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QUETIAPINE FOR THE PREVENTION OF MIGRAINE REFRACTORY TO THE COMBINATION OF ATENOLOL + NORTRIPTYLINE + FLUNARIZINE

An open pilot study

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Abstract – **Background:** Migraine is a prevalent neurological disorder. Although prevention is the mainstream treatment, some patients are refractory to standard therapies. **Aim:** To evaluate the use of quetiapine (QTP) in the preventive treatment of refractory migraine, defined as previous unresponsiveness to the combination atenolol + nortriptyline + flunarizine. **Method:** Thirty-four consecutive patients (30 women and 4 men) with migraine (ICHD-II) and headache attacks on less than 15 days per month not overusing symptomatic medications were studied. The main inclusion criterion was the lack of response (<50% reduction in attack frequency) after ten weeks to the combination of atenolol (60 mg/day) + nortriptyline (25 mg/day) + flunarizine (3 mg/day). The patients started on QTP as the sole treatment in a single daily dose of 25 mg, titrated to 75 mg. After ten weeks, headache frequency, consumption of rescue medications and adverse events were analyzed. **Results:** Twenty nine patients completed the study. Among completers, 22 (75.9%; 64.7% of the intention-to-treat population) presented >50% headache reduction. The mean frequency of migraine days decreased from 10.2 to 6.2 and the average consumption of rescue medications decreased from 2.3 to 1.2 days/week. Adverse events were reported by 9 (31%) patients. **Conclusion:** Although limited by the open design, this study provides a pilot data to support the use of quetiapine in preventive treatment of refractory migraine.

KEY WORDS: migraine, quetiapine, preventive treatment, refractory.

Quetiapina para a prevenção da migrânea refratária à combinação de atenolol + nortriptilina + flunarizina: estudo piloto aberto

Resumo – **Introdução:** A migrânea é uma doença neurológica prevalente. Embora a prevenção seja o esteio principal do tratamento, alguns pacientes são refratários aos tratamentos tradicionais. **Objetivo:** Avaliar o uso da quetiapina (QTP) no tratamento preventivo da migrânea refratária definida como ausência de resposta ao uso prévio da combinação de atenolol com nortriptilina e flunarizina. **Método:** Trinta e quatro pacientes consecutivos (30 mulheres e 4 homens) com migrânea (CIC-II) e crises de cefaléia em menos de 15 dias/mês sem uso excessivo de sintomáticos foram estudados. O critério de inclusão principal foi a não obtenção na redução da frequência de cefaléia >50% após 10 semanas de uso da combinação de atenolol (60 mg/dia) + nortriptilina (25 mg/dia) + flunarizina (3 mg/dia). Os pacientes iniciaram a QTP como tratamento único na dose de 25 mg à noite e aumentaram-na até 75 mg. Após 10 semanas de uso, a frequência da cefaléia, o consumo de sintomáticos e os efeitos colaterais foram avaliados. **Resultados:** Vinte e nove pacientes completaram o estudo. Entre os que completaram, 22 (75.9%; 64.7% dos pacientes que foram incluídos) obtiveram redução da frequência >50%. A frequência média de dias com migrânea por mês decresceu de 10,2 para 6,2. O consumo médio de sintomáticos caiu de 2,3 para 1,2 dias/semana. Efeitos colaterais foram relatados por 9 (31%) pacientes. **Conclusão:** Apesar de limitado pela metodologia aberta, esse estudo oferece dados iniciais para a possível utilidade da QTP na prevenção da migrânea refratária.

PALAVRAS-CHAVE: migrânea, quetiapina, tratamento preventivo, refratário.

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Migraine is a highly prevalent disorder manifesting clinically as headache attacks of moderate to severe intensity. The headache attacks generally induce disability among sufferers resulting in considerable economic and social losses[1-4]. The pathophysiology of migraine is complex and presents a clear genetic basis. During migraine attacks, neural events result in the dilatation of meningeal blood vessels, which in turn, results in pain, further nerve activation and inflammation[5]. The head pain during migraine attacks may 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 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[6-9]. Clinical evidence seem to indicate an involvement of dopamine in the pathophysiology of the migraine attack. Nausea, vomiting, and hypotension as well as postdromal symptoms (mood changes, drowsiness and tiredness) may be related to dopaminergic activation. The dopaminergic system could also play a role in the headache phase, either by taking part in nociceptive mechanisms or by regulating cerebral blood flow. A body of pharmacological findings seems to support this involvement[10]. In addition, dopaminergic neurotransmission has been shown to influence nociceptive traffic through the trigeminal nucleus caudalis (TNC)[11], whose inhibition may be correlated to prevention of migraine in animals[5,12].

The use of dopamine antagonists in the treatment and prevention of migraine has been reported by some authors[13-15]. The new atypical antipsychotics, which act as dopamine antagonists as well, have fewer extrapyramidal side effects than the first generation antipsychotics, and therefore became attractive as potential treatment and prevention of migraine attacks[14,15]. Moreover, atypical psychotics are indicated for the treatment of acute mania, and migraine prevalence in bipolar subjects is high and commonly underdiagnosed[15]. The preventive treatment for migraine attacks is the mainstream approach in patients with frequent headache attacks, as well as in individuals with attack-related disability who are not responsive to acute therapy alone. In general populations of migraineurs, it is estimated that no more than 60% of patients achieve more than 50% reduction in headache frequency with the use of standard pharmacological options[16,17]. In specialty care, these may be even lower, despite treatment attempts with combination of different drugs, commonly practiced by headache specialists[16-20]. This highlights the unmet treatment needs of refractory migraineurs, thereby justifying the execution of small pilot studies, to gather preliminary data on this issue.

