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Original Article

Omeprazole (Risek®) Use in Inpatient and Outpatient Departments: A Post-Marketing Surveillance Investigation

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ABSTRACT

Proton pump inhibitors (PPIs) are widely used for the treatment of acid-related gastrointestinal disorders. However, their overuse or inappropriate prescription can lead to adverse effects, increased healthcare costs, and development of antibiotic-resistant infections. **Objectives:** To ascertain whether the Omeprazole (Risek®)-PPIs prescription patterns by practitioners in the inpatient and outpatient departments of various healthcare facilities in Pakistan are in compliance with the therapeutic indications and to evaluate the safety profile associated with each therapeutic indication. **Methods:** A cross-sectional multicenter study was conducted for 4 months at various healthcare facilities inpatient and outpatient departments. A total of 1384 patients ≥ 18 years prescribed Omeprazole (Risek®) were enrolled while pregnant or lactating women, patients with chronic diarrhea, those with a history of Omeprazole allergic reaction, and with diagnosed malignancy of the GI tract were excluded. The drug use was determined based on the prescribed frequency, dosage, and duration of therapy with respect to each indication. **Results:** Of the total, 29.8% were already taking oral PPI or Histamine H2-Receptor Antagonists. The common indication for Omeprazole (Risek®) was Gastroesophageal Reflux Disease (GERD), followed by peptic ulcer. Mostly the drug was infused/injected in 40 mg dosage, once daily and for five days among 76.6% and 41.8%, respectively. Around 13.3% of patients experienced mild adverse events like flatulence, fever, vomiting, abdominal pain, constipation, diarrhea, nausea, rash, etc. Most off-label uses were observed in GERD concerning the duration of therapy (55.9%), prescribed frequency (19.7%), and dosage (5.9%). The Omeprazole (Risek®) treatment was also prescribed for stress ulcer prophylaxis and upper GI bleeding against the treatment protocol for the particular therapeutic indication. The adverse events were most frequent among patients with GERD, followed by NSAID-induced ulcers. **Conclusions:** This study provides clinical evidence on the Omeprazole (Risek®) use in concordance with the product label, in both inpatient and outpatient departments of Pakistan for various therapeutic indications.

INTRODUCTION

Proton pump inhibitors (PPIs) are commercially available since more than 30 years ago and have been the mainstay of treating upper gastrointestinal disorders[1]. Since then, they have proven to be valuable, safe, and effective agents for the management of a variety of acid-related disorders. Although members in this class act in a similar fashion, inhibiting active parietal cell acid secretion, there are slight differences among PPIs relating to their pharmacokinetic properties, metabolism, and their approved clinical indications[2]. PPIs are available in intravenous (IV) and

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oral forms (enteric-coated delayed-release, microencapsulated beads in a capsule or suspension, and unprotected drug with sodium bicarbonate). Currently, the IV PPI are approved by the US Food and Drug Administration (US-FDA) for treating patients who are unable to tolerate oral medications due to complicated erosive esophagitis, and in patients with Zollinger-Ellison syndrome with pathological hypersecretory states. In real life practices, the use of IV PPI is much more widespread [3]. PPIs are among the most frequently prescribed drugs globally. While they are highly cost-effective when used appropriately, studies across a wide range of populations continue to identify that they are prescribed without a clear indication in 50 to 70% of cases [4, 5]. One of the most frequently prescribed drug classes worldwide is that of proton-pump inhibitors (PPIs), which include Omeprazole. It has grown in popularity for off-label use in inpatient and outpatient settings, despite its primary indication being the treatment of GERD. It has a long history of effective treatment inside and outside hospitals. Omeprazole is increasingly used off-label despite being effective. When the frequency of hospitalizations brought on by adverse drug reactions were assessed, it was found that Omeprazole was the medication most frequently linked to hospital admission [6]. A drug's safety may also alter over time due to increased usage and alterations in patient characteristics. Therefore, a risk assessment is necessary. Reports on omeprazole abuse and irrational prescription of this medication can help to clarify this context. As a result, studies have documented the risks (adverse events (AEs)) of using Omeprazole, including changes in gastric proliferative tissue; increased levels of urea and creatinine cause acute interstitial nephritis[7, 8], which raises the risk of developing chronic kidney disease, a higher risk of asthma when gastroesophageal reflux is present, increased danger of contracting Clostridium difficile infection, reduced vitamin B absorption, cystic fibrosis-related steatorrhea, fracture with reduced calcium absorption, gynecomastia, anaphylactic reactions to Omeprazole, etc., [9]. Additionally, Omeprazole was listed as one of the drugs that may have contributed to the hospitalization in studies that assessed the frequency of hospital admission due to adverse drug events, suggesting that Omeprazole is frequently used outside of the recommended dosage range [5]. Off-label drug use refers to the use of medications for unapproved purposes. It typically affects polymedicated patients and serves as prophylactic gastric protection for some medications, including antimicrobials and non-steroidal anti-inflammatory drugs. This post-marketing surveillance investigation was designed to ascertain whether Omeprazole (Risek®) prescription patterns by practitioners in the inpatient and outpatient departments of various healthcare facilities in Pakistan are in conformity with the therapeutic indications.

