Effectiveness of Intranasal Zolmitriptan in Acute Cluster Headache

A Randomized, Placebo-Controlled, Double-blind Crossover Study

Elizabeth Cittadini, MD; Arne May, MD; Andreas Straube, MD; Stefan Evers, MD; Gennaro Bussone, MD; Peter J. Goadsby, MD, PhD

Background: Cluster headache is a form of primary headache in which attacks are rapid in onset with very severe pain. The mainstays of acute therapy are inhaled oxygen and sumatriptan succinate injection.

Objective: To evaluate zolmitriptan nasal spray in the acute treatment of cluster headache.

Methods: Ninety-two patients, aged 40±10 years (mean±SD) (80 men and 12 women), with Internation Headache Society–defined cluster headache were randomized into a placebo-controlled, double-blind crossover study. Patients treated 3 headache attacks using placebo for 1 attack, 5 mg of zolmitriptan nasal spray (ZNS5) for 1 attack, and 10 mg of zolmitriptan nasal spray for 1 attack. The primary end point was headache relief at 30 minutes, defined as reduction from moderate, severe, or very severe pain to no or mild pain. The study was approved by the appropriate ethics committees.

Results: Sixty-nine patients were available for an intention-to-treat analysis. The 30-minute headache relief rates were placebo, 21%; ZNS5, 40%; and ZNS10, 62%. Modeling the response as a binary outcome, the Wald test was significant for the overall regression (χ²=29.4; P<.001), with both ZNS5 and ZNS10 giving significant effects against placebo. Headache relief rates for patients with episodic cluster headache were 30% for placebo, 47% for ZNS5, and 80% for ZNS10, while corresponding rates for patients with chronic cluster headache were 14%, 28%, and 36%, respectively. Zolmitriptan was also well tolerated.

Conclusion: Five-milligram and 10-mg doses of zolmitriptan intranasal spray are effective within 30 minutes and well tolerated in the treatment of acute cluster headache.

Trial Registration: controlled-trials.com Identifier ISCRN27362692.

Arch Neurol. 2006;63:1537-1542

Author Affiliations: Institute of Neurology, The National Hospital for Neurology and Neurosurgery, Queen Square, London, England (Drs Cittadini and Goadsby); Department of Neurology, University of Hamburg, Hamburg, Germany (Dr May); Department of Neurology, University of Munich, Munich, Germany (Dr Straube); Department of Neurology, University of Munster, Munster, Germany (Dr Evers); Department of Neurology, "C. Besta" Neurological Institute, Milan, Italy (Dr Bussone).

CME course available at www.archneur.com

to work swiftly. The best placebo-controlled evidence for acute-CH treatment is for sumatriptan succinate by intranasal and subcutaneous administration. Limited evidence exists to treat acute attacks of CH with oxygen inhalation, intranasal lidocaine, and intranasal dihydroergotamine mesylate. Intranasal dihydroergotamine was reported to be better than placebo, but the time to onset of a response was not defined and the study used pre—International Headache Society diagnostic criteria. Inhalation of oxygen is effective and safe but may be impractical for some patients. Oral zolmitriptan has been demonstrated to be effective in acute episodic CH, albeit at higher doses than normally used in migraine. There remains a considerable unmet need in CH for therapies with a clear evidence base.

Zolmitriptan is a serotonin, 5-HT₁B/1D, receptor agonist that has actions at the peripheral and central ends of the trigeminovascular system. Zolmitriptan is an effective, well-tolerated treatment of acute migraine, with oral and intranasal formulations. The newly developed intranasal formulation has an onset of action that is earlier than the oral formulation, and there is clear evidence for intranasal absorption. A comparison of the pharmacokinetics of intranasal zolmitriptan with in-
transnasal sumatriptan suggests that intranasal zolmitriptan should be effective in acute CH. A preliminary, single-blind study has suggested zolmitriptan by the intranasal route may be effective in acute CH.

In the present study, we aimed to investigate whether intranasal zolmitriptan is superior to placebo in the acute treatment of CH attacks lasting at least 45 minutes using the primary outcome measure of headache response at 30 minutes. We wished to test 2 doses, 5 and 10 mg, and take advantage of the clinical presentation of CH with reproducible attacks over short periods, and bearing in mind its relatively rarity, to conduct a crossover study. We have presented the results in preliminary form.

