Double-Blind Evaluation of Domperidone in Acute Vomiting and Dyspeptic Disorders

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The anti-emetic effects of domperidone were evaluated under double-blind conditions in twenty-four patients with acute vomiting randomly assigned to treatment either with 10 mg i.m. domperidone (six females, five males) or with placebo (seven females, six males). The therapeutic results were better with domperidone and the differences from placebo were statistically significant ($p < 0.02$).

In a second randomized, crossover, double-blind trial, domperidone (10 mg t.i.d.) evaluated according to a nine-symptom rating scale, in eighteen dyspeptic patients, proved significantly more effective than placebo. The duration of treatment was 6 weeks and the drugs were crossed-over after 3 weeks. The difference between the two groups was most marked during the second phase of the trial.

No side-effects were reported.

Introduction

Specific receptors stimulated by dopamine and blocked by traditional anti-dopaminergic agents (phenothiazines, butyrophenones) have been identified in the periphery and seem to exert a significant role in the autonomic regulation (Thorner 1975). Relaxation of the proximal part of the stomach observed during the vomiting act, mainly occurs by gastro-gastric vagal relaxatory fibres which concomitantly activate a spinal gastro-gastric adrenergic inhibitory reflex (Abrahamson 1974, Christensen 1974). Apomorphine, a dopaminergic agonist, acting on the CNS, induces gastric relaxation and emesis and in smaller doses has a delaying effect on gastric emptying. This effect cannot be blocked by atropine (parasympatholytic) or guanethidine (sympatholytic) but only with vagotomy (Abrahamson, Jansson and Martinson 1973). Consequently vagal relaxatory fibres inducing gastric relaxation and emesis should stimulate receptors belonging very probably to the dopaminergic system. Blocking of these receptors may prevent relaxation and hypomotility disorders of the stomach.

Domperidone is a potent and specific dopamine antagonist devoid of any in vivo central effects (Laduron & Leysen 1979). It antagonizes the slowing effect of apomorphine on the stomach without affecting gastric secretion (Broekaert 1979). In healthy
volunteers, administered orally and parenterally, it improves the motor function in the proximal part of the upper gastro-intestinal tract (Baeyens et al 1979) and stimulates the rhythmic activity of the antrum (Schmidt et al 1978).

Because of its properties, domperidone has been recently evaluated, with positive results, in acute vomiting of various aetiologies in adults (D’Souza, Reyntjens & Thornes 1980, Korttila, Kauste & Auvinen 1979, Zissis et al 1979) and in children (Dhont et al 1978) as well as in chronic dyspeptic disorders (Arts et al 1979, Englert & Schlich 1979, Haarman et al 1979).

The aim of our trial was to verify under double-blind crossover conditions the therapeutic effects of domperidone in acute vomiting and dyspeptic disorders as well as to evaluate its unwanted effects.

**Material and Methods**

**Anti-emetic trial**

Twenty-four patients of both sexes with at least two vomiting episodes during the last 2 hours, consented to participate, after full information had been imparted to them, in a double-blind, prospective, randomized, placebo controlled trial aiming to evaluate the therapeutic effects of domperidone in acute vomiting (Domperidone Group: six females, five males; mean age 52.7, median age 55, min. 34, max. 78 years; mean body-weight 60.2 kg, median 60 kg, min. 50, max. 70 kg – Placebo Group: seven females, six males; mean age 53.8, median age 55, min. 25, max. 90 years; mean body-weight 67.7 kg, median 64 kg, min. 58, max. 90 kg). The mean number of previous vomiting episodes in the Domperidone Group was 4.1 (median 4) and in the Placebo Group 3.3 (median 3). The aetiology of vomiting is presented in Table 1. All patients were evaluated after 1, 2, 4, 6 and 8 hours according to the following scale: 0 = no nausea-vomiting, 1 = slight nausea, 2 = moderate nausea, 3 = severe nausea, 4 = one vomiting episode, 5 = more than one vomiting episode. Unwanted effects (score: 0 = absent, 1, 2, 3, 4 = very severe) and the subjective evaluation of the therapeutic results by the investigators were also recorded. All patients received i.m. 2 ml of either placebo or 10 mg domperidone. In the event of insufficient therapeutic response a second 2 ml injection was administered at the end of the first hour.

**Anti-dyspeptic trial**

Eighteen patients of both sexes presenting with at least three of the following symptoms: Flatulence = full feeling after normal-sized meals, inability to finish normal-sized meals, distended abdomen; Dyspepsia = belching, burning discomfort in upper abdomen, heartburn (burning discomfort in chest), regurgitation of bitter fluid to mouth (Johnson 1978), epigastric pain and epigastric distress in very severe or severe degree, were included in a separate double-blind, randomized, prospective, crossover trial concerned with the effects of domperidone in chronic dyspepsia. Other evaluating criteria were the total score of all symptoms as well as the unwanted effects related to treatment. The effect of treatment on anorexia and defaecation disorders was also evaluated.

Nine patients (seven females, two males; mean age 46, median 46, min. 27, max. 60 years; mean body-weight 64.7 kg, median 65 kg, min. 51, max. 73 kg) were included in the active drug-placebo sequence and nine patients (seven females, two males; mean age 42.2, median 41, min. 28, max. 56 years; mean body-weight 69.4 kg, median 70, min. 56, max. 93 kg) in the placebo-active drug sequence. Informed consent was obtained from all patients. The dyspeptic disorders were due to functional disorders in seventeen patients and in one, belonging to the domperidone-placebo sequence, were due to drug response.
Results

Anti-emetic effect

The mean scores of nausea-vomiting in both groups, as well as the statistical evaluation of the differences between the two groups, are presented in Figure 1. Patients were randomly assigned to the two treatment sequences according to a pre-established randomization code. The dosage schedule consisted of three tablets daily (10 mg domperidone or placebo tablets) administered 30 minutes before meals. Patients were evaluated weekly according to the following rating scale for all symptoms and side-effects: 0 = absent, 1 = slight, 2 = moderate, 3 = severe, 4 = very severe. The mean scores of flatulence and dyspepsia were calculated from the scores of symptoms contained in these two factors.

Patients treated with other anti-emetics, anticholinergics, or metoclopramide were excluded from the trial. All other treatment modalities, and especially antacids and minor tranquillizers, were permitted only where they had existed before the trial.

### Table 2

<table>
<thead>
<tr>
<th></th>
<th>Domperidone</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Very good</td>
<td>9 patients</td>
<td>0 patients</td>
</tr>
<tr>
<td></td>
<td>(81.8%)</td>
<td></td>
</tr>
<tr>
<td>Good</td>
<td>1 patient</td>
<td>3 patients</td>
</tr>
<tr>
<td></td>
<td>(9.1%)</td>
<td>(23.1%)</td>
</tr>
<tr>
<td>Moderate</td>
<td>0 patients</td>
<td>2 patients</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(15.4%)</td>
</tr>
<tr>
<td>No change</td>
<td>1 patient</td>
<td>8 patients</td>
</tr>
<tr>
<td></td>
<td>(9.1%)</td>
<td>(61.5%)</td>
</tr>
</tbody>
</table>

Anti-dyspeptic effect

The factor of flatulence, consisting of the symptoms full-feeling after normal-sized meals, inability to finish normal-sized meals and distended abdomen, improved during the first 3 weeks in both treatment groups. However during the subsequent 3 weeks and after the treatments were crossed-over, only those patients who received domperidone were further improved while the condition of those under placebo did not change significantly (Figure 2). The difference between the two groups at the end of the 6th week was statistically significant ($p < 0.02$ Mann-Whitney U test, two-tailed probability) and
favoured the group that received domperidone last.

Improvement in both groups without significant differences between them was observed in the factor of dyspepsia and the symptom of defaecation disorders. Very few patients suffered from anorexia.

The total score of dyspeptic symptoms decreased in both groups during the first 3 weeks and compared to the pre-trial period the differences were statistically significant (p<0.01). However, after the crossover of treatments the total scores in the Placebo Group hardly changed while patients treated with domperidone were further improved (Figure 3). During the second phase of the crossover trial a statistically significant decrease of the total symptom score was observed only in the group treated with domperidone last (Figure 3).

Side-effects under treatment with domperidone were not observed.

Discussion

The results of the present trial confirm earlier reports (D’Souza et al 1980, Korttila et al 1979, Zissis et al 1979) that domperidone constitutes an effective treatment in acute vomiting. During the trial some decrease of the vomiting score had also been observed with placebo, however, the differences between the two groups were statistically significant (p<0.02). It is important to underline the fact that no side-effects were observed after the i.m. administration of domperidone.

The placebo effect is a common phenomenon in psychosomatic diseases. Our chronic dyspeptic patients during the first 3 weeks of the crossover trial improved either with domperidone or with placebo. The net difference between them appeared only after the crossover of treatments when patients receiving domperidone improved further, while those who were transferred to placebo remained unchanged. A statistically significant improvement of the total symptom score during the second phase of the crossover trial was observed only in the active drug group.

It is concluded that domperidone with its peripheral anti-dopaminergic effects exerts a significant anti-emetic action and counteracts disorders due to hypomotility of the proximal part of the gastro-intestinal tract.

Fig 3 Evolution of total score of dyspeptic symptoms. Statistical evaluation concerns the differences with the previous periods within the same group:

- *p < 0.01
- **p < 0.02 (Wilcoxon matched pairs signed-ranks test, two tailed probability)
- n.s. = non-significant

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