PROPRANOLOL vs FLUNARIZINE vs FLUNARIZINE PLUS
PROPRANOLOL IN MIGRAINE WITHOUT AURA PROPHYLAXIS

A DOUBLE-BLIND TRIAL

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ABSTRACT - Forty-five migraine without aura patients underwent a parallel double-blind trial aiming the comparison of the effects of propranolol 60 mg/day to flunarizine 10 mg/day and to propranolol 60 mg/day plus flunarizine 10 mg/day simultaneously. There were 3 groups, each one with 15 patients. After a 20-day-baseline period, each group received one kind of treatment during 120 days. Migraine index on propranolol was 23.4*, on flunarizine 18.7* and on both drugs 14.4*, mean frequency of attacks on propranolol was 1.26**, on flunarizine 1.2** and on both drugs 1.13** (*p<0.05, ** p < 0.01 compared to baseline) and global evaluation was reduced with all forms of treatment. It was not found statistical differences between groups, nevertheless there was a trend in the group using two drugs reaching lower values in migraine index, frequency of attacks and global evaluation. In individuals using flunarizine (alone or associated with propranolol) the therapeutic effect was largely maintained up to 45 days after drug withdrawal.

KEY WORDS: migraine trial, propranolol and migraine, flunarizine and migraine, migraine and polytherapy.

Ensalo duplo-cego comparando propranolol, flunarizina e flunarizina associada ao propranolol na profilaxia da migrânea sem aura

RESUMO - Quarenta e cinco pacientes com migrânea sem aura submeteram-se a ensaio paralelo e duplo-cego visando comparar os efeitos de propranolol (PPN), flunarizina (FNZ) e uso associado de propranolol mais flunarizina. Foram divididos em três grupos de 15 indivíduos. Após período preliminar de 20 dias sem a administração de qualquer droga, um grupo recebeu PPN 60 mg/dia, outro grupo FNZ 10 mg/dia, e o terceiro grupo PPN 60 mg/dia associado à FNZ 10 mg/dia. O tempo de tratamento foi 120 dias. O índice de dor no grupo sob PPN passou de 39,3 para 23,4 (p<0,05) no grupo sob FNZ de 33,7 para 18,7 (p<0,05) e no grupo recebendo ambas as drogas de 33,5 para 14,4 (p<0,05). Não houve diferenças entre os índices de dor dos três grupos após o tratamento. A frequência de crises no grupo sob PPN passou de 2,8 para 1,26 (p<0,01) no grupo sob FNZ de 2,6 para 1,2 (p<0,01) e no grupo recebendo ambas as drogas de 2,9 para 1,13 (p<0,01). Não houve diferenças entre as frequências de crises dos três grupos após o tratamento. Foram confirmadas as eficácia das drogas na profilaxia da migrânea sem aura. A associação das drogas não logrou benefício ulterior no que concerne à diminuição dos índices de dor ou da frequência de crises. Entretanto, na avaliação global por parte do paciente, os melhores resultados estavam entre os que usaram duas drogas. Nos grupos que usaram FNZ (isolada ou associada ao PPN), as melhoras alcançadas persistiram mesmo após 45 dias da retirada dos fármacos.

PALAVRAS CHAVE: migrânea, propranolol na migrânea, flunarizina na migrânea, migrânea e politerapia.

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Migraine is a chronic episodic disease. For a given individual, attack frequency varies throughout life. Sometimes, if migrainous headaches are recurring twice a month or more, a prophylactic treatment is required. There is a variety of medication usually employed in the migraine prophylaxis, a hint that none is entirely effective. Moreover, usually there are patients who do not respond to one or more prophylactic drugs. Besides, there are individual differences in the responsiveness to different prophylactic agents and even sometimes, an inability to sustain an initial good response to a particular agent. Such facts may be arguments for the concomitant use of two modalities of drugs in migraine prophylaxis.

Propranolol and flunarizine have proven to be useful tools in migraine prophylaxis. This trial aims the comparison of the efficacy of propranolol to flunarizine and to propranolol plus flunarizine in migraine prophylaxis.

**PATIENTS AND METHODS**

Outpatients of both sexes between 17 and 48 years old diagnosed as migraine without aura according to the criteria set forth by the International Headache Society, suffering for at least one year and having a frequency of 2 to 6 attacks a month during the last six months were eligible for inclusion in the study. Patients were recruited from the Outpatient Headache Clinic at the University Hospital of Ribeirão Preto School of Medicine, Brazil.

