Prophylactic Use of Omeprazole Associated with a Reduced Risk of Peptic Ulcer Disease among Maintenance Hemodialysis Patients

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Abstract

Background. Patients undergoing maintenance hemodialysis (MHD) have a high prevalence of peptic ulcer disease (PUD). Omeprazole is a proton pump inhibitor with proven efficacy in the prevention and treatment of PUD. However, there is little data on the prophylactic use of omeprazole in reducing the risk of PUD among MHD patients.

Methods. This prospective study included 93 patients undergoing MHD at Zen-Ho Dialysis Center between July 2008 and December 2009. Fifty-three patients were assigned to receive 20 mg of omeprazole daily for 18 months and 40 patients served as control. The Kaplan-Meier method was applied to calculate the cumulative incidence of PUD.

Results. The per-protocol population comprised 85 patients (omeprazole group, 49; control group, 36). Both groups had similar baseline characteristics. The need for endoscopy was found to be significantly less (10.2 vs. 44.4%, P = 0.001) in the omeprazole group than in the control group. Dialysis patients in the omeprazole group required fewer blood transfusions and erythropoietin doses than did the control group patients. Kaplan Meier analysis revealed a higher cumulative ulcer rate in the control group (log-rank test, P = 0.04). However, omeprazole did not reduce the risk of PUD in MHD patients on regular aspirin or warfarin.

Conclusions. We conclude that prophylactic use of omeprazole might be effective to lower the incidence of PUD among MHD patients without regular aspirin or warfarin use. Further large-scale controlled trials should be carried out to confirm our findings.

Introduction

Dialysis patients are known to have an elevated bleeding risk. Although the pathogenesis of excessive bleeding in patients with end stage renal disease (ESRD) is multifactorial, defects of platelet function and platelet-vessel wall interaction are thought to play a major role [1-2]. Moreover, because of a high risk of cardiovascular or cerebrovascular diseases in dialysis patients, a high prevalence of antiplatelet or warfarin use further contributes to an increased bleeding risk [2]. It has been reported that a majority of the bleeding events originate from the gastrointestinal tract [2-3]. Gastroduodenal ulcers, i.e., peptic ulcer disease (PUD), have been reported to account for nearly 60% of upper GI bleeding episodes among patients receiving maintenance hemodialysis (MHD) [3-4]. Systemic/local circulatory failure, hypergastrinemia, high ammonia levels, and enhanced inflammation were considered to contribute to GI mucosal injury in MHD patients [1,4]. Even though more and more studies explore this topic, several important issues still remain unsettled.

Several reports have indicated that dialysis patients, despite having a lower prevalence of *Helicobacter pylori* (*H. pylori*) infection, have a higher occurrence of PUD than those without renal failure [5-6]. Since dialysis patients have a high risk of GI mucosal damage, these patients with PUD should be managed as a high-risk group [1], and strategies to reduce its incidence need to be developed. Omeprazole is a proton pump inhibitor (PPI) widely used in the treatment of PUD or gastroesophageal reflux disease [7]. By blocking the production of gastric acid, omeprazole helps in healing the ulcerated gastric mucosa and relieving dyspepsia [7]. The efficacy of PPIs in the prevention of non-steroidal anti-inflammatory drug (NSAID)-associated ulcers has been largely established in the general population [8-10]. Accumulating studies have also shown PPIs to have good safety and efficacy in dialysis patients with PUD [11]. However, prophylactic use of omeprazole to reduce the risk of PUD

has rarely been reported among MHD patients. Therefore, the primary objective of this study was to determine whether MHD patients on omeprazole have a lower risk for PUD than those not receiving omeprazole. We also assessed the safety and cost-effectiveness of omeprazole use among MHD patients.

