The HT4-agonist Cisapride (CIS) and the peripheral D2-antagonist Domperidone (DOMP) have distinct prokinetic actions. We compared their clinical efficacy in 127 dyspeptic patients. Patients with upper abdominal complaints of > 1 month duration, who had a normal UGE were allocated to the REFLUX-group (RG) (predominance of heartburn, acid regurgitation or retrosternal pain) or if devoid of this specific symptomatology to the DYSPEPSIA-group (DG) in a double-blind randomised fashion and allocated to 10 mg CIS or 20 mg DOMP qid (RG) or tid (DG) for 1 month and followed-up for further 2 months. In RG (N = 43, p < 0.05) the response rates were clearly in favour of CIS, but not in DG (N = 84). In RG DOMP was more effective against nausea. The benefit of both therapies was largely maintained in the follow-up period.

Cisapride and domperidone were effective in the treatment of dyspepsia. Cisapride was more effective than domperidone in the REFLUX-Group.

Key words: dyspepsia, functional, GORD, Domperidone, Cisapride, therapeutic trial, endoscopy.

INTRODUCTION

The use of prokinetics in the treatment of functional dyspepsia and gastroesophageal reflux disease (GORD) is widely accepted. The two prokinetic agents, domperidone and cisapride, have both been shown to be effective in these indications (1, 2). However, the pharmacological mechanisms of action of the two compounds are quite different: domperidone is a peripheral dopamine D2-antagonist with anti-emetic properties (1) and cisapride is a HT4-agonist which enhances cholinergic activity and also reduces colonic transit time (2). Therefore, it is reasonable to expect some differences in their therapeutic activity profiles.
Peripheral dopamine antagonists have gained important clinical use because of their effect on the motility of the upper gastrointestinal tract. Domperidone elicits an increase in lower oesophageal sphincter pressure (LOSP) and stimulates gastroduodenal motility and gastric emptying. Consequently, domperidone effectively alleviates the symptoms of chronic postprandial dyspepsia and nausea and vomiting due to a wide variety of underlying causes and, in some studies, has been superior to metoclopramide (3—6).

Cisapride stimulates the motility of the smooth muscle lining the oesophagus, stomach, small intestine and colon both in vitro and in vivo. In controlled investigations, cisapride was superior to placebo in relieving symptoms associated with reflux oesophagitis, non-ulcer dyspepsia and gastroparesis. In comparative studies, similar symptoms and healing effects were observed with cisapride and histamine H2-antagonists in reflux oesophagitis. Cisapride is well tolerated with adverse effects being limited primarily to the gastrointestinal tract (2).

Based on the pharmacological profiles of domperidone and cisapride, different clinical results could be expected in patients with functional upper gastrointestinal symptoms. To our knowledge, there are no published studies directly comparing the clinical efficacy of the two prokinetics, although it has been reported that cisapride is superior to placebo in domperidone- or metoclopramide-resistant cases of dyspepsia (7). Therefore, the present trial was designed to compare the two drugs in different subgroups of patients with functional upper gastrointestinal symptoms consulting their primary care physician and to assess the duration of the improvement obtained.

METHODS

Study design and patient selection

The study was performed as a randomised double-blind parallel group multicentre trial with four weeks of therapy and follow-up at four and eight weeks after the end of active treatment.

Adult patients who had experienced one of the following as (a) main symptom(s) for at least the previous four weeks were eligible to enter the study: epigastric pain or discomfort, nausea, vomiting, postprandial bloating or fullness, early satiety, fat intolerance, regurgitation, or heartburn. At entry, patients underwent endoscopic examination of the upper gastrointestinal tract. H. pylori status was assessed in all subjects with gastric biopsies and the CLO-urease test. Independent of H. pylori status only patients with a normal oesophago-gastro-duodenoscopy were admitted. Additional exclusion criteria were: known major pathology, previous major abdominal surgery, abnormal values in routine haematology and blood chemistry, severe symptoms of irritable bowel syndrome, and previous regular treatment with antisecretory agents or a prokinetic drug for the current episode of symptoms.

