Brief Communication

Olanzapine in the Treatment of Refractory Migraine and Chronic Daily Headache

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Background.—Olanzapine, a thienobenzodiazepine, is a new "atypical" antipsychotic drug. Olanzapine's pharmacologic properties suggest it would be effective for headaches, and its propensity for inducing acute extrapyramidal reactions or tardive dyskinesia is relatively low. We thus decided to assess the value of olanzapine in the treatment of chronic refractory headache.

Methods.—We reviewed the records of 50 patients with refractory headache who were treated with olanzapine for at least 3 months. All previously had failed treatment with at least four preventative medications. The daily dose of olanzapine varied from 2.5 to 35 mg; most patients (n = 19) received 5 mg or 10 mg (n = 17) a day.

Results.—Treatment resulted in a statistically significant decrease in headache days relative to baseline, from 27.5 ± 4.9 before treatment to 21.1 ± 10.7 after treatment ($P < .001$, Student *t* test). The difference in headache severity (0 to 10 scale) before treatment (8.7 ± 1.6) and after treatment (2.2 ± 2.1) was also statistically significant ($P < .001$).

Conclusion.—Olanzapine may be effective for patients with refractory headache, including those who have failed a number of other prophylactic agents. Olanzapine should receive particular consideration for patients with refractory headache who have mania, bipolar disorder, or psychotic depression or whose headaches previously responded to other neuroleptic medications.

Key words: olanzapine, chronic refractory headache, atypical neuroleptics

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Olanzapine, a thienobenzodiazepine, is a new "atypical" antipsychotic drug (Figure). It is a selective 5-$HT_{2A,2B,2C}$ (serotonin), dopamine D_{1-4}, muscarinic M_{1-5}, and α_1-adrenergic receptor antagonist with high binding affinity. "Atypical" antipsychotic drugs impose less risk of tardive dyskinesia and acute extrapyramidal reactions (especially dystonias) than do "typical" antipsychotic agents such as haloperidol.[1]

Olanzapine has been used to treat schizophrenia, psychotic depression, mania, affective mood disorders, substance abuse disorders, dementia in the elderly, and behavioral problems in patients with mental retardation or developmental delay.[2] One placebo-controlled, double-blind trial showed that olanzapine had superior efficacy for the symptoms of acute mania.[3] In an open-label trial, olanzapine was also effective for Tourette disorder.[4]

Olanzapine has exhibited an antinociceptive effect in the mouse tail flick pain model, and its analgesic effect is believed to be mediated by agonistic activity at α_2-adrenoreceptors.[5]

In addition to serotoninergic dysfunction, migraineurs may have hyperfunction of the dopaminergic system.[6] Individuals with migraine with aura have an increased frequency of the D_2 dopamine receptor allele (DRD2 *Nco*I C allele), and migraineurs demonstrate a higher incidence of dopaminergic symptoms (nausea, vomiting, drowsiness, yawning, dizziness, sweat-

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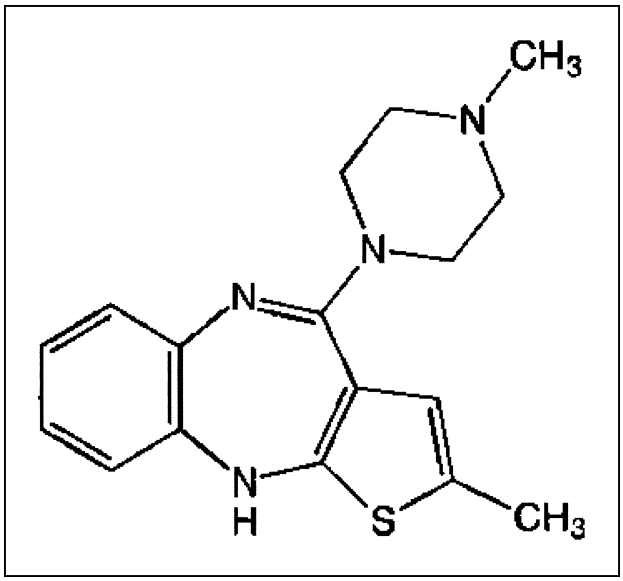

Olanzapine's chemical structure. Reprinted with permission from Neuropsychopharmacology.[18]

ing) than normal subjects after apomorphine administration.[7,8] Many dopamine antagonists are used for acute migraine therapy, including droperidol, chlorpromazine, prochlorperazine, metoclopramide, domperidone, and haloperidol.[9-14] The preventative effect of flunarizine may come from its antidopaminergic properties.[15] The antidopaminergic properties of olanzapine suggest that it may be an effective agent in migraine therapy.

Methysergide, a serotonin antagonist at the 5-$HT_{2B/C}$ receptors, is an effective migraine preventative treatment, whereas metachlorophenylpiperazine, a nonselective 5-HT_2 agonist, induces migraine in susceptible individuals.[16,17] Olanzapine's serotonin antagonism also could contribute to its utility as a migraine preventative.