Materials and Methods

Patient population and study design

This prospective study initially included 124 dialysis patients receiving chronic hemodialysis at Zen-Ho Dialysis Center (Taichung County, Taiwan) between July 2008 and December 2009. Patients were considered eligible for inclusion if they underwent HD for more than 3 months; had no GI symptoms at enrollment; and if they agreed to receive an endoscopic examination if either typical GI symptoms for PUD [7], positive fecal occult blood test, or an unexplained hematocrit drop over 3% was noted during the study period. The exclusion criteria were a history of gastric surgery; allergy to omeprazole; use of PPI or histamine$_2$ receptor antagonists within 1 year prior to enrollment; and presence of coagulopathy, thrombocytopenia, liver cirrhosis, or cancer. We also excluded dialysis patients with a history of endoscopically confirmed PUD. Ninety-three eligible subjects were enrolled in this study. Fifty-three patients were assigned to receive 20 mg of omeprazole (Okwe, Nang-Kuang Pharmaceutical Co. Ltd, Tainan County, Taiwan) daily for 18 months and 40 patients who did not receive omeprazole served as controls. All patients were followed-up to investigate the occurrence of PUD during the study period. Patients on medications such as warfarin, nonsteroidal anti-inflammatory drugs (NSAIDs), cyclooxygenase-2 inhibitors, corticosteroids, and/or antiplatelet drugs prior to the study were allowed to continue use of these medications during the study period. However, new medications were prohibited until the end of the study. The end point was PUD, as defined by a gastric or duodenal ulcer, diagnosed by endoscopy without other identified causes during the 18-month study period. This clinical study followed the principles of the Declaration of Helsinki and was compatible with the policies of the local ethics committee. The anonymity of all enrolled subjects was carefully protected and informed written consent was obtained from all participants.

Collection of clinical data

During the study period, a monthly evaluation of complete blood count, serum biochemical data, and fecal occult blood was performed. Hemoglobin and hematocrit levels were obtained bi-weekly and dialysis adequacy (i.e., Kt/V) and parathyroid hormone levels were determined every 3 months. Drug compliance, use of prohibited medications, and drug safety and tolerability were also assessed monthly. Failure to take > 80% of the omeprazole doses was considered unsatisfactory compliance. The assessment of safety and tolerability was based on spontaneously reported adverse events and open questionnaires administered by the dialysis staff. We also examined clinical parameters of endoscopically confirmed PUD events, including (i) clinical presentations; (ii) endoscopic treatments, findings, and diagnoses; and (iii) clinical outcomes (transfusion requirements, complications, and mortality). Blood transfusion was performed in cases if hematocrit levels dropped below 25% or in cases of symptomatic anemia. All the lesions detected by high-definition video endoscopy (EVIS LUCERA GIF-H260; Olympus Optical Co., Ltd, Tokyo, Japan) were examined by experienced endoscopists [12]. During endoscopic diagnosis of PUD, all biopsy samples were taken with sterile biopsy forceps to detect *H. pylori* infection by the rapid urease test. Patients were considered *H. pylori*-positive if the color change occurred within 24 hours. An ulcer was defined as a circumscribed mucosal break at least 5 mm in diameter and having a perceptible depth [7-10]. Erosion was defined as a flat mucosal break of any size occurring in the presence of blood in the stomach or duodenum [7-10].

Statistical analysis

Efficacy analyses were carried out only for the per-protocol population. Continuous variables were expressed as means ± standard deviation, and categorical variables were expressed as number or percentage for each parameter, unless otherwise stated. Data were routinely tested

for normality of distribution and equality of standard deviations before analysis. All collected hematological and biochemical parameters during the study period were averaged for analysis. For comparison of continuous variables between the omeprazole and control groups, unpaired variables were compared by Student's t-test or Mann–Whitney U-test, and paired variables by Student's t-test or Wilcoxon test, as appropriate. For categorical variables, a cross-table with Fisher exact test was used. The Kaplan-Meier method was applied to calculate the cumulative incidence of PUD, and the difference was determined by the log-rank test. All statistical analyses were performed using Statistical Packages for Social Sciences (SPSS) 13.0 for Windows (SPSS Inc., Chicago, IL). The criterion for significance was the 95% confidence interval (CI) to reject the null hypothesis.