Excluded were patients with obesity, cardiovascular diseases, diabetes mellitus, past history of psychiatric disease and allergy. Patients with other types of headache or abusing of abortive agents for headache attacks were later excluded. Fertile women should be using a satisfactory method of contraception. Women on oral contraceptives were excluded.

Fifty-two patients entered the study. Seven did not complete the study for the following reasons: one got pregnant, one was seen to have major depression, two were abusing on analgesics and three lost the follow-up. These patients were not included, thus 45 (41 females and 4 males) did complete the trial.

The study was designed as a double-blind, parallel, controlled, randomized 185 days study. Patients gave informed consent and were informed they would use known prophylactic anti-migraine drugs.

Drugs were prepared at the University Hospital Pharmacy in solutions containing either propranolol 20 mg/ml, or flunarizine 3.3 mg/ml or yet propranolol 20 mg/ml plus flunarizine 3.3 mg/ml.

The daily dosage schedule for the treatments were 1ml of the solution t.i.d., thus there were 3 groups of 15 patients, one group using 60 mg/day of propranolol, one other using 10 mg/day of flunarizine and a third group using 60 mg/day of propranolol plus 10 mg/day of flunarizine. Each of the treatments were used by 15 individuals. Distributions for sex and age are seen in Table 1.

During the first interview a complete physical and neurological examination was carried out in every patient, and the result of this examination and the diagnostic history were considered in determining the patient's eligibility for the study.

If the patient was to be accepted in the study, his (her) weight was recorded, then he (she) was asked to rest during 15 minutes in supine decubitus; thereafter, blood pressure (BP) and heart rate (HR) were measured.

Patients were given a headache diary card and asked to note the intensity of pain on a 4-point scale: 1= mild, not interfering with usual activities; 2= moderate, disturbing usual activities; 3= intense, prohibits activities; 4= extremely intense, must go to bed.

During the first 20 days period (baseline) no prophylactic drug should be used. At the end of this period a drug was introduced, the headache diaries were checked, BP, HR and weight were recorded.

The drug was used for a 120-day period. Follow-up visits were carried out every 40 days (Fig1) after introducing the drug. After this period, drugs were withdrawn, and the patients were further followed-up for 45 days, when the study was considered to be completed.

Efficacy was assessed by comparing the 3 treatments with regard to migraine index (the sum of daily scores of headache), frequency of attacks, global evaluation (the patients were asked to classify their response to the treatment as poor, good, very good or excellent). Migraine index and attack frequency were calculated per 20 days.
Attack abortive agents were allowed if necessary. The amount of these agents taken by the patients were not recorded.

Statistical methods: the variable migraine indexes and attack frequency are non-continuous and with an unknown distribution. Non-parametric tests are proper in these situations. In this study both Kruskall-Walis and parametric tests were used, and it was seen that they led to similar results. Whenever comparisons were of data of a given group, Wilcoxon test was used. For the study of HR, BP and weight, Student t-test was used.

RESULTS

Migraine index: No differences were found between the 3 groups in the baseline period. Comparing the values from the last 20 days on drug period, no differences were found between the 3 groups either (Table 2).

For the 3 groups, the migraine index from the last 20 days on drugs period was significantly reduced from those of the baseline period, meaning that all treatments were effective (Table 3).

Table 1. Sex and age distributions of 45 migraine without aura patients completing the trial.

<table>
<thead>
<tr>
<th></th>
<th>males (n)</th>
<th>females (n)</th>
<th>mean age (years)</th>
</tr>
</thead>
<tbody>
<tr>
<td>propranolol</td>
<td>1</td>
<td>14</td>
<td>30.2</td>
</tr>
<tr>
<td>flunarizine</td>
<td>2</td>
<td>13</td>
<td>31.2</td>
</tr>
<tr>
<td>propranolol plus flunarizine</td>
<td>1</td>
<td>14</td>
<td>32.2</td>
</tr>
</tbody>
</table>

Table 2. Mean values of migraine index. Baseline and last 20 days on drug period.

<table>
<thead>
<tr>
<th></th>
<th>baseline</th>
<th>last 20 days on drug</th>
</tr>
</thead>
<tbody>
<tr>
<td>propranolol</td>
<td>39.3</td>
<td>23.4</td>
</tr>
<tr>
<td>flunarizine</td>
<td>33.7</td>
<td>18.7</td>
</tr>
<tr>
<td>propranolol plus flunarizine</td>
<td>33.5</td>
<td>14.4</td>
</tr>
</tbody>
</table>

Table 3. Mean values of migraine index throughout the study.

