Venlafaxine versus amitriptyline in the prophylactic treatment of migraine: randomized, double-blind, crossover study

Serpil Bulut a,∗, M. Said Berilgen a, Aslihan Baran a, Aslan Tekatas, Murad Atmaca b, Bulent Mungen a

a Department of Neurology, Faculty of Medicine, Firat University, TR 23119 Elazig, Turkey
b Department of Psychiatry, Faculty of Medicine, Firat University, TR 23119 Elazig, Turkey

Received 25 June 2003; received in revised form 3 March 2004; accepted 18 March 2004

Abstract

In patients with migraine with or without aura the prophylactic effect of amitriptyline (AMT) and venlafaxine (VLF) was compared in a randomized double-blind crossover study. Intolerable side effects resulted in drop out of five patients on AMT (due to hypersomnia, difficulty in concentration and orthostatic hypotension) and one patient on VLF (because of nausea and vomiting). Following the run-in period the patients (n = 52) were randomly treated with one of the study medications for 12 weeks. After a wash-out period lasting 4 weeks the patients were treated with the other drug for further 12 weeks. Both drugs had significant beneficial effect on pain parameters. Total number of side effects of VLF was low when compared with the side effect profile of AMT. In conclusion, it is suggested that VLF may be considered for the prophylaxis of migraine because of its low and/or tolerable side effect properties.

© 2004 Elsevier B.V. All rights reserved.

Keywords: Migraine; Prophylaxis; Amitriptyline; Venlafaxine

1. Introduction

Since the mechanisms underlying migraine headache are still insufficiently known, different kinds of medications are used in migraine prophylaxis. The efficacy of tricyclic antidepressants (TCA) in migraine treatment has been shown to be independent of their antidepressant action [1,2]. Amitriptyline (AMT), a TCA, is one of the most commonly prescribed migraine-preventive drugs [3,4]. It inhibits the neuronal reuptake of nor epinephrine (NE) and serotonin (5-HT) in the brain [5]. Despite AMT’s use in migraine prophylaxis as an alternative pharmacological treatment [6], side effects including sedation, orthostatic hypotension, cognitive impairment, dry mouth, nausea, and cardiac abnormalities limit its use [6–9].

The bicyclic antidepressant venlafaxine (VLF), a structurally novel antidepressant, is a phenyl ethylamine. It inhibits the reuptake of 5-HT, NE and dopamine. Although its mechanism of action is similar to the TCA’s, it acts more specifically at those receptors and does not bind to the receptors responsible for the side effects of TCAs [3,10].

The purpose of the present study was to compare the prophylactic effects and the side effects of VLF and AMT in migraineurs.

2. Patients and methods

Migraine was classified according to criteria of the Headache Classification Committee of the International Headache Society (IHS) [11]. The criteria for inclusion were age between 16 and 50 years, a history of migraine for more than one year, and at least two attacks per month based on the average of the last three months before admission. Exclusion criteria were use of other drugs ordered for prophylactic treatment of migraine in the four weeks before randomization, depression or other psychiatric disorders, allergy to VLF and/or AMT, serious somatic diseases including hepatic or renal dysfunction, heart disease, and pregnancy or breast-feeding.
3. Study design

The study was a randomized, double-blind crossover trial of 36 weeks duration. All patients gave their informed consent before entering the study and the protocol of this study was approved by Firat University Local Ethics Committee. Each patient had a complete physical and neurological examination before entering the study. An ECG was recorded and the blood pressure and body weight were measured. All patients were evaluated by using Hamilton Rating Scale for Depression (HAM-D), and those with marked to moderate depression according to this scale were excluded from the study.