Since olanzapine's pharmacologic properties suggest it may be effective for headache treatment and since its propensity for inducing acute extrapyramidal reactions or tardive dyskinesia is relatively low, we decided to assess the value of olanzapine in the preventative treatment of chronic refractory headache.

METHODS

We retrospectively reviewed the charts of patients who were treated with olanzapine at the Jefferson Headache Center and interviewed a portion of those patients by telephone. We analyzed data from 50 patients with refractory chronic daily headache (CDH) who were treated with olanzapine for at least 3 months. All patients previously had failed at least four preventative medications, often in combination, at adequate doses and for an adequate duration. The daily dose of olanzapine varied from 2.5 to 35 mg; most patients received 5 (n = 19) or 10 (n = 17) mg a day.

As outcomes measures, we analyzed the self-reported patient satisfaction questionnaires, adverse events profiles, number of days with headache, intensity of headache, and the number of patients with daily headaches who converted to episodic headache (less than 15 days of headache a month). Patient sat-

Table 1.—Pretreatment Headache Characteristics*

Feature	Patient Group (n = 50)
Baseline intensity†	3 (0-7)
Maximum intensity†	9 (5-10)
Acute medication overuse	49 (98)
Prodrome	29 (58)
Aura	18 (36)
Triggers	
Menses (n = 40)	23 (57)
Stress	37 (74)

*Values are number (percentage) unless otherwise indicated.
†Intensity measured on a scale of 0 to 10 (median).

Table 2.—Adverse Events*

Adverse Event	Patient Group (n = 50)
Weight gain	19 (38)
Somnolence	9 (18)
Nausea	2 (4)
Dystonia	0
Agitation	1 (2)
Dizziness	4 (8)
Constipation	3 (6)
Akathesia	1 (2)
Muscle aches	2 (4)
Tremor	3 (6)
Edema	5 (10)
None	13 (26)

*Values are number (percentage).

isfaction was categorized as: "better," if there had been significant headache improvement; "same," if significant improvement had not occurred; or "worse," if there had been worsening of the headaches.

RESULTS

Forty patients were women, and 10 were men. Duration of headache history ranged from 2 to 53 years (mean, 26 years), and duration of CDH ranged from 3 months to 25 years (mean, 5.5 years). Thirty patients (60%) had chronic (transformed) migraine, 12 (24%) had chronic posttraumatic headache, 4 (8%) had new daily persistent headache, and 4 (8%) had chronic tension-type headache. Chronic daily headache subtypes and acute medication overuse were defined according to the criteria of Silberstein et al.[19] Forty-nine patients (98%) were overusing acute medication. Eighteen patients (36%) had a history of suicidal ideation, and 12 (24%) had a history of psychiatric hospitalization. Beck Depression Inventory scores ranged from 1 to 38 (median, 20). Headache characteristics are listed in Table 1.

There was a statistically significant decrease in headache days, from 27.5 ± 4.9 before treatment to 21.1 ± 10.7 after treatment ($P < .001$, Student t test). The difference in headache severity (0 to 10 scale) before treatment (8.7 ± 1.6) versus after treatment (2.2 ± 2.1) was also statistically significant ($P < .001$).

Eighteen patients (36%) converted to episodic headache on olanzapine. Of the 50 patients in total, 37 (74%) reported that their headache syndrome was better, 12 (24%) reported that it was the same, and 1 reported that it was worse. Satisfaction with treatment was "good to excellent" in 18 patients (36%), "fair" in 12 (24%), and "poor" in 8 (16%).

Adverse events were rated as "very bothersome" by 12 patients (24%). Weight gain and somnolence were the most common adverse events (Table 2).

COMMENTS

This is the first report of olanzapine's effectiveness for headache prevention. The role of the dopaminergic function in the pathophysiology of migraine has long been recognized, and olanzapine is not the only preventative medication that targets the dopaminergic system.[20] Flunarizine's mechanism of action in suppressing headache is not completely understood, but its pharmacologic effects include dopamine antagonism as well as calcium channel blockade. Flunarizine is not available in the United States or many other countries, and it may cause parkinsonism and depression.

Our study was retrospective and unblinded. Placebo-controlled trials will be required to confirm our findings. Even so, as our subjects were all treatment-refractory and previously had failed four or more other preventative medications in adequate doses, we doubt that placebo effect significantly influenced our results.

Olanzapine may be considered for headache prevention in patients refractory to better established agents, and particularly in those with comorbid mania, bipolar disorder, psychotic depression, or Tourette disorder. Although this currently is speculative, olanzapine may be particularly effective as a preventative treatment for patients who previously have responded well to neuroleptics used for acute headache treatment.

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