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Original article

Appropriateness of proton pump inhibitors use in noncritically ill hospitalized children in a tertiary hospital in Saudi Arabia

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ABSTRACT

Background: Studies assessing the appropriate use of proton pump inhibitors (PPIs) for hospitalized non-critically ill pediatric patients are lacking. Therefore, this study aimed to assess the suitability of PPI prescriptions in noncritically ill pediatric patients.

Methods: This cross sectional retrospective study was conducted at a maternity hospital in Qassim, Saudi Arabia from November 2020 to January 2021. All noncritically ill hospitalized children aged 14 years and below who received PPIs were included. The endpoints included the number and percentage of patients who appropriately received PPIs in general and in each age category. The collected data were analyzed using Microsoft Excel (version 2208, Microsoft Corp., Redmond, WA, USA).

Results: In total, 332 medical records were screened, of which 246 were included. Of all patients, 49.2% were children and 50.8% were infants, with the average age at admission being 5.39 ± 5.4 years. More than half of the patients were female, and the average weight of patients was 19.8 kg. Omeprazole was appropriately used in 95 (38.5%) patients. Based on age groups, omeprazole was appropriately used in 66.3% of children and 38.4% of infants.

Conclusion: The use of omeprazole in noncritically ill pediatrics was only deemed appropriate in 38.6% of the study population. This result indicates that this medication was overused in the institution. Additional research is required to confirm this on a nationwide scale.

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1. Introduction

Proton pump inhibitors (PPIs) are antisecretory drugs that have transformed the management of acid-related diseases (Scarpignato et al., 2016), as the most potent inhibitors of gastric acid production (Sachs, 1997). PPIs effectively suppress the final step of acid secretion through the inhibition of the H⁺, K⁺-ATPase enzyme. (Aihara et al., 2003) Since PPIs can only inhibit activated enzymes,

successful inhibition relies heavily on the timing of administration. The concentration of H⁺, K⁺-ATPase present in the parietal cells is at its highest after a prolonged fast. Therefore, the PPIs are preferably administered before the first meal of the day. A single dose is usually adequate to produce a suitable level of acid inhibition throughout the day for most patients, although some patients may require a second dose before an evening meal. (Huang & Hunt, 2001).

PPIs are used to prevent and treat various gastric conditions in pediatric patients, including inflammation of the upper gastrointestinal tract, gastroesophageal reflux disease (GERD), erosive esophagitis, eosinophilic esophagitis, gastric and duodenal ulcers, and *Helicobacter pylori* gastritis. (Dellon et al., 2013; Koletzko et al., 2011; Vandenplas et al., 2009) PPIs are generally well tolerated, and their safety profile is better established in adults than in children, and to a lesser extent, in infants. (Shakhnovich et al., 2012; Tolia & Boyer, 2008) The most common adverse reactions

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observed in pediatric patients are headaches, diarrhea, constipation, and nausea.(Ward & Kearns, 2013).

The prescription of PPIs for children has increased noticeably in the last three decades, with studies showing that PPIs are overprescribed and are sometimes prescribed for inappropriate indications.(Barron et al., 2007; De Bruyne et al., 2014) Moreover, emerging evidence contradicts the previously assumed safe long-term use of PPIs,(Wilhelm et al., 2013) raising concerns regarding the increased risk of infections, vitamin and mineral deficiencies, adverse bone health, and drug interactions.(Safe et al., 2016; Tjon et al., 2013).

Data have shown that PPIs are overprescribed to noncritically ill hospitalized adults, increasing the risk of adverse outcomes and costs. Studies assessing the appropriateness of PPI prescription to hospitalized, noncritically ill pediatric patients are lacking. Therefore, this study aimed to assess the appropriateness of PPI prescription in noncritically ill hospitalized pediatric patients.

2. Methods

2.1. Study design, settings and ethical approval

This cross-sectional retrospective observational study was conducted at a maternity hospital in Qassim, Saudi Arabia from November 2020 to January 2021. This study was approved and registered at the National Committee of Biomedical and Medical Ethics under registration number H-04-Q-001.

2.2. Inclusion criteria, data collection and study outcomes

All noncritically ill hospitalized children aged 14 years and below who received PPIs between November 2020 and January 2021 were included. Children admitted to the intensive care unit (ICU) during hospitalization were excluded.

