The inhaler is designed to automatically discharge at a specific point in the patient's breath, eliminating the need for coordination of breathing and hand movements, minimizing oropharyngeal deposition and maximizing delivery of DHE deep into the lung. MAP0004 has similar T_{max} and area under the curve (and lower C_{max}) as that of intravenous DHE infusion [13].

> "Levadex™ is a novel and proprietary formulation of dihydroergotamine designed to optimize the delivery of dihydroergotamine and minimize the side effects associated with older formulations."

A Phase II study of Levadex 0.5 or 1.0 mg systemic equivalent dose (1.0 or 2.0 mg nominal dose) showed onset of pain relief for acute migraine pain in as fast as 10 min (32 vs 0%; $p < 0.05$). The pain-free result at 2 h was significantly greater with 0.5 mg than with placebo (44 vs 7%; $p = 0.015$). The sustained pain-free rate from 2–24 h exhibited a therapeutic gain of 31% ($p = 0.037$) versus placebo. Levadex was well tolerated with no serious or severe adverse events, while no clinically relevant changes were noted in spirometry, vital signs, electrocardiogram or clinical laboratory values [14].

The Phase III randomized, double-blind, placebo-controlled, multicenter study in 908 subjects has not yet been fully published. It evaluated 0.6 mg of DHE and used a four-point co-primary efficacy end point at 2 h post dose: pain relief (59 vs 35%; NNT: 4.2), phonophobia-free (53 vs 34%; NNT: 5.3) photophobia-free (47 vs 27%; NNT: 5) and nausea-free (67 vs 59%; NNT: 12.5). Three of the end points were significant versus placebo at the $p < 0.001$ level (nausea-free was $p = 0.02$). Sustained pain freedom from 2–24 h was achieved by 23.1% of the DHE patients versus 6.7% of the placebo patients (NNT: 6.1; $p < 0.0001$). With respect to adverse events, Levadex was generally well tolerated. The most common adverse event reported was taste

complaints (6.4 vs 1.7%). Symptoms typically associated with triptans, such as chest discomfort and chest pain, were rare (1 vs 0.7%). No patient treated with active treatment reported chest pain compared with one patient receiving placebo [15].

Conclusion

A non-oral route of drug delivery may be optimal for migraineurs with nausea, vomiting and poor gastrointestinal absorption and although injection and nasal delivery systems do exist, these approaches may be associated with limiting adverse events and/or lack of efficacy for some patients. Recent developments in drug delivery systems include a novel breath-actuated device for intranasal sumatriptan delivery, an iontophoretic transdermal delivery system of sumatriptan and a new inhaler system for administration of DHE through the lung via oral inhalation. These new approaches, all currently under either Phase II or Phase III development, may prove to offer clinical benefits and become the choice for patients experiencing symptoms consistent with gastrointestinal dysfunction associated with migraine.

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