

Testing the combination beta-blocker plus topiramate in refractory migraine

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Objective – To test treatment combining a beta-blocker plus topiramate in migraine patients previously resistant to the two medications in monotherapy. **Patients and methods** – Those patients who had not responded to a beta-blocker and topiramate received combined treatment. **Results** – Fifty-eight patients (47 women, age 25–76 years) received the combined treatment. Thirty-three (57%) met criteria for chronic migraine/medication overuse headache, 18 (31%) for migraine without aura and seven (12%) with aura. Ten (17%) discontinued due to adverse events. Among the 48 patients who tolerated the combination, 36 (75%, 62% of the total series) showed response (> 50% reduction in frequency), while 12 (25%) did not. The number of days with headache/month decreased from 15.1 to 6.5 (–57%). Sixteen (44% of responders) showed an excellent (> 75%) response. Eighteen patients (38%) experienced a total of 26 adverse events (mild-moderate). **Conclusions** – The combination of beta-blocker plus topiramate showed a benefit in around 60% of patients who had not previously responded to monotherapy. Adverse events led to discontinuation in one out of six patients. From these open results, it seems reasonable to recommend this combination, complementary in terms of mechanism of action, as a potential strategy in patients with refractory migraine.

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Introduction

Preventive treatment is mandatory in migraine patients who are experiencing frequent attacks. Preventive treatment is not an easy task in many patients. Migraine preventatives with well-demonstrated efficacy include beta-blockers, the neuro-modulators valproate and topiramate, flunarizine and amitriptyline. The efficacy of these drugs is limited. In clinical practice, only about 50–60% of patients improve on these medications (1).

In an open trial reported several years ago, we explored whether combining a beta-blocker plus sodium valproate could lead to an advantage in 52 migraine patients who were previously resistant to the two medications in monotherapy for at least 2 months (2). Combination therapy appeared to be a good migraine preventive in over 50% of previously resistant migraine cases. Our aim was to test the efficacy and tolerability of a preventive treatment which combines a beta-blocker plus

topiramate in migraine patients previously resistant to the two medications in monotherapy.

Patients and methods

Patients with a history of International Headache Society-classified migraine were treated with a combination of beta-blockers (propranolol or nadolol) plus topiramate in an open-label fashion. Study subjects needed to have a history of migraine of at least 1 year. All patients were initially treated with a beta-blocker, propranolol or nadolol, for at least 1.5 months without improvement and, subsequently, with topiramate, again with no response for at least 1.5 months. Topiramate was kept at the same dose and the initial beta-blocker was added. A study diary was provided to each participant. Patients were evaluated once at the end of the first month of this combined treatment to try to look for an optimal dose of the two drugs and to check tolerability.

Efficacy results were evaluated on a second visit in the third month when tolerability issues were again examined. The primary outcome measure ('response') was a >50% reduction in the number of days with headache in the third month of treatment with the combination, compared with the number of days with headache the month prior to when the combination was started. We considered a response as 'excellent' if the reduction in headache days was >75%. Only non-steroidal anti-inflammatory drugs or triptans were allowed as symptomatic treatment during the entire therapy phase. The study was approved by our ethics committee.

Results

Fifty-eight patients (47 women, age range 25–76 years) met the inclusion criteria and were treated with the combination. Fifty-one (88%) had been on the two drugs for two complete months. Only 7 received either beta-blocker or topiramate or both for at least 6 weeks. Most of these patients (41, 71%) were referred to our clinics following a lack of response or intolerance to flunarizine in a GP setting. According to current criteria (3, 4), 20 (34.5%) met criteria for chronic migraine, 13 (22.4%) were migraineurs meeting criteria for medication overuse headache, 18 (31%) for migraine without aura and seven (12%) for migraine with aura. At the third month, mean, median and range of daily dosages were for beta-blockers 52, 60 and 40–80 mg, and for topiramate 82, 100 and 50–200 mg. Twenty-four patients received propranolol and 34 nadolol.

