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Proton pump inhibitors use in short bowel patients at a Thai tertiary hospital: A 10-year retrospective observational study

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ABSTRACT

Background: Proton pump inhibitors (PPIs) reduce the gastric acid secretion in short bowel patients. However, the absorptive areas of these patients are limited. In case of residual jejunum length <50 cm, the intravenous administration of PPIs should be considered. **Objective:** The objective of the study was to evaluate the appropriateness of PPIs use in short bowel patients regarding their remaining bowels. **Methods:** Data were collected from medication orders from 2008 to 2018 for short bowel patients admitted at King Chulalongkorn Memorial Hospital, Thailand. The medication costs were also evaluated. **Results:** Ten patients aged from newborn to 64 years were included in the study. Six patients were undergone extensive bowel resection needing intravenous PPIs. From a total number of 340 medication orders, omeprazole was the only PPIs prescribed to the patients. In the two-thirds of prescriptions, the routes of PPIs administration were not appropriate according to the physiology of patients' remaining bowels. They costed 235.20 USD or 7,301.00 baht. **Conclusion:** Inappropriate prescriptions of omeprazole in short bowel patients were found. However, there were unclear of patients' clinical conditions and the limitations of medication administration in practice. Further studies about the cost-effectiveness of PPIs in short bowel patients should be warranted.

Keywords: Antisecretory agent, intestinal failure, omeprazole, proton pump inhibitor, short bowel

INTRODUCTION

Short bowel syndrome (SBS), the most common type of intestinal failure (IF), is defined as a group of symptoms occurred in patients with a remaining length of the small intestine <200 centimeters.[1] Since the initial phase, removal of the bowel; especially jejunum and ileum, results in reduction of cholecystokinin and secretin hormones which control gastrin secretion. Increased gastrin level stimulates secretion of gastric acid by the parietal cells of the stomach and enhances gastric motility.[2,3] The gastric acid hyperacidity and hypersecretion occurred in short bowel patients reduces bowel pH, inactivates pancreatic enzyme functions, precipitates bile salts, and damages small bowel mucosa. Loss of electrolytes through gastric juices together with malabsorption lead to fluid and electrolyte imbalance in short bowel patients. In addition to parenteral nutrition, anti-secretory agents become important treatments for gastric acid hypersecretion of these patients.[1-4]

Proton pump inhibitors (PPIs) are widely used for treatment of excessive gastric acid secretion disorders. Active forms of PPIs bind covalently to the gastric hydrogen/potassium adenosine triphosphatase (H+, K+-ATPase, or proton pump) resulting in irreversible inhibition of acid secretion from the secretory canaliculi of the parietal cells.[5,6] New proton pumps need to be endogenously synthesized for full restoration of acid secretion which takes about 96 h.[7] Unlike other anti-secretory agents, PPIs have prolonged duration of action so that once a day of administration is enough for effective treatment.[5] However, because of acid-labile properties, PPIs were orally delivered by enteric-coated dosage forms to protect them from gastric

acid before absorption through proximal small bowel mucosa. Gastrointestinal pH, structural, and functional integrity of the gastrointestinal mucosa are involved in the absorption of the medications. Increased gastric pH by repeated dosing of PPIs reduces drug degradation and improves the bioavailability, especially in omeprazole.[6,7] The location and function of the remaining bowel are also important. The expected length of healthy jejunum for effective absorption capacity of PPIs was reported as 50 cm.[4] Including duodenum, overall proximal bowel should be at least 75 cm to obtain the satisfied treatment outcome of PPIs. Patients who had undergone extensive small bowel resection may face with impaired absorption due to insufficient intestinal mucosa and low pH of bowel lumen; therefore, intravenous administration of PPIs should be considered. A better knowledge regarding the pattern of PPIs use in clinical practice is important to identify appropriate treatment protocol of SBS. Consequently, the objective of this study was to identify the pattern of PPIs use regarding the route of administration and small bowel residue in short bowel patients. The appropriateness of administered PPIs related to the patients' remaining bowel physiology was also evaluated. The expense of such prescriptions was assessed through the cost of PPIs dispensing.

