Multi-center Randomized Control Trial of Etizolam Plus NSAID Combination for Tension-type Headache

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Abstract

Objective  Benzodiazepines are commonly used for the treatment of tension-type headache (TTH), however, there are few randomized controlled trials recommending the use of these drugs in Japan. This study was undertaken to evaluate the efficacy of etizolam, a thienodiazepine derivative, in combination with a non-steroidal anti-inflammatory drug (NSAID) as an acute treatment for TTH.

Methods  The study design was a multi-center randomized control trial and included 144 patients. The diagnosis of TTH was based on the criteria of the International Classification of Headache Disorders-1 and all patients were diagnosed with episodic tension-type headache (ETTH). Changes in the severity of headache and shoulder pain were graded using a Visual Analogue Scale (VAS) before and after administration of drugs. Patients were randomized into NSAID alone (NSAID, mefenamic acid, 250 mg) group and NSAID (mefenamic acid, 250 mg) plus etizolam (0.5 mg) (NSAID-ET) group prior to treatment.

Results  Although both groups showed a significant drop in VAS for headache and shoulder pain (p<0.01), there was no overall significant difference between the NSAID-ET and NSAID groups. However, headache was improved significantly in female patients (p<0.05), and shoulder pain was improved in young and female patients (p<0.05, p<0.04) in the NSAID-ET group.

Conclusion  This study indicates that the combination treatment of etizolam and NSAID is useful in young or female patients.

Key words: episodic tension-type headache, non-steroidal anti-inflammatory drugs, etizolam

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Introduction

Tension-type headache (TTH) is one of the most common primary headaches. Its lifetime prevalence in the general population ranges in different studies from 30 to 78% (1, 2). The infrequent subtype has very little impact on the individual and does not command much attention from the medical profession. However, frequent sufferers can encounter considerable disability that sometimes warrants expensive drugs and prophylactic medication.

The most widely used evidence-based drugs for the management of TTH are the non-steroidal anti-inflammatory drugs (NSAIDs) in acute treatment and antidepressants for preventive treatment (3-14). Benzodiazepines are commonly used for the treatment of TTH (15-18), however, there are few randomized controlled trials (RCTs) recommending the use of these drugs (19). Etizolam is a thienodiazepine derivative, which is a short-acting and ultra-rapidly eliminated benzodiazepine (20) and the only approved benzodiazepine for administration to TTH patients under the Japanese health insurance system. As for NSAIDs, Aspirin, acetaminophen and mefenamic acid (21) are approved for administration to TTH patients under the Japanese health insurance system, including for episodic tension-type headache (ETTH). However, no RCT studies have been done for these drugs. The aim of this study was to evaluate the efficacy of etizolam combined with an NSAID as an acute treatment for ETTH
Patients and Methods

The study design was a multi-center RCT of 144 patients with TTH. This study was conducted in 2003-2004 at six centers throughout Japan. The study was approved by institutional review boards appropriate for each investigator and all study participants gave written informed consent. Outpatient volunteers with a clinical history of TTH that had been generally relieved in the past with over-the-counter (OTC) analgesics were recruited. The diagnosis was based on ICHD-I (22) criteria, and all TTH patients were diagnosed with ETTH.

Patients who were taking continuous treatment with prescription doses of analgesics, NSAIDs, tranquilizers, or muscle relaxants (concomitant medications that might confound the pharmacological effects of the study drugs) were excluded.

The following additional exclusion criteria were stipulated: chronic non-drug treatment for headaches, use of an OTC headache remedy within 12 hours or use of a prescription headache remedy within 1 day prior to taking the study drug, unless approved by the investigator. Pregnant or breast-feeding women or patients who had participated in an investigational drug trial in the past 30 days were also prohibited from entering the study.

The changes in degree of headache and shoulder pain were graded using the Visual Analogue Scale (VAS) before and after administration of drugs. NSAID (mefenamic acid 250 mg) alone (NSAID) and etizolam (0.5 mg) plus NSAID (mefenamic acid 250 mg) (NSAID-ET) drug packaging was identical in shape, size, weight and color. The reason why we used mefenamic acid as an NSAID was that the drug stability could be guaranteed in drug packaging with etizolam. These two drugs were randomized and given to the patients. Ten packs were given to each patient.