The IT team provided a list of patients who received PPIs during the specified period, and the three authors reviewed and retrieved data using the hospital's electronic health records. Several demographic and clinical variables, including age, sex, weight, reason for admission, comorbidities, medication history, prescriber specialty, dose, frequency, route of administration, and PPIs duration, were also collected.

The main outcome included the number and percentage of patients who appropriately received PPIs in general and in each age category (infant or child). In our institution, infant age is defined as 1 month to less than 24 months of age, while child age is from 2 years to 14 years of age. It is important to note that patients up to 14 years of age are treated in our maternity and children's hospitals. Two independent healthcare providers reviewed the patients' charts and assessed the appropriateness of PPI prescriptions based on a prespecified criterion adopted from Scarpignato et al. (Scarpignato et al., 2016) These criteria indicate that the use of PPIs is deemed inappropriate in several conditions, including corticosteroid use without concurrent nonsteroidal anti-inflammatory drugs therapy, hypertensive gastropathy in cirrhotic patients, acute pancreatitis, and stress ulcer prophylaxis in noncritically ill hospitalized patients who are not at high risk for gastrointestinal (GI) bleeding. Moreover, the authors suggested that the use of PPIs is of uncertain benefit in PPI-nonresponsive and extra-digestive GERD.

2.3. Statistical analysis

We used descriptive analysis to present the results continuous. Variables were presented as means and standard deviations (SD), or medians and interquartile ranges (IQR). Categorical variables

were presented as numbers and percentages. The collected data were analyzed using Microsoft Excel (version 2208, Microsoft Corp., Redmond, WA, USA).

3. Results

In total, 332 medical records were screened, of which 246 were included. The baseline characteristics of the included patients are presented in Table 1. Of all patients, 49.2% were children and 50.8% were infants, with the mean age at admission being 5.39 ± 5.4 years. More than half of the patients were female, and the mean weight of patients was 19.8 ± 18.4 kg. The reasons for admission varied, with gastrointestinal disorders being the most common. Comorbidities were recorded in 108 patients (43.9%), with heart disease being the most common comorbidity, followed by seizures and lung diseases. Before admission, insulin was the most commonly administered medication, followed by diuretics and iron/multivitamin supplementation (Table 1).

Omeprazole was the only PPI used during hospitalization, with intravenous omeprazole 40 mg once daily given to 68.3% of the included patients. Oral omeprazole 20 mg once daily was administered to 20.7% of patients, while data for 11 patients (4.5%) were

Table 1
Patients' baseline characteristics (n = 246).

Characteristics	n (%)
Age, years (mean \pm SD)	5.39 \pm 5.4
Age category	
Child	121 (49.2)
Infant	125 (50.8)
Sex	
Female	137 (55.7)
Male	109 (44.3)
Weight, kg (mean \pm SD)	19.8 \pm 18.4
Reason for admission	
Gastrointestinal disorders	60 (24.4)
Infectious and inflammatory disorders	39 (15.9)
Respiratory disorders	28 (11.4)
Cardiovascular disorders	25 (10.2)
Metabolic complications	19 (7.7)
Neurological disorders	3 (1.2)
Others	66 (26.8)
No data available	6 (2.4)
Comorbidities (n = 173^a)	
Heart diseases	32 (18.5)
Seizure	16 (9.3)
Lung diseases	16 (9.3)
Type 1 diabetes	15 (8.7)
Liver and spleen diseases	12 (6.9)
Down syndrome	11 (6.4)
Anemia	9 (5.2)
Gastroesophageal reflux disease	8 (4.6)
Eczema and skin rash	7 (4.0)
Gastrointestinal bleeding	3 (1.7)
Others	44 (25.4)
Medication history (n = 119^b)	
Insulins	32 (26.9)
Diuretics	15 (12.6)
Iron or multivitamin supplements	12 (10.1)
Blood pressure medications	10 (8.4)
Anticonvulsants	9 (7.6)
Steroids	6 (5.0)
Analgesics	5 (4.2)
Barbiturates	4 (3.4)
Benzodiazepines	4 (3.4)
Others	22 (18.5)

Data are presented as numbers (%) unless stated otherwise. Abbreviations, n, number of samples, SD, standard deviation.

