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REVIEW

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Treatment of migraine with aura: comments and perspectives

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Abstract Migraine with aura (MwA) is a primary headache that affects about 30% of migraine sufferers. The main questions for the physician caring for the patient who has MwA are: when to use preventive medications, what medications to use in acute and preventive treatment, and whether the aura should be treated. The aim of this paper is to review the various therapeutic options for MwA proposed in the current literature and to evaluate their efficacy.

Key word Migraine • Aura • Therapy

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Introduction

Migraine with aura (MwA) is a primary headache disorder that affects about 30% of migraine sufferers [1]. In some patients, MwA is associated with attacks of migraine without aura [1] and this coexistence in individuals has sparked a debate as to whether these two forms of migraine are actually clinically distinct entities. The International Headache Society's (IHS) diagnostic criteria for MwA [2] provide a clinical description of the aura, the disorder's most distinctive feature: aura consists of transient, unilateral or bilateral visual, sensory or motor symptoms considered to arise from a recurrent reversible, idiopathic dysfunction of the cortex or brainstem.

The most challenging task for the physician confronted with this easy-to-diagnose form of migraine is to select the most effective treatment course. A thorough history is important to uncover possible triggering factors such as oral contraceptives and light stimuli. Once these have been identified, the main questions are what drugs to use and whether a preventive regimen is justified. A not less important consideration is whether the aura should be specifically treated or whether attention should be confined to the pain. The aim of this review is to examine the various therapeutic options for MwA and to suggest answers to these questions. To this aim, we performed a literature search (databases used were MEDLINE on PubMed, Embase, Healthstar, Cochrane databases and CINAHL); the principal search terms were MwA, classical migraine and therapy.

Migraine headaches vary considerably in terms of the severity of pain, the presence of associated symptoms, the degree of disability they cause and effects they have on the patient's quality of life [3–5]. The drug prescribed for acute treatment should therefore be tailored to the needs of the patient and the characteristics of the attack. For example if, in the patient's experience, a certain type of aura usually precedes a particularly severe attack, then this is a sign that a "strong" medication should be prescribed. As all medications have possible side effects, patients should be made explicitly aware of these so that they may be questioned about them

during follow-up and, if necessary, the dose should be altered or the medication changed.

Acute treatment of MwA

A number of studies have been published on the acute treatment of MwA. Flunarizine was one of the first drugs tested in a double-blind, placebo-controlled study involving patients with MwA [6]. However, only 17 of the 60 patients recruited to the trial had MwA. The medication (20 mg flunarizine administered intravenously) was given in the first half of the attacks to the patients in the treatment group. Patients were defined as responders if the treatment reduced the intensity of the pain and accompanying manifestations by at least 50% within 60 minutes after administration. There were 23 responders (74.2%) in the treated group and 9 (27.6%) in the placebo group. The only side effect attributable to flunarizine was slight sedation in 9 patients. Flunarizine was equally effective in both forms of primary headache as far as pain relief and manifestations accompanying the pain were concerned. No mention was made of any effect on the aura**.** Studies involving the intravenous administration of flunarizine for the acute treatment of migraine have not been repeated, and flunarizine for injection is not available in many countries. It is not available at all in the U.S.A.

Two published studies have used the 5-HT_1 agonist sumatriptan. The first [7], a randomized, double-blind, parallel group, placebo-controlled trial, investigated the efficacy of oral sumatriptan at 200 mg on three attacks of MwA over three months in 76 patients divided into two groups. The end points were reduction in the intensity or total disappearance the pain and associated manifestations two hours after administration. Sumatriptan was significantly (p=0.0023) more effective than placebo in reducing or abolishing pain and reducing the associated manifestations for the first attack only. For the second and third attacks, the clinical response to the drug did not differ significantly from placebo. The effect of sumatriptan on the aura was not mentioned. The second study was a multicenter, double-blind, placebo-controlled, parallel group study carried out by the Sumatriptan Aura Study Group [8] specifically to assess the effect of sumatriptan on aura in 171 patients who had MwA. The drug was administered subcutaneously during aura at a dose of 6 mg. The mean duration of the aura was not modified in patients treated with sumatriptan (25 minutes) versus patients treated with placebo (30 minutes). Interestingly the study found that sumatriptan was ineffective in preventing the pain when taken at the onset of aura, as pain crises occurred in 68% of patients against 75% of patients who were given placebo.