Results

Study population characteristics

Ninety-three patients were enrolled in this study and received HD with a high flux dialyzer during the study period. In the omeprazole group, one patient discontinued its use because of adverse events and one patient was excluded because of unsatisfactory compliance. During the study period, one patient in the omeprazole group died of malignancy, one in the control group died of sepsis, and one in the control group died of cardiovascular diseases. Additionally, one patient in the omeprazole group and two patients in the control group were excluded from the per-protocol analysis owing to the use of other medications during the study period. Finally, the per-protocol population comprised 85 patients (omeprazole group, 49; control group, 36). As shown in Table 1, the omeprazole and control groups were similar with respect to baseline characteristics.

Gastrointestinal events (Table 2)

During the study period, 5 patients in the omeprazole group and 16 in the control group underwent endoscopy because of typical symptoms of PUD, a positive fecal occult blood test, or unexplained hematocrit drop over 3%. Of these, all 5 patients in the omeprazole group were found to have PUD (2 gastric ulcers, 2 duodenal ulcers, 1 both gastric and duodenal ulcers). Of the 16 patients in the control group that underwent endoscopy, 15 were found to have PUD (12 gastric ulcers, 6 duodenal ulcers, 3 both gastric and duodenal ulcers). The need for endoscopy was significantly less in the omeprazole group than in the control group (10.2% vs. 44.4%, P = 0.001). Stigmata of recent hemorrhage (SRH) occurrence was significantly lower in the omeprazole group than in the control group. Among the per-protocol population, the incidence of PUD was higher in the control group (15 patients,

41.7%) than in the omeprazole group (5 patients, 10.2%) (P = 0.001, Fisher's exact test). However, similar *H. pylori* infection and recurrent bleeding rates were observed between the two groups. Four of the 24 aspirin users in the omeprazole group and 3 of 18 in the control group developed PUD. It is surprising that omeprazole did not reduce the risk of PUD among MHD patients with regular use of aspirin. Similar results were also found in warfarin users: 2 of 5 in the omeprazole group and 1 of 4 in the control group developed PUD. Dialysis patients in the omeprazole group had fewer requirements of blood transfusion than the control group patients (2% vs. 11.1%, P = 0.009). Although mean hematocrit levels in both groups were not statistically different, patients in the omeprazole group received lower erythropoietin (EPO) doses than those in the control group while achieving similar hematocrit levels (1469 ± 287 vs. 1904 ± 398 units, P = 0.024). There was no difference in the percentage of patients receiving iron supplementation between the two groups (12/49 vs. 10/36, P > 0.05). Kaplan-Meier analysis revealed a higher cumulative ulcer rate in the control group (Fig 1, P = 0.04). Nevertheless, we found two patients with GI bleeding diagnosed as having colonic angiodysplasia, instead of gastric or duodenal lesions.

Assessment of safety and side effects

During the study period, there were no serious adverse events in the omeprazole group. One patient in this group prematurely discontinued the study due to palpitation. There was no significant change in body weight before and after omeprazole treatment (57.6 ± 9.4 versus 58.6 ± 10.0 kg, P > 0.05). In the omeprazole group, one 45-year-old female with secondary hyperparathyroidism and one 78-year-old female with severe osteoporosis had femoral neck fractures because of accidental falls during the study period.

Discussion

This prospective study was conducted to investigate the effects of prophylactic omeprazole on the occurrence of PUD in dialysis patients. Our results demonstrated that prophylactic omeprazole use not only reduced the risk of PUD but also decreased the requirement for blood transfusion and EPO doses among MHD patients. Furthermore, our study revealed the cost-effectiveness of omeprazole use, particularly with respect to the expense of EPO as well as hospitalization for bleeding complications. However, this efficacy was not seen in dialysis patients on regular aspirin or warfarin.