Subjects were instructed to ingest the study medication only after experiencing an acute TTH of at least moderate severity. They were also instructed to record in a diary the date and time of ingestion, pain intensity before treatment and pain relief after treatment recorded at final ingestion in the two to four weeks until the next visit to an outpatient office. Pain intensity was recorded on a VAS in a headache case report form. For subjects with concomitant conditions that required drug therapy, those conditions, and any side effects and the medications used were recorded on the case report form.

The primary efficacy parameter was the changes in degree of headache and shoulder pain by VAS before and after administration of drugs. NSAID (mefenamic acid 250 mg) alone (NSAID) and etizolam (0.5 mg) plus NSAID (mefenamic acid 250 mg) (NSAID-ET) drug packaging was identical in shape, size, weight and color. The reason why we used mefenamic acid as an NSAID was that the drug stability could be guaranteed in drug packaging with etizolam. These two drugs were randomized and given to the patients. Ten packs were given to each patient.

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Figure 2. Top: VAS for headache decreased from 5.69±2.36 to 2.36±2.09 in the NSAID-ET group (N-E) (p<0.01), and from 5.40±2.07 to 2.67±2.15 in the NSAID group (N) (p<0.01). However, there was no significant difference between the NSAID-ET and NSAID groups. Bottom: VAS for shoulder pain decreased from 6.10±2.29 to 3.67±2.45 in the NSAID-ET group, and from 6.00±2.37 to 4.02±2.52 in the NSAID group (p<0.01). However, there was no significant difference between the NSAID-ET and NSAID groups. Data are mean ± SD.

Figure 3. Headache improved significantly in the female patients (*p<0.05,) of the NSAID-ET group (N-E). Data are mean ± SD.

Table 1. Background of Participating Subjects and Change in VAS

<table>
<thead>
<tr>
<th></th>
<th>NSAID + Etizolam (n=65)</th>
<th>NSAID (n=64)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (median)</td>
<td>40.3 ± 14.2* (37)</td>
<td>39.6 ± 14.4* (37)</td>
</tr>
<tr>
<td>Sex (male)</td>
<td>17</td>
<td>17</td>
</tr>
<tr>
<td>Drug intake (packs)</td>
<td>4.6 ± 0.7*</td>
<td>4.6 ± 0.7*</td>
</tr>
<tr>
<td>VAS for headache</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Before</td>
<td>5.7 ± 2.4*</td>
<td>5.4 ± 2.1*</td>
</tr>
<tr>
<td>After</td>
<td>2.4 ± 2.1*</td>
<td>2.7 ± 2.2*</td>
</tr>
<tr>
<td>VAS for shoulder pain</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Before</td>
<td>6.1 ± 2.3*</td>
<td>6.0 ± 2.4*</td>
</tr>
<tr>
<td>After</td>
<td>3.7 ± 2.4*</td>
<td>4.0 ± 2.5*</td>
</tr>
</tbody>
</table>

*Data are mean ± SD.

*p<0.01, compared with before treatment.

Results

Although 144 patients were included in the study, complete follow-up was possible in only 129 patients: 15 patients dropped out during the treatment period (Fig. 1). The mean and median age of subjects was 39.9 and 37 years, respectively, so we divided the participants into a “young” and “old” groups based on age less or greater than 39 years. There were no significant differences in age, sex, or number of subjects within the two treatment groups. The mean drug intake (packs) after administration was 4.6±0.7 packs in the NSAID-ET group, and 4.6±0.7 packs in the NSAID group (Table 1).

The VAS for headache decreased from 5.7±2.4 to 2.4±2.1 in the NSAID-ET group (p<0.01), and from 5.4±2.1 to 2.7±2.2 in the NSAID group (p<0.01, Table 1, Fig. 2). For shoulder pain, VAS decreased from 6.1±2.3 to 3.7±2.4 in the NSAID-ET group, and from 6.0±2.4 to 4.0±2.5 in the NSAID group (p<0.01, Table 1, Fig. 2). On the other hand, there was no significant difference between the NSAID-ET and NSAID groups in terms of overall efficacy for headache.
Figure 4. There was no significant difference in degree of headache between young and old patients. Data are mean ± SD.