METHODS

PATIENTS

Patients, men or women between 18 and 65 years of age, with an established diagnosis of CH according to the International Headache Society criteria, were recruited by 5 study centers (3 in Germany, 1 in Italy, and 1 in the United Kingdom). Patients were required to have CH attacks lasting at least 45 minutes when untreated. Patients should have used zolmitriptan in the past; zolmitriptan-naive patients were included if, in the opinion of the investigator, it was safe to do so. We excluded patients unsuitable for zolmitriptan tablet or nasal spray use in the country in which the study was being conducted according to the drug label or regulatory approved use in that country. We also excluded patients with more than 2 risk factors for cardiovascular disease, patients using regular ergotamine derivatives or analgesics, and patients with an ears, nose, and throat disorder that would preclude the use of intranasal zolmitriptan.

DESIGN

This was a randomized, double-blind, 3-attack crossover study of 5-mg or 10-mg zolmitriptan nasal spray and matching placebo. Cluster headache is relatively uncommon, so a crossover study facilitated recruitment as well as provided homogeneity for comparisons between treatments and placebo. The disadvantage of a carryover effect in a crossover design is minimal because the treatment has a short half-life relative to the interval we specified and the interaction is easily modeled in the analysis used. Patients were asked to treat 3 attacks, at least 24 hours apart, with study medicine. They were instructed to grade their pain on an ordinal categorical (5-point) scale of none, mild, moderate, severe, or very severe and to apply 1 study dose in the contralateral nostril when the headache had at least reached a moderate severity. Subsequent assessments were at 5, 10, 15, and 30 minutes. Escape medication was allowed at 30 minutes postdose, using oxygen or an analgesic but not a triptan or ergotamine derivative. The sponsor provided the study medication but, consistent with recent guidelines, had no influence on or involvement in the conduct of the study, the analysis, or publication of the results. As per our protocol, the sponsor was provided with a copy of the manuscript.

Efficacy Assessments

The primary protocol-specified outcome measure was headache response at 30 minutes, defined as a reduction in headache from moderate, severe, or very severe to no or mild pain. Secondary outcome measures included the percentages of patients headache free at 30 minutes and rate of relief of associated symptoms. Associated symptoms, such as vomiting, nausea, photophobia, phonophobia, lacrimation, nasal congestion, other autonomic features, and restlessness and agitation, were recorded immediately prior to treatment and at 30 minutes. Finally, adverse events were assessed by comparison of tolerability of nasal zolmitriptan to placebo.

STATISTICAL ANALYSIS

Based on the effect of sumatriptan nasal spray and our clinical experience of what would be a meaningful effect, we planned for a treatment difference between placebo and active treatment of 20%. We estimated that we would require 100 patients to have 65 evaluable for at least 1 attack with a power of 80% (1-β) and an α of 5% for the primary end point. Initial power was calculated with ties to be discarded as if to use the McNemar test. The outcome data were to be treated as binary. The ties were estimated from the results of a crossover study of subcutaneous sumatriptan vs placebo and allowed for some difference in therapeutic responses seen between sumatriptan injections and the nasal spray in migraine. Our planned analysis specifically allowed for the dichotomous outcome and used a generalized linear model and logistic regression approach to determine the effect of active treatment and treatment order, sex, site, and CH type (ie, episodic vs chronic CH). Considering that the 3 attacks are not strictly independent because the patients remain the same, a multilevel multivariate analysis was performed using the software developed by the Multilevel Project, MLwiN. To avoid multiple comparisons, we did not test the effect of study treatment on associated symptoms, preferring to report the numerical outcome.

APPROVAL

The appropriate institutional review boards or ethics committees of the participating sites reviewed and approved the protocol prior to the study commencing. All patients gave informed consent before entering the study. The study protocol was initially written by 1 of us (P.J.G.). The pharmaceutical company provided the study medication but, consistent with recent guidelines, had no influence on or involvement in the conduct of the study, the analysis, or publication of the results. As per our protocol, the sponsor was provided with a copy of the manuscript.

RESULTS

A total of 92 patients was recruited, 80 men and 12 women, with a mean±SD age of 40±10 years, between June 12, 2003, and May 24, 2005.

DISPOSITION OF PATIENTS

Of the 92 patients recruited, 17 came to the end of the bout, which is to say their attacks stopped before completing the study; 4 of these treated the first attack, and 4 treated the first and second attacks. Eight patients withdrew before treating any attacks. Three patients withdrew after treating the first attack, 2 of these without a clear reason and 1 because of an adverse effect. Six patients were completely lost to follow-up and whether they treated their attacks was not clear. We have regarded them as though they did not treat any attacks. The average duration of an untreated attack was 45 minutes. Use of es-
Cape medication before 30 minutes after treatment was reported in 1 attack, which was scored as a treatment failure (Figure 1).

