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What's new in the treatment of acute migraine

Abstract With the rapid advances in the treatment of migraine attacks in the last few years, a number of non-specific anti-migraine drugs have been developed for clinical use. The most important class of drugs for the treatment of migraine attacks is represented by the triptans, which show 5-HT_{1B/1D} receptor selectivity. Although their efficacy has been clearly demonstrated in controlled clinical trials and by meta-analyses, triptans are still far from being perfect drugs; they can potentially constrict human coronary arteries at therapeutic doses and therefore contraindications in the presence of cardiovascular disease remain the main limitation to their use. Another problem with these agents is the recurrence of moderate-to-severe pain within 24 h of initial headache relief. The mechanisms underlying the differences in headache recurrence have been elucidated in the last few years and reside in their pharmacological and pharmacokinetic properties. This prompted the development of new agents with selective agonistic effects for 5-HT_{1D} and also 5-HT_{1F} receptors without cardio- and cerebrovascular side effects. In initial clinical studies, the former were shown to be ineffective for migraine

treatment, whereas the latter were demonstrated to be potentially useful for migraine attacks. However, the higher doses at which their effectiveness is exerted suggest that their main target at these doses is not the 5-HT_{1F} receptors but mainly the 5-HT_{1B} receptors, which seem to mediate the most important effect of all triptans, vasoconstriction of the cerebral vessels. Efforts have been made in recent years to develop other anti-migraine alternatives acting via the direct blockade of vasodilator mechanisms. They include calcitonin gene-related peptide (CGRP) receptor antagonists, capsaicin/vanilloid receptor agonists, adenosine A₁ agonists and cannabinoid analogues acting on CB₁ receptors, antagonists at 5-HT₇ receptors and inhibitors of nitric oxide biosynthesis. These alternatives will hopefully be effective in treating migraine attacks and lead to fewer side effects. The first promising clinical results in this regard were recently obtained for the highly specific and potent CGRP antagonist, BIBN 4096 BS.

Key words Triptans • Selective 5-HT_{1D} and 5-HT_{1F} agonists • CGRP receptor antagonists • Cannabinoid analogues

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Introduction

The last two decades have witnessed an explosion in the understanding of migraine pathophysiology, which has resulted in the development of various new options in the armamentarium for the acute treatment of migraine.

Results of controlled studies showed the efficacy of 5-HT_{1B/1D} agonists as first-line drugs in the treatment of not only the attacks of migraine headache but also the accompanying symptoms (photo- and phonophobia, nausea and vomiting) and functional disability. A consistent efficacy in the treatment of multiple attacks and long-term effectiveness has also been demonstrated. Although studies comparing the oral formulations of triptans are available, it is not possible at the moment to identify a reliable parameter of overall efficacy which establishes the greater efficacy of one triptan over another [1, 2].

Attempts to identify new molecules in the triptan class have been addressed at improving safety profiles due to their increased receptor selectivity. Despite these attempts, triptans are still far from being ideal drugs for migraine attacks; all of them have potential coronary artery constrictor effects and no significant improvement in efficacy was obtained with the new triptans. Other adverse events are even more rare, and include the potential for drug-drug interactions, based on their metabolic elimination pathways. The serotonin syndrome has been a concern, but reports on this issue are limited. Another problem with these agents is the recurrence of moderate-to-severe pain within 24 h of initial headache relief.

Novel drugs selectively targeting other mechanisms underlying the pathophysiology of migraine attack, such as calcitonin gene-related peptide (CGRP) antagonists, are currently under investigation.

New insights in triptan research

In the last few years, the search for new triptan molecules has been directed toward identifying drugs with a greater affinity for 5-HT_{1B/1D} receptors and a greater selectivity for cerebral vessels, which could be characterized by a greater efficacy and lower potential for headache recurrence.

Several second-generation triptans have been introduced that differ in pharmacological profiles relative to each other and to sumatriptan. Recently, a meta-analysis was conducted on data from 53 double-blind, randomized, placebo or active-controlled trials involving over 24,000 patients receiving oral triptans [1]. Results indicated that almotriptan 12.5 mg, rizatriptan 10 mg, and eletriptan 80 mg are slightly superior to sumatriptan 100 mg based on individual treatment attributes, such as pain relief, sus-

tained freedom from pain, consistency of response, and tolerability. Meta-analyses are limited, however, as the analysis can only be performed for individual end points, whereas patients and physicians balance a variety of treatment attributes when assessing drug acceptability. A flexible overall scoring system, "Tripstar", has recently been proposed to compare triptans to a hypothetical "ideal" drug using meta-analysis [3] data combined with ratings of the relative importance of clinically relevant treatment criteria. The informal test of the Tripstar model showed that sumatriptan is most similar to a hypothetical ideal for both mild and severe migraine, but this is prevalently due to its high clinical exposure worldwide. However, after exclusion of worldwide exposure as a contributing factor, almotriptan 12.5 mg appeared to be the most similar drug to the ideal, principally because of its good tolerability. Further tests that will verify the relative importance of a broader range of attributes of this model are planned.