Patients suffering from migraine with and without aura according to International Headache Society criteria were randomly assigned to treatment. During the first 4 weeks, run-in period, the patients received no prophylactic treatment and had to record in a headache diary the number of migraine attacks, the duration of attacks in hours and the severity. The severity was graded on 1–3 scale: (1) able to work throughout the attack; (2) unable to work, but not staying in bed; (3) staying in bed. Acute medications were used as needed. Following the run-in period the patients who randomly treated with one of the study medications for 12 weeks. After a wash-out period lasting 4 weeks the patients were treated with the other drug for 12 weeks. The patients were re-evaluated after a 4 weeks wash-out period. At every visit in the trial, side effects were reported in response to physician’s asking. The patients receiving VLF in the first period of the treatment (4–16 weeks), and AMT in second period of the treatment (20–32 weeks) were considered as Group 1; while the patients receiving the AMT in the first period of the treatment (20–32 weeks) and VLF in the second period of treatment were considered as Group 2. Both drugs were identical in appearance, were packed in identical bottles and contained 37.5 or 75 mg VLF or 10 or 25 mg AMT. VLF was dosed as follows: 37.5 mg per day for 3 days, 75 mg per day for 3 days and 150 mg for 78 days. AMT was dosed as follows: 10 mg per day for 3 days, 25 mg per day for 3 days, 50 mg per day for 3 days and 75 mg per day for 75 days. Since it has been reported that the extended release (XR) form of venlafaxine is more effective in migraine prophylaxis the XR form of this agent was given to the both groups [3]. Follow-up visits took place 4, 16, 20, 32 and 36 weeks after inclusion. The patients were requested to record in a headache diary the number of migraine attacks, the duration of attacks in hours and the severity of attacks (as described above) and in these follow up visits they provided information on the outcome measures for migraine and the side effects of medication. Evaluations were done by a neurologist blind to the treatment given.

4. Statistical analysis

Data were statistically analyzed using SPSS for Windows (version 10.01). Paired T test, one-way ANOVA were used for comparison between the groups and Tukey B and Scheffe tests were used post hoc comparisons. Mann-Whitney U-test was used for comparison between independent groups. P < 0.05 was considered to be significant.

5. Results

Fifty-two out of 76 patients involved in this study were completed the study. Among the drop-outs; there was a follow up problem in 12 and adherence problems to the given treatment protocol in 5 individuals. Intolerable side effects resulted in drop out of five patients on AMT and one patient on VLF. Another patient underwent surgery during the study and was excluded from the analysis. Of the patients who completed the study, 8 were male and 44 were female and their median age was 31.9 years (16–50 years). Twelve patients had migraine with aura and 40 patients had migraine without aura. Each group included 26 patients.

It was determined that both drugs had significant beneficial effect on pain parameters (P < 0.01, ANOVA test, Tables 1 and 2). There was no significant difference between the two drugs in Group 1 with respect to migraine attack frequency, attack duration and intensity of the pain when compared in run-in period, post treatment and wash-out periods (P > 0.05, paired-samples T test, (Tables 1 and 2). There was no significant difference between the two drugs in Group 2 with respect to migraine attack frequency, attack duration and intensity of the pain when compared in run-in period, post treatment and wash-out periods (P > 0.05, paired-samples T test, Tables 1 and 2).

There was no statistically significant difference between post treatment migraine parameters for VLF treatment in Group 1 and AMT treatment in Group 2 (P > 0.05, Mann-Whitney U-test).

When the data were compared, after the groups were crossed over, the pain parameters were significantly improved in both groups compared to the wash-out period (P < 0.05, paired-samples T test), but there was no significant difference between the groups (P > 0.05, Mann-Whitney U-test).

In both periods, five (8.6%) of AMT-receiving patients dropped out of the study due to hypersomnia, difficulty in concentration and orthostatic hypotension, and one (1.7%) of VLF-receiving patients due to nausea and vomiting.

When the side effects of drugs were compared, in the AMT-treated group 42 (80.7%) of the patients had hypersomnia, 36 (69.2%) dry mouth, 28 (53.8%) difficulty in concentration and 18 (34.6%) sedation whereas in the VLF-receiving group the most frequent complaints were nausea/vomiting (12 patients, 23.0%) and palpitation/tachycardia (8 patients, 15.2%) (Table 3). The remaining patients described the side effects as slight and they were transient in all cases. It was necessary to reduce the dose in order to minimize the AMT-related side effects. The most frequent complaint side effect of VLF was nausea,
### Table 1
Comparison of Group I pain parameters during two treatment periods

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Group I: VLF</th>
<th>Group I: AMT</th>
<th>P value (paired-samples T test)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Attacks per month</td>
<td>Attack duration (h)</td>
<td>Attack intensity</td>
</tr>
<tr>
<td>Pre-treatment (I)</td>
<td>4.15 ± 2.24</td>
<td>15.69 ± 7.65</td>
<td>2.65 ± 0.36</td>
</tr>
<tr>
<td>During 12-week treatment (II)</td>
<td>1.77 ± 1.39</td>
<td>4.71 ± 2.69</td>
<td>1.38 ± 0.85</td>
</tr>
<tr>
<td>4 weeks after treatment (III)</td>
<td>3.27 ± 1.61</td>
<td>10.04 ± 3.00</td>
<td>2.42 ± 0.58</td>
</tr>
<tr>
<td>P value (ANOVA test)</td>
<td>†P &lt; 0.001 (I–II)</td>
<td>†P &lt; 0.001 (I–II)</td>
<td>†P &lt; 0.001 (I–II and II–III)</td>
</tr>
<tr>
<td></td>
<td>‡P &lt; 0.01 (II–III)</td>
<td>‡P &lt; 0.01 (II–III)</td>
<td>‡P &lt; 0.01 (II–III)</td>
</tr>
</tbody>
</table>

NS: non significant.

