Combined therapy for migraine prevention? Clinical experience with a β-blocker plus sodium valproate in 52 resistant migraine patients

J Pascual, R Leira[1] & JM Láinez[2]

Service of Neurology and Department of Medicine (UC), University Hospital 'Marqués de Valdecilla', Santander, [1]Service of Neurology, University Hospital Santiago de Compostela, and [2]Service of Neurology, Hospital 'Clínico Universitario', Valencia, Spain

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The aim was to explore whether combining a β-blocker and sodium valproate could lead to an advantage in efficacy in patients with migraine previously resistant to the two medications in monotherapy. Fifty-two patients (43 women) with a history of episodic migraine with or without aura, and previously unresponsive to β-blockers and sodium valproate in monotherapy, were treated with a combination of propranolol or nadolol and sodium valproate in an open-label fashion. Eight patients (15%) discontinued due to adverse events. Fifteen (29%) did not respond. The remaining 29 cases (56%) showed response (>50% reduction in migraine days). The response was excellent in nine (17%). From this open trial, combination therapy with a β-blocker and sodium valproate appears to be a good migraine preventative in some previously resistant migraine cases. Controlled trials are now necessary to determine the true advantage in efficacy of this combination in difficult to treat migraineurs. □*Migraine, migraine prevention, nadolol, propranolol, sodium valproate*

Dr Julio Pascual, University Hospital Marqués de Valdecilla, 39008 Santander, Spain. Tel. +34 9 4220 2707, fax +34 9 2420 2655, e-mail juliopascual@telefonica.net *Received 14 September 2002, accepted 2 April 2003*

Introduction

Preventive treatment of migraine is not an easy task in many patients. Beta-blockers and sodium valproate are among the drugs showing the best risk-to-benefit ratio for migraine prophylaxis and available in most countries. Adverse events, however, are not infrequent with these medications and, for those without tolerability problems, they are not efficacious in at least one-third of cases (1). The aim of this work was to explore whether combining these two treatments could lead to an advantage in efficacy in patients with migraine previously resistant to the two medications in monotherapy.

Subjects and methods

Fifty-two patients (43 women, age range 22–71 years) with a history of International Headache Society classified episodic migraine with ($n = 3$) and without aura were treated with a combination of β-blockers (propranolol or nadolol) plus valproic acid in an open-label fashion. Study subjects needed to have a history of migraine of at least 1 year. Twenty-two were referred to us due for failing on amitriptyline and 17 for failure on flunarizine.

All patients were initially treated by us with a β-blocker, propranolol or nadolol, for at least 2 months (maximum time 3 months) without impairment and, subsequently, with sodium valproate, again with no response for between 2 and 3 months. During this phase, study participants suffered from rather frequent migraine as they experienced a minimum of six migraine attacks per month (migraine days per month ranging from 8 to 24). Then sodium valproate was kept at the same dose and the initial β-blocker was added. A study diary was provided for 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, mainly, to check tolerability, including potential abnormalities in liver enzymes and other routine blood tests. 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 number of days with migraine headache in the previous 2 months compared with the mean number of days with migraine headache during the months treated with either a β-blocker or sodium naproxen in monotherapy. We considered a response as 'excellent' if the reduction of migraine days was >75% in the previous 2 months. Only sodium naproxen or ibuprofen plus a triptan, if necessary, were allowed as symptomatic treatment during the entire therapy phase.

Results

The maintenance dose of sodium valproate ranged from 300 to 1000 mg daily. Most patients took low doses of this drug (mean = 390 mg daily) using the slow-release formulation of sodium valproate (30 took one 300-mg tablet and 16 one 500-mg tablet at night). The remaining six took between 600 and 1000 mg daily distributed in two or three daily doses of conventional 200- or 500-mg tablets. Regarding β-blockers, the patients were offered nadolol (one dose per day) or propranolol (three doses per day). Thirty-one patients were treated with nadolol (maintenance dose 40–160 mg/day; mean dose 59 mg daily) and 20 with propranolol (maintenance dose 40–160 mg/day; mean dose 73 mg daily).

Eight patients (15%) who had previously tolerated the two medications well separately discontinued prematurely due to adverse events: gastric intolerance ($n = 3$), sedation ($n = 3$) and hand tremor ($n = 2$) All were mild to moderate and clearly drug related; no abnormalities in blood tests were detected. Fifteen patients (29%) did not respond. The remaining 29 cases (56%) showed response to this combination. In nine (17%) the response was excellent.

Discussion

Monotherapy should be the rule in migraine prevention (2). No rigorous clinical trials have yielded convincing evidence of the additive effects of a second or third preventive drug. Such a strategy also increases side-effects, while potential interactions among drugs are not fully understood. Nevertheless, drug combinations are commonly used in clinical practice for patients suffering from resistant migraine (3). It could be argued that drugs with different mechanisms of action could have summatory effects for the preventive treatment of this condition. The positive efficacy data shown here should be interpreted with caution, coming as they do from an open-label investigation in an entity with a high placebo response (4) and with a protocol in which a carry-over effect from the previous monotherapy should be expected. We are also aware that the doses of the single prophylactic drugs, reflecting the usual practice in our country, could be interpreted as rather low. Our results, moreover, confirm that using the two drugs is associated with an increase in adverse events, with almost 20% of our patients being unable to tolerate even usually low doses of this combination. These adverse events were either mild or moderate and did not differ from those seen with the two drugs used separately. They could theoretically be due to a metabolic effect or to a bioavailability change on either drug.

From this trial, however, combination therapy with a β-blocker and sodium valproate appears to be a good migraine preventive in over 50% of previously resistant migraine cases. To our knowledge, this combination had never been tested before for migraine prevention. The respective mechanisms of action of β-blockers and sodium valproate in migraine prevention seem to be on different neurochemical systems. Therefore, combining these two drugs with the best documented efficacy appears a conceptually reasonable option for the preventative treatment of resistant migraine patients. Nevertheless, controlled trials are necessary to determine the true advantage in efficacy of this combination, at different dosages, in difficult migraineurs.

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