Consistently, the aim of this study was to evaluate the use of quetiapine (QTP), a multi-acting antipsychotic drug, in the prevention of refractory migraine, defined as previous failure to a prospective challenge using a combination of three traditional agents.

METHOD

Thirty four consecutive patients (30 women and 4 men, age 24 to 53, mean 39 years) with migraine (according to the ICHD-II, 2004)[3] and headache attacks on less than 15 days per month were prospectively studied. Patients with clinical or psychiatric co-morbidities as well as women in child-bearing age not using stable contraceptive methods were not included. All of the subjects were regular patients from a tertiary center who had not presented greater than 50% frequency reduction in migraine days after 3 months using the combination of atenolol (60 mg/day) + nortriptyline (25 mg/day) + flunarizine (3 mg/day). The combination of pharmacological agents was presented in single capsules given twice daily (2 weeks for initial titration and 10 weeks using the described dosages). Daily diaries had recorded migraine frequency for 1 month prior to commencement of therapy with the combination of preventive agents. All patients continued to maintain daily diaries throughout the titration and maintenance phase with this combination.

Despite the use of the described therapy, the patients continued to experience an average of 2-3 migraine days per week. No patients had a greater than 50% reduction in migraine days at the 10th and final week compared to the 30-day baseline period.

After the suspension of the preventive medication (one capsule a day for seven days followed by total interruption), quetiapine was prescribed to all patients as the only treatment in a single daily bedtime dose of 25 mg titrated to 75 mg (25 mg each 6 days). The acute treatment was maintained as previously, with a maximum allowed frequency twice a week, comprising the combination of a triptan plus a non-steroidal anti-inflammatory drug (NSAID) to be taken as needed. Additionally, the patients were clearly oriented to fill out a detailed headache calendar every time a headache attack occurred. The average consumption of rescue medications among the studied population was evaluated when quetiapine was prescribed. After 10 weeks, the patients were reevaluated and headache frequency, measured as migraine days/week along with consumption of rescue medications were analyzed and compared between phases. Adverse events were also analyzed.

All patients gave their informed consent. In addition, the study was approved by the ethics committee of the Universidade Federal Fluminense.

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 re-

Table. Results of frequency of attacks and adverse events.

Frequency reduction of attacks	**Greater than 50%**	**No reduction**	**Increasing number of headache attacks**
Per protocol group (29 patients)	22 patients (75.9%)	3 patients (10.3%)	4 patients (13.8%)
Intention-to-treat population (34 patients)	64.7%	8.8%	11.8%
Adverse events (AE)	**Total number of patients**	**Patients presenting more than one AE**	**Patients not presenting AE**
	9 (31%)	6 (20.7%)	20 (69%)
Rescue medication consumption	**Before QTP* treatment**	**After QTP* treatment**	
	2.4 days/week	1.2 days/week	

*Quetiapine.

sponsible for withdrawal were excessive sedation in two patients and mental confusion in one subject). Two other patients (5.9%) did not return and were lost to follow up. Among the 29 subjects who completed the trial, 22 patients (75.9%; 64.7% of the intention-to-treat – ITT – population) (21 women and 1 man) presented frequency reduction of greater than 50% after two months (12 days of titration and 48 days on 75 mg/day).

Although the one-month time-point outcome (12 days of titration and 18 days on 75 mg/day) was not initially evaluated, the rates of response were lower. Among the completers, headache frequency reduction of greater than 50% was observed in 9 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 5 subjects who did not complete the study were not having more than 10 migraine days per month at the time of the inclusion. The consumption of rescue medications decreased from an average of 2.3 days/week (despite the clear instruction regarding limits) to an average of 1.2 days/week, considering all patients who completed the study. Adverse events reported included worsening of headache, drowsiness, somnolence, increased appetite, weight gain and nausea, occurring in 9 (31%) patients. Six patients reported more than one adverse event (Table).

The mean frequency of migraine days per month was also assessed in this study, and it was 10.2 at the time of inclusion for all 34 patients. After two months, the mean frequency of migraine days per month among those who completed the study had decreased to 6.2.

DISCUSSION

Refractory migraine remains a challenge in clinical practice, especially in tertiary referral 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 preventive drugs employed for the treatment of migraine[19-22]. This group of patients was considered refractory to such preventive medications since they had 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 a useful agent for migraine prevention, particularly the atypical antipsychotics, since they have fewer propension to induce extrapyramidal side effects[24-26]. QTP was first suggested for migraine prevention in a study involving 24 migraineurs with a history of not responding to at least 2 pharmacological agents. At an average dose o-f 75 mg daily, 21 of the 24 patients showed significant improvement in either migraine frequency, severity or both. The disability evaluated by the MIDAS score, improved by at least 1 grade in 18 of the patients. None of the patients presented serious side effects or extrapyramidal symptoms. One patient discontinued the drug because of sedation[25]. The conclusion was that QTP may represent an important resource for patients with refractory migraine or patients with co-morbid psychological disturbances[25], 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 aripiprazole[15].

Cautions have to be used with this study. The major limitations are 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 use as monotherapy[19-22]. Moreover, the use of lower dosages in this study was justified based on the fact that the drugs were used in combination. Combining preventive agents is a strategy based on using different pharmacological agents with different mechanisms of action to address multi-mechanism diseases such migraine[16,27]. There is evidence that combining preventive medications is effective for the preventive treatment of migraine and the strategy is widely employed in tertiary headache practice[16-18,27,28]. The advantage of this study is the fact 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 addition, the presentation of refractory migraine is common in clinical practice and to date, this patient population has been systematically excluded from migraine prevention trials. In fact, most migraine prevention studies exclude patients who have failed to respond to more than two preventive medications[19-21,29]. Therefore, this small trial, while very preliminary, requires a further larger randomized placebo-controlled study in a population of migraine patients refractory to other well-established preventive medications.

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