### Table 2
Comparison of Group II pain parameters during two treatment periods

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Group II: AMT</th>
<th>Group II: VLF</th>
<th>P value (paired-samples T test)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Attacks per month</td>
<td>Attack duration (h)</td>
<td>Attack intensity</td>
</tr>
<tr>
<td>Pre-treatment (I)</td>
<td>3.28 ± 2.12</td>
<td>19.69 ± 8.56</td>
<td>2.61 ± 0.50</td>
</tr>
<tr>
<td>During 12-week treatment (II)</td>
<td>1.23 ± 1.14</td>
<td>3.30 ± 2.61</td>
<td>1.00 ± 0.571</td>
</tr>
<tr>
<td>4 weeks after treatment (III)</td>
<td>3.23 ± 1.66</td>
<td>16.15 ± 8.39</td>
<td>2.50 ± 0.51</td>
</tr>
<tr>
<td>P value (ANOVA test)</td>
<td>†P &lt; 0.001 (I–II and II–III)</td>
<td>†P &lt; 0.001 (I–II)</td>
<td>†P &lt; 0.001 (I–II and II–III)</td>
</tr>
<tr>
<td></td>
<td>‡P &lt; 0.01 (II–III)</td>
<td>‡P &lt; 0.01 (II–III)</td>
<td>‡P &lt; 0.01 (II–III)</td>
</tr>
</tbody>
</table>

NS: non significant.
The treatment efficacy of the prophylactic agents has to be assessed after 2 or 3 months, during which the patient must keep a headache diary [12,24]. In the present study the therapy period was continued for 12 weeks for evaluation of the efficacy of the both drugs.

Although the sample size of this study is rather small, both drugs showed efficacy in the prophylactic treatment of migraine. No significant differences were noted between treatments for any efficacy parameter. However, significantly more patients in the amitriptyline group had at least one adverse event. Most of the patients those failed to complete the study because of the side effects could not tolerate the AMT. Especially in those working in jobs demanding intense concentration the AMT induced sedation, hypersonmia and concentration deficit caused difficulties in toleration of the drug. Although within the therapeutically limits all patients received a relatively high dose of AMT and this may contribute for the high side effects noted. Nausea/vomiting were the most prominent side effect of VLF that caused failure to complete the study. To other patients with nausea/vomiting an anti-emetic (metoclopramide HCl 10 mg) was given for the first 3 days of the treatment and they reported significant benefit from this.

These results should support the efficacy and tolerability of venlafaxine in comparison with amniptryline for preventing migraine headache. As a result from this study it was concluded that VLF could be preferred for migraine prophylaxis in patients involved in intense daily activities at work.

But for a more conclusive statement there is a need for further studies involving larger group of patients.

6. Discussion

Prophylactic treatment of migraine is mainly intended to reduce the attack frequency, duration, and severity of migraine. The choice of the drug to start with depends on several considerations. One of them is the possible side effect of the prophylactic agent [12,13].

The efficacy of AMT has already been established by earlier clinical studies and appeared that significantly reduced the severity, frequency, and duration of headache attacks, but it caused severe side effects (especially drowsiness) in migraineurs [14–16]. AMT is still one of the most effective current migraine preventive agents [17]. Several studies of TCAs have pointed to their joint effect on 5-HT and NE as a major reason for their effectiveness [18,19]. This combination of 5-HT and NE reuptake inhibition has been provided a strong pain-relieving [19–21].

VLF chemically unrelated to the TCAs is a dual 5-HT-NE reuptake inhibitor [22]. VLF prevents headaches in much the same way as the AMTs but with a much more tolerable side effect profile [3].

In an open study intended to show the prophylactic value of venlafaxine in migraine, the author concluded that venlafaxine was an effective drug in prophylaxis of migraine patients [23]. The efficient dose was reported in that study for VLF was 37.5 mg per d. But in a retrospective study by Adelman et al. [3] it was reported that the efficient dose of VLF in migraine prophylaxis was 150 mg per day and extended release form being more effective. The dose of VLF used in the present study was also 150 mg per day and the XR form.