METHODS

A cross-sectional multicenter study was designed to assess the conformity and concordance of the prescription of Omeprazole (Risek®) as per the product label, in various healthcare facilities of Pakistan. Before study initiation, ethical approval was obtained from the independent Ethical Committee of AEIRC [Ref# ERC/S20/P-004; Dated January 30, 2021]. Data were collected using purposive sampling technique. All patients ≥ 18 years reporting to and diagnosed by treating physicians for acid-related disorders prescribed Omeprazole (Risek®) were enrolled. Pregnant or lactating women, patients with chronic diarrhea, those with a history of Omeprazole allergic reaction, and with diagnosed malignancy of the GI tract were excluded. The prescription was considered non-compliant/off-label if any of these three criteria were met i.e. prescribed frequency, dosage, and duration of therapy (with respect to each indication in non-compliance with the marketing authorization). The treating physician that collected and submitted data used an electronic data capture system (Microsoft Forms) for this study. The required data were assembled as a patient registry, specifically designed electronic medical records at the study sites for the study. For sample size following formula was used at 50% proportion $N = z^2 p (1- p) / d^2$. Final sample size was n=384 with 20% attrition it was n=450. The data collected in June to September 2022. The final analysis presented in this study includes data from n=1384 patients. Each enrolled case was labeled with a specific identifier and the data confidentiality was retained. Patient demographic and clinical information, including age, gender, current medication history related to PPI or Histamine H2-Receptor antagonists use, concomitant drug consumed, and patient complaints, were registered. Omeprazole (Risek®) off-label and on-label use was determined based on the indication for which it was used, prescribed dosage, frequency, and duration of therapy given. The safety profile was also monitored, data regarding any adverse events reported, action taken to manage them, and clinical improvement in patient symptoms after treatment with Omeprazole (Risek®) was recorded. Data analysis was performed on SPSS Version 22.0, and all variables were evaluated for normality using the Shapiro-Wilk test. Continuous variables were expressed as mean ± standard deviation and categorical variables were described in frequencies and percentages. As the comparisons included categorical variables, the chi-square test was applied for the normally distributed data. A p-value < 0.05

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was considered significant for all significance tests applied.

RESULTS

For n=1384 cases analyzed, the mean patient age was 43.79 ± 13.63 years, with slightly more male patients (58.2%) than females (41.8%). It was found that 413(29.8%) patients were already taking oral PPI, and 106(25.67%) were consuming Omeprazole (Risek®). The patients mostly complained about heartburn 898(64.9%), followed by gastritis. GERD was the predominant indication for which the Omeprazole (Risek®) was infused or injected. Other details regarding the prescribed dosage, frequency, and duration of therapy are given in Table 1.