As far as headache recurrence is concerned, a recent meta-analysis suggested that it is statistically related to potency at 5-HT_{1B} receptors but not to potency at 5-HT_{1D} receptors [4]. This observation is consistent with the current opinion that the mechanism of the therapeutic effects of triptans in acute migraine is most likely vascular and exerted by the 5-HT_{1B}-mediated reversal of cranial vasodilation.

This hypothesis is further supported by recent data from a study by Gomez-Mancilla et al. [5], who demonstrated that PNU-142633, a selective 5-HT_{1D} receptor agonist, is ineffective in the acute treatment of migraine. In contrast, recurrence rates appeared unrelated to the receptor binding affinity profile of the drug. Other parameters that should be taken into account are the intrinsic activity or kinetics of ligand-receptor interactions. As far as intrinsic activity is concerned, differences in triptan behaviour seem unlikely to be related to recurrence rate, as shown in the Chinese hamster ovary (CHO) cell-line model, where all triptans appeared to be full agonists for 5-HT_{1B} receptors and were able to induce the same biological effect as 5-HT [6].

Differences in the kinetics of triptan-receptor interactions could be more relevant for the clinical response. The most striking example in this regard comes from eletriptan, which exhibits faster association and lower dissociation rates than sumatriptan. From a pharmacological point of view, the long residence time of the drug on its receptor is associated with larger cellular effects and may result in greater or more prolonged clinical effects [7]. The second advantage for eletriptan is the partial agonist activity at the 5-HT_{1B} receptor, reducing the potential for cardiovascular side effects compared to the other triptans.

Another advantage of eletriptan also lies in its lipophilicity, consisting of an increased rate of absorption and T_{max}

compared to sumatriptan. This is reflected in a modest advantage over sumatriptan in terms of speed of onset, both headache response and freedom from pain at 2 h.

The mechanism of migraine recurrence in the course of triptan treatment is complex and remains to be fully elucidated. Although triptan half-life and recurrence seem to be closely correlated (lower recurrence rates have been found for naratriptan and frovatriptan, which have longer half-lives; 5.5 and 25.7 h, respectively), there is no strict correspondence between the magnitude of difference in elimination half-life and the magnitude of difference in mean recurrence as could be expected if the relationship between these two parameters were absolute [4]. Additional factors should be involved, which need to be investigated in future research.

Independently of the search for mechanisms underlying headache recurrence in up to one-third of triptan responders, the efforts of clinical researchers were aimed at identifying strategies for reducing their incidence in clinical practice.

The concomitant use of a non-steroidal anti-inflammatory drug (NSAID) with a triptan has been recommended for this purpose. The combination of sumatriptan plus naproxen sodium or tolfenamic acid in small pilot studies has been demonstrated to significantly decrease migraine recurrence compared with sumatriptan alone [8, 9].

In another open study, the combination of a fast-acting triptan, rizatriptan, with a selective anti-COX-2 drug, rofecoxib, resulted in a lower recurrence rate than in a group treated with rizatriptan alone. This combination was well tolerated and appeared to be more effective than the use of the triptan alone [10]. The proposal of also using dexamethasone in a limited population of migraineurs still presenting with headache recurrence after combined treatment of a triptan with an NSAID, such as naproxen sodium or tolfenamic acid, should be considered with caution. The usefulness of this approach needs to be confirmed, as in previous clinical experiences, by case-control studies and studies with a randomized double-blind design [11]. With the affinity of triptans for 5-HT_{1F} receptors, it is hypothetically possible that they could be a further potential target in acute migraine. 5-HT_{1F} receptors are present in the trigeminal system, and may participate in blocking migraine pain transmission through the trigeminal ganglion and nucleus caudalis. These receptors are located on glutamate-containing neurones and their activation has been demonstrated to inhibit glutamate release, which has been shown to play a potential role in central sensitization and release of sensory neuropeptides during migraine attacks. Selective 5-HT_{1F} receptor agonists, such as LY334370 and LY344864 compounds, have been demonstrated to be effective in inhibiting neurogenic inflammation, and a high correlation has been demonstrated

between their potency in the guinea pig dural plasma protein extravasation assay and their 5-HT_{1F} receptor binding affinity [12]. Therefore, these preclinical studies support their potential role as novel therapeutic options for migraine attacks. The efficacy of LY334370 for migraine relief was tested in a recent randomized controlled trial. At the higher dosages (60, 200 mg) the drug appeared to be superior than placebo in headache response, sustained headache response, freedom from pain and sustained freedom from pain. Side effects included asthenia, somnolence and dizziness, which were experienced by a greater number of patients treated with LY334370 than with placebo [13].