CLINICAL FEATURES OF STUDY COHORT

The mean ± SD duration of CH history was 12 ± 7 years. Fifty-nine patients had episodic CH and 33 had chronic CH. The mean ± SD bout length of the patients with episodic CH was 8 ± 6 weeks. The mean ± SD attack duration at recruitment was reported by the patients to be 95 ± 43 minutes. Sixty-seven patients had previously used subcutaneous sumatriptan, 40 patients had used intranasal sumatriptan, 18 patients had used oral zolmitriptan, and 72 patients had used oxygen (Table 1).

Efficacy

The primary end point of the study was the combined (attacks 1, 2, and 3) headache response rate at 30 minutes compared with placebo. The Wald test was significant for the overall regression ($\chi^2$=29.4; $P<.001$), with the treatment term and CH type being significantly different from zero. There was no significant effect of treatment order or patient sex.

Efficacy Results for the Cohort as a Whole

In total, 65 attacks were treated with 5 mg of zolmitriptan nasal spray; 63 attacks, with 10 mg of zolmitriptan nasal spray; and 61 attacks, with placebo. In the attacks treated with 5 mg of zolmitriptan nasal spray, 27 patients (42%) reported headache relief at 30 minutes, and in the attacks treated with 10 mg of zolmitriptan nasal spray, 38 patients (61%) reported headache relief at 30 minutes, compared with 14 patients (23%) who treated an attack with placebo ($P=.002$) (Figure 2). Eighteen patients (28%) were pain free at 30 minutes when treated with 5 mg of zolmitriptan nasal spray and 31 patients (50%) were pain free at 30 minutes when treated with 10 mg of zolmitriptan nasal spray, compared with 10 patients (16%) who treated an attack with placebo ($P=.003$). At 15 minutes after treatment, 1.6% of patients using placebo, 9% using 5 mg of zolmitriptan nasal spray, and 19% using 10 mg of zolmitriptan nasal spray reported headache relief (Table 2).

Episodic vs Chronic CH

Of the treated cohort, 40 patients had episodic CH and 29 had chronic CH, with a total of 104 attacks treated by the episodic CH group and 85 by the chronic CH group. For headache relief at 30 minutes in the episodic CH group, 10 attacks (30%) of the 33 treated with placebo had a response, while 17 (47%) of 36 had relief using 5 mg of zolmitriptan nasal spray and 28 (80%) of 35 had relief using 10 mg of zolmitriptan nasal spray. In comparison, for the patients with chronic CH, 4 (14%) of 28 who treated attacks with placebo had relief, 8 (28%) of 29 had relief using 5 mg of zolmitriptan nasal spray, and 10 (36%) of 28 had relief using 10 mg of zolmitriptan nasal spray (Figure 3).

Table 1. Demographic Data and CH Characteristics of Included Patients

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Patients, No. (%)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y, mean ± SD</td>
<td>40 ± 10</td>
</tr>
<tr>
<td>Sex</td>
<td>Male 80 (87); Female 12 (13)</td>
</tr>
<tr>
<td>Type of CH</td>
<td>Episodic 59 (64); Chronic 33 (36)</td>
</tr>
<tr>
<td>Average attack duration, min</td>
<td>45 (2); &gt;45-60 31 (34); 60-90 22 (24); 90-180 31 (34); &gt;180 4 (4); Unknown 2 (2)</td>
</tr>
<tr>
<td>Duration of bout, wk, mean ± SD</td>
<td>8 ± 6 (episodic patients, n = 59)</td>
</tr>
<tr>
<td>Type of CH</td>
<td>Episodic 59 (64); Chronic 33 (36)</td>
</tr>
<tr>
<td>Previous use of</td>
<td>Sumatriptan injection 67 (73); Sumatriptan nasal spray 40 (43); Zolmitriptan oral 18 (20); Oxygen 72 (78)</td>
</tr>
<tr>
<td>Abbreviation: CH, cluster headache.</td>
<td></td>
</tr>
</tbody>
</table>

*Unless otherwise indicated.
To evaluate the associated symptoms, only patients who had the symptom immediately before treatment were included in the analysis. Conjunctival injection/lacrimation, nasal congestion/rhinorrhea, and ptosis/eyelid edema were the most frequently mentioned associated symptoms. In the attacks treated with zolmitriptan nasal spray, numerically more patients reported relief from associated symptoms at 30 minutes (Figure 4).