METHODS

This retrospective observational study reviewed the medication orders from 2008 to 2018 for short bowel patients who were admitted to King Chulalongkorn Memorial Hospital, Bangkok, Thailand, a public general and tertiary-referral teaching hospital with approximately 1500 beds. The study protocol was approved by the Institutional Review Board of the Faculty of Medicine, Chulalongkorn University, Thailand (Approval No 945/2019, IRB No. 497/62) with the exemption of informed consent. All data were exported from the electronic dataset and reported anonymously.

Data contained two main components including patients' demographic data and medication orders. All age ranges and gender of the patients were included in the study. Age of the patients starting diagnosed with SBS was recorded. Causes of SBS including bariatric surgery, and surgery for cancer removal were reviewed. Written surgical notes were carefully read over to identify the physiology of the remaining bowel of the patients. Exclusion criteria were the medication orders of the patients who did not receive PPIs. Patients with unclear pathophysiology of remaining small bowel were excluded from the study. Patients who were treated as the out-patient settings or home-care basis were also excluded.

The list of medications prescribed to short bowel patients was reviewed. PPIs refer to omeprazole, lansoprazole, dexlansoprazole, pantoprazole, esomeprazole, and rabeprazole. Dose, dosage regimen, and routes of administration of PPIs to these patients were recorded. The appropriateness of PPIs uses was considered the routes of PPIs administration corresponding to the physiology of the remaining intestines of patients. "Appropriateness" implied that the drug administration method was consistent with the physiology of the remaining intestines. For example, if the length of healthy jejunum of the patient was <50 cm or the proximal small bowel was shorter than 75 cm, the intravenous PPIs administration was prescribed to such patient. Otherwise, the oral routes should be prescribed to the patients with extended small bowels. The direct medical costs of the PPIs used in short bowel patients were calculated, according to the products provided at the Department of Pharmacy, King Chulalongkorn Memorial Hospital. All descriptive data are shown as frequencies and percentages.

RESULTS

During 2008–2018, there were 45 short bowel patients admitted to King Chulalongkorn Memorial Hospital, Bangkok, Thailand, with PPIs prescriptions. Of those, 35 patients were excluded due to either unclear physiology of remaining bowel or unspecified dosage form of prescribed PPIs. Thereafter, the data of this study were collected from a total of ten patients. The patients' age diagnosed with the SBS were varied from newborn to 64 years old. The causes of SBS were mainly surgical resection of bowel gangrene, cancers, etc. No patient had gastric surgery. Each patient had different remnant intestine. There was a patient with no remaining duodenum while three patients had no jejunum. The ileal section of most patients had been partially or totally removed. Nine patients had colon in continuity. Six out of ten patients had the remaining proximal small bowel <75 cm; therefore, the appropriate PPIs administration methods of these patients were considered as intravenous routes. The characteristics of the patients are shown in Table 1.

