Flunarizine as a Supplementary Medication in Refractory Childhood Epilepsy: A Double-Blind Crossover Study

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ABSTRACT: We report a double blinded cross-over study involving Flunarizine versus placebo in the treatment of refractory childhood epilepsy. The patients studied were between the ages of 2 and 18; and were having more than 4 seizures per month not responsive to regular anticonvulsant medications. Of the 34 patients treated, 8 had a 50% decrease in their seizures during the placebo phase, 5 had a 50% decrease during the Flunarizine phase, and 1 patient had a 50% increase in seizures while taking Flunarizine. The remaining 25 patients showed no change in seizure activity in either phase. Patients having partial seizures with secondary generalization tended to do better on Flunarizine than those with other seizure types. Monitoring serum Flunarizine levels showed no significant difference between patients having improved seizure control and those who were unimproved. No significant side effects were noted with this medication, nor were any significant drug interactions noted.

RESUME: La flunarizine comme médication adjuvante dans l'épilepsie réfractaire de l'enfance: un essai à double insu avec permutation

Nous rapportons une étude à double insu avec permutation de la Flunarizine versus un placebo dans le traitement de l'épilepsie réfractaire de l'enfance. Les patients étudiés étaient âgés de 2 à 18 ans et présentaient plus de 4 crises par mois ne répondant pas à la médication anticonvulsivante usuelle. Parmi les 34 patients traités, 8 ont vu leurs crises diminuer de 50% pendant la phase placebo, 5 ont eu une diminution de 50% des crises sous Flunarizine et 1 patient a eu une augmentation de 50% des crises sous Flunarizine. Les 25 autres patients n'ont manifesté aucun changement de l'activité épileptique pendant l'une ou l'autre phase. Les patients qui présentaient des crises partielles avec généralisation secondaire semblaient mieux se porter sous Flunarizine que ceux qui présentaient d'autres sortes de crises. La surveillance des taux sanguins de Flunarizine n'a pas montré de différence significative entre les patients qui ont éprouvé un meilleur contrôle des crises et ceux qui n'ont pas été améliorés. Aucun effet secondaire de la médication et aucune interaction médicamenteuse significative n'a été noté.


It has been proposed that the inward movement of calcium into cells plays a dominant role in neuronal hyperexcitability. If these fluxes could be reduced or prevented, then the control of seizures might be improved. This hypothetical role of calcium entry blockers has lead to a search for drugs that are particularly effective as calcium channel blockers in the central nervous system. Flunarizine, a long acting difluoro derivative of cinnarizine, has been postulated to be such a drug. In animal models it has shown anticonvulsant affects against pentylenetrazole, electro-shock, and allylglycerine-induced seizures as well as preventing amygdala kindling. The few reported open trials in humans have shown promise with regard to improvement in seizure control. The purpose of this paper is to present the findings of a double blind crossover study of Flunarizine versus placebo in the treatment of refractory childhood epilepsy.

METHODS

Patients chosen for this study had to be aged 2 to 18 years; have four or more seizures per month which had been refractory to the appropriate anti-convulsant medications for their seizure
From the data gathered in this study, for the dosage used, Flunarizine appeared to be a safe drug without major side effects. It could be used with other anticonvulsant drugs as an add-on medication without significant drug interaction occurring. Its role as an anticonvulsant medication in clinical practice remains unanswered. Initial open-ended trials showed a significant reduction in seizure frequency (i.e., greater than 50%) in a great number of patients given the drug. Binnie et al7 showed 16 out of 47 patients had such a response; Curatolo et al8 8/21 patients; Overweg et al10 18/77 patients; and Sorel9 10/20

**DISCUSSION**

No significant side effects were reported in any of the patients during the time they were taking Flunarizine as compared to the placebo phase for the same patient. Changes in serum levels of other anticonvulsant medications were not seen. No changes in EEG, complete blood count, platelets, differential, SGOT levels occurred at any time during this study.

For analysis, the seizures were divided into major and minor groups. The seizures were considered to be minor if there was no generalized tonic clonic component. Major seizures consisted of at least some generalized tonic clonic activity. Seizure frequency for each phase was calculated for each patient. A 50% or greater improvement of seizure frequency with Flunarizine in comparison to baseline period was considered to be a clinical success. Any patient who had to be removed from the study because of increased seizure frequency or side effects was considered a failure. The patients that withdrew from the study for other reasons, (for example, lack of compliance or transfer to another city or centre) were not included in the final analysis.

**RESULTS**

<table>
<thead>
<tr>
<th>Seizure types</th>
<th>Total Number</th>
<th>Number Nonresponders</th>
<th>Number Responders</th>
</tr>
</thead>
<tbody>
<tr>
<td>Partial</td>
<td>16</td>
<td>16 (100%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Partial with generalization</td>
<td>6</td>
<td>2 (33%)</td>
<td>4 (67%)</td>
</tr>
<tr>
<td>Generalized only</td>
<td>12</td>
<td>11 (92%)</td>
<td>1 (8%)</td>
</tr>
</tbody>
</table>

**Table 1: Various Seizure Types and Their Outcomes**
patients. The daily dosages of Flunarizine ranged from 10 to 25 mg per day, but serum Flunarizine levels of the responders were not reported. In the double-blind studies of this drug reported the results are not nearly as convincing. Using the same criteria for successful outcome as listed above, Overweg et al. reported 7 out of 30 patients (23%) had a successful outcome on Flunarizine; Froscher et al. had 4 out of 28 patients (28%). Daily dosage of Flunarizine in their studies was between 10-15 mg per day. Flunarizine serum levels were not readily available in these studies for comparison between patients with successful outcome and nonresponders.

Though the responses to Flunarizine reported in the literature have been generally better than our group, the numbers are not as striking as in the open trials. Daily dosages on Flunarizine received were similar in all studies. However, like our study, the duration of time the patient was taking the medicine was short in relationship to the reportedly long half-life of the drug. This means any changes in the daily dosages would take a significant time before being reflected in the drug’s steady state level. It is possible that optional drug serum and tissue concentrations had not been reached in our study. An open study with increased drug dosages and serum level correlation with seizure frequency change would be necessary to further study this possibility. It is possible that the other drugs the children were taking resulted in lower Flunarizine levels without significant changes in regular anticonvulsant drug levels being seen. Even though significant serum differences between responders and nonresponders were not seen in our study, the numbers are too small to draw definite conclusions in this regard.

From review of the type of patients studied in this and other trials, it is quite possible that patient selection played a pivotal role in determining outcome. In our study patients with partial seizures with secondary generalization tended to have better response than patients with either partial seizures or generalized seizures alone. Whether this is a bias of sampling or not cannot be answered from our study due to the small number. From reviewing the literature, it was difficult to ascertain which seizure types tended to respond to Flunarizine due to inadequate patient population definition. In order to answer this question a larger number of patients with a single seizure type would have to be studied. The phases for such a study would have to be significantly longer to account for the pharmacokinetic properties of the drug. The daily dosage of the drug might also have to be substantially increased.

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References