<table>
<thead>
<tr>
<th></th>
<th>21 to 40</th>
<th>41 to 60</th>
<th>61 to 80</th>
<th>81 to 100</th>
<th>101 to 120</th>
<th>121 to 140</th>
<th>165 to 185</th>
</tr>
</thead>
<tbody>
<tr>
<td>propranolol</td>
<td>31.3</td>
<td>28.3*</td>
<td>23.6**</td>
<td>23.2**</td>
<td>23.6**</td>
<td>23.4**</td>
<td>25.3**</td>
</tr>
<tr>
<td>flunarizine</td>
<td>28.3</td>
<td>25.1*</td>
<td>16.5**</td>
<td>09**</td>
<td>15.5**</td>
<td>18.7**</td>
<td>18.7**</td>
</tr>
<tr>
<td>propranolol plus flunarizine</td>
<td>27.3</td>
<td>25.7</td>
<td>15.1**</td>
<td>18.5**</td>
<td>13.5**</td>
<td>14.4**</td>
<td>18.7**</td>
</tr>
</tbody>
</table>

* p<0.05; **p<0.001. Compared to baseline.
The mean migraine index reached significant difference from baseline during the 21th- to-40th-day period in individuais on propranolol and in those on flunarizine, whereas those using both drugs the difference reached a significant level in the period from the 41th to the 60th day.

**Frequency of attacks:** No differences were found in the baseline period between the 3 groups. Comparing the values from 3 groups during the last 20 days on drugs period, no differences were found either (Table 4).

**Table 4. Mean frequency of migraine attacks per 20 days. Baseline and last 20 days on drug period.**

<table>
<thead>
<tr>
<th></th>
<th>baseline</th>
<th>last 20 days on drug</th>
<th>p (#)</th>
</tr>
</thead>
<tbody>
<tr>
<td>propranolol</td>
<td>2.8</td>
<td>1.26</td>
<td>**</td>
</tr>
<tr>
<td>flunarizine</td>
<td>2.6</td>
<td>1.2</td>
<td>**</td>
</tr>
<tr>
<td>propranolol plus flunarizine</td>
<td>2.9</td>
<td>1.13</td>
<td>**</td>
</tr>
<tr>
<td>p (##)</td>
<td>0.52</td>
<td>0.81</td>
<td></td>
</tr>
</tbody>
</table>

# Wilcoxon test; ## Kruskall-Walis test. ** p < 0.01

**Table 5. Global evaluation (percent values), at the drug withdrawal, and 45 days thereafter.**

<table>
<thead>
<tr>
<th></th>
<th>poor A</th>
<th>B</th>
<th>good A</th>
<th>B</th>
<th>very good A</th>
<th>B</th>
<th>excellent A</th>
<th>B</th>
</tr>
</thead>
<tbody>
<tr>
<td>propranolol</td>
<td>0</td>
<td>7</td>
<td>26</td>
<td>46</td>
<td>66</td>
<td>40</td>
<td>7</td>
<td>0</td>
</tr>
<tr>
<td>flunarizine</td>
<td>7</td>
<td>7</td>
<td>20</td>
<td>13</td>
<td>33</td>
<td>53</td>
<td>40</td>
<td>27</td>
</tr>
<tr>
<td>propranolol plus flunarizine</td>
<td>7</td>
<td>7</td>
<td>7</td>
<td>13</td>
<td>66</td>
<td>60</td>
<td>20</td>
<td>20</td>
</tr>
</tbody>
</table>

A, at the time of drug withdrawal; B, 45 days later.

The mean migraine index reached significant difference from baseline during the 21th- to-40th-day period in individuals on propranolol and in those on flunarizine, whereas those using both drugs the difference reached a significant level in the period from the 41th to the 60th day.

**Frequency of attacks:** No differences were found in the baseline period between the 3 groups. Comparing the values from 3 groups during the last 20 days on drugs period, no differences were found either (Table 4).

Table 4 also shows, that for all 3 groups, mean frequency of attacks during the period of the last 20 days on drug was significantly reduced if compared to the baseline period.

**Global evaluation:** By the time of drug withdrawal, the rate of “very good” or “excellent” was 86.6% for propranolol plus flunarizine, the groups on monotherapy these values amounted to 73.3%. 45 days after the drug withdrawal, rates of “very good” or “excellent” was 80% for groups on flunarizine, while for the group on propranolol the rate was 47% (Table 5).

**Weight (kg):** Mean weight in propranolol group was 60.6 in baseline and 60.3 after treatment (p=0.431), in flunarizine group such values were 62.8 and 64.1 (p=0.018) and in the group using both drugs, 60.3 and 60.8 (p=0.442).