Table 1: Clinical characteristics (indications, dosage, frequency of Omeprazole (Risek®) IV, AEs) of inpatients and outpatients

Variables		n(%)
Already taking oral PPI or Histamine H2-Receptor Antagonists	No	971(70.2)
	Yes	413(29.8)
Drugs consumed by the patients (n=413)	Esomeprazole	119(28.81)
	Omeprazole	106(25.67)
	Pantoprazole	43(10.41)
	Famotidine	31(7.51)
	Rabeprazole	30(7.26)
	Lansoprazole	30(7.26)
	Dexlansoprazole	26(6.30)
	Ranitidine	15(3.63)
	Cimetidine	8(1.94)
	Others	5(1.21)
Concomitant drugs consumed	None	1055(76.2)
	Clopidogrel (Antiplatelet)	126(9.1)
	Digoxin (Cardiac Glycosides)	63(4.6)
	Clarithromycin (Macrolide)	53(3.8)
	Diazepam (Anxiolytic)	38(2.7)
	Ketoconazole (Antifungal)	31(2.2)
	Methotrexate (Antimetabolites)	13(0.9)
	Rifampicin (Antitubercular)	10(0.7)
	Tacrolimus (Immunosuppressant)	5(0.4)
	Phenytoin (Anticonvulsants)	2(0.1)
	Others	35(2.5)
Symptoms or patient complaints	Heartburn	898(64.9)
	Gastritis	456(32.9)
	Nausea Or Vomiting	414(29.9)
	Dyspepsia	403(29.1)
	Abdominal Pain	374(27.0)
	Dysphagia	230(16.6)
	Bloating Or Blenching	177(12.8)
	Blood In Stool (Melena)	38(2.7)
	Others	11(0.8)
Indication for infusion/injection Omeprazole	GERD	1024(74.0)
	Peptic Ulcer	387(28.0)
	Upper G.I Bleed	250(18.1)
	Stress Ulcer Prophylaxis	232(16.8)
	NSAIDs Induced Ulcers	221(16.0)
	Erosive Esophagitis	117(8.5)
	Helicobacter Pylori Infection	
	Zollinger-Ellison Syndrome	90(6.5)
Route of drug administration	IV Injection	504(36.4)
	IV Infusion	819(59.2)
	Both	61(4.4)
Prescribed dosage	20 mg	79(5.7)
	40 mg	1266(91.5)
	60 mg	35(2.5)
	120 mg	4(0.3)
Prescribed frequency	OD	1060(76.6)
	BD	288(20.80)
	TDS	36(2.6)
Duration of therapy (days)	1 Day	241(17.4)
	2 Days	120(8.7)
	3 Days	282(20.4)
	More Than 3 Days	579(41.8)
	SOS	162(11.7)
Adverse event(s)*	No	1200(86.7)
	Yes	184(13.3)
Symptoms	Flatulence	56(4.0)
	Fever	54(3.9)
	Vomiting	54(3.9)
	Abdominal Pain	54(3.9)
	Constipation	47(3.4)
	Diarrhea	46(3.3)
	Nausea	39(2.8)
	Rash	39(2.8)
	Dizziness	36(2.6)
	Tingling Feelings	36(2.6)
	Vertigo	35(2.5)
	Edema	34(2.5)
	Kidney Functions Abnormality	33(2.4)
	Headache	32(2.3)
	Others	60(4.3)
Action taken due to adverse event(s) (n=184)	No Action or Therapy Required / Transient Adverse Events	52(28.26)
	Therapy Required for Management of Adverse Events and Continuation of Omeprazole	59(32.06)
	Therapy Required for Management of Adverse Events and Discontinuation of Omeprazole	73(39.67)
Patient symptom(s) improved clinically after treatment with IV Omeprazole	No	53(3.8)
	Yes	1331(96.2)
Patients discharged on oral Omeprazole	No	90(6.5)
	Yes	1294(93.5)

*164 patients had single AE. Multiple cases with more than one AE were observed, patients with 2 AEs=18, 3 AEs=1, 4 AEs=1, and a total of 32 had all AEs

The off and on-label use was determined based on the prescribed frequency, dosage, and duration of therapy (Figure 1). Most off-label uses were observed in GERD cases in terms of therapy duration 572(55.9%), prescribed frequency 202(19.7%), and dosage 60(5.9%). The PPI treatment was also prescribed for stress ulcer prophylaxis (n=232; 100%) and upper GI bleeding (n=250; 100%) against the treatment protocol for the particular therapeutic indication.

