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RESEARCH ARTICLE

Association between omeprazole use and *Clostridium difficile* infection among hospitalized patients: A case–control study of the Saudi population

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ABSTRACT

Background: While few international studies have assessed the association between omeprazole use and the risk of *Clostridium difficile* infection (CDI), research into this is lacking in Saudi Arabia and the Middle East region. The aim of this study was to determine whether exposure to omeprazole is associated with the risk of *Clostridium difficile* infection in a sample of hospitalized Saudi patients.
Methodology: A retrospective matched case–control study was conducted at the King Abdulaziz Medical City in Riyadh, Saudi Arabia, from 1 August 2010 through 31 July 2015. The analysis included a total of 200 patients: 100 CDI cases and 100 matched controls.
Results: The majority (60%, 120 out of 200) of patients had received proton pump inhibitors (PPIs), and a minority (18.5%, 37 out of 200) had received omeprazole. The PPI use was insignificantly higher in CDI cases than in controls. However, the use of omeprazole was significantly higher in CDI cases compared with controls. Specifically, patients receiving omeprazole were two times more likely to develop CDI compared with controls (aOR = 2.1, 95% confidence interval (CI) = (1.007 – 4.437)). After adjusting for potential predictors of CDI, watery diarrhea (aOR = 59.1, 95% CI = 19.831 – 175.974) and abdominal pain (aOR = 7.5, 95% CI = 2.184 – 25.445) were found to be independent predictors of CDI.
Conclusions: The data suggests that PPIs were commonly used in patients admitted to King Abdulaziz Medical City in Riyadh: six out of ten patients received PPIs. The findings support a possible association

between the use of omeprazole and a high risk of CDI. To confirm causality, the link between omeprazole and CDI should be assessed in a large interventional study.

Keywords: *Clostridium difficile* infection, omeprazole, watery diarrhea, abdominal pain, Saudi Arabia

BACKGROUND

Clostridium difficile infection (*CDI*) is characterized by a wide range of symptoms from diarrhea to life-threatening or severe colitis.[1] Over the last decade, the prevalence and severity of *CDI* has increased significantly worldwide,[1–4] and it is a major and unpleasant complication of antibiotic therapy, especially in older patients.[5]

The recent use of proton pump inhibitors (PPIs) has increased tremendously and causes major public health implications.[6] Although PPIs reduce gastric-acid-related disorders, they may also increase the risk of *CDI*. Many published studies have revealed that PPI use increases the risk of *CDI* among patients;[7–15] however, there are conflicting findings as some studies have not obtained sufficient evidence that PPIs increase the risk of CDI.[5,6,16,17] One systemic review and meta-analysis found insufficient evidence for the association between the use of PPIs and *CDI*.[18] Furthermore, Lowe et al., and Naggie et al., reported that the relationship between PPI use and *CDI* may depend on antibiotic use.[6,16] This includes the number of antibiotics received, antibiotic class, and the timing of antibiotic therapy.[6,16]

The incidence of *CDI* continues to increase in patients admitted to King Abdulaziz Medical City in Riyadh, as well as the use of gastrointestinal drugs (e.g., omeprazole and esomeprazole). In this study, we assess the association between gastrointestinal drug use and *CDI* among hospitalized Saudi patients who had been treated with antibiotics.

Few studies have assessed the relationship between different classes of PPIs and *CDI*, namely omeprazole (Losec 20 mg tablet, AstraZeneca UK) and esomeprazole (Nexium 20, 40 mg tablet and 40 mg vial for IV injection, AstraZeneca UK) therapies. The use of omeprazole therapy was associated with increased risk of *CDI* in hospitalized patients.[19] Hegarty et al., reported that omeprazole therapy reduces the gene expression, which may promote *CDI*.[20] In a study conducted in Bangkok, Thailand, on patients with confirmed *CDI* toxin A, almost half of the population studied (44.6%, 25 out of 55) received either ranitidine or omeprazole.[21] More epidemiological investigations in different populations are needed to examine PPIs separately for each therapy (esomeprazole and omeprazole) as potential risk factors for *CDI*.

No previous study was found to examine the association between gastrointestinal drugs (including omeprazole and esomeprazole) and *CDI* in Saudi Arabia or the Middle East. The study tested whether there was sufficient evidence that PPI (omeprazole or esomeprazole therapy) use increases the risk of *CDI* in a sample of hospitalized Saudi patients who had taken antibiotics during the previous 30 days.

METHODOLOGY

A retrospective matched case–control study was completed at the King Abdulaziz Medical City in Riyadh (KAMC-R), Ministry of National Guard, Saudi Arabia. KAMC-R was established in May 1983 and initially provided medical, obstetrical, surgical, and critical care services to the National Guard population and their dependents. Expansion of services over the years has resulted in more than 1800 beds, as well as specialized services such as oncology and organ transplant. This study was approved by the IRB office at King Abdullah International Medical Research Center (KAIMRC), Research Protocol #SP15/116.

Study subjects

The study included hospitalized patients with suspected *CDI* who had taken antibiotics during the previous 30 days. The study population (*CDI* cases and controls) was selected by screening microbiology laboratory databases from 1 August 2010 to 31 July 2015. The Microbiology Laboratory at KAMC-R uses stool cultures to diagnose the presence of *CDI* and its toxins. Positive *CDI* results were identified using the A04.7 code, in accordance with the guidelines found in the International Statistical Classification of Diseases and Related Health Problems. Cases were defined as hospