Trimebutine, A New Antispasmodic in the Treatment of Dyspepsia

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Indigestion, flatulent dyspepsia, nausea, vomiting, abdominal pain or discomfort are among the commonest complaints in adults attending their doctor’s surgery or medical out-patient department (Switz, 1976). Investigations by x-ray or endoscopy may show a peptic ulcer, diseased gall-bladder or other lesion, but in many cases objective investigations are negative. Symptoms in these patients may be caused by disordered gastro-intestinal motility rather than a well-localised lesion, and restoration of normal motility may alleviate symptoms. Trimebutine has been shown to have a relaxant effect on gastro-intestinal smooth muscle and a regulatory effect on contractility (Frexinos, 1971). The present study was carried out to compare the symptomatic effect of Trimebutine with placebo in patients with x-ray and endoscopically negative dyspepsia.

Patients and Methods
Initially, 30 patients entered the study: all were out-patients, referred to the gastroenterology department in the Regional Hospital, Galway from other physicians and surgeons or by their general practitioners. There were 14 males and 16 females, age range 18-70, average age 34.5 years. All patients had complained of dyspepsia or other upper gastrointestinal symptoms (Table 1) for at least three months: average duration of symptoms was three years. Each patient had negative findings on barium meal, cholecystogram and upper gastrointestinal endoscopy. On admission to the trial, each patient was asked to specify his main complaint and 10 individual symptoms were also assessed and graded in terms of severity on a 0-3 point rating scale. These symptoms were nausea, vomiting, anorexia, abdominal pain, heartburn, epigastric discomfort, acid regurgitation, feeling of distension, inability to finish meals and eructation.

Patients were treated with Trimebutine 200 mg three times daily and with placebo three times daily, each treatment lasting for four weeks and allocated on a randomised pre-arranged double-blind cross-over basis. Patients were assessed after each 4-week treatment period for check on their progress and symptom re-grading, full blood count and biochemical monitoring of renal and hepatic function. After completion of both 4-week treatment periods, patients were asked to say which treatment was the more effective (or were both equally good or equally ineffective).

Table 1

<table>
<thead>
<tr>
<th>Chief Complaint</th>
<th>(Entering Study)</th>
<th>(Completing Study)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Flatulence/flatulent dyspepsia</td>
<td>10</td>
<td>7</td>
</tr>
<tr>
<td>Heartburn</td>
<td>7</td>
<td>5</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>9</td>
<td>9</td>
</tr>
<tr>
<td>Nausea</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>Regurgitation</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Total</td>
<td>30</td>
<td>24</td>
</tr>
</tbody>
</table>

Results
Twenty-four of the initial 30 patients completed the study and 19 of the 24 expressed a marked treatment preference (Table 2). Thirteen patients (54%) found Trimebutine more effective and 6 (25%) preferred placebo. Two patients found both placebo and Trimebutine equally effective, and two patients found both treatments to be ineffective. There was no overall significant difference between either treatment preference ($p = 0.27$ multinominal test). However, when order of treatment was taken into consideration, it was found that, of the 12 patients given Trimebutine first, no clear treatment preference was seen. Of the other twelve patients (who received placebo first) a significantly higher proportion (10/12) preferred Trimebutine ($p = 0.038$ multi-nominal test). All patients who found both treatments equally effective (three or ineffective (two) had received Trimebutine first. Six patients dropped out of the study. Three of these failed to attend for their first check-up (two on Trimebutine, one on placebo). One patient left the country before the first check-up, and one was admitted to another
hospital with suspected perforation of duodenal ulcer: there were no positive findings and the patient was discharged home. The sixth patient dropped out of the trial because she developed an acute anxiety state two weeks after starting treatment, which was discontinued.

**Table 2**

<table>
<thead>
<tr>
<th>Preference</th>
<th>All Patients</th>
<th>Trimebutine First</th>
<th>Placebo First</th>
</tr>
</thead>
<tbody>
<tr>
<td>Trimebutine</td>
<td>13</td>
<td>3</td>
<td>10</td>
</tr>
<tr>
<td>Placebo</td>
<td>6</td>
<td>4</td>
<td>2</td>
</tr>
<tr>
<td>Equally good</td>
<td>3</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>Equally bad</td>
<td>2</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Total</td>
<td>24</td>
<td>12</td>
<td>12</td>
</tr>
</tbody>
</table>

Biochemical and haematological tests monitored included ESR, full blood count, blood urea and electrolytes, alkaline phosphatase, bilirubin, SGOT and urinalysis: no significant abnormality was recorded. No side-effects occurred which necessitated discontinuing treatment though three patients complained of feeling tired while taking Trimebutine, and one of these developed a transient penile rash.

**Discussion**

X-ray negative dyspepsia always presents a therapeutic problem. With the advent of readily available endoscopy, a more complete assessment of the upper gastrointestinal tract can be made, and persistence of symptoms when radiological and endoscopic investigations are non-diagnostic poses a problem to the clinician. Association of upper gastrointestinal symptoms with disorder of bowel habit may point to a diagnosis of irritable bowel syndrome (Manning et al., 1978) and considerable relief maybe obtained by increasing roughage such as bran in the diet.

Trimebutine was originally used because of its antispasmodic and relaxant effect on the lower bowel (Frexinos, 1971). In the present study, Trimebutine has been used to alleviate symptoms associated with an upper gastrointestinal disorder on the assumption that symptoms were related to a disorder of motility.

Though, overall, no statistically significant difference between treatment with Trimebutine and placebo could be demonstrated, a significant number of the patients who received Trimebutine in the second 4-week period of treatment obtained considerable symptomatic relief when compared with placebo. It is difficult to evaluate symptomatic relief:

Sturdevant et al. (1977) showed that antacids and placebo could produce similar relief of pain in patients with duodenal ulcer, while Thompson and Venables (1976) questioned the desirability of relieving ulcer pain as opposed to achieving objective evidence of ulcer healing. Objective studies of intestinal gas in relationship to functional abdominal pain (Lasser et al., 1975; Levitt et al., 1976) indicate that ‘normal’ volume and pressure of intestinal gas may be associated with severe symptoms of distension, pain and flatulence, resulting from disordered intestinal motility in combination with an abnormal pain response.

In the present study, individual symptoms varied widely (Table 1) but all, in the absence of radiological or endoscopic evidence of gut pathology, were suggestive of an upper gastrointestinal motility disorder. Trimebutine, when given after 4 weeks’ treatment with a placebo, gave a significant symptomatic improvement, most marked in patients complaining of flatulent dyspepsia. Numbers are small, but larger studies may confirm the clinical impression that Trimebutine could be of value in treating patients with x-ray and endoscopically negative dyspepsia.

**Summary**

In a double-blind cross-over study, twenty-four patients with x-ray and endoscopically negative dyspepsia were treated with the antispasmodic Trimebutine 200 mg three times daily and placebo, each for a consecutive period of four weeks. The effect of each treatment upon individual symptoms was noted, and patient treatment preference recorded on completion of the trial. No overall significant difference between Trimebutine and placebo was found, though there was a significant symptomatic improvement in patients who received Trimebutine as their second treatment (10/12) compared with placebo (p = 0.038). No evidence of clinical or biochemical toxicity was observed.

**Acknowledgements**

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**References**