Whether ergotamine is safe to use as a treatment for MwA has long been a subject of debate in view of the drug's potent vasoconstrictor properties and the fact that the onset of aura seems to coincide with a reduction in cerebral blood flow (CBF) that persists into the pain phase [9]. However, more recently a study using functional MRI (fMRI) has shown hyperemia with a >300% increase in CBF at the onset of aura [10]. Studies on migraineurs and controls reported no effect of ergotamine (0.2 mg or 1 mg intramuscularly) on cerebral blood flow [11, 12]. In another study, 0.5 mg ergotamine or 1.0 mg dihydroergotamine administered intravenously did not modify cerebral blood flow in eight healthy volunteers [13]. Nevertheless persons sensitive to ergot toxicity may develop symptomatic cerebral vasospasm confirmed by angiography [14]. The prudent conclusion is not to use ergotamine to treat migraine attacks preceded by major aura.

Nimodipine was used at a dose of 40 mg in oral and sublingual capsules in a cross-over study against placebo on 43 patients with MwA [15]. The efficacy was tested in two attacks. Questionnaires were used to monitor the duration of aura, the duration of the pain, side effects and the preferences of the patients. For none of these variables was nimodipine superior to placebo. The study concluded that nimodipine probably has no place in the treatment of MwA attacks.

Two papers on the use of nifedipine have been published. One was a case report of a 15-year-old patient who presented a unique crisis characterized by difficulty in reading, speaking, and understanding speech accompanied by headache that lasted for hours. Following sublingual administration of nifedipine the symptoms rapidly resolved [16]. The second paper reported a double-blind, crossover study against placebo in 17 patients divided into two groups. Six attacks were treated with the drug (20 mg) which was taken during the aura. In the first phase of the study, oral capsules were used and in the second a sublingual preparation was used. By both administration routes, nifedipine was associated with increased duration of pain attack and had no effect on the aura [17]. We conclude that neither nimodipine nor nifedipine should be used to treat MwA attacks.

Recent publications [18, 19] indicate that status migrainosus with aura can be effectively treated with furosemide or acetazolamide. Status migrainosus with aura is a condition in which the attacks occur several times a day for days or weeks. The aura is generally visual and not usually accompanied by headache; between auras the patient is asymptomatic. The use of furosemide was reported in two patients who had suffered from repeated and prolonged visual auras for years. The first patient was a 34-year-old woman who had been suffering from loss of right peripheral vision, facial and limb paresthesias and headache for 11 days. She was treated with a 20-mg intravenous infusion of furosemide. A few hours later the aura disappeared and did not return. In the preceding days the patient had received intravenously prochlorperazine (10 mg/day), methylprednisolone (200 mg/day) and valproate (300 mg/day) without effect.

The second patient was a 37-year-old woman who presented with marked bilateral visual aura (fortification spectra) and headache. After three days of persistent crisis she was admitted to hospital and treated intravenously with 20

mg furosemide; the visual symptoms disappeared about two hours later. Previously, magnesium as well as droperidal and methylprednisolone (both intravenously) had been tried but had had no effect on the aura [18]. Three patients with status migrainosus were treated with 250 mg acetazolamide 2–3 times per day, which resulted in "dramatic" resolution of all symptoms, after propanolol and valproate had proved ineffective [19].

Ketamine given as a 25-mg nasal spray was used in a group of 11 patients with familial hemiplegic migraine, all of whom had disabling aura. Five patients (14 attacks treated) reported a marked reduction in the duration of the auras, particularly those associated with motor deficit. The drug was ineffective against the aura of the 11 attacks reported by the other six patients. However all patients reported marked side effects of ketamine that included a sense of alienation and modest ataxia. Only two patients experienced an improvement in the severe headache that accompanied the aura [20].

