Agomelatine and migraine management: a successfully treated case series

Beatriz O. Plasencia-García, Samuel L. Romero-Guillena, Alicia Quirós-López and Sergio Ruiz-Doblado

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Correspondence to:
Beatriz O. Plasencia-García, MD
Psychiatric and Mental Health Services, Osuna Hospital, Avda. Constitución, 2, 41640, Osuna, Seville, Spain
dra.plasencia@gmail.com

Samuel L. Romero-Guillena, MD
Psychiatric and Mental Health Services, Macarena Hospital, Seville, Spain

Alicia Quirós-López, MD
Sergio Ruiz-Doblado, MD, PhD
Psychiatric and Mental Health Services, Osuna Hospital, Seville, Spain

Introduction

Headache is the most common reason for consultation in neurology departments in Spain. Despite the greater prevalence of tensional type headache, it is migraine that accounts for most visits to specialists because it is a medical condition causing more disability. The burden caused by headaches is well documented in the literature. It results in days of work or school missed, reduced labour productivity, etc.

This field has undergone significant changes in recent years, such as the inclusion of chronic migraine in the new diagnostic classification [Headache Classification Subcommittee of the International Headache Society, 2004], a concept that urgently needed to be revised [Headache Classification Committee *et al.* 2006] to adapt it to the real situation experienced by patients. New therapeutic approaches include the use of triptans in acute treatment and the use of neuromodulators, particularly topiramate, as preventive therapy [Linde *et al.* 2013].

Melatonin is physiologically associated with sleep induction and maintenance [enhancing the GABAergic system by modulating γ-aminobutyric acid (GABA) receptor activity], dose-dependent analgesic effects [unknown mechanism related to μ-opioid or GABA(B) receptors], antioxidant effect (prevents free radical induced damage and increases the activity of various antioxidant enzymes such as glutathione S-transferase, glutathione reductase and catalase), chronobiotic properties, a moderate antihypertensive effect and even intraocular pressure-reducing effects [Kurdi and Patel, 2013]. It also acts as a membrane stabilizer, serotonin modulator and GABA potentiator, and protects against glutamate-mediated neurotoxicity [Peres *et al.* 2006].

Agomelatine is a modern antidepressant with a novel mechanism of action. It is an MT1 and MT2 melatonin receptor agonist and a selective 5-HT2C receptor antagonist. Its efficacy, which is similar to that of standard antidepressants, and low risk of sexual side effects, insomnia and discontinuation syndromes, make it an interesting alternative for the management of depression [Taylor *et al.* 2014]. Some evidence from pilot and experimental clinical trials [Guglielmo *et al.* 2013; Tabeeva *et al.* 2011] suggests that the melatonergic system plays a role in the pathogenesis of migraine and that drugs that act on melatonin receptors may have an effect have on migraine.

We present the case of six patients with depression and comorbid migraine who were successfully treated for both conditions with agomelatine.

Presentation of cases and discussion

A total of 6 patients (measurement data shown in Table 1), all of them women, with a mean age of 38.16 ± 10.45 years, were seen at outpatient mental health clinics for Recurrent Major Depressive Disorder [American Psychiatric Association's Diagnostic and Statistical Manual of Mental Disorders IV Text Revision (DSM-IV-TR)]. All presented a moderate depressive episode [mean Montgomery-Asberg Depression Rating Scale (MADRS) score of 26.66 ± 3.72] at the time of assessment. Their personal history included migraine (based on the diagnostic criteria of the International Headache Society, 2004), with a mean age of onset of 20 ± 3.22 years, a mean number of attacks per month of 3.83 ± 1.83 and a pain intensity of 9 ± 0.89 measured on a Visual Analogue Scale (VAS). In all the cases prophylactic treatment for headaches (amitriptyline,

Table 1. Case series: characteristics of the patients.

Age	Onset of migraine	Episodes of migraine/ month (baseline)	VAS (baseline)	MADRS (baseline)	Episodes of migraine/ month (4th month)	VAS (4th month)	MADRS (4th month)
45	19	7	10	33	2	3	2
52	17	5	9	25	2	4	0
34	16	3	10	23	0	2	1
29	24	2	8	29	0	1	3
44	21	3	9	24	0	2	1
25	23	3	8	26	0	0	0

MADRS, Montgomery-Asberg Depression Rating Scale; VAS, Visual Analogic Scale.

beta-blockers and topiramate) had been withdrawn due to lack of response or adverse effects.

Treatment with agomelatine at a dose of 25 mg was initiated for the depressive episode. A total of 4 of the 6 patients required an increase in dose to 50 mg/24 hours due to lack of remission after 8 weeks. After 4 months of follow up, the depressive episode was in remission (MADRS 1.16 $\pm$ 1.16) and there had been a considerable reduction in the frequency of migraine attacks/month (0.66 $\pm$ 1.41) and in the intensity of the attacks (2 $\pm$ 1.41). This considerable reduction in frequency of attacks was observed from the first month of treatment.

In all these cases, we attribute the improvement to the treatment with agomelatine, since past treatment with other antidepressants (venlafaxine, sertraline, duloxetine and mirtazapine) had had no effect on migraine episodes, despite remission of the depressive symptomatology.

Our results are similar to those of two other studies, also case series, previously published on the efficacy of agomelatine in migraine prophylaxis [Guglielmo *et al.* 2013; Tabeeva *et al.* 2011], although it must be mentioned that all the patients in our sample had a concomitant depressive disorder, which could introduce bias. The antimigraine effect appears to be related to the synergic action between melatonin agonism and 5-HT2C antagonism, though further studies are needed to clarify the pathophysiological and neurochemical mechanisms involved in the specific antimigraine response.

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Conflict of interest statement

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