

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).

Association de rabéprazole et d'hydrotalcite : Efficace chez les patients souffrant de gastrite par reflux biliaire post-cholécystectomie

HISTORIQUE : Peu importe la technique chirurgicale, les patients qui ont subi une cholécystectomie semblent prédisposés à la gastrite par reflux biliaire.

OBJECTIF : Évaluer l'efficacité du rabéprazole et de l'hydrotalcite chez les patients qui souffrent de gastrite par reflux biliaire post-cholécystectomie.

MÉTHODES : Après la cholécystectomie, des patients souffrant de gastrite par reflux biliaire confirmée au moyen de l'endoscopie et de la surveillance de la bilirubine gastrique sur 24 heures ont été assignés aléatoirement à l'une des quatre interventions de huit semaines suivantes : observation (groupe A), rabéprazole seul (groupe B), hydrotalcite seul (groupe C) et rabéprazole en association avec hydrotalcite (groupe D). Tous les patients ont subi une endoscopie et un dosage de la bilirubine gastrique des 24 heures de contrôle après le traitement. Les symptômes digestifs hauts, tels douleurs abdominales, ballonnements, brûlures d'estomac, goût amer, ainsi que les signes endoscopiques et histologiques et le reflux biliaire ont été évalués avant et après le traitement.

RÉSULTATS : Après l'administration des médicaments, les symptômes des patients des groupes B, C et D ont été soulagés et de façon plus marquée dans le groupe D ($P < 0,05$). On n'a noté aucune différence significative quant à l'hyperémie endoscopique et l'inflammation histologique entre les groupes ($P > 0,05$). Toutefois, l'activité histologique, le nombre d'épisodes de reflux et le nombre d'épisodes de reflux d'une durée de plus de cinq minutes ont significativement diminué uniquement dans le groupe D ($P < 0,05$). Le pourcentage total du temps d'absorption de la bilirubine (valeur de 0,14 unités ou plus) a diminué dans les groupes B, C et D et de façon plus marquée dans le groupe D ($P < 0,05$).

CONCLUSION : Le rabéprazole allié à l'hydrotalcite est une option thérapeutique efficace dans le traitement des patients qui souffrent de gastrite par reflux biliaire post-cholécystectomie.

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 duodenogastric reflux, has provided relief of reflux symptoms. Several

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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 cholelithiasis 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 underwent observation only; group B 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 C consisted of 29 patients who received 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 mononuclear 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

TABLE 1
Clinical symptom scores pre- and post-treatment

Symptoms	Group A (observation)			Group B (rabeprazole)			Group C (hydrotalcite)			Group D (combination)		
	Pre	Post	P	Pre	Post	P	Pre	Post	P	Pre	Post	P
Epigastric pain	3.24±0.71	3.39±0.53	0.054	3.24±0.79	2.39±0.86	0.041*	3.32±0.08	2.06±1.00	0.033*	3.36±0.65	1.88±0.86	0.035*†
Heartburn	3.31±0.64	2.91±0.59	0.061	3.31±0.64	2.21±0.95	0.031*	3.23±0.69	1.96±0.07	0.026*	3.12±0.67	1.72±0.79	0.041*†
Bloating	3.27±0.86	3.10±0.94	0.093	3.22±0.71	2.16±0.91	0.029*	3.21±0.70	2.06±0.91	0.031*	3.25±0.68	1.69±1.01	0.022*†
Bitter taste	3.25±0.78	3.22±0.99	0.075	3.24±0.71	2.27±0.96	0.024*	3.29±0.73	2.16±0.92	0.013*	3.10±0.64	1.75±0.79	0.032*†

Pre- and post-treatment data presented as mean ± SD. Symptom scores ranged from 0 (not present) to 5 (very severe). * $P < 0.05$ compared pre- and post-treatment in each group; † $P < 0.05$ compared among the four groups

a 24 h period. The distal tip of the probe contains a 2 mm space through which fluids can flow. The portable unit contains two light-emitting diodes, one emitting a wavelength of 470 nm (ie, close to the absorbance peak of bilirubin at 453 nm) and the other at 565 nm (reference signal). Optical signals reflected back to the probe are converted into electrical impulses by a photodiode. A microcomputer calculates the difference between the absorbance at 470 nm and 565 nm. This difference is commonly known as the absorbance value and may range from 0 (plain water) to 1 (total screen); however, the working range of the instrument has been shown to span absorbance values from 0.14 to 0.60 only (9).

In the present study, after calibration of the instrument, the probe was inserted transnasally with local anaesthesia and guided by fluoroscopy. The tip of the probe was inserted through one side of the nasal cavity into the stomach and placed approximately 10 cm beneath the lower esophageal sphincter. All medications that could alter motility and gastrointestinal secretion were suspended (eg, histamine antagonists and prokinetic agents for at least 48 h, and PPIs for at least two weeks before the test). All participants were advised to eat three standard meals per day, which were composed of nutrients that could not significantly interfere with bilirubin detection (eg, water, milk, boiled chicken breast, boiled potatoes, white bread, rice, bananas and apples). Alcohol and smoking were also prohibited. All patients were free to pursue regular activities (except those that aggravated their symptoms) and sleep.

