Rabeprazole combined with hydrotalcite is effective for patients with bile reflux gastritis after cholecystectomy

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BACKGROUND: Regardless of surgical technique, patients who have undergone cholecystectomy appear to be predisposed to the development of bile reflux gastritis.

OBJECTIVE: To assess the efficacy of rabeprazole and hydrotalcite in patients with bile reflux gastritis after cholecystectomy.

METHODS: Postcholecystectomy patients with bile reflux gastritis confirmed by endoscopy and 24 h gastric bilirubin monitoring were randomly assigned to one of four eight-week treatments: observation (group A), rabeprazole alone (group B), hydrotalcite alone (group C) and rabeprazole in combination with hydrotalcite (group D). Endoscopy and 24 h gastric bilirubin monitoring were repeated in all patients after treatment. Dyspeptic symptoms of abdominal pain, bloating, heartburn, bitter taste, endoscopic and histological finding, and biliary reflux were evaluated before and after treatment.

RESULTS: After administering medication, patient symptoms in groups B, C and D were relieved—most significantly in group D (P<0.05). There were no significant differences in endoscopic hyperemia and histological inflammation among the groups (P>0.05). However, histological activity, the number of reflux episodes and the number of reflux episodes lasting longer than 5 min were significantly decreased only in group D (P<0.05). The total per cent of bilirubin absorption (value of 0.14 units or greater) time was decreased in groups B, C and D, and most significantly in group D (P<0.05).

CONCLUSION: Rabeprazole combined with hydrotalcite is an effective therapeutic option in the treatment of patients with bile reflux gastritis after cholecystectomy.

Key Words: Bile reflux; Gastritis; Hydrotalcite; Rabeprazole

A considerable number of patients complain about persistent dyspeptic symptoms after cholecystectomy, including epigastric pain, bloating, heartburn and bitter taste. The development of these dyspeptic symptoms could be due to many factors. In the absence of a gallbladder, disequilibrium in the rate of bile released into the duodenum may lead to duodenogastric bile reflux, resulting in gastric cellular membrane degeneration and, thus, bile reflux gastritis (BRG) (1). In contrast, antroduodenal dysmotility after cholecystectomy has also been implicated in the pathogenesis of BRG (2).

BRG has now been accepted by the Sydney system (3) as a distinct entity. Apart from severe metaplastic gastritis, carcinogenesis could also be induced by duodenogastric reflux (4,5). To date, BRG remains a poorly understood entity, with no current effective pharmacological strategies for the management of postcholecystectomy BRG and related dyspeptic symptoms (6).

The use of proton pump inhibitors (PPIs), which strongly inhibit gastric acid secretion and reduce duodenogastroesophageal reflux, has provided relief of reflux symptoms. Several
studies have shown that treatment with PPIs dramatically decrease both acid and bile reflux into the esophagus, as measured by Bilitec 2000 (Medtronic Synetics, Sweden) monitoring and a pH probe (7-9). However, the available literature suggests that PPIs are not as effective at suppressing duodenogastric reflux as they are at inhibiting acid reflux (8,9). The effect of PPIs in the management of duodenogastric reflux needs to be reinvestigated.

Because cellular membrane degeneration is involved in the pathogenesis of BRG, mucosal protective therapy may also have a favourable prophylactic and therapeutic effect on mucosal injury caused by the prolonged exposure of the gastric mucosa to bile contents and gastric acid.

As a PPI agent, rabeprazole has a strong antisecretory action (10). Moreover, it has a definite cell protective effect in the process of chemically induced mucosal injury (11,12). Hydrotalcite, a frequently used gastric mucosal protectant, has dual effects in both bile complexation and acid neutralization (13). Rabeprazole and hydrotalcite both seem to be appropriate candidates for the treatment of duodenogastric bile reflux.

The aim of the present study was to investigate the efficacy of different therapeutic regimens of rabeprazole and hydrotalcite by assessing the improvements in dyspeptic symptoms, gastric mucosal inflammation and bile reflux in patients with apparent dyspeptic symptoms caused by bile reflux after cholecystectomy.

METHODS

Patients

From May 2006 to October 2007, 120 postcholecystectomy BRG patients satisfying the entry criteria were included in the study.