Prophylaxis of MwA

No studies have addressed the problem of when to start prophylaxis in patients who experience MwA. Typically these attacks present 3- or 4- times per year [21], in which case prophylaxis would not seem to be justified. If however the attacks are much more frequent (i.e. once per month or more), then we suggest that prophylaxis should be considered after organic causes have been excluded. Metoprolol, propanolol, flunarizine and lamotrigine have been studied as preventive agents for migraine [22–29]. Metoprolol was studied first and four papers have been published [22–25]. The first was a multicenter, double-blind, placebo-controlled, parallel group study of 71 patients, 34 of whom received metoprolol at a dose of 200 mg/day. The study lasted eight weeks. The drug significantly reduced the number of attacks ($p<0.01$), the number of days with migraine ($p<0.05$), the severity score (days with headache x intensity, $p<0.05$), and the consumption of symptomatic drugs, assessed over four weeks ($p<0.01$). Side effects were tiredness, sleep disturbances and rarely bradycardia [22]. The second study compared metoprolol (in slow-release tablets, 200 mg/day) with placebo in a double-blind, cross-over design with a four-week run-in, four-week wash-out and eight weeks of either treatment. Seventy-three patients completed the study. Metoprolol was more effective than placebo in reducing attack frequency, mean global rating and analgesic consumption per attack [23]. The third was a double-blind, cross-over study comparing propanolol (80 mg twice daily) with metoprolol (in slow-release tablets, 200 mg daily). The patients received placebo for a four-week run-in after which they were allocated to metoprolol or propanolol for eight weeks followed by placebo for a four-week wash-out and were thereafter switched to the other drug for a further eight weeks. There were no significant differences between the two drugs in terms of attack frequency, migraine days, severity score (intensity x migraine days) and consumption of acute medication [24]. The fourth study investigated the effect on the aura as well as on the pain. The study compared the frequency of aura symptoms in 360 attacks in patients treated with placebo and 314 "residual headaches" in patients treated with metoprolol. There were no significant differences in frequency of scotoma, hemianopsia or zig-zag lines. Scintillations ($p=0.0003$) and paresthesia ($p=0.004$) were more frequent with metoprolol treatment whereas speech disturbances were less frequent ($p=0.001$) [25].

Flunarizine has been tested as a migraine-with-aura preventive medication. A placebo-controlled study involved 20 patients randomized to active treatment or placebo. After a 1-month run-in without medication, nine patients received flunarizine (10 mg/day) and 11 received placebo for three months. The end points assessed were number of attacks per month, duration, severity, migraine index (number of attacks per month x mean severity) and the corrected migraine index (migraine index x mean duration of attacks). Flunarizine was significantly more effective than placebo in all end points. However no mention was made of the effect of the drug on aura in residual attacks [26].

Lamotrigine is an antiepileptic introduced in the late 1990s. Its efficacy against partial and generalized seizures is attributed to its ability to reduce neuronal hyperexcitability by blocking voltage-dependent sodium channels and glutamate release. It is known that hyperexcitability is considered the basic cause of migraine aura [27]. This prompted the use of lamotrigine in two open label studies on MwA. In the first, after a 1-month run-in, 24 patients with high frequency attacks of MwA (6.1±4.1 attacks per month) received lamotrigine (initially 25 mg/day with gradual weekly increases up to the final dose of 100 mg/day) for three months. The number of attacks per month and the duration of the aura were monitored. Lamotrigine treatment was associated with a significant reduction in attack frequency (1.1±1.6 per month) compared to pre-treatment ($p<0.0001$). The attacks in 13 patients disappeared completely during the third month of treatment and in four patients the duration of aura decreased. In one patient treated for daily aura without headache, the auras disappeared [28]. In the second study, 15 patients received various doses of lamotrigine gradually increased (25–100 mg/day) for four months followed by three months without the drug. The treatment significantly reduced the number and duration of auras ($p<0.001$) compared to pre-treatment. When the drug was stopped the number and duration of the auras increased significantly compared to the treatment phase ($p<0.001$) [29]. On the contrary a placebo-controlled trial with lamotrigine in migraine patients with and without aura failed to show superiority over placebo in 77 patients (31 with aura, 46 without aura) [30], however in this study the 2 groups of patients are considered together and we have no data about the specific efficacy on the aura.

Finally lamotrigine was reported to be effective in a patient with persistent positive visual phenomena [31].