At the end of the 24 h study, the probe was removed and data were downloaded and analyzed (Esophogram, GastroSoft Inc, USA). An absorbance value of 0.14 was used as the threshold value for reflux episodes in all patients. The software calculated the percentage of time that bilirubin absorption was greater than 0.14 units during the total monitoring time. It also recorded the total number of reflux episodes for the same time period and the number of biliary reflux episodes lasting longer than 5 min.

Statistical analysis

SPSS version 13.0 (SPSS Inc, USA) software was used to analyze the data. For normally distributed continuous variables with equal variances among groups, an ANOVA model was used to compare baseline differences of the four groups, including age and total per cent time of bilirubin absorbance greater than 0.14 units. For categorically and non-normally distributed continuous variables (including scores of dyspeptic symptoms, endoscopic gastritis, histological inflammation, and degree of

bile reflux), the Kruskal-Wallis test was used to assess differences among the four groups. The Wilcoxon test was used to assess differences before and after the treatment in each group. For normally distributed continuous variables with equal variances (total per cent time of bilirubin absorbance greater than 0.14), the paired *t* test was used and $P < 0.05$ was considered to be statistically significant.

RESULTS

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

Inflammation	Group A (observation)			Group B (rabeprazole)			Group C (hydrotalcite)			Group D (combination)		
	Pre	Post	P	Pre	Post	P	Pre	Post	P	Pre	Post	P
Endoscopic scores												
Hyperemia	2.25±0.74	2.18±0.81	0.053	2.13±0.87	2.15±0.79	0.083	2.20±0.85	2.16±0.77	0.069	2.18±0.69	2.00±0.80	0.102
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. Scores of chronic inflammation and activity were graded on mononuclear cells and polymorphonuclear infiltration, respectively (0 = normal, 1 = mild, 2 = moderate and 3 = severe). *P<0.05 compared pre- and post-treatment in each group

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

Bile reflux	Group A (observation)			Group B (rabeprazole)			Group C (hydrotalcite)			Group D (combination)		
	Pre	Post	P	Pre	Post	P	Pre	Post	P	Pre	Post	P
Reflux episodes	69.04±23.00	63.46±21.34	0.091	68.64±22.70	62.68±22.40	0.060	67.64±21.59	63.04±21.88	0.059	68.38±22.12	53.85±19.40	0.039*
Reflux episodes >5 min	17.89±1.78	18.02±1.63	0.068	19.37±2.70	17.97±1.30	0.085	18.40±2.70	15.20±2.51	0.100	18.26±1.80	9.70±1.20	0.037*
Total percent time ABS >0.14 units	49.67±21.45	46.76±19.00	0.089	48.64±23.10	38.12±13.80	0.032*	47.18±16.79	36.87±12.90	0.047*	48.02±11.93	33.60±8.80	0.042†

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 Syntetics, 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 post-cholecystectomy 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, timely, effective treatments should be carefully considered, with the aim of symptom relief and reduction of mucosal damage due to reflux. Unfortunately, BRG remains a poorly understood entity and there are still no well-established, evidence-based pharmacological approaches to its management in postcholecystectomy patients (21). To date, treatment with prokinetic agents have merely focused on clinical symptoms or acid reflux exclusively, often with controversial results (22-25). Furthermore, prokinetic agents administered alone cannot completely eliminate the risk of cancerization due to bile reflux. In the present study, we investigated the efficacy of different therapy regimens of rabeprazole and hydrotalcite for patients with BRG after cholecystectomy.

Bile reflux is often accompanied by acid reflux in patients with BRG (26). Acid suppressive therapy seems to be helpful in reducing the harmful effects of gastric acid and bile. Acid

suppressive therapy was supported in a study in which both acid and bile reflux was significantly suppressed by PPI therapy (9). The present study provides further support for the use of acid suppressant therapy, which found that after treatment with rabeprazole, scores of dyspeptic symptoms and total percent time of bilirubin absorbance greater than 0.14 units (from 49% to 38%) declined. The mechanisms involved in clearance of nonacid reflux may be explained by the following: PPIs have been shown to augment the antral and duodenal phase III migrating motor complex in healthy individuals, thereby accelerating antroduodenal passage of gastric contents, which should reduce duodenogastric reflux episodes and, thus, volume of both acid and bile refluxing into the stomach (27,28). In addition, the possible explanation for symptom relief and endoscopic and histological improvement may also implicate the cytoprotective properties of rabeprazole against chemically induced gastric damage (11).

Is a mucosal protective agent useful in patients with BRG? Santarelli et al (29) compared the efficacy of rabeprazole and sucralfate in the management of BRG – their findings demonstrated that both were effective (29). Sucralfate, a classic cytoprotective agent, is able to form a physical barrier between the gastric mucosa and damaging agents such as bile contents. This cytoprotective effect is not dependent on antisecretory action. In our study, hydrotalcite rather than sucralfate was selected as a treatment agent because of its additional antacid and antibile conjugation 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%).

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 per cent 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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