Inclusion criteria were as follows: patients with a history of cholecystectomy due to cholecystolithiasis in the past two years, accompanied by apparent dyspeptic symptoms according to the validated Leeds Dyspepsia Questionnaire (LDQ) (14), apparent endoscopic gastritis (assessed by the same endoscopist according to the Kleba endoscopic criteria [15]) and abnormal bile reflux exposure confirmed by Bilitec 2000 monitoring.

Exclusion criteria were as follows: Helicobacter pylori infection, the use of nonsteroidal anti-inflammatory drugs, adrenal cortex hormone therapy, the use of acid inhibitors or antacid agents in the four weeks preceding endoscopy, abuse of alcohol, pancreatic diseases, major abdominal surgery, previous peptic ulcer disease, pregnant or lactating women, and other organic or severe psychiatric disorders as assessed by history, appropriate consultations and laboratory tests.

The study protocol was approved by the Shanghai Renji Hospital Ethics Committee (Shanghai, China). Informed written consent was obtained from each patient.

Treatment

Patients were designated to one of four eight-week treatment groups selected by a computer-generated random number assignment in opaque, sealed envelopes: group A was comprised of 30 patients who were administered 20 mg rabeprazole (Pariet, Janssen Pharmaceutical Ltd, United Kingdom) once a day, 30 min before breakfast; group B was comprised of 30 patients who were administered 1.0 g hydrotalcite (Talcid, Bayer Pharmaceutical Ltd, Germany) three times a day, chewed after dinner; and group D consisted of 31 patients who received a combination of both rabeprazole 20 mg once daily and hydrotalcite 1.0 g three times per day, chewed after dinner. During the eight-week therapeutic period, all of the patients were advised against taking other medications such as PPIs, and antacid or prokinetic agents.

Patients were blinded to the possible therapeutic effects of treatment throughout the study period. Patients in group A were told that there were no currently effective therapies for BRG and that they would be observed without any treatment for eight weeks. Patients in groups B, C and D were told that the efficacy of the medications were not confirmed and could only be evaluated based on symptoms, endoscopic appearance and bilirubin monitoring results after treatment.

Evaluations

Symptomatic evaluation: Each subject was sent a structured dyspepsia questionnaire based on the validated LDQ to assess dyspeptic symptoms at baseline and symptom improvements after eight weeks of treatment. The LDQ (14), which is administered in a face-to-face interview, measures four dyspepsia symptoms (upper abdominal pain, heartburn, bloating and bitter taste) on a six-grade scale (grade 0 = not present; 1 = very mild; 2 = mild symptoms, noted when the patient was reminded by the physician; 3 = moderate complaints with no interference of daily life activities; 4 = severe complaints, with occasional interference in daily life activities; and 5 = very severe).

Endoscopic and histological evaluation: For all patients, three biopsies from the antrum and two biopsies from the body of the stomach during endoscopy were obtained. H pylori infection was assessed by modified Giemsa stain and rapid urease test (positive results in both tests were considered affirmative for H pylori infection). Four biopsies were used for routine hematoxylin and eosin histology.

Presently, there are no histological markers for the diagnosis of BRG. Our criteria for endoscopic diagnosis of BRG were established according to endoscopic criteria proposed by Kleba (15). Gastritis was evaluated based on endoscopic evidence of mucosal edema and hyperemia: 0 = none; 1 = mild; 2 = moderate; and 3 = severe.

Hematoxylin and eosin histological findings were independently graded semiquantitatively by two experienced pathologists according to the updated Sydney System (3). Scores of chronic inflammation and activity were graded on monocellular cells and polymorphonuclear infiltration, respectively (0 = normal, 1 = mild, 2 = moderate and 3 = severe). Improvements of histological alterations were evaluated after a second endoscopic examination.

Both the endoscopist and the pathologists were blinded to the treatment regimen assigned to each patient. Furthermore, the study materials were kept in a location that could only be accessed by a study nurse. Patients were advised not to discuss the study treatment or their responses to it with the endoscopist.

