An Open Pilot Study Assessing the Benefits of Quetiapine for the Prevention of Migraine Refractory to the Combination of Atenolol, Nortriptyline, and Flunarizine

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Abstract

Background. Migraine is a prevalent neurological disorder. Although prevention is the core of treatment for most, some patients are refractory to standard therapies. Accordingly, the aim of this study was to evaluate the use of Quetiapine (QTP) in the preventive treatment of refractory migraine, defined as previous unresponsiveness to the combination of atenolol, nortriptyline, and flunarizine.

Methods. Thirty-four consecutive patients (30 women and 4 men) with migraine (ICHD-II), fewer than 15 days of headache per month, and not overusing symptomatic medications were studied. All participants had failed to the combination of atenolol (60 mg/day), nortriptyline (25 mg/day), and flunarizine (3 mg/day). Failure was defined as <50% reduction in attack frequency after 10 weeks of treatment. After other medications were discontinued, QTP was initiated at a single daily dose of 25 mg, and then titrated to 75 mg. After 10 weeks, headache frequency, consumption of rescue medications, and adverse events were analyzed.

Results. Twenty-nine patients completed the study. Three patients withdrew and two were lost to follow-up. Among those who completed, 22 (75.9%; 64.7% of the intention-to-treat population) had greater than 50% headache reduction. The mean frequency of migraine days decreased from 10.2 to 6.2 per month. Use of rescue medications decreased from 2.3 to 1.2 days/week. Adverse events were reported by nine (31%) patients.

Conclusions. Although limited by the open design, this study provides pilot data to support the use of QTP in the preventive treatment of refractory migraine. Controlled studies are necessary to confirm these observations.

Key Words. Migraine; Quetiapine; Preventive Treatment; Refractory

Background

Migraine is a highly prevalent disorder clinically manifested by headache attacks of moderate to severe intensity. Attacks typically induce disability and result in considerable economical and social losses [1–4].

The pathophysiology of migraine is complex and a genetic basis is evident. During migraine attacks, neural events result in the dilatation of meningeal blood vessels, which in turn cause pain, further nerve activation, and inflammation [5]. In migraine, headaches can be understood as a combination of altered perception (due to peripheral or central sensitization) of stimuli that are usually not painful, with activation of a neurovascular dilator mechanism mainly located in the ophthalmic division of the trigeminal nerve [5]. Therefore, migraine is considered as a neurovascular headache [5–8]. The pathophysiology of migraine involves multiple compartments of the nervous system, as well as multiple neurotransmitters, including dopamine and serotonin [5–9].

Clinical evidence suggests the involvement of dopamine in the pathophysiology of migraine. Nausea, vomiting, hypotension, as well as postdrome symptoms (mood changes, drowsiness and tiredness) may be related to dopaminergic activation. The dopaminergic system may also play a role in the headache phase, either by being involved in the nociceptive mechanisms, or by regulating the cerebral blood flow. Pharmacological findings seem to support this involvement [10]. Indeed, dopaminergic neurotransmission has been shown to influence nociceptive traffic through the trigeminal nucleus caudalis (TNC) [11]. Inhibition of the TNC correlates with migraine prevention in animals [5,12].

The use of dopamine antagonists in the acute and preventive treatment of migraine has been investigated [13–15]. Atypical antipsychotics, which act as dopamine antagonists as well, have fewer extrapyramidal side effects as compared with the first generation of antipsychotics, and therefore became attractive for the preventive treatment of migraine attacks [14,15]. Quetiapine (QTP)
was targeted as potentially useful for migraine based on its high affinity for central 5-HT₂ serotonergic and α₁-adrenergic receptors, in addition to its specificity for D₂ dopaminergic receptors in the mesolimbic pathways. As migraine is a neurological disease involving multiple neurotransmitter systems, QTP may simultaneously address multiple molecular targets involved in migraine. Furthermore, atypical psychotics are indicated for the treatment of acute mania, and the prevalence of migraine is increased (and migraine is often missed) in subjects with bipolar disease [15].

The preventive treatment of migraine attacks is the core approach for patients with frequent headache attacks, as well as in individuals with attack-related disability who are not responsive to acute therapy alone. However, no more than 60% of migraineurs experience greater than 50% reduction in headache frequency after using standard pharmacological options [16,17]. In specialty care, rates may be even lower, despite the frequent use of combination of different drugs, commonly practiced by headache specialists [16–20]. These rates highlight the unmet treatment need for refractory migraineurs, thereby justifying the execution of small pilot studies, in order to gather preliminary data on the topic.

Accordingly, the aim of this study was to evaluate the use of QTP, a multiacting antipsychotic drug, in the prevention of refractory migraine, defined as previous failure to a prospective treatment trial using a combination of three traditional agents.

Methods

Thirty-four consecutive patients (30 women and 4 men, with mean age of 39 years and range from 24 to 53) with migraine (according to the ICHD-II, 2004 [3]) and fewer than 15 days of headache per month were prospectively studied. We excluded patients with clinical or psychiatric comorbidities, as well as fertile women not using contraceptives.

All participants were regular patients from a tertiary center, and had not presented greater than 50% reduction in the number of headache days after 3 months using the combination of atenolol (60 mg/day), nortriptyline (25 mg/day), and flunarizine. The combination of pharmacological agents was formulated as single capsules given twice daily (2 weeks for initial titration and 10 weeks using the described dosages). Daily diaries recorded baseline headache frequency (1 month), as well as during the treatment with the combination.

Despite the use of the described therapy, patients continued to experience an average of 2–3 migraine days per week. None experienced greater than 50% reduction in migraine days at the 10th and final week, as compared with the baseline period.