Conclusions

Although the main aim of treatment is usually not to reduce the aura but the pain and associated signs and symptoms of the migraine attack, a drug also effective against aura is particularly useful if the patient is rendered anxious or incapacitated by its occurrence, particularly if it lasts for more than 60 minutes. Note also that prolonged aura may rarely be the initial symptom of acute ischaemic cerebral accident and should therefore be treated [32]. For this purpose rapidly absorbed drugs that quickly reach therapeutic concentrations are required. Unfortunately such drugs are not available, and this explains why studies on the treatment of aura are few and their results equivocal [33, 34]. In the American Academy of Neurology's guidelines for migraine headache [35] (as in those of the Società Italiana Studio Cefalee [36]), there is no distinction between the treatment of migraine with and without aura, and from an analysis of the literature we observe a lack of information regarding the specific treatment of migraine with aura (Tables 1, 2). Sumatriptan, one of the triptans used for migraine without aura, was ineffective

Table 1 Evidence for the efficacy of pharmacological therapy for acute migraine, according to the guidelines of ANN [35], and effectiveness of these therapies on migraine aura, as indicated in the literature

Acute migraine therapy	Efficacy on migraine			Evidence for efficacy on aura		
	Quality of evidence	Scientific effect	Clinical impression of effect	Study design	Results	Reference
Triptans						
Sumatriptan spray	A	+++	+++	–	–	–
Naratriptan	A	++	++	–	–	–
Rizatriptan	A	+++	+++	–	–	–
Sumatriptan (oral)	A	+++	+++	Double-blind placebo-controlled	Ineffective	[7, 8]
Zolmitriptan	A	+++	+++	–	–	–
Sumatriptan (sc)	A	+++	+++	–	–	–
Ergot alkaloids						
Dihydroergotamine (iv)	B	++	+++	–	–	–
Dihydroergotamine (sc/im)	B	+++/++	+++	–	–	–
Dihydroergotamine (iv) plus antiemetics	B	+++	+++	–	–	–
Dihydroergotamine (nasal spray)	A	++	++	–	–	–
Ergotamine	B	+	++	–	–	–
NSAIDs and nonopiate analgesics						
Acetaminophen	B	0	+	–	–	–
Ketorolac (im)	B	+	++	–	–	–
Aspirin	A	++	++	–	–	–
Diclofenac	B	++	++	–	–	–
Flurbiprofen	B	+	++	–	–	–
Ibuprofen	A	++	++	–	–	–
Naproxen	B	+	++	–	–	–
Naproxen sodium	A	++	++	–	–	–
Combination analgesics				–	–	–
Acetaminophen, aspirin, caffeine	A	+++	++	–	–	–
Barbiturate hypnotics				–	–	–
Butalbital, aspirin, caffeine	C	?	+++	–	–	–
Butalbital, aspirin, caffeine, codeine	B	++	+++	–	–	–

cont. →

Table 1 continued

Acute migraine therapy	Efficacy on migraine			Evidence for efficacy on aura		
	Quality of evidence	Scientific effect	Clinical impression of effect	Study design	Results	Reference
Opiate analgesics						
Butorphanol (nasal spray)	A	+++	+++	–	–	–
Opiates (oral combination)	A	++	++	–	–	–
Acetaminophen, codeine combinations						
Opiates (parenteral)	B	++	++	–	–	–
Other medications						
Corticosteroids	C	+	++	–	–	–
Isometheptene (compound)	B	+	++	–	–	–
Lidocaine (intranasal)	B	++	?	–	–	–
Nimodipine	–	–	–	Cross-over against placebo	Ineffective	[15]
Nifedipine	–	–	–	Double-blind cross-over	Ineffective	[17]
				Case report	Effective	[16]
Furosemide	-	-	-	Case report	Effective	[18]
Acetazolamide	-	-	-	Case report	Effective	[19]

Quality of evidence: *A,* optimal scientific support; *B*, scientific support was not optimal; *C*, absence of relevant randomized controlled trials; *Scientific effect: O,* ineffective or harmful; +, not statistically or clinically significant; ++, exceeds the minimally clinically significant benefit; +++, far exceeds the minimally significant benefit. *Clinically impression of effect*: *0*, ineffective; +, somewhat effective; ++, effective; +++, very effective. *SC*, subcutaneous administration; *iv*, intravenous administration; *im*, intramuscular administration; *NSAIDs*, non-steroidal anti-inflammatory drugs

Table 2 Evidence for the efficacy of pharmacological prophylaxis against migraine, according to the guidelines of ANN [35], and effectiveness of these therapies on migraine aura, as indicated in the literature