Ten (17%) patients who had previously tolerated the two medications well in monotherapy, prematurely discontinued due to a total of 15 adverse events: cognitive impairment ($n = 5$), paresthesias ($n = 3$), depression ($n = 3$), digestive symptoms ($n = 3$) and exaggerated weight loss ($n = 1$). Among the 48 patients who tolerated the combination, 36 (75%, 62% of the total series) showed a response, while 12 (25%, 21% of the total series) did not (Fig. 1). The number of days with headache per month decreased from 15.1 to 6.5 (–57%). Sixteen patients (44% of responders) showed an excellent response. Eighteen (38% of those patients continuing in the study) experienced a total of 25 adverse events, always mild-moderate: cognitive impairment ($n = 13$), paresthesias ($n = 5$), digestive symptoms ($n = 5$), renal colic ($n = 1$) and impotence ($n = 1$). A total of 24 patients (50% of those remaining in the study) lost weight (mean 5.3 kg), when compared with prior use of topiramate in monotherapy.

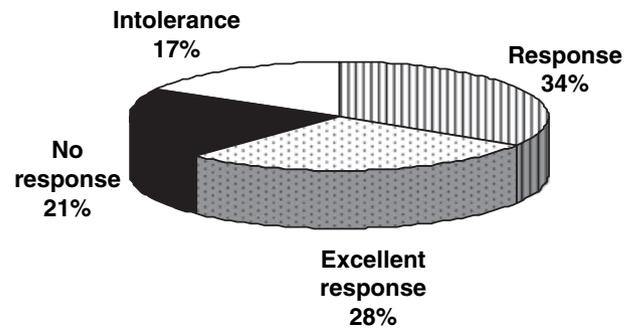


Figure 1. Summary of results.

Discussion

Combining a beta-blocker plus topiramate showed benefit in around 60% of those patients who had not responded to the treatment in monotherapy. Even though monotherapy remains the rule in migraine prevention (1), drug combinations are commonly used in clinical practice for patients suffering from resistant migraine (5). The good efficacy results obtained here must be interpreted with caution, as they come from an open-label research in a condition with a high placebo response rate and with a protocol in which a carry-over effect from two previous monotherapy trials is theoretically possible (6). Our responder rate of 62%, given the small study numbers, would not have a confidence interval that could differentiate from the topiramate response rate (7). The previous refractoriness of these patients and the rate of excellent response, higher than that seen in the previous combination trial with valproate (2), however, support that the benefit with this combination is real. As occurred in the previous combination trial, using together a beta-blocker and topiramate increases adverse events with one out of every six patients being unable to tolerate them and with almost 40% of patients experiencing some *de novo* mild-moderate adverse events, which did not require discontinuation (2). While potential interactions among these drugs have not been specifically studied, these adverse events could theoretically be due to a change in bioavailability or to a metabolic effect of either drug.

As pointed out above, in clinical practice at least one-third of the cases coming to our clinics do not improve on preventatives. Considering migraine pathophysiology, one explanation for this insufficient efficacy of current preventatives is the partial and indirect mechanisms of action of these drugs. Therefore, theoretically, compounds acting at different levels of migraine pathophysiology could have summatory effects in preventive treatment. If we picture migraine as a channelopathy, for

example, none of the available drugs is specific for a particular channel but they act either in a several of them (e.g., topiramate) or indirectly on the consequences of channel malfunctioning (e.g., beta-blockers) (8). This approach is not new in our specialty and we routinely prescribe combined therapy, based on this reasoning of complementary mechanisms of action, in many neurologic conditions, such as epilepsy, Parkinson's disease, etc. The respective mechanisms of action of beta-blockers and topiramate are on different neurochemical targets. Consequently, combining these two drugs with the best documented efficacy in migraine prevention appears a conceptually reasonable option for the preventive treatment of resistant migraine patients (9). The same is true for symptomatic migraine treatment where refractory patients can respond to NSAIDs plus a triptan in combination (10, 11).

In conclusion, our data suggest that in clinical practice combining a beta-blocker plus topiramate is a recommendable strategy in patients with refractory migraine. Nevertheless, controlled trials are necessary to clearly determine a real advantage of this combination in difficult migraines.

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