After the withdrawal of the preventive medication (one capsule a day for 7 days followed by total interruption), QTP was initiated as the only treatment, initially as a single nocturnal dose of 25 mg, and then titrated to 75 mg (25 mg each 6 days). The acute treatment was maintained, with a maximum allowed frequency of twice per week, and consisted of the combination of a triptan plus a nonsteroidal anti-inflammatory drug. Patients were instructed to fill a detailed headache calendar anytime they experienced a headache attack. The number of days using rescue medications was captured.

After 10 weeks, patients were reevaluated and headache frequency, as well as use of rescue medications, was measured. The treatment phase was compared with the baseline.

The study was carried out at the Headache Center of Rio. All patients gave their informed consent. In addition, the study was approved by the Ethics Committee of the Universidade Federal Fluminense, in Rio de Janeiro.

Results

Twenty-nine (85.3%) patients completed the study. Three (8.8%) patients did not tolerate the medication and interrupted before the first follow-up visit (side effects consisted of excessive sedation in two patients and mental confusion in one subject). Two other patients (5.9%) were lost to follow-up. Among the 29 subjects completing the trial, 22 patients (75.9%; 64.7% of the intention-to-treat [ITT] population, 21 women and 1 man) experienced greater than 50% decrease in their headache frequency after 2 months (12 days of titration and 48 days on 75 mg/day).

Although the 1-month time-point (12 days of titration and 18 days on 75 mg/day) was not initially evaluated, response rates were lower. Among those who completed the study, reduction of greater than 50% in headache frequency at 1 month was observed in nine patients (31%; in ITT population, 26.5%). Three patients (8.8%) reported worsening of headache and four patients (11.8%) experienced no reduction in migraine frequency.

The five subjects not completing the study had less than 10 migraine days per month at the time of the exclusion. Consumption of rescue medications decreased from a mean of 2.3 days/week (1–4 days/week, despite the clear instruction regarding limits) to a mean of 1.2 days/week (0.8–2 days/week), for completers.

Mean monthly migraine days was also assessed in this study; it was 10.2 at the time of inclusion, for all 34 patients. After 2 months, it decreased to 6.2 among completers.

Adverse events included worsening of headache, drowsiness, somnolence, increased appetite, weight gain and nausea, occurring in nine (31%) patients. Six patients reported more than one adverse event (Table 1).
Refractory migraine remains a challenge in clinical practice, especially in tertiary headache clinics [16,17]. Prevention should be considered when frequent, severe, and long-lasting headache attacks occur, or when there is excessive and/or regular use of symptomatic medications [16,17]. Tricyclic antidepressants, calcium channel blockers, and beta-blockers are well-established migraine preventive drugs [19–22]. Patients were considered refractory, in our study, as they failed to demonstrate a greater than 50% reduction in migraine frequency after a 10-week course of combination therapy using flunarizine, nortriptyline, and atenolol [18].

Dopamine antagonists, which have demonstrated efficacy in the acute treatment of migraine [23], could be useful for prevention as well, particularly the atypical antipsychotics, as they carry lower risks of inducing extrapyramidal side effects [2,4,24–26].

QTP has been studied for the treatment of migraine not responding to at least two pharmacological agents. At an average dose of 75 mg daily, 21 of the 24 patients showed significant improvement on migraine frequency, severity or both. Disability (MIDAS score) improved by at least one grade in 18 of the patients. None of the patients had serious side effects or extrapyramidal symptoms. One patient discontinued the drug because of sedation [5]. The conclusion was that QTP may represent an important resource for patients with refractory migraine or patients with psychological disturbances [5], although the results were never published as a full manuscript and the population studied was not considered refractory.

Other atypical antipsychotics have been suggested for migraine prevention as well. Silberstein et al. [14] reviewed the records of 50 patients with refractory headache who were treated with olanzapine for at least 3 months. The results were favorable to olanzapine. In another recent study, a decrease of migraine frequency and severity was described in three patients taking the atypical antipsychotic, aripiprazole [15].

Cautions have to be used with this study. The major limitation regards its open-label design and the relatively small number of patients. In addition, one may argue that the dosage of the preventive medications used were suboptimal. However, the standard dosages of beta-blockers, calcium channel blockers, and tricyclic antidepressants used for migraine prevention are recommended for monotherapy use [19–22]. The use of lower dosages in this study was justified based on the fact that they were used in combination. Combining preventive agents is a strategy based on using pharmacological agents with different mechanisms of action for the treatment of biologically complex disorders, such as migraine [16]. Evidence suggests the efficacy of combining preventive medications, and the strategy is widely used in tertiary headache centers [16–18,27,28]. The strength of this study is the fact that it was carried out in a real-world setting. All patients were closely followed in a tertiary referral headache clinic, completed daily diaries, and were clearly shown to be refractory to a combination of preventive medications. In fact, most migraine prevention studies exclude patients who have failed to respond to more than two preventive medications [19–21,29].

Accordingly, although limited by the open design, this study provides pilot data to support the use of QTP in the preventive treatment of refractory migraine. Controlled studies are necessary to confirm these observations.

### Table 1

<table>
<thead>
<tr>
<th>Change in Headache Frequency</th>
<th>Reduction of 50% or more</th>
<th>Less than 50% reduction</th>
<th>Increased frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Per protocol group (N = 29)</td>
<td>22 (75.9%)</td>
<td>3 (10.3%)</td>
<td>4 (13.8%)</td>
</tr>
<tr>
<td>Intention to treat (N = 34)</td>
<td>64.7%</td>
<td>8.8%</td>
<td>11.8%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Adverse Events</th>
<th>Number with at least one adverse event</th>
<th>Number with more than one adverse event</th>
<th>No adverse events</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>9 (31%)</td>
<td>6 (20.7%)</td>
<td>20 (69%)</td>
</tr>
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