Migraine prophylaxis	Efficacy on migraine			Evidence for efficacy on aura		
	Quality of evidence	Scientific effect	Clinical impression of effect	Study design	Results	Reference
Antiepileptics						
Carbamazepine	B	++	0	–	–	–
Divalproex sodium/sodium valproate	A	+++	+++	–	–	–
Gabapentin	B	++	++	–	–	–
Topiramate	C	?	++	–	–	–
Lamotrigine	?	?	?	Open study	Effective	[28]
				Open study	Effective	[29]
				Double-blind placebo-controlled	Ineffective	[30]
				Case report	Effective	[31]
Tricyclic antidepressants						
Amitriptyline	A	+++	+++	–	–	–

cont. →

Table 2 continued

Migraine prophylaxis	Efficacy on migraine			Evidence for efficacy on aura		
	Quality of evidence	Scientific effect	Clinical impression of effect	Study design	Results	Reference
Nortriptyline	C	?	+++	–	–	–
Protriptyline	C	?	++	–	–	–
Doxepin, imipramine	C	?	+	–	–	–
Selective serotonin reuptake inhibitors						
Fluoxetine	B	+	+	–	–	–
Fluvoxamine, paroxetine, sertraline	C	?	+	–	–	–
Monoamine oxidase inhibitors						
Phenelzine	C	?	+++	–	–	–
Other antidepressants						
Bupropion, mirtazepine, trazodone, venflaxine	C	?	+	–	–	–
Beta-blockers						
Atenolol	B	++	++	–	–	–
Metoprolol	B	++	+++	Double-blind placebo-controlled	Effective on headache, aura not mentioned	[22]
				Double-blind crossover	Effective on headache, aura not mentioned	[23]
				Double-blind crossover	Effective on headache, aura not mentioned	[24]
				Double-blind placebo-controlled	Ineffective	[25]
Nadolol	B	+	+++	–	–	–
Propanolol	A	++	+++	–	–	–
Timolol	A	+++	+	–	–	–
Calcium channel blockers						
Diltiazem	C	?	0	–	–	–
Nimodipine	B	+	++	–	–	–
Verapamil	B	+	++	–	–	–
NSAIDs						
Aspirin	B	+	+	–	–	–
Fenoprofen	B	+	+	–	–	–
Flurbiprofen	B	+	+	–	–	–
Mefenamic acid	B	+	+	–	–	–
Ibuprofen	C	+	+	–	–	–
Ketoprofen	B	+	+	–	–	–
Naproxen/naproxen sodium	B	+	+	–	–	–
Serotonin antagonist						
Cyproheptadine	C	?	+	–	–	–
Methysergide	A	+++	+++	–	–	–
Other drugs						
Feverfew	B	++	+	–	–	–
Magnesium	B	+	+	–	–	–
Vitamin B12	B	+++	++	–	–	–
Flunarizine	-	-	-	Placebo-controlled	Effective on headache, no data on aura	[26]

NSAIDs, non-steroidal anti-inflammatory drugs

when given subcutaneously during aura, against both the aura and the subsequent pain. This suggests that 5-HT_1 receptor blockade during aura is ineffective in preventing pain because the central serotoninergic and peripheral trigeminovascular systems are not activated in the early stages of an attack. Nevertheless we have seen from the results reviewed here that the two phases (aura and migraine) may be influenced differently by different medications. Metoprolol, propanolol and flunarizine, drugs commonly used for the prevention of MwA, reduced the frequency of migraine crises in controlled trials but did not prevent the auras in headaches that did not respond to the treatment (residual headaches). By contrast lamotrigine appears promising against the aura as well as the pain: in the few cases where headache persisted despite treatment the aura was generally absent and when it did occur it was shorter than normal. Further studies are necessary to determine the efficacy of lamotrigine on MwA. Lamotrigine acts by blocking voltage-sensitive sodium-channels leading to inhibition of the neuronal release of glutamate. The reduction in the frequency and duration of aura by this drug suggests that the glutamatergic system may be involved in the mechanism of aura [37], once more raising the question as to the role of excitatory amino acids in the pathogenesis of MwA.

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Sommario *L'emicrania con aura è una forma di cefalea primaria che colpisce circa il 30% dei pazienti emicranici. I principali problemi che il medico deve affrontare nella gestione dei pazienti con emicrania con aura riguardano quando iniziare una terapia di profilassi, quali farmaci utilizzare nel trattamento dell'attacco e nella terapia di profilassi e se l'aura debba essere trattata in modo specifico. Lo scopo di questa* review *è di considerare le varie opzioni terapeutiche per l'emicrania con aura presenti nella letteratura corrente e valutare la loro efficacia.*

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