From a total number of 340 medication orders included in this study, omeprazole was the only PPIs prescribed to the patients [Table 2]. According to the price of products provided at the Department of Pharmacy, King Chulalongkorn Memorial Hospital, 1 capsule of local made omeprazole capsules 20 mg (Miracid, Berlin Pharmaceutical Industry, Bangkok, Thailand) cost 0.048 USD (1.50 Thai baht [THB]) and 1 vial of omeprazole powders for solutions for injections 40 mg/1 vial (Zefxon®, Biolab, Samutprakarn, Thailand) cost 2.432 USD (75.50 THB; 1 USD equivalent to 31.042 THB, U.S. Federal Reserve Bank G5.A annual average rate 2019). Duration of treatment with omeprazole of each patient was varied from 7 days to 4 years. Regarding the route of administration and the physiology of remaining small bowel in short bowel patients, only 112 omeprazole prescriptions (32.9%) were appropriate. There were 274 prescriptions of oral omeprazole of which 80% did not conform to the patients' bowel residue. We found a newborn undergone extensive bowel resection had received oral omeprazole for a month (patient no.5). A patient with remnant proximal duodenum only 15 cm without jejunum and ileum had received oral omeprazole for almost 4 years (patient no. 6). A patient with the proximal bowel 25 cm and distal ileum 5 cm had received oral omeprazole for 7 months (patient no. 8). Another patient with remaining proximal bowel <30 cm had received oral omeprazole for 4 months (patient no. 10). Meanwhile, ten prescriptions (15%) of intravenous omeprazole were inappropriate. A newborn with whole duodenum as well as the length of jejunum plus ileum as 100 cm was prescribed intravenous omeprazole for 23 days (patient no. 1). We also found a cancer patient with whole proximal bowel receiving omeprazole 40 mg intravenously for 2 days (patient no. 3). Even though the number of prescriptions was low, the intravenous administration obviously costed higher than the oral one.

Table 1: Characteristics of the patients and the appropriate route of PPIs administration*

Patient no.	Gender	Age of diagnosis (years)	Causes of surgical resection	Physiology of remaining small bowel	Ileocecal valve	Colon	Appropriate route of PPIs administration	Duration of the prescribed PPIs (days)	Number of PPIs prescription (prescriptions)		
									All	Appropriate PPI prescription	Inappropriate PPI prescription
1	F	Newborn	Small bowel disproportion	Whole duodenum Jejunum plus ileum 100 cm	N	Y	Oral	70	24	16	8
2	F	59	Intestinal perforation from cervical cancer treatment	The remnant proximal small bowel 80 cm. with no ileum	Y	Y	Oral	270	24	24	0
3	M	59	Rectal cancer with liver and lung metastasis	Whole duodenum and jejunum with no ileum	N	N	Oral	163	10	8	2
4	M	64	Unspecified	Whole duodenum and jejunum with no ileum	N	Y	Oral	307	8	8	0
5	F	Newborn	Congenital bowel gangrene	The remnant jejunum 5 cm No duodenum and ileum	N	Y	Intravenous	35	12	1	11
6	M	Newborn	Gastroschisis with multiple atresia	The proximal duodenum 15 cm No jejunum and ileum	N	Y	Intravenous	1,460	145	13	132
7	M	1	Necrotizing enterocolitis	The remnant proximal small bowel 45 cm. with no ileum	N	Y	Intravenous	7	1	0	1
8	F	4	Large mesenteric cyst	The proximal duodenum 15 cm, jejunum 10 cm Distal ileum 5 cm	Y	Y	Intravenous	229	57	7	50
9	M	37	Unspecified	The proximal duodenum 8 cm. and distal ileum 8 cm. No jejunum	Y	Y	Intravenous	71	23	23	0
10	F	51	Small bowel ischemia, bowel gangrene	The remnant proximal duodenum <30 cm No jejunum and ileum	Y	Y	Intravenous	142	36	12	24

*F=Female; M=Male; Y=Yes; N=No

Table 2: Appropriateness and cost of omeprazole use in short bowel patients

Routes of administration	*N*	Appropriate prescriptions			Inappropriate prescriptions		
		n	Costs (USD)	Costs (THB)	n	Costs (USD)	Costs (THB)
All	340	112	883.63	27,429.50	228	235.20	7,301.00
Oral	274	56	85.87	2,665.50	218	113.59	3,526.00
Intravenous	66	56	797.76	24,764.00	10	121.61	3,775.00

In addition to PPIs, other gastrointestinal agents were prescribed to the patients [Table 3]. Loperamide capsules, oral rehydration salts powders, simethicone chewable tablets, domperidone suspension, and cholestyramine powders were usually ordered. All patients received total parenteral nutrition; either commercial or compounding bags. Intravenous antibiotics such as ceftazidime, cloxacillin, meropenem, and vancomycin were common. Oral antibiotics such as metronidazole suspensions were few. Oral medications for chronic diseases included gemfibrozil and furosemide tablets. Miscellaneous oral medications included lorazepam, paracetamol, bromhexine, ambroxol, and ursodeoxycholic acid. Evaluation of the appropriateness of these medications use was beyond the scope of this study.

