Olanzapine as an add-on treatment in migraine status: A randomized double-blind, placebo-controlled, pilot study

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ABSTRACT – Background and Objectives: The authors assessed the effectiveness of olanzapine as an adjunctive treatment in migraine status.

Methods: Randomized, double-blind, placebo-controlled study. Subjects consecutively admitted to a day program of tertiary referral (97% women; age: 35.8 ± 11.8 yrs.) were assigned to olanzapine (n = 14, 5-10 mg/day) or placebo (n = 17), added to the standard neurological treatment during 4 days. Primary measures were the change in pain and the return to regular daily activities. Secondary and safety measures were the magnitude of sedation, constipation and glucose level changes.

Results: No significant differences were observed in the overall analysis of the primary measures. However, change in pain significantly correlated with age in the olanzapine group (p = 0.03). In the ≥ 40 year-old group, olanzapine (n = 5) displayed a significantly higher reduction in pain than placebo (n = 4) at days 1 (p = 0.048) and 3 (p = 0.045). No significant differences were observed in the change of serum glucose levels.

Conclusions: Olanzapine was well tolerated and sedation was welcomed by most subjects. The positive effect in subjects aged ≥ 40 years awaits replication.
Introduction

The management of migraine attacks in neurological and psychiatric patients is a formidable challenge. Therapy consists of analgesics such as aspirin, acetaminophen, opioids, steroidal and nonsteroidal anti-inflammatory drugs, and migraine-specific agents, such as ergotamine, dihydroergotamine and the triptans. Very often, a washout, drug-free period is necessary to recover drug responsiveness, with high intra- and inter-individual variability.

There is a long off-label, anecdotic tradition in using antipsychotics in the treatment of migraine attacks. Typical antipsychotics are limited by the risk of unwanted neurological effects. Atypical antipsychotics display a favorable profile in open labeled studies and are promising agents. Olanzapine has easy dosage, analgesic, sedative and ansiolytic properties which are related to its effects on serotonergic, dopaminergic and histaminergic neurotransmission. No randomized, placebo-controlled clinical trial with olanzapine has been published.

Methods

This add-on, randomized, double-blind, placebo-controlled study was conducted from January 1st to December 31st, 2010 at the Migraine Clinic for tertiary referral at Los Andes University Hospital, Mérida, Venezuela. It was approved by the local Ethic Committee, and participants signed an informed consent for voluntary participation.

Procedure

Consecutively admitted patients aged ≥ 18 years consulting after failed non-standardized pharmacological treatment for a migraine attack lasting at least three consecutive days and diagnosed of Status Migrainosus were randomized either to olanzapine (Zyprexa Zydis®, in 5-mg tablets) or identical placebo pills during 4 days. The neurologist in-charge used the drug treatment considered as the best for a particular patient.

Only the study coordinator (TB) knew the treatment allocation (olanzapine or placebo) but he did not conduct any clinical evaluation. Randomization was achieved by alternating treatment distribution every first, second or third consulting subject in the initial, middle and last phases of the study respectively.

Olanzapine (5-10 mg, a dose range expected to induce mild sedation) or placebo were administered b.i.d. Each subject was contacted daily by phone at 17:00 hr by J.M. who administered the scales and by the study coordinator who adjusted the dose according to the sedation level.

At day 0 (figure 1), we assessed in the morning the migraine attack duration, incapacity (number of days without working or attending school) and the administered pharmacological treatment.

The primary measure was change in pain assessed with an analogical visual scale (AVS) where “0” was no pain and “10” was unbearable pain. Daily individual scores were obtained by subtracting punctuation at days 1 to 4 from basal values at day 0.

Secondary measures with unstandardized scales were:

a) Return to normal life and constipation, with 4 items: normal, intermediate, barely and none.

b) Sedation, with “0” as no sedation and “10” as maximal in a VAS.

c) Since olanzapine tends to induce hyperglycemia, serum glucose levels were assessed at day 0 and 5.
Change in pain was analyzed with an ANOVA for repeated measures, with treatment (olanzapine or placebo) and age (under or over 40 yrs.) as between subject factors. Effect size was calculated according to Cohen. Glucose level change and sedation were analyzed with the two-tailed \( t \) test for unrelated samples. Return to normal life and constipation were analyzed with the Mann-Whitney U test. Correlations were conducted with the Spearman coefficient. Results were considered significant when \( p < 0.05 \).
Results

A Last Observation Carried Forward protocol was used, but it was only applied in one subject. The study was completed by 14 olanzapine subjects (age: 35.7 ± 11.8 yrs; 13 females, 1 male) and 17 placebo subjects (age: 35.2 ± 8.3 yrs; 17 women). Seven patients (23%) had migraine with aura and 24 (77%) without aura (p = 0.15).

In the overall analysis no between-group significant differences were observed in pain change: $f (1, 26) = 1.9, p = 0.18$. However, a positive association was observed between pain change and age only in the olanzapine group: day 1: bivariate correlation analysis: ($r \ [14] = 0.58, p = 0.031$); day 3 ($r = 0.68, p = 0.008$). A significant interaction was observed between age and treatment $f (1, 26) = 6.9, p = 0.01$. Specifically, pain reduction was significantly higher after olanzapine administration in subjects aged $\geq 40$ yrs (Table 1), with a medium-large effect size (0.6-0.7). Baseline pain intensity and duration, degree of disability and basal glycaemia did not differ between the treatments in the $\geq 40$ yr. subjects ($p > 0.05$). Demographics and pharmacological treatments in this group are described in Table 2; olanzapine-treated patients were older: $53.8 \pm 8.1$ vs. $44.8 \pm 2.5$, $t \ (7) = 2.1, p = 0.07$.