In the past, PUD with its high rate of morbidity and mortality was a major threat to the general population [13]. With the advance in medical therapies and the discovery of *H. pylori*, PUD outcomes have greatly improved [7]. However, despite great progress in endoscopic and pharmacologic treatments, a high risk for PUD-related bleeding complications still exist in the dialysis population [3,4,14,15]. The recurrence rate of PUD has been reported to be significantly higher in dialysis patients than in those with normal kidney function [4]. Frequent occurrence of PUD in long-term dialysis patients not only affects the quality of life but also decreases the levels of hematocrit, a predictor of morbidity and mortality in these patients [16]. Therefore, the development of strategies to lower the incidence and severity of PUD is important in clinical practice. Since eradication of *H. pylori* did not prevent PUD recurrence in ESRD patients [4], other methods to reduce ulcer rates need to be developed. Our results indicate that prophylactic omeprazole use might be an effective strategy for preventing PUD among MHD patients.

One interesting finding of our study was that prophylactic omeprazole had no effect on the ulcer rate of MHD patients with regular aspirin or warfarin use. This result has several

interpretations. First, most of our patients with aspirin or warfarin use were > 60 years of age and had multiple comorbid conditions. Holden et al. reported the hazard ratio for the first major bleeding event to be 3.59 for warfarin exposure and 5.24 for aspirin exposure, with respect to MHD patients without warfarin or aspirin use [2]. Hence, an intervention involving PPIs alone might not change the incidence of PUD in this very high-risk group. Second, the small patient size limited the statistical power, which implies that the results of larger-scale studies may differ. Finally, some patients on aspirin or warfarin in both groups would intermittently stop it if they felt abdominal discomforts during the study period, which might explain why we did not find a significant effect of prophylactic omeprazole on the incidence of PUD in these patients.

During the study period, we did not notice serious adverse events associated with omeprazole use. Although long-term use of PPI has been shown to lead to body weight gain in the general population by relieving the symptoms of PUD and increasing appetite [17], our result was not consistent with this finding. It is possible that the limited water intake as well as diet control in the dialysis population minimized this undesired effect. Another concern regarding chronic omeprazole use among MHD patients is its effect on bone metabolism. Omeprazole has been shown to impair gastric acid secretion and have a negative influence on calcium homeostasis and bone mass, thus increases the risk of fracture in the general population [18]. Kirkpantur et al. also indicated that PPI therapy might be associated with lower serum calcium levels, higher intact PTH levels, and lower bone mineral density among MHD patients [19]. However, our study did not find any differences in serum calcium, phosphorus, and intact PTH levels between the two groups. Even though we observed that two postmenopausal women in the omeprazole group had events of traumatic femoral neck fracture during the study period, no statistically significant increase in the risk of bone

fracture was observed in our study. We propose two factors to account for the discrepancies between previous reports and our results. First, a complex relationship exists among calcium, phosphorus, vitamin D, parathyroid hormone, and bone mineral density, especially in the dialysis population. Further, bone fracture in the dialysis population could be caused by metabolic bone disease, senile osteoporosis, or other factors, despite lack of PPI use [20]. Thus, the association between bone fracture and PPI use in patients undergoing MHD remains unclear. Second, we strictly controlled serum calcium, phosphorus, and parathyroid hormone levels according to K-DOQI guidelines [21], which possibly decreased the effects of omeprazole on bone metabolism.

Our study has several limitations. First, we did not perform periodic endoscopic examinations on all subjects, which might underestimate peptic ulcer rates in both groups. Second, most enrolled subjects in our study had several risk factors of PUD, particularly old age and coexisting medical conditions [7]. It is uncertain whether prophylactic omeprazole would have similar effects on young dialysis patients without multiple comorbidities. Third, we did not measure serum 25-OH vitamin D levels or bone mineral density to investigate changes in bone metabolism among patients receiving omeprazole. Finally, our study was limited to a small number of patients and a single center. Further prospective, multicenter, large-scale controlled trials should be carried out to confirm our findings.

In conclusion, the prophylactic use of omeprazole in MHD patients might lower the incidence of PUD and reduce treatment cost of these patients. However, out study did not demonstrate its efficacy in MHD patients on regular aspirin or warfarin. Furthermore, its safety should be assessed by longer-term and larger-scale controlled studies.