Table 3: Other medications prescribed to the patients

Medications	Cumulative prescription frequency (*n*)
Antibiotics (both oral and intravenous route)	159
Gastrointestinal agents	90
Anticoagulant drugs	64
Medications for chronic diseases (hypertension, dyslipidemia)	61
Miscellaneous	108

DISCUSSION

ESPEN guideline recommended PPIs for gastric hypersecretion treatment secondary to loss of inhibitory enteral hormones in short bowel patients, especially those with high stool output (more than 2 L/day).[1] Mechanisms of actions are the reduction of fluid and electrolyte secretion into the digestive tract and slowing the gastric emptying rate. Unfortunately, the oral drug absorption in short bowel patient is impaired due to a reduction or bypass of the absorptive mucosal surface resulting in difficulty of pharmacotherapy treatment. The degree of drug absorption mainly depends on the patient factors (physiology of remnant bowels, age, and other comorbidities) and the drug factors (physicochemical properties, formulation, rates and sites of absorption, etc.).[8] A study of Nightingale *et al*.[9] reported that the patients who had remaining jejunum 30 cm showed better response after switching 40 mg omeprazole orally into intravenously. Reduction of stool wet weight and sodium excretion had improved by intravenous omeprazole. Intravenous administration of omeprazole 80 mg/day showed superior effect than 300 mg/day ranitidine injections on the absorption of wet weight and stool sodium of short bowel patients.[10] Moreover, Tang *et al*.[11] showed that intravenous PPI was effective in the treatment of the upper gastrointestinal bleeding in a patient with complete intestinal resection who had failed the treatment with intravenous H_2-receptor antagonists. Because of the heterogeneity and dynamicity of the diseases, the treatment plan should be carefully considered according to an individual basis. To optimize the treatment outcome, the routes of drug administration need to be prescribed according to the physiology of the remnant bowel of the patients. The gastric acid hypersecretion was also reported as transient and resolved within a few months after surgery due to the gastrointestinal adaptation and rehabilitation.[3,12] The benefit of PPIs treatment was obvious during the first 6 months following resection; thereafter, the benefit may minimize.[1,2] In this study, we found one patient with remnant proximal duodenum 15 cm had received oral omeprazole for almost 4 years. Another patient with the proximal bowel 25 cm and distal ileum 5 cm had received oral omeprazole for 7 months. These patients may not get any beneficial effect from the omeprazole treatment due to insufficient absorptive areas, even though we did not have any objective measurement of the outcomes. The recommendations for improving medication prescriptions and frequent clinical monitoring are important.

Despite the availability of many PPIs including lansoprazole, dexlansoprazole, pantoprazole, esomeprazole, rabeprazole, and omeprazole was the only PPIs prescribed to this group of patients. The cost-effectiveness and economic factors may affect drug selection. Omeprazole is the only one of the PPIs in the National Lists of Essential Medicines (NLEM) of Thailand to allow full reimbursement for all Thais under the public universal health insurance system.[13] Price of the omeprazole is relatively low compared to other PPIs with comparable treatment outcomes.[14,15] At the equivalent doses, esomeprazole and rabeprazole may show superiority than omeprazole on gastric acid suppression by lowering the mean 24-h intragastric pH[14] but there was no clinical evidence showing that both drugs provided better treatment outcomes in short bowel patients. Clinical advantages of other PPIs over omeprazole at equivalent doses have not yet been proved. Our setting, King Chulalongkorn Memorial Hospital, is the public general teaching hospital which follows the rational drugs use protocol regarding NLEM. No other PPIs were prescribed to the patients included in this study. In addition to economic issue, we need to pay more attention to the appropriate prescription of PPIs use in short bowel patients regarding their remaining bowels.