^a The total number indicates the total number of comorbidities, and patients might have more than one comorbidity.

^b The total number indicates the total medications, and a patient might have more than one medication.

Table 2
Information regarding proton pump inhibitors (PPI) used during hospitalization.

	n (%)
PPI administered to patients	
Oral omeprazole 20 mg once daily	51 (20.7)
Oral omeprazole 20 mg twice daily	2 (0.8)
IV omeprazole 40 mg once daily	168 (68.3)
IV omeprazole 40 mg twice daily	14 (5.7)
No data available	11 (4.5)
Duration of using PPIs, days	
Mean ± SD	4.7 ± 6.2
Median (IQR)	8 (2, 5)
<7	208 (84.6)
8–14	18 (7.3)
>14	9 (3.6)
No data available	11 (4.5)
Prescriber level of specialty	
Consultants	232 (94.3)
Residents	4 (1.6)
No data available	10 (4)

Data are presented as numbers (%), unless stated otherwise.

Abbreviations: n, number of samples; SD, standard deviation; IQR, interquartile range.

Table 3
Appropriateness of proton pump inhibitors use according to age category.

	Child	Infant	Total
Appropriate n (%)	63 (66.3)	32 (33.7)	95 (38.6)
Not appropriate n (%)	58 (38.4)	93 (61.6)	151 (61.4)

Data are presented as numbers (%). n, number of samples.

Table 4
Appropriateness of proton pump inhibitor prescription according to prescriber level of specialty.

	Consultants	Residents
Appropriate, n (%)	84 (36.2)	1 (25)
Not appropriate, n (%)	148 (63.8)	3 (75)

Data are presented as numbers (%). n, number of samples.

not available (Table 2). The mean duration of omeprazole use was 4.7 ± 6.2 days. Omeprazole was used for less than 7 days in 208 (84.6%) patients, 8–14 days in 18 patients (7.3%), and more than 14 days in 9 patients (3.6%). Most prescribers were consultants, with only four medical residents prescribing omeprazole, and data were not available for four patients (Table 2).

The appropriateness of PPI use is shown in Table 3. Omeprazole was used appropriately in 95 (38.5%) patients. When divided by age group, omeprazole was used appropriately in 66.3% of children and 38.4% of infants (Table 3). Table 4 demonstrates the appropriateness of omeprazole use based on the prescriber's level of expertise. The findings revealed that 84 (36.2%) of the consultants' prescriptions were appropriate.

4. Discussion

This study aimed to assess the appropriateness of PPI prescriptions for hospitalized, noncritically ill pediatric patients. The results of this study have shown that omeprazole was used appropriately in 38.6% of the entire population. Moreover, omeprazole was used appropriately in 66.3% of children and 38.4% of infants. To the best of our knowledge, no earlier studies in Saudi Arabia have provided insights into the high rate of inappropriate omeprazole use in noncritically ill pediatric patients.

PPIs are associated with drug-related problems (DRP) in hospital settings. In an observational study involving neonates in the ICU, (Leopoldino et al., 2019) omeprazole accounted for 2.2% of the DRP cases and 3% of the prescriptions. Omeprazole was among the list of drugs that have shown a statistically significant increase in DRP, with an adjusted odds ratio (OR) of 1.66 (95% CI: 1.02 to 2.59). In addition, omeprazole is listed among the medications with a high risk of DRP, most of which are a result of the drug use process, logistics, or dose selection. (Leopoldino et al., 2019).

Studies regarding the appropriate use of acid suppressants in noncritically ill pediatric patients are lacking. Most of the available results are from studies involving noncritically ill adult patients. The unjustified use of acid suppressants, including PPIs, ranges from 19.0% to 96.4%, with an average of more than 50.0%. (Akkawi & Elnaem, 2020; Alsultan et al., 2010; Bez et al., 2013; Hong et al., 2015; Hwang et al., 2007; Judd et al., 2009; Meli et al., 2015; Mohamad et al., 2015; Parente et al., 2003; Sheikh-Taha et al., 2012; Villamañán et al., 2015; Zink et al., 2005) In our study, inappropriate use was observed in 61.4% of noncritically ill pediatric patients, which is somewhat comparable to what has been observed in the adult population. It is important to note that our study only included omeprazole, whether administered orally or intravenously, whereas the previously mentioned studies included different PPIs or PPIs in addition to other acid suppressants such as H-2 receptor antagonists and sucralfate.

