Ketotifen in prevention of indomethacin-induced gastropathy

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Background: Therapeutic benefits of nonsteroidal anti-inflammatory drugs (NSAIDs) are offset by their gastrointestinal side effects. We evaluated whether oral ketotifen, which prevents experimental NSAID-induced gastric mucosal injury, is superior to placebo in preventing NSAID-induced gastropathy. Design: Prospective, randomized, double-blind, placebo-controlled clinical trial. Setting: Rheumatology clinic in a tertiary care hospital. Participants: A majority of the 53 subjects had rheumatoid arthritis (n=36) or osteoarthritis (12). Those with comorbidity, gastrointestinal (GI) symptoms or abnormal endoscopic findings at entry were excluded. Persons on steroids or NSAIDs in the previous month were also excluded. The subjects were started on indomethacin 25 mg thrice daily. Intervention: Subjects were randomly allocated to receive 2 mg ketotifen or placebo tablets. Compliance was measured by tablet count. Outcome measure: At the end of every week a questionnaire was administered to elicit GI symptoms or adverse effects. Every patient underwent endoscopy after four weeks. Results: Of 53 patients recruited (27 drug, 26 placebo), three (2 drug, 1 placebo) dropped out. The age, sex, NSAID use and clinical conditions were similar in the two groups. Eight in the drug group and 16 in the placebo group developed GI symptoms and/or endoscopic lesions (relative risk 0.51, 95% CI 0.27 - 0.95). The difference was significant on intention-to-treat analysis. Conclusions: Ketotifen significantly reduced the risk of GI side effects in patients on indomethacin. [Indian J Gastroenterol 1999;18:76-77]

Key words: Nonsteroidal anti-inflammatory drugs

The beneficial effects of nonsteroidal anti-inflammatory drugs (NSAIDs) are offset by their serious, sometimes life-threatening, gastrointestinal side effects. Gastrointestinal lesions produced by NSAIDs (NSAID gastropathy) may produce no symptoms or symptoms varying from mild dyspepsia to life-threatening hemorrhage.

The drugs used for preventing NSAID gastropathy are histamine H2-receptor blockers,1 proton pump inhibitors,2 prostaglandin analogues3 and mucosal protective agents.4 Using nitric oxide-releasing NSAID5 or non-prostaglandin NSAIDs6 are other options.

Ketotifen is an anti-inflammatory drug, a mast cell stabilizer, which reduces the release of ulcerogenic platelet-activating factor (PAF), substance P and tumor necrosis factor (TNF). These substances have been implicated in the pathogenesis of NSAID gastropathy. Experimental studies have shown that ketotifen reduces indomethacin- and alcohol-induced gastrointestinal lesions in rats.7,8 This study evaluates whether oral ketotifen is superior to placebo in reducing NSAID gastropathy.

Methods

This double-blind, randomized, placebo-controlled trial was done in a tertiary care referral hospital. The study subjects were new cases attending the rheumatology clinic over a period of two years, who gave written consent for the trial and also for the initial and follow-up endoscopies. Subjects with gastrointestinal (GI) symptoms (n=4), comorbidity (6) or abnormal initial endoscopy (3) were excluded from the study. Patients who were on steroids or NSAIDs for one month before the study were also excluded.

The characteristics of the subjects who satisfied the inclusion criteria and their rheumatologic diagnoses are given in the Table. All cases were started on indomethacin 25 mg thrice daily.

The subjects were randomized to receive tablets containing 2 mg ketotifen or placebo daily for 30 days. Antacids were allowed when the patient developed symptoms. No other drugs were given. Compliance to the trial drug was assessed by tablet count at the end of the study.

After the end of every week the patient filled a questionnaire regarding the presence or absence of GI symptoms or any adverse effect of the drug. A repeat endoscopy was done after thirty days of the trial medication.

Results

Fifty-three patients (27 on drug, 26 on placebo) were enrolled into the trial. Two persons in the drug group and one from the placebo group did not complete the study.

Eight patients in the ketotifen group developed GI symptoms (5 heartburn, 3 epigastric pain) whereas 10 (all heartburn) had GI symptoms in the placebo group. The

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Ketotifen</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male:female</td>
<td>5:20</td>
<td>6:19</td>
</tr>
<tr>
<td>Age (mean ± SD)</td>
<td>35.4 (9.3)</td>
<td>37.4 (10.1)</td>
</tr>
<tr>
<td>Smokers</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>Rheumatoid arthritis</td>
<td>18</td>
<td>18</td>
</tr>
<tr>
<td>Osteoarthritis</td>
<td>5</td>
<td>7</td>
</tr>
<tr>
<td>Ankylosing spondylitis</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Spondylitic arthropathy</td>
<td>1</td>
<td>0</td>
</tr>
</tbody>
</table>

Table: Baseline characteristics in patients receiving ketotifen and placebo

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Ketotifen in NSAID gastropathy.

Ketotifen has also been shown to be protective against indomethacin-induced small intestinal ulceration in the rat. Thus, the drug not only appears to be promising for the prevention of NSAID gastropathy, but should be evaluated for prophylaxis against NSAID-induced intestinal lesions as well.

References


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