The complexity characteristics of SBS lead to widespread polypharmacy. Adjunctive to total parenteral nutrition and PPIs, there were multiple symptomatic pharmacotherapies. For example, loperamide slows down intestinal transit together with increased time for fluid and electrolytes absorption; therefore, it has been advocated for diarrhea treatment in short bowel patients.[1,4,12,16] In case of bile salt

diarrhea which is a common problem in patient with colon continuity, bile acid sequestrants may be introduced to relieve the symptom. Bile acid sequestrants also inhibit intestinal oxalate absorption resulting in prevention of urinary oxalate excretion and kidney stone formation.[12,17] The oral antibiotics such as metronidazole, ciprofloxacin, and sulfamethoxazole/trimethoprim, are recommended for the treatment of small bowel bacterial overgrowth which commonly occurs in patients without ileocecal valve or presented with gastrointestinal dysmotility.[1,15] The patients may present with recurrent symptoms of bloating, abdominal distention, and abdominal pain which need periodic antibiotic therapy. However, the effect on gut microbiome of routine antibiotics in short bowel patients is still ambiguous. From the contents mentioned above, it is a challenge to monitor the pharmacological treatment outcomes of the short bowel patients who have uncertain absorptive capacity of remnant bowel mucosa together with complexity of the disease characteristics itself. The complication of the treatment would be increased if the patients have many comorbidities such as hyperlipidemia, heart diseases, and liver failure requiring additional medications. In this situation, careful consideration of drug selection by the evidence-based approach or therapeutic drug monitoring is critically needed. The specialty pharmacist plays an important role in the management of these patients to manipulate dose adjustment and offer alternative route of drug administration appropriately to the patients' conditions. The pharmacist takes the responsibility to notify the team to aware of the drug-drug or drug-nutrient interaction. Termination of the inappropriate drug use or switching to other routes of administration including parenteral, rectal, and transdermal routes; if applicable, may optimize the efficacy and minimize the cost of the medications for the short bowel patients. It was confirmed that the multidisciplinary teams including physicians, surgeons, nurses, dietitians, and pharmacists are required for the SBS management.[8,18,19]

As our best knowledge, this is the first study evaluated the appropriateness of PPIs use in clinical practice regarding the route of administration and small bowel residue in short bowel patients. The results will help physicians be aware of prescribing PPIs. Regularly reviews of the medication lists of these patients are needed more attention. The inappropriate drug use and their costs may be lessened. However, there were some limitations in this study. First, this study was a retrospective design. There was no clear information on the patients' clinical status. Some patients may be unable to obtain venous access and face with the limitations of medication administration in practice. Degree of clinical improvement that could be expected from PPIs use was also difficult to measure in clinical situation. Second, aside from PPIs, this study did not thoroughly review the use of other medications. Due to the heterogeneous characteristics of the short bowel patients, a wide range of drugs and dosage regimens were given to these patients resulting difficulty of data gathering and summary into the recommendation. Third, the data represented only the findings from a single public hospital. The number of patients was limited, and the medical cost analysis was based on local hospital billing rates, disregarding other indirect costs. Therefore, further studies about efficiency and worthiness using anti-secretory agents in short bowel patients should be performed.

CONCLUSION

In most of the prescription included in this study, the route of PPIs administration in short bowel patients was inappropriate regarding to the physiology of patients' remaining bowels. The orders of omeprazole in the oral dosage forms were high risk of inappropriate drug use. Careful review of the medications and enforcement of rational PPIs prescribing should be performed for effective outcome and cost reduction. However, the clinical treatment outcome of gastric acid hypersecretion by PPIs administration has not yet confirmed by the retrospective design. Future researches are needed for the cost-effectiveness analysis of PPIs use in short bowel patients.

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