### Escape Medication

The frequency of the use of escape medication was lower in the zolmitriptan-treated attacks compared with those treated with placebo (placebo, 30 [50%]; 5 mg of zolmitriptan nasal spray, 23 [35%]; and 10 mg of zolmitriptan nasal spray 17 [27%]).
Tolerability

No serious adverse events were reported in either the zolmitriptan-treated or placebo-treated attacks. The important adverse effects that led to withdrawal occurred in a patient treated with 5 mg of zolmitriptan nasal spray and were shortness of breath, vomiting, and rheumatic pain.

The data demonstrate that 5 or 10 mg of intranasal zolmitriptan are better than placebo in the acute treatment of CH at 30 minutes posttreatment. The very minimal dropout rate and low number of adverse events reported suggest that intranasal zolmitriptan is well tolerated in patients treating acute CH. The data provide evidence that zolmitriptan nasal spray can be used as a first-line abortive therapy, along with sumatriptan nasal spray or inhaled oxygen, in the management of CH.

Given the relative rarity of CH, we chose a crossover approach to study this patient group. This approach has the advantages of providing both patients and health care professionals with the practical knowledge of how the active medicine compares with placebo within an individual. Similarly, it enables intrapatient comparison of adverse events so that the balance of adverse effect vs efficacy can be directly assessed. Given that CH attacks occur frequently, it is possible to treat 3 attacks over a short period, rendering it likely that the attacks are relatively homogenous. Dropouts are an important consideration in a crossover study, and we had few. This is likely because the patient group was well motivated and, in part, because our centers have a close working relationship with the patient groups such that the study was explained to them and their participation agreed before it commenced. An issue that cannot be avoided in crossover studies is that the observations can never be truly independent since they come from the same individuals. The multilevel analysis approach that we have used explicitly accounts for this problem and is a great advantage in this study. A further issue in our study is that the patients were all recruited at specialist centers. This must limit the generalizability of the result, although it might be argued that the patients attending such centers are more likely to be refractory to treatment and thus the results herein are possibly conservative.

The current gold-standard treatment of acute CH is subcutaneous sumatriptan. It is clearly effective and well tolerated. It has been shown in a similar study to the current one, a single-way crossover study, that 20 mg of sumatriptan succinate nasal spray is also effective in acute CH at 30 minutes. The new data are consistent with this. It had been previously reported that zolmitriptan when administered orally at the 10-mg dose was effective in acute CH. Given the pharmacokinetics of the zolmitriptan spray, it could be predicted that both the 5- and 10-mg sprays would be effective and that is what has been seen. Given that there are good safety data for zolmitriptan’s use in a daily dose of 15 mg, albeit not in CH but in migraine, it seems a possible advantage that patients with CH may be able to use three 5-mg doses in 24 hours. For the patient with CH not responding well to oxygen and limited to 2 sumatriptan injections per 24 hours, this seemingly small advantage, day after day, will accrue. Such an approach must be made with caution since we have no long-term data in CH and we have no systematic information collected as to what the propensity for rebound headache with regular, more frequent use may be. Given the long-term safety data for subcutaneous sumatriptan, it seems unlikely that a specific problem will emerge with zolmitriptan in CH.

Accepted for Publication: June 28, 2006.
Published Online: September 11, 2006 (doi:10.1001/archneur.63.11.nct60002).
Correspondence: Peter J. Goadsby, MD, PhD, Institute of Neurology, The National Hospital for Neurology and Neurosurgery, Queen Square, London WC1N 3BG, United Kingdom (peterg@ion.ucl.ac.uk).
Author Contributions: Drs Cittadini and Goadsby made the initial analysis of the data and wrote the first draft of the manuscript. Study concept and design: May, Bussone, and Goadsby. Acquisition of data: Cittadini, May, Straube, Evers, and Goadsby. Analysis and interpretation of data: Evers and Goadsby. Drafting of the manuscript: Evers and Goadsby. Critical revision of the manuscript for important intellectual content: Cittadini, May, Straube, Evers, Bussone, and Goadsby. Statistical analysis: Cittadini and Goadsby. Obtained funding: Goadsby. Administrative, technical, and material support: Straube, Evers, and Goadsby. Study supervision: Evers, Bussone, and Goadsby.
Financial Disclosure: None reported.
Funding/Support: AstraZeneca supported this work but did not initiate, design, or analyze the study; interpret the data; or have any role in the writing of the manuscript.

REFERENCES


Visit www.archneurol.com. As an individual subscriber to Archives of Neurology, you have full-text online access to the journal from 1998 forward. In addition, you can find abstracts to the journal as far back as 1975.