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Table 1. Baseline characteristics of the Omeprazole and Control groups

Variables	Omeprazole group (N = 49)	Control group (N = 36)	P value
Age, years	64.4 ± 12.3	62.6 ± 13.3	NS
Female gender (n [%])	29 (59.2)	20 (55.6)	NS
HD vintage, years	5.7 ± 3.9	5.5 ± 2.7	NS
Diabetes mellitus (n [%])	15 (30.6)	12 (33.3)	NS
Current smoking (n [%])	7 (14.3)	4 (11.1)	NS
Current alcohol consumption (n [%])	2 (4.1)	2 (5.6)	NS
Heparin dose (IU/session)	3568 ± 743	3416 ± 699	NS
Aspirin use (n [%])	24 (48.9)	18 (50.0)	NS
Warfarin use (n [%])	5 (10.2)	4 (11.1)	NS
NSAID/COX-2 inhibitors (n [%])	10 (20.4)	7 (19.4)	NS
Corticosteroids (n [%])	1 (2.0)	1 (2.8)	NS
Hematocrit (%)	32.13 ± 2.86	32.87 ± 3.03	NS
Ferritin (μ g/L)	368 ± 148	338 ± 257	NS
Kt/Vurea (Daugirdas)	1.65 ± 0.31	1.60 ± 0.37	NS
Albumin, g/dl	3.93 ± 0.47	3.95 ± 0.41	NS
ALT, IU/L	18.7 ± 4.1	19.1 ± 3.7	NS
i-PTH, pg/dl	247.9 ± 236.5	236.8 ± 227.9	NS
Corrected calcium, mg/dl	9.5 ± 0.7	9.2 ± 0.4	NS
Phosphate, mg/dl	5.0 ± 1.4	4.9 ± 1.3	NS

Abbreviations: NS = not significant; HD = hemodialysis; NSAID/COX-2 inhibitors = nonsteroidal anti-inflammatory drugs/cyclooxygenase-2 inhibitors; Kt/Vurea = adequacy of dialysis dose; ALT = alanine transaminase; i-PTH = intact parathyroid hormone.

Table 2. Comparison of outcomes between the Omeprazole and Control groups

Variables	Omeprazole group (N = 49)	Control group (N = 36)	P value
Endoscopic findings			
Received endoscopy (n [%])	5 (10.2)	16 (44.4)	0.001
Reflux esophagitis (n [%])	1 (2.0)	4 (11.1)	0.158
Gastric ulcer (n [%])	3 (6.1)	12 (33.3)	0.002
Duodenal ulcer (n [%])	3 (6.1)	6 (16.7)	0.159
Peptic ulcer disease [a] (n [%])	5 (10.2)	15 (41.7)	0.001
SRH (n [%])	1 (2.0)	6 (16.7)	0.038
H. pylori status (histologically) [b]	1/5	4/15	1.000
Clinical findings			
Recurrent bleeding [c] (n [%])	1 (2.0)	4 (11.1)	0.158
Transfusion required [d] (n [%])	1 (2.0)	7 (19.4)	0.009
Mean hematocrit (%)	33.2 ± 3.21	31.1 ± 3.38	0.059
Mean EPO doses (units/session)	1469 ± 287	1904 ± 398	0.024

[a] Peptic ulcer disease: including patients with gastric or/and duodenal ulcer.

[b] *H. pylori* status histologically: detected by the rapid urease test.

[c] Recurrent bleeding: re-bleeding within 30 days.

[d] Transfusion required: received 2 units of red blood cell transfusion when hematocrit levels dropped to <25%.

Abbreviations: SRH = stigmata of recent hemorrhage; EPO = erythropoietin.

Figure captions

Figure 1 Cumulative incidence of peptic ulcer disease in the omeprazole and control groups by per-protocol analysis. The omeprazole group had a lower cumulative incidence during the 18-month study period (log-rank test, P = 0.04).