24 h gastric bilirubin monitoring: The Bilitec 2000 was used to quantify ambulatory bile reflux using bilirubin as a marker for the presence of duodenal contents. It is a portable optoelectronic instrument fitted with a fibre optic probe capable of monitoring the presence of bilirubin in the foregut lumen over...
Combination rabeprazole/hydrotalcite therapy for BRG

**TABLE 1**
Clinical symptom scores pre- and post-treatment

<table>
<thead>
<tr>
<th>Symptoms</th>
<th>Group A (observation)</th>
<th>Group B (rabeprazole)</th>
<th>Group C (hydrotalcite)</th>
<th>Group D (combination)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Pre</td>
<td>Post</td>
<td>P</td>
<td>Pre</td>
</tr>
<tr>
<td>Epigastric pain</td>
<td>3.24±0.71</td>
<td>3.39±0.53</td>
<td>0.054</td>
<td>3.24±0.79</td>
</tr>
<tr>
<td>Heartburn</td>
<td>3.31±0.64</td>
<td>2.91±0.59</td>
<td>0.061</td>
<td>3.31±0.64</td>
</tr>
<tr>
<td>Bloating</td>
<td>3.27±0.86</td>
<td>3.10±0.94</td>
<td>0.093</td>
<td>3.22±0.71</td>
</tr>
<tr>
<td>Bitter taste</td>
<td>3.25±0.78</td>
<td>3.22±0.99</td>
<td>0.075</td>
<td>3.24±0.71</td>
</tr>
</tbody>
</table>

*P<0.05 compared pre- and post-treatment in each group; †P<0.05 compared among the four groups.

Patient characteristics
All patients completed the study. Group A consisted of 30 patients (17 men, 13 women) with a mean age of 54 years (range 33 to 70 years). Group B consisted of 30 patients (18 men, 12 women) with a mean age of 55 years (range 35 to 71 years). In group C, a total of 29 patients (15 men, 14 women) with a mean age of 57 years (range 32 to 66 years) were observed. There were 31 patients in group D (17 men, 14 women), with a mean age of 53 years (range 33 to 70 years).

Baseline parameters including age, sex, dyspeptic symptom scores, endoscopic gastritis, histological inflammation, and degree of bile reflux evaluated by endoscopy and Bilitec 2000 monitoring before treatment, were homogeneously distributed among the four groups (P>0.05).

Dyspeptic symptom scores
There were no statistically significant differences in pre- and postdyspeptic symptom (abdominal pain, bloating, bitter taste and heartburn) scores in group A, whereas the scores of patients in group B, C and D were all decreased – most significantly in group D (P<0.05) (Table 1).

Endoscopic and histological inflammation scores
After treatment, there was no statistically significant difference in the baseline histological score of chronic inflammation in each group, while the histological activity score was significantly decreased in group D (Table 2).

Bile reflux evaluated by Bilitec 2000 monitoring
There were no significant differences in the number of bile reflux episodes evaluated by Bilitec 2000 monitoring between pre- and postobservation in group A. Although the number of reflux episodes and the number of reflux episodes lasting longer than 5 min decreased after treatment in groups B, C and D, statistical significance was found only in group D (P<0.05). Moreover, the total per cent of time in which absorbance was greater than 0.14 units also significantly decreased in groups B, C and D, and most significantly in group D (P<0.05) (Table 3).
TABLE 2
Endoscopic and histological inflammation scores pre- and post-treatment

<table>
<thead>
<tr>
<th>Inflammation</th>
<th>Group A (observation)</th>
<th>Group B (rabeprazole)</th>
<th>Group C (hydrotalcite)</th>
<th>Group D (combination)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Pre</td>
<td>Post</td>
<td>P</td>
<td>Pre</td>
</tr>
<tr>
<td>Endoscopic scores</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hyperemia</td>
<td>2.25±0.74</td>
<td>2.18±0.81</td>
<td>0.053</td>
<td>2.13±0.87</td>
</tr>
</tbody>
</table>
| Edema               | 2.10±0.75 | 2.09±0.64 | 0.071 | 2.09±0.63 | 1.99±0.73 | 0.051 | 2.13±0.81 | 2.01±0.78 | 0.052 | 2.11±0.77 | 1.50±0.67 | 0.027*
| Histological scores |        |      |      |        |      |      |        |      |      |        |      |      |
| Chronic inflammation| 3.54±0.70 | 3.55±0.65 | 0.062 | 3.40±0.79 | 3.65±0.46 | 0.091 | 3.29±0.81 | 3.31±0.79 | 0.421 | 3.31±0.76 | 3.47±0.66 | 0.054 |
| Activity            | 2.90±0.72 | 2.57±0.85 | 0.077 | 2.95±0.68 | 2.76±0.91 | 0.060 | 2.45±0.54 | 2.50±0.47 | 0.051 | 2.87±0.72 | 1.97±0.78 | 0.029*

Pre- and post-treatment data presented as mean ± SD. *P<0.05 compared pre- and post-treatment in each group.