Blocking CGRP receptor

Calcitonin gene-related peptide (CGRP), a potent vasodilatory neuropeptide released from capsaicin-sensitive trigeminal sensory nerves, has been demonstrated to be involved in the pathophysiology of migraine attacks, based on the observations of a clear association between headache phase and increase in its levels both in the external and internal jugular blood [14, 15]. Drugs already available with an antagonistic action on CGRP release are the triptans, which mediate not only the vasoconstriction of intracranial vessels but also a presynaptic inhibition of sensory trigeminal endings, resulting in the normalization of CGRP levels [16].

The central role played by CGRP stimulated the search for molecules targeting CGRP receptors or inhibiting CGRP release through a mechanism of action different from that exerted by the triptans.

Selective peptidergic and non-peptidergic antagonists of CGRP (i.e. SB-273779 e SK-N-MC compounds) have been developed, which have been demonstrated to inhibit trigeminovascular activation in experimental models. These emerging molecules were proposed as innovative therapeutic strategies with promising potential for acute migraine attacks [17].

Based on the above positive preclinical findings, a recent international, multicentre, double-blind, randomized, placebo-controlled, clinical trial was promoted by Olesen et al. [18], aimed at testing the efficacy of a highly specific and potent CGRP antagonist, BIBN 4096 BS, in the symptomatic treatment of migraine. The 2.5-mg dose showed a responder rate of 65.6% vs. 26.8% for placebo ($p < 0.001$). Significant superiority compared to placebo was also observed for most secondary parameters: freedom from pain at 2 h, sustained freedom from pain over 24 h, headache recurrence, nausea, phonophobia and phonophobia, improvement in functional capacity and

time to meaningful relief. The effects on migraine appeared after 30 min and increased over the next few hours. The overall adverse event rate was 25% after 2.5 mg and 20% for all active doses vs. 12.2 % for placebo. The adverse events were transitory and not serious and the most frequent consisted of paresthesias. The results of this first clinical experience establish a new approach based on the pivotal role played by CGRP in migraine attacks, which opens a new era in the acute treatment of migraine.

Another interesting approach for migraine attacks is the use of vanilloid receptor agonists, such as civamide. This drug, which also exerts an antagonistic action on calcium channels, was shown to inhibit the neural release of CGRP and substance P (SP) and deplete the neurones of the trigeminal plexus of their neurotransmitter content [19].

The results of an open study carried out with civamide administered intranasally (20 or 150 mg) for acute migraine are promising [20]. The drug appeared to be effective in the relief of pain for patients with migraine both with and without aura and showed only few, slight and transitory side effects, such as nasal burning and lacrimation. No systemic side effects were observed. Based on the results of this study, intranasal civamide has been hypothesized to be effective in the acute treatment of migraine headache. Moreover, given civamide's proposed mechanism of action, intranasal civamide has also been suggested for migraine prophylaxis.

GR79236, a highly potent and selective adenosine A1 receptor agonist with analgesic and anti-inflammatory actions in humans and animals, should be mentioned among the emerging approaches for acute migraine treatment targeting CGRP release. In animal models it has been demonstrated to inhibit trigeminal nerve firing and CGRP release mediated by protein kinase A, which has been shown to play a pivotal role in migraine pathophysiology.

The selective adenosine A1 receptor agonist, GR190178 (30–1,000 mg/kg i.v.), was shown to inhibit superior sagittal sinus (SSS)-evoked neuronal activity in a dose-dependent fashion [21]. In this model of trigemino-vascular nociception, adenosine A1 receptor activation leads to neuronal inhibition without concomitant vasoconstriction, suggesting a novel avenue for the acute treatment of migraine and cluster headache.

Further evidence supporting the potential possible therapeutic role of GR79236 in primary headache disorders derives from a randomized, double-blind, placebo-controlled, cross-over trial investigating the effect of this adenosine A1 receptor agonist on trigeminal nociceptive pathways, as measured by the blink reflex. Using nociceptive-specific electrodes, GR79236 produced a non-significant reduction of the ipsilateral R2 component compared with placebo and a significant reduction contralaterally without significant adverse events, supporting the

ability of this adenosine A1 receptor agonist to inhibit trigeminal nociception in humans, an effect which could be relevant for a potential anti-migraine efficacy [22].