**HR (beats per minute):** There has been significant decrease in individual using propranolol (from 80 to 72), and in those using propranolol plus flunarizine (from 77 to 72), whereas those using only flunarizine no difference was found.

**Systolic BP (Hg mm):** There has been significant decrease in individual using propranolol (from 132 to 121), and in those using propranolol plus flunarizine (from 127 to 116), whereas those using only flunarizine no difference was found (from 125 to 124).

**Side effects:** 2 patients on propranolol reported side effects. One reported a feeling of fear without a clear reason and the other one reported that he was feeling anxious. 3 patients on flunarizine
reported side effects. One complained of somnolence and anxiety, one somnolence and increasing appetite and another one, tiredness. On both drugs, 4 patients reported side effects. Two reported anxiety, one somnolence and one tiredness. No patient dropped out due to side effects.

**DISCUSSION**

Whether migraine without aura and migraine with aura should or should not be considered identical conditions is a controversial issue\(^{10,16}\). For the sake of homogeneity, we dealt only with migraine without aura patients.

The non-cross-over design, although less powerful than the cross-over design\(^5\), has the advantage of avoiding the carryover effect, a feature of great importance in migraine prophylaxis trials, as it is seen in Table 3.

Prusinski\(^11\) argues that in the pathophysiology of a migraine attack there could be several parallel chains of events, then if we use drugs acting on different chains, probably we could get better results. In spite of the perfect mechanisms of propranolol in migraine prophylaxis are not perfectly known\(^9\), but it probably differs from the mechanism of flunarizine\(^14,15\). Moreover studies on polytherapy for migraine prophylaxis are scarcely seen.

Having all these facts in mind, we have endeavoured to perform this trial.

Migraine index and attack frequency: No differences were found between the 3 groups in the baseline period as for both parameters. This fact suggests that there has been homogeneity between the three groups.

Comparing the values from the last 20 days on drug period, differences were found between the 3 groups neither for migraine index, nor for mean frequency of attacks, suggesting that the 3 treatments had similar efficacy.

Data from Table 3 shows that it takes about two months before the migraine index reaches a "stable level". So, we should wait for at least two months before giving up from one of such a kind of treatment.

For the 3 groups the mean migraine index from the last 20 days on drugs period was significantly reduced from those of the baseline period, meaning that all treatments were effective. The percentage decrease in migraine index for the propranolol group was 41.5% (from 39.3 to 23.4), for the flunarizine group was 44.2% (from 33.7 to 18.7) and for the two-drugs group was 57% (from 33.5 to 14.4). So, there is a trend of the migraine index to be reduced to a greater extent in patients using two drugs.

Table 4 shows that for all 3 groups, mean frequency of attacks during the period of the last 20 days on drug was significantly reduced if compared to the baseline period. The percentage decrease in the frequency of migraine attacks for propranolol group was 55% (from 2.8 to 1.26), for the flunarizine group was 54% (from 2.6 to 1.2) and for two-drugs group was 61% (from 2.9 to 1.13). Here too, there is a trend towards a greater extent of decrease in patients using two drugs.

Global evaluation: at the time of drug withdrawal, there was a trend in propranolol plus flunarizine group fare better than the monotherapy groups.

Fourty-five days after drug withdrawal, in the groups on flunarizine, the therapeutic effect was largely maintained, whereas in the group using only propranolol there was a decrease in the percent of individuals rating the treatment as "very good" or "excellent".

When to discharge a migraineur is an unanswered question. Perhaps it is worth treating the patient for 4 months and then try to withdraw the drug, provided that for many patients the improvement will be maintained.
Flunarizine led to an increase in weight, a feature that we must have in mind when prescribing this drug, a fact that has already been reported. On the other hand, flunarizine did not alter either systolic BP or HR, suggesting that this kind of calcium-channel blocker lacks cardiovascular effects. Propranolol led to a decrease in both HR and systolic BP.

As for PPN, there are reports suggesting to begin the treatments with small dosages, in order to decrease the incidence of adverse effects. The dosage used in the current trial may be seen as a small one, therefore the small amount of these effects were predictable.

Parkinsonism, akathisia and major depression are serious adverse effects related to to FNZ use. Indeed, the package insert warns about its use in elderly and in women with previous history of depression.

The percentage in side effects (somnolence, tiredness, anxiety) found in the current trial was minor in all groups probably due to the strict eligibility criteria.

In summary, there were trends (migraine index, attack frequency, global evaluation) in patients on polytherapy to obtain better results than patients on monotherapy. This is an important fact. It is suggested that wider, possibly multicentric studies should be carried out in order to have this question completely resolved.

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REFERENCES