All patients fulfilling the above criteria were deemed to have functional dyspepsia and entered the double-blind, parallel group, therapeutic study. Patients suffering from one or more of the following predominant symptoms were allocated to the GORD-group: acid regurgitation and/or
heartburn and/or retrosternal pain. The remainder were allocated to the DYSPEPSIA-group. The patients were randomly allocated to four weeks treatment with identically looking tablets containing 10 mg cisapride (CIS) or 20 mg domperidone (DOMP) to be taken four times daily by the patients in the GORD-group (at breakfast, lunch, dinner and before bed) and three times daily by the patients in the DYSPEPSIA-group. All the patients were seen at again four weeks and eight weeks after the end of active treatment.

The study was approved by the ethics committees of the University Hospital, Inselspital of Berne and by the Cantonal Boards of Geneva and Ticino, Switzerland. Informed consent to participate was obtained from each patient before inclusion.

Clinical assessments

A general medical history including routine haematological and blood chemistry assessments were obtained before entry. At each visit (days 0, 7, 28, 56, 84) the severity of the patient's condition was rated from 0 to 3 by reviewing the target symptoms in four categories: no symptom; mild symptom(s) (that is mentioned spontaneously or affirmative answer by the patient when asked), relevant symptom(s) (mentioned spontaneously by the patient as requiring treatment; severe symptom(s) (relevant symptoms clearly disrupting the patient's daily activities). The target symptoms actively asked about were acid regurgitation, heartburn, epigastric pain, epigastric discomfort, postprandial fullness, bloating, early satiety, nausea, fat intolerance, vomiting, diarrhoea, constipation and lower abdominal pain (relieved by defaecation or not). At each visit the patients were also asked if they had had any adverse drug events (ADE) in the previous two weeks, and if so, their nature, severity and duration were recorded. At each visit the investigator and the patient had to report a global assessment of the results (very good/good/sufficient/insufficient).

Statistical analysis and criteria for assessment of therapeutic success or failure

Demographic data are reported as mean values ±SD and compared using the two-sided student-t-test for independent samples. Unless stated otherwise, once a patient entered the double-blind active treatment phase of the trial, the data were statistically analysed on an LOCF basis (Last Observation Carried Forward). Categorical data were compared by means of two-tailed Chi-square analysis (with the Yates' correction for continuity in small samples) and the Chi-squared test for trend (for categories in natural order): results were regarded as significant if p < 0.05.

Patients were considered to be responders to the treatment if they reported a symptoms' score reduction by more than two-thirds (> 66% of the initial score) at the end of active therapy and during the follow-up period. Relapser was a patient who, having been a responder, reported an increase in the total symptoms' score of greater than 50% of the score at admission. Once the patient has 'relapsed' he was considered as such until the end of the study. Non-responder was a patient whose symptoms' score did not attain a two-thirds reduction of the initial score.

RESULTS

Patients

Of the 172 patients originally screened by the participating GPs, 127 fulfilled the criteria of functional GORD or dyspepsia. 32 patients were excluded from the study because of upper gastrointestinal pathology (including
erosions). A further 13 patients were excluded for series of organic conditions: malignancies (3, whereas 2 were of extra gastrointestinal origin), increased amylase and lipase values (2 patients), increased liver enzymes (2 patients), gallbladder disease (3 patients), and other systemic diseases (3 patients).

Of the 127 patients available for analysis, 43 were allocated to the GORD-group and 84 to the DYSPEPSIA-group: 59 received domperidone and 68 were treated with cisapride. The two treatment groups were comparable in terms of patient demographics and symptoms at the start of the study (Table 1). A significantly larger number of patients assigned to domperidone withdrew from the study due to ineffectiveness or relapse (details see below).

Table 1. Demographic data in GORD and dyspepsia patients

<table>
<thead>
<tr>
<th>DOMPERIDONE</th>
<th>AGE</th>
<th>HEIGHT</th>
<th>WEIGHT</th>
<th>DURATION*</th>
<th>Initial Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>GORD</td>
<td>43±14</td>
<td>167±10</td>
<td>70±23</td>
<td>32±50</td>
<td>10.6±3.8</td>
</tr>
<tr>
<td>Dyspepsia</td>
<td>40±16</td>
<td>168±8</td>
<td>67±9</td>
<td>26±45</td>
<td>9.4±3.4</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>CISAPRIDE</th>
</tr>
</thead>
<tbody>
<tr>
<td>GORD</td>
</tr>
<tr>
<td>Dyspepsia</td>
</tr>
</tbody>
</table>

*) in weeks

<table>
<thead>
<tr>
<th>DOMPERIDONE</th>
<th>Nt</th>
<th>MALES</th>
<th>SMOKERS</th>
<th>SURGERY</th>
<th>CLO-TEST*</th>
</tr>
</thead>
<tbody>
<tr>
<td>GORD</td>
<td>22</td>
<td>7</td>
<td>3</td>
<td>6</td>
<td>7</td>
</tr>
<tr>
<td>DYSPEPSIA</td>
<td>37</td>
<td>15</td>
<td>12</td>
<td>5</td>
<td>14</td>
</tr>
<tr>
<td>CISAPRIDE</td>
<td>21</td>
<td>8</td>
<td>6</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>DYSPEPSIA</td>
<td>47</td>
<td>13</td>
<td>16</td>
<td>6</td>
<td>11</td>
</tr>
</tbody>
</table>

| Nt | 127 | 43 | 37 | 21 | 37 |

GORD: global evaluation of therapy

Of the 43 GORD-patients, 22 received domperidone and 21 received cisapride. In the domperidone-group 15 patients completed the study, 1 patient withdrew due to an ADE (exanthema) and 6 withdrew due to lack of efficacy of the treatment either during the active treatment phase or in the follow-up period. In the cisapride-group, one patient each withdrew due to lack of efficacy or due to relapse in the follow-up phase resp.

As is shown in Table 2, the global evaluation of the therapeutic results reported by the investigators was marginally favouring cisapride at the end of the 4 weeks treatment (p < 0.1).
Table 2. Global evaluation at end of therapy in GORD and in dyspepsia

<table>
<thead>
<tr>
<th></th>
<th>Insufficient</th>
<th>Sufficient</th>
<th>Good</th>
<th>Very Good</th>
<th>Nt</th>
</tr>
</thead>
<tbody>
<tr>
<td>GORD</td>
<td>Domperidone</td>
<td>6</td>
<td>1</td>
<td>6</td>
<td>9</td>
</tr>
<tr>
<td></td>
<td>Cisapride</td>
<td>1</td>
<td>1</td>
<td>8</td>
<td>11</td>
</tr>
<tr>
<td>Dyspepsia</td>
<td>Domperidone</td>
<td>6</td>
<td>6</td>
<td>9</td>
<td>16</td>
</tr>
<tr>
<td></td>
<td>Cisapride</td>
<td>4</td>
<td>6</td>
<td>19</td>
<td>18</td>
</tr>
<tr>
<td>TOTAL</td>
<td>Domperidone</td>
<td>12</td>
<td>7</td>
<td>15</td>
<td>25</td>
</tr>
<tr>
<td></td>
<td>Cisapride</td>
<td>5</td>
<td>7</td>
<td>27</td>
<td>29</td>
</tr>
</tbody>
</table>

**GORD: response rates at end of therapy and follow-up**

No differences between the two treatment groups were observed at day 7. After 4 weeks of treatment, however, 95% of the cisapride-treated patients were responders compared with 64% of the domperidone patients and this difference was significant (p < 0.05). Although the difference in response rates in favour of cisapride numerically persisted during the follow-up period (days 56 and 84) this was no longer significant (Table 3).

**GORD: symptoms’ scores**

The total and individual mean symptoms’ scores improved consistently and significantly in both therapeutic groups. In terms of the individual symptoms of GORD (heartburn, regurgitation, retrosternal pain, the heartburn score fell more markedly in the cisapride-group, particularly on day 28 (p < 0.05). The other symptoms did not show significant differences with the exception of nausea, which had a lower mean score on day 7 in the domperidone-group (p < 0.05). Diarrhoea was consistently but not significantly less in the domperidone-group.