Cannabinoid receptors as potential targets of future acute anti-migraine drugs

Arachidonylethanolamide (AEA or anandamide) is an endogenous ligand of the cannabinoid CB1 and CB2 receptors. CB1 receptors, in particular, have been found on fibres in the spinal trigeminal tract and spinal trigeminal nucleus caudalis and have been hypothesized to play a potential role in migraine attack pathophysiology. Known behavioural effects of anandamide are anti-nociception, catalepsy, hypothermia and depression of motor activity. In a recent study carried out by Akerman et al. [23] using intravital microscopy, anandamide was able to inhibit dural blood vessel dilation brought about by electrical stimulation by 50%, CGRP by 30%, capsaicin by 45% and nitric oxide by 40%. This effect was reversed by the CB1 receptor antagonist, AM251. The involvement of CB1 receptors in the NO/CGRP-mediated events and dural blood vessel dilation underlying migraine attack has been suggested based on the evidence of a pre-synaptic action of anandamide in preventing CGRP release from trigeminal sensory fibres and of a post-synaptic action in inhibiting CGRP-induced NO release in the smooth muscle of dural arteries. This opens the possibility of identifying these receptors as potential targets of new therapeutic strategies for migraine attacks.

Conclusions

The discovery of the 5-HT_{1B/1D} agonist sumatriptan constitutes a substantial advance in the acute treatment of migraine, although it displays a number of non-negligible shortcomings. Directions in second-generation triptans for migraine have been focused on agents that exhibit high intrinsic activity at 5-HT_{1B/1D} receptors, offer a good safety profile, and demonstrate long-lasting action which might also be considered in migraine prophylaxis [24].

Today, a number of second-generation drugs derived from tryptamine are marketed worldwide for the acute treatment of migraine. These drugs have been demonstrated to be very effective as acute migraine drugs and are considered first-line therapy for moderate to severe attacks.

However, at marketed doses, all oral triptans are effective and well tolerated. Differences among them are in general relatively small, but clinically relevant for indi-

vidual patients. Triptan use is associated with headache recurrence, and this has been reported as one of the main reasons for patient dissatisfaction with the treatment. The mechanism of recurrence is not clear, and the incidence of recurrence varies with the triptan used. Migraine recurrence does not appear to be related to initial clinical efficacy, but is influenced by the pharmacological and pharmacokinetic properties of the individual triptans. Triptans with longer half-lives and greater 5-HT_{1B} receptor potency seem to be associated with the lowest rates of headache recurrence. A strategy which has been proposed to overcome headache recurrence in triptan responders is combination with an NSAID, and more recently, with anti-COX-2 drugs; however, clinical experience in this regard is limited and needs to be confirmed.

The search in the triptan field has also been aimed at identifying drugs acting specifically on some pivotal mechanisms of migraine attacks. In line with the vascular and neurogenic theories of migraine, selective carotid vasoconstriction (via 5-HT_{1B} receptors) and presynaptic inhibition of the trigeminovascular inflammatory responses implicated in migraine (via 5-HT_{1D}/5-HT_{1F} receptors) have been recognized to be the main targets. Moreover, selective agonists at 5-HT_{1D} (PNU-142633) and 5-HT_{1F} (LY344864) receptors have been shown to inhibit the trigeminovascular system without producing vasoconstriction. Nevertheless, PNU-142633 proved to be ineffec-

tive in the acute treatment of migraine, whereas LY344864, which has been demonstrated to be effective in preclinical migraine models, did show some efficacy when used in doses that interact with 5-HT_{1B} receptors, leading to the hypothesis that the main mechanism of action of the triptans is represented by 5-HT_{1B} agonism on cerebral vessels.

Although triptans are effective anti-migraine agents producing mainly selective cranial vasoconstriction, efforts are being made to develop other effective anti-migraine alternatives acting via the direct blockade of CGRP-mediated direct or indirect mechanisms (i.e. antagonists at CGRP receptors, vanilloid agonists, cannabinoid ligands) with hopefully fewer side effects.

In particular, evidence of the central role played by CGRP in migraine and cluster headache pathophysiology has led to the search for small-molecule CGRP antagonists, which are predicted to have fewer cardiovascular side effects than the triptans [25]. The pharmacological profile of such a group of compounds has recently been disclosed [26]. One of these compounds with high selectivity for human CGRP receptors has recently been shown to be significantly efficacious in the relief of acute attacks of migraine with few side effects, and this first clinical evidence opens a new era in the pharmacological approach to acute migraine, targeting pivotal mechanisms in the pathophysiology of attacks.

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