TABLE 3
Bilitec 2000 24 h bile acid monitoring pre- and post-treatment

<table>
<thead>
<tr>
<th>Bile reflux</th>
<th>Group A (observation)</th>
<th>Group B (rabeprazole)</th>
<th>Group C (hydrotalcite)</th>
<th>Group D (combination)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Pre</td>
<td>Post</td>
<td>P</td>
<td>Pre</td>
</tr>
<tr>
<td>Reflux</td>
<td>69.04±23.00</td>
<td>63.46±21.34</td>
<td>0.091</td>
<td>68.64±22.70</td>
</tr>
<tr>
<td>episodes</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Reflux</td>
<td>17.89±1.78</td>
<td>16.02±1.63</td>
<td>0.068</td>
<td>19.37±2.70</td>
</tr>
<tr>
<td>episodes</td>
<td>&gt;5 min</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total per-</td>
<td>49.67±21.45</td>
<td>46.76±19.00</td>
<td>0.089</td>
<td>48.64±23.10</td>
</tr>
<tr>
<td>cent time</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ABS &gt;0.14</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Pre- and post-treatment data presented as mean ± SD. *P<0.05 compared pre- and post-treatment in each group; †P<0.05 compared among the four groups. ABS Absorbance. Bilitec 2000, Medtronic Synetics, Sweden

Adverse events

Regarding drug-associated side effects, only mild diarrhea was found to be associated with the use of hydrotalcite alone in a few patients; however, no patients discontinued the use of hydrotalcite because of this side effect. It was noted that no relevant side effects were observed in other three groups. Therefore, rabeprazole and hydrotalcite were confirmed to be well tolerated after eight weeks of continuous use, even in combination.

DISCUSSION

Previous studies (16,17) have shown that 51% to 89% of postcholecystectomy patients have pathological duodenal gastric reflux, and a significant correlation exists between intragastric bile acid levels and the severity of duodenogastric reflux. Bile acids are capable of altering the permeability barrier of the gastrointestinal tract, which would lead to severe metaplastic gastritis and, possibly, carcinogenesis (4,18-20). Therefore, a treatment agent because of its additional antacid and antibile conjagation effects owing to an active hydrated carbonate moiety, which is able to maintain the optimal acid environment (approximate pH of 3 to 5) in the stomach and protect gastric mucosa, resulting in prompt symptom relief (13). We found that hydrotalcite had a similar effect in symptom relief and reduction of total percentage of bilirubin absorbance time of greater than 0.14 units (from 47% to 37%).

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With the use of rabeprazole or hydrotalcite alone, symptoms persisted in some patients because the degree of biliary reflux reduction was insufficient. Regarding the effect of combination rabeprazole/hydrotalcite therapy, our study expectedly showed that symptoms, endoscopic and histological evaluation and reduction of bile reflux, the number of biliary reflux episodes, the number of reflux episodes lasting longer than 5 min and the percent time of bilirubin absorbance greater than 0.14 units, were all significantly improved in patients undergoing combination treatment compared with patients who were treated with either agent alone.

The present study had several limitations. First, patient blinding was not feasible because it would have required the same dosage form of both medication and placebo. The control group in the present study was treated observed only and did not receive a placebo. Thus, conclusions regarding possible placebo effects on postcholecystectomy dyspeptic symptoms could not be drawn. Second, as mentioned above, BRG remains a poorly understood entity and dyspeptic symptoms reported by the patients may not necessarily be a function of bile gastritis, but may have been due to other factors such as abnormal motility following cholecystectomy. Only treatments aimed at relieving BRG symptoms were investigated in the present study. Whether combination therapy with prokinetic agents would provide additional improvement requires further study.

**CONCLUSION**

Hydrotalcite (an antacid) combined with rabeprazole (a PPI) may be a relatively more effective option for the management of postcholecystectomy BRG. The exact mechanisms of action remain to be investigated, and trials longer than eight weeks are necessary to confirm the current findings and determine whether the benefits persist after treatment is discontinued.

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