**DYSPEPSIA: global evaluation of therapy**

Of the 84 DYSPEPSIA-group patients, 37 received domperidone and 47 received cisapride. The demographic data of the two treatment groups were comparable. In the domperidone-group, 2 patients withdrew due to an ADE (abdominal cramps) and 6 patients withdrew due to inefficacy of the treatment either during the active treatment phase or in the follow-up period. In the cisapride-group 1 patient withdrew due to an ADE (diarrhoea) and 5 patients due to inefficacy either during the active treatment phase or in the follow-up
period. As is shown in Table 2, the global evaluation of the therapeutic results reported by the patients and by the investigators was similar in both groups at the end of active treatment (day 28).

**DYSPEPSIA: response rates at end of therapy and follow-up**

At all visits, during treatment and during the follow-up period, the response rates were similar with both treatments. The benefit obtained with both treatments persisted during the follow-up period (Table 3).

Table 3. Response rates* in GORD & dyspepsia
* symptom scores reduced by > 66%; **p < 0.05

<table>
<thead>
<tr>
<th></th>
<th>Therapy</th>
<th>day 7</th>
<th>day 28 End of therapy</th>
<th>day 56 Follow-up</th>
<th>day 84 End of follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dyspepsia</td>
<td>Domperidone</td>
<td>59%</td>
<td>76%</td>
<td>78%</td>
<td>78%</td>
</tr>
<tr>
<td></td>
<td>Cisapride</td>
<td>51%</td>
<td>79%</td>
<td>79%</td>
<td>81%</td>
</tr>
<tr>
<td>GORD</td>
<td>Domperidone</td>
<td>41%</td>
<td>64%</td>
<td>73%</td>
<td>73%</td>
</tr>
<tr>
<td></td>
<td>Cisapride</td>
<td>48%</td>
<td>95%(**)</td>
<td>90%</td>
<td>86%</td>
</tr>
</tbody>
</table>

**DYSPEPSIA: symptoms' scores**

The individual symptoms' scores improved consistently in both therapeutic groups with a marginally greater improvement in the cisapride-group. The difference between the treatment groups did not, however, reach statistical significance. In terms of individual symptoms the regurgitation score was consistently but not significantly lower in the cisapride-group. Diarrhoea was consistently but not significantly higher in the cisapride-group.

**Safety assessments**

No major or unexpected adverse events were registered during this trial. There were 3 treatment withdrawals attributed to ADEs in the patients treated with domperidone (2 due to abdominal cramps, 1 due to an exanthema) and 1 case in the patients treated with cisapride (diarrhoea).

**DISCUSSION**

In this double-blind controlled study performed in 127 patients suffering from functional dyspepsia the two prokinetics, cisapride and domperidone resulted in an overall similar degree of symptom reduction. We observed,
however, differences in the comparative therapeutic efficacy of cisapride and domperidone in the treatment of subgroups of functional dyspepsia.

Cisapride (10 mg qid) was more effective than domperidone (20 mg qid) in the treatment of GORD-like dyspepsia while the two prokinetics had similar efficacy in the therapy of dyspepsia where reflux symptomatology was not predominant. Furthermore, cisapride-treated patients with GORD-like symptomatology, all of whom received the higher dose (qid), clearly showed greater improvement than the other dyspepsia patients treated with the lower cisapride dose (tid) and than both subgroups treated with domperidone.

In terms of the symptomatology, there was a greater reduction in the cluster of symptoms related to gastroesophageal reflux in the cisapride-treated patients than in those receiving domperidone. In the patients treated with the higher dosage of domperidone, the drug appeared to have a stronger anti-nausea effect than cisapride in the first week of treatment only. Diarrhoea was slightly but not significantly more often occurring in the cisapride-treated group which could be expected from this prokinetic's pharmacological action of increasing colonic motility.

The relapse rates after two months of follow-up were less than 2% in the domperidone-group (1:59 patients) and 7% in the cisapride-group (5:68 patients). These relapse rates are lower than those reported recently by Rösch (10) and Heyse et al. (11).

The differences between the two prokinetics at the symptomatic level are relatively modest but are well in line with those which could be expected from their respective pharmacological profiles since cisapride has a more potent activity than domperidone on gastroesophageal reflux and colonic stimulation during the active treatment phase or in the follow-up period.

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REFERENCE


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