Acid suppressants, typically PPIs, are commonly used in the adult ICU to prevent bleeding secondary to stress-related gastrointestinal mucosal damage. ("ASHP Therapeutic Guidelines on Stress Ulcer Prophylaxis. ASHP Commission on Therapeutics and Approved by the ASHP Board of Directors on November 14, 1998,," 1999; Scarpignato et al., 2016; Ye et al., 2020) This indication is referred to as stress ulcer prophylaxis (SUP) and is supported by several international guidelines. ("ASHP Therapeutic Guidelines on Stress Ulcer Prophylaxis. ASHP Commission on Therapeutics and Approved by the ASHP Board of Directors on November 14, 1998,," 1999; Dellinger et al., 2013) Patients with a high risk of bleeding, such as those on mechanical ventilation or with coagulopathy, should receive SUP. ("ASHP Therapeutic Guidelines on Stress Ulcer Prophylaxis. ASHP Commission on Therapeutics and Approved by the ASHP Board of Directors on November 14, 1998,," 1999; Scarpignato et al., 2016; Ye et al., 2020) Similar to the adult population, PPIs are commonly used for SUP in pediatric ICUs. (Duffett et al., 2020) The benefits among pediatric patients are inconsistent, with some studies reporting a decrease in GI bleeding and others failing to find a significant reduction. (Abu El-Ella et al., 2021; Reveiz et al., 2010; Sochet et al., 2020) This might be explained, in part, by the fact that although GI bleeding is common in critically ill pediatric patients, the rate of clinically significant bleeding remains very low. (Abu El-Ella et al., 2021; Chaïbou et al., 1998) Data regarding the benefits and risks of PPIs as SUP in noncritically ill pediatric patients are lacking, necessitating a more cautious approach to the routine use of PPIs beyond the ICU.

The overuse of PPIs in practice, especially in noncritically ill adult patients, is evident, resulting in a possible increase in patient harm and costs. (Barletta et al., 2002; Farley et al., 2013; Farrell et al., 2010; Zink et al., 2005) Several studies have suggested that PPIs may increase the risk of hospital-acquired pneumonia and *Clostridium difficile*-associated diarrhea in hospitalized adult patients. Data from the ICU appeared to be more limited than those from general medical wards. Wang et al., in a network meta-analysis, found that PPIs may increase pneumonia risk in the ICU, but suggested that more high-quality clinical trials are needed to provide a definitive answer. (Wang et al., 2020) On the other hand, among noncritically ill adult patients, more evidence suggested a strong association between the use of PPIs and nosocomial infec-

tions.(Arriola et al., 2016; Buendgens et al., 2014; Filion et al., 2014; Johnstone et al., 2010; Kwok et al., 2012; Tariq et al., 2017; Ye et al., n.d.) Among hospitalized pediatric patients, the data are inconclusive, and large clinical trials are needed to shed light on the safety of PPIs in this delicate population.

This study has some limitations. First, this was a single-center study with a small sample size. Second, this was a descriptive study that did not investigate factors that might have increased the chances of patients receiving omeprazole. This study focused on the indications for omeprazole and whether it was appropriate; however, it did not consider whether the dose of omeprazole was appropriate. Finally, missing data were encountered during the data collection process, and it was not possible to report whether the patients continued to use omeprazole after discharge.

In our study, we observed the overuse of omeprazole in noncritically ill pediatric patients. We suspect that these observations may be applicable to other institutions in the country. Thus, several efforts are required to reduce the inappropriate use of PPIs. This could include the utilization of an alert function in the computerized prescriber order entry if inappropriate use is suspected. Moreover, the development of a protocol for PPI use in the pediatric population, educational sessions for health care providers, and pediatric clinical pharmacist involvement in medical team for evidence-based data utilization.

5. Conclusion

In 38.6% of the study's sample of hospitalized and noncritically ill pediatric patients, the use of omeprazole was deemed appropriate. This result indicates that this medication was overused in the clinical settings. Additional research is required to confirm this on a nationwide scale, and serious efforts are needed to reduce the inappropriate use of PPIs in the pediatric population.

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Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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