No significant differences were observed in constipation intensity and return to normal life. However, sedation was more pronounced at day 1 after olanzapine ($p = 0.023$) and at day 4 after placebo ($p = 0.025$). No significant differences were observed in glucose change between the groups ($p = 0.7$).

When the single male subject was excluded, the results were identical (data not shown).

Table 1
Change in pain severity

<table>
<thead>
<tr>
<th></th>
<th>Olanzapine (n = 9)</th>
<th>Placebo (n = 13)</th>
<th>95% CI of the difference</th>
<th>t (p)</th>
<th>Cohen’s effect size</th>
</tr>
</thead>
<tbody>
<tr>
<td>Day 1</td>
<td>4.4 ± 3.3</td>
<td>4.5 ± 4.0</td>
<td>–</td>
<td>NS</td>
<td>–</td>
</tr>
<tr>
<td>Day 2</td>
<td>4.8 ± 3.9</td>
<td>7.0 ± 2.3</td>
<td>–</td>
<td>NS</td>
<td>–</td>
</tr>
<tr>
<td>Day 3</td>
<td>4.0 ± 3.5</td>
<td>6.3 ± 4.5</td>
<td>–</td>
<td>NS</td>
<td>–</td>
</tr>
<tr>
<td>Day 4</td>
<td>5.9 ± 3.6</td>
<td>6.3 ± 3.4</td>
<td>–</td>
<td>NS</td>
<td>–</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>Olanzapine (n = 5)</th>
<th>Placebo (n = 4)</th>
<th>95% CI of the difference</th>
<th>t (p)</th>
<th>Cohen’s effect size</th>
</tr>
</thead>
<tbody>
<tr>
<td>Day 1</td>
<td>8.6 ± 2.1</td>
<td>3.8 ± 2.8</td>
<td>0.96-8.7</td>
<td>2.9 (0.02)</td>
<td>0.7</td>
</tr>
<tr>
<td>Day 2</td>
<td>8.4 ± 1.1</td>
<td>4.0 ± 3.7</td>
<td>0.28-8.5</td>
<td>2.5 (0.03)</td>
<td>0.6</td>
</tr>
<tr>
<td>Day 3</td>
<td>9.0 ± 1.2</td>
<td>4.0 ± 3.6</td>
<td>1.0-8.9</td>
<td>2.9 (0.02)</td>
<td>0.7</td>
</tr>
<tr>
<td>Day 4</td>
<td>7.2 ± 4.2</td>
<td>4.5 ± 3.3</td>
<td>–</td>
<td>NS</td>
<td>–</td>
</tr>
</tbody>
</table>

Values represent mean ± standard deviation.
Daily individual scores were obtained by subtracting scores at days 1 to 4 from basal values at day 0 (higher value mean more pain reduction).
CI: 95% confidence interval.
$t = $ statistics of the student $t$ test and associated probability.
Discussion

We report a positive effect of olanzapine on pain management in subjects older than 40 years and a safe profile. Sedation was considered as positive by most subjects, and glucose change was similar in both groups. The discussion will focus on women who constituted most of our sample.

The influence of age may be related to the hormonal environment of perimenopause and menopause. Low serum estradiol levels associated to the luteal phase and perimenopause may be involved in migraine aggravation. Normal or elevated estradiol levels are observed during olanzapine administration, but these effects are unlikely to be involved, since the estradiol level change occurred after prolonged treatment. Besides, olanzapine is devoid of effects on 5HT1B and 5HT1D receptors which are critical for the antimigraine effects. Therefore, the beneficial effects observed here may be related to antihistaminic effects or serotonin and dopamine transmission modulation.

Since the ≥ 40 year old group comprised only 5 women, our findings must be considered as preliminary. Given the potential efficacy and safety of olanzapine in migraine attacks, this study should be replicated and extended.

Acknowledgments


Conflicts of interests: Neither the sponsor agency nor Eli Lilly participated in the design, data analysis or manuscript preparation.

References


Table 2
Demographics and pharmacological treatment administered by the neurologist in subjects above 40 years

<table>
<thead>
<tr>
<th>Add-on treatment</th>
<th>Age (yrs.)</th>
<th>Neurological treatment during the study</th>
<th>Average change in pain (a)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Olanzapine</td>
<td>42</td>
<td>Acemetacin, diclofenac</td>
<td>7.0 ± 4.8</td>
</tr>
<tr>
<td>Olanzapine</td>
<td>50</td>
<td>Lornoxicam</td>
<td>8.3 ± 1.5</td>
</tr>
<tr>
<td>Olanzapine</td>
<td>55</td>
<td>Ketoprofen, dexametasone</td>
<td>7.3 ± 1.7</td>
</tr>
<tr>
<td>Olanzapine</td>
<td>59</td>
<td>Ketoprofen</td>
<td>9.0 ± 0.0</td>
</tr>
<tr>
<td>Olanzapine</td>
<td>63</td>
<td>Ketoprofen, dexametasone, ibuprofen</td>
<td>10.0 ± 0.0</td>
</tr>
<tr>
<td>Placebo</td>
<td>42</td>
<td>Dexametasone, ketoprofen, lornoxicam</td>
<td>3.3 ± 1.0</td>
</tr>
<tr>
<td>Placebo</td>
<td>44</td>
<td>Dexametasone, amitriptyline</td>
<td>7.5 ± 3.0</td>
</tr>
<tr>
<td>Placebo</td>
<td>45</td>
<td>Tramadol, ibuprofen</td>
<td>1.3 ± 1.0</td>
</tr>
<tr>
<td>Placebo</td>
<td>48</td>
<td>Ketoprofen, dexametasone</td>
<td>4.3 ± 2.9</td>
</tr>
</tbody>
</table>

(a) Values represent the average ± standard deviation of 4 days of treatment.


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