Figure 5. Shoulder pain improved significantly in the female patients (**p<0.04) of the NSAID-ET group (N-E). Data are mean ± SD.

Discussion

The most widely used evidence-based acute treatment for management of TTH is with NSAIDs. The analgesic agents [acetaminophen (3-7), aspirin (3, 6), ibuprofen (5, 7-13), ketoprofen (6, 12, 13), and naproxen (4, 12)] are all effective as analgesics in TTH.

The underlying pain mechanisms in TTH are highly dynamic and both central and peripheral mechanisms seem to be important (23). The exact contributions of the peripheral mechanism (muscle contraction) and central mechanism in TTH are still unclear. Benzodiazepines are commonly used for TTH treatment, as agents that address both the central and peripheral mechanisms (15-18). The efficacy of the benzodiazepine compound alprazolam has been confirmed for chronic TTH (19). In addition, a long-term protocol of relaxation exercises combined with diazepam is reported to produce the best long-term results in decreasing muscle tension and reducing pain complaints, as found by Lavallee et al in chronic anxiety patients (24). However, few RCTs have assessed objectively the efficacy of the drugs. Comparison of the relative efficacy of drugs, including analgesics, in TTH is complicated by the self-limiting nature of this indication and a high placebo response rate (25). In order to improve the quality of controlled trials in TTH, RCTs are needed.

Caffeine is known to have analgesic adjuvant activity, as reviewed by Laska et al (26), in a variety of pain conditions. In this study, we investigated the analgesic adjuvant activity of etizolam. Although the present study demonstrated no significant decrease of headache and shoulder pain overall in the subjects, there was a significant reduction of symptoms in young or female patients receiving NSAID-ET. The reason that etizolam exerted an apparent adjuvant effect only in young or female patients is not clear at present. However, we speculate the following mechanism. Boggards and ter Kuile reported in their meta-analysis that 78% of the general population is reported to have experienced a TTH during their lifetime, and that TTH is reported more frequently by women (88%) than by men (69%) (2). Treatment effects were unrelated to duration and transfer of treatment. Treatment outcome was related to all patient characteristics studied: younger patients improved more than did older patients, and studies with a higher percentage of female patients and
Figure 6. In young patients, shoulder pain improved significantly (*p<0.05) in the NSAID-ET group (N-E). Data are mean ± SD.

Table 2. Incidence of Adverse Events

<table>
<thead>
<tr>
<th>Adverse effects</th>
<th>NSAID + Etizolam (n=65)</th>
<th>NSAID (n=64)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n (%)</td>
<td>n (%)</td>
</tr>
<tr>
<td>sleepiness or fatigue</td>
<td>6 (9.2)</td>
<td>0</td>
</tr>
<tr>
<td>dizziness</td>
<td>2 (3.1)</td>
<td>1 (1.5)</td>
</tr>
<tr>
<td>nausea</td>
<td>0</td>
<td>1 (1.5)</td>
</tr>
<tr>
<td>diarrhea</td>
<td>0</td>
<td>1 (1.5)</td>
</tr>
</tbody>
</table>

self-referred patients tended to have better results (2). The mean age of the sample was interrelated and negatively related to treatment outcome; patients with more chronic TTH and those who were older had less benefit from treatment (2). Furthermore, very minor osteoarthritis of the neck or shoulder may exist in some of aged patients. Such a skeletal problem may reduce the adjuvant effect etizolam.

Although we observed some side effects from etizolam (sleepiness or fatigue in 9.2% of patients of the NSAID-ET group), no patient dropped out due to a side effect. This result suggests that etizolam in combination with NSAIDs is well tolerated for treatment of ETTH.

Although patients in both the NSAID and NSAID-ET groups showed significant decreases in VAS for headache and shoulder pain, etizolam in combination with an NSAID was effective for headache and shoulder pain treatment in young and female patients. The present study indicates that combination treatment with NSAID and etizolam is useful in young and female patients.

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References


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