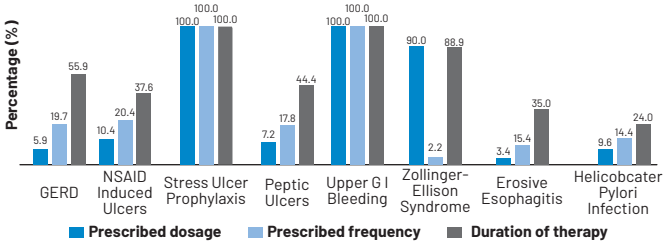

Figure 1: Off-label use of Omeprazole (Risek®) by physicians

The adverse events were most frequent among patients

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with GERD, i.e., 360(35.1%) AEs were observed among the patients prescribed Omeprazole (Risek®) for GERD, followed by NSAID-induced ulcers (Table 2).

Table 2: Adverse events with respect to indications

Adverse Events	Indications							
	GERD	NSAID Induced Ulcers	Stress Ulcer Prophylaxis	Peptic Ulcer	Upper G.I Bleed	Zollinger-Ellison Syndrome	Erosive Esophagitis	Helicobacter Pylori Infection
Headache	23(2.2)	13(5.9)**	7(3.0)	1(0.3)**	2(0.8)	1(1.1)	2(1.7)	2(1.9)
Diarrhea	30(2.9)	18(8.1)**	10(4.3)	3(0.8)**	2(0.8)**	1(1.1)	3(2.6)	3(2.9)
Constipation	30(2.9)	16(7.2)**	10(4.3)	2(0.5)**	3(1.2)*	2(2.2)	4(3.4)	4(3.8)
Abdominal Pain	28(2.7)**	15(6.8)**	12(5.2)	5(1.3)**	5(2.0)	4(4.4)	5(4.3)	2(1.9)
Flatulence	27(2.6)**	18(8.1)**	9(3.9)	10(2.6)	4(1.6)*	2(2.2)	3(2.6)	4(3.8)
Fever	25(2.4)**	16(7.2)**	11(4.7)	8(2.1)*	5(2.0)	3(3.3)	3(2.6)	3(2.9)
Vomiting	26(2.5)**	16(7.2)**	11(4.7)	6(1.6)**	5(2.0)	2(2.2)	6(5.1)	3(2.9)
Nausea	25(2.4)	14(6.3)**	7(3.0)	3(0.8)**	4(1.6)	2(2.2)	2(1.7)	2(1.9)
Rash	24(2.3)	13(5.9)**	9(3.9)	3(0.8)**	4(1.6)	1(1.1)	2(1.7)	2(1.9)
Edema	24(2.3)	13(5.9)**	8(3.4)	1(0.3)**	2(0.8)	1(1.1)	2(1.7)	2(1.9)
Dizziness	25(2.4)	13(5.9)**	8(3.4)	1(0.3)**	3(1.2)	1(1.1)	2(1.7)	3(2.9)
Tingling Feelings	26(2.5)	15(6.8)**	8(3.4)	2(0.5)**	3(1.2)	1(1.1)	3(2.6)	3(2.9)
Vertigo	23(2.2)	15(6.8)**	8(3.4)	1(0.3)**	2(0.8)*	1(1.1)	2(1.7)	2(1.9)
Kidney Functions Abnormality	24(2.3)	13(5.9)**	7(3.0)	1(0.3)**	2(0.8)	1(1.1)	2(1.7)	2(1.9)
	360	208	125	47	46	23	41	37

*p<0.05; **p<0.01 is considered statistically significant

DISCUSSION

In our study, off-label use of Omeprazole (Risek®) has been reported in both inpatient and outpatient departments. In this research, GERD and peptic ulcer disease were the most frequently reported off-label indications. Omeprazole (Risek®) was also used for other indications, such as upper GI bleeding (18.1%) and stress ulcers (16.8%), which were non-compliant with the marketing authorization (Table 1). Our findings are consistent with other published studies regarding the over-prescription of PPIs[5]. These authors also discovered that doctors did not follow the consensus statements because they overprescribed PPIs without fully evaluating the impact of anti-H2 agents, did not adequately reevaluate the need for continuing PPI treatment, and were not sufficiently persuaded of the benefits of stopping drugs that aggravated reflux. An in-hospital retrospective study of surgical inpatients from the Netherlands found 46.6% of cases of non-compliance with guidelines, with overprescribing accounting for 93.1% of these [10]. Similarly, an Italian study reported that the off-label use of medications is widespread in the intensive care environment. PPIs account for the highest ratio, i.e., the off-label use observed in intensive care units is as high as 55% [11]. Likewise, Ali *et al.*, documented inappropriate prescribing of PPIs among 54.7% of cases [5]. Other studies have examined the underlying justification for PPI prescriptions and their continued use [12, 13]. Despite educational and stewardship strategies, there are frequently ambiguous justifications and low compliance with rules[14, 15]. The most frequent justifications for long-term PPI use were stress ulcer prophylaxis, improper treatment of dyspepsia, and prophylaxis for low-risk patients taking NSAIDs or corticosteroids (in secondary care) [16]. Healthcare providers should monitor patients closely and assess their response to treatment with Omeprazole (Risek®). Patients should also be informed of the potential risks associated with using Omeprazole (Risek®) off-label and encouraged to report any concerns or side effects they may experience. Although we observed that 96.2% of patients clinically improved after treatment with IV Omeprazole, 93.5% were discharged on oral Omeprazole, and no serious adverse events were reported (Table 1). Minor adverse events were reported in 13.3% of cases, the most common being flatulence (4%), followed by fever, vomiting, abdominal pain, etc. Moreover, with reference to the most frequent off-label use and associated AEs, these adverse events were also most frequent among patients with GERD, followed by NSAID-induced ulcers. Therapy was required to manage adverse events and discontinuation of Omeprazole among 73(39.67%) patients. Although several studies report potential adverse effects associated with long-term PPI use, their relevance is unclear, and most of them are based on low-grade evidence[17, 18]. However, caution should be exercised when prescribing this medication due to potential adverse events. Clopidogrel was among the most frequently used concomitant medication in the studied patients, i.e., 126(9.1%) (Table 1). A major concern is linked to the drug interactions associated with the use of Clopidogrel and Omeprazole; it significantly accelerates

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the platelet reactivity index [19, 20]. Individuals who use PPIs and clopidogrel concurrently may have an elevated risk of major adverse cardiovascular events (MACE) but not of mortality, according to several systematic reviews and meta-analyses. Two meta-analyses examining the interactions between distinct PPIs and clopidogrel did not establish any direct links to worse CV outcomes [21]. Another systematic review, including 16 observational studies (183,546 participants) and 6 randomized controlled trials (RCTs) with 6930 people each, revealed no statistically significant differences between the PPI groups and the non-PPI groups receiving dual antiplatelet therapy (DAPT) in the incidences of MACEs, MI, and all-cause mortality [22]. The guidelines greatly vary on the concomitant use of PPIs and DAPT. Smaller RCTs, numerous meta-analyses, and observational studies have offered mixed evidence regarding the effectiveness of this regimen[23].

CONCLUSIONS

Omeprazole (Risek®), according to the study's findings, is widely used for gastrointestinal conditions such as acid reflux and peptic ulcers. However, most of the prescriptions did not adhere to the marketing authorization. For instance, administering Omeprazole for longer than suggested durations or for diseases like upper GI bleeding and stress ulcers would be against the prescribed course of care for the particular therapeutic indication. Moreover, with reference to the most frequent off-label use and associated AEs, adverse events were also most frequent among GERD patients.

Authors Contribution

Conceptualization: JKK, SHD, MNS
Methodology: JKK, SHD, MNS
Formal analysis: RM, SS, MU
Writing-review and editing: JKK, SHD, MNS

All authors have read and agreed to the published version of the manuscript.

Conflicts of Interest

The authors declare no conflict of interest.

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