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ORIGINAL ARTICLE

Sodium Valproate versus Propranolol in paediatric migraine prophylaxis

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Summary In a randomized clinical trial the effect of Sodium Valproate in pediatric migraine prophylaxis was compared with that of Propranolol. One hundred and twenty patients with common migraine (migraine without aura) aged from 3 to 15 years who met the defined criteria enrolled into the study. Randomly the patients were divided in two groups of A and B, treating with sodium Valproate and Propranolol, respectively. Three phases of baseline period (phase I), titration and adjustment period (phases II) and fixed -dose treatment period (phase III) have been designed. A total of 57 patients in group A, and 58 patients in group B completed all phases of the trial. Seventy two percent of patients in group A and 69% of patients in group B have responded to Sodium Valproate and Propranolol, respectively, as a reduction of more than 50% in headache frequency per month. Further more both drugs have shown efficacy in reducing the severity and duration of headache and also better response to rescue medications (p value <0.01). There was no significant difference in all previously mentioned therapeutic effects between two groups (p value <0.05).

Introduction

Propranolol has been prescribed for migraine prophylaxis since 1966, when Rabkin et al. discovered serendipitously its effectiveness in migraine headache in their patients who were being treated for angina pectoris.[1] Anti-convulsant drugs for migraine prophylaxis have been tested since 1970 with Carbamazepine as the first drug of this group.[2] Sorensen reported the potential effectiveness of Sodium Valproate in migraine prophylaxis in 1988.[3] Multiple clinical trials have been published in literature comparing the efficacy of these drugs and also with placebo. Most of these studies have been performed in adult population and also have small sample sizes. There are few studies evaluating the efficacy of different medication groups or comparing their effects as

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preventive migraine agents in pediatric population.[4] Here we report our trial for comparison of Sodium Valproate versus Propranolol in prophylaxis of childhood migraine.

Materials and methods

We designed a multicenter, randomized clinical trial to compare the efficacy of Sodium Valproate with that of Propranolol in pediatric common migraine prophylaxis. To be enrolled patients had to be 3–15 years of age and had to meet the diagnostic criteria for pediatric common migraine defined by the 1988 International headache society.[5] We could not consider the revised diagnostic criteria and classification system of IHS 2004 because it was released while a major part of our study was accomplished. In IHS classification 2004, 'common migraine'was replaced by 'migraine without aura'. Furthermore the patients with frequent or nearly daily migraine (>15 headache/month) were categorized as chronic migraineurs.[6] Other inclusion criteria were one of the following:

1. More than two headaches per month
2. Severe disabling or intolerable headache
3. No reduction of headache with rescue medications
4. Poorly tolerated or unwanted rescue medications.

All of the patients were asked to keep a headache calendar. The frequency, severity and duration of headache and also response to rescue medications were recorded for a period of 4 weeks (phase I) before initiation of drug prophylaxis. Complete physical and neurological examination, baseline laboratory screening tests and if needed neuroimaging studies were performed on entering the study. Exclusion criteria were as follows:

1. Past trial of migraine prophylactic agent
2. Persistent increasing headache
3. Change of behavior and school performance
4. Increased pain with Valsalva maneuvers
5. Abnormal physical examination (e.g. papilledema)
6. Persistent focal neurological signs
7. Neuroimaging studies indicative of focal neurological lesion
8. Contraindications for Propranolol or Sodium Valproate (e.g. asthma, hepatic disease).

Randomly 120 patients with common migraine (migraine without aura) who met the selection criteria were divided in two groups. Sixty patients in group A were treated with Sodium Valproate while patients in group B ($n=60$) received Propranolol. After a 4 weeks period of titration and adjustment (phase II), patients reached to a fixed-dose treatment period lasting for at least 2 months (phase III). Sodium Valproate was started at a dose of 10 mg/kg/day in two divided doses and slowly increased up to 40 mg/kg/day according to patient's response and tolerance. For Propranolol this was 1–3 mg/kg/day divided in two doses. Keeping the headache calendar and recording the headache frequency, severity and duration and also response to rescue medications in the phase III enabled us to assess and compare the efficacy of drugs in two groups.

Headache severity was scored on a 1–3 point scale with 1 presenting no effect on daily activity, 2 for partial inhibition of daily activity and 3 for loss of daily activities. Response to rescue medications 2 h after taking an agent of acute therapy, e.g. NSAIDs or acetaminophen was scored on a 1–4 point scale as Clinical impression of effect: 1 for ineffective, 2 for somewhat effective, 3 for effective and 4 for very effective. The drug is considered effective as a prophylactic agent in migraine headache if it could reduce more than 50% the baseline headache frequency per month. Reduction of headache severity and duration and also better response to rescue medications were evaluated as other aspects of preventive pharmacotherapy. Paired sample *T*-test, *Z*-test and chi-square have been used in statistical analysis. Values of $p<0.05$ in *Z* and *T* test and values of $p<0.01$ in chi-square were considered significant.

Results

A total of 57 patients on Sodium Valproate (group A) and 58 patients on Propranolol (group B) completed all phases of the trial. Three cases of group A were withdrawn because they did not have compliance to be treated with anti-epileptic drugs and two patients of group B who were lost to follow up were excluded. Fortunately withdrawal of treatment was not required in any case due to drugs side effects. Occasional minor side effects appeared to be fairly well tolerated by patients of both groups. Demographic characteristics and pre-treatment headache frequency had no significant differences between two groups (Tables 1 and 2), e.g. male to female ratio of 2/1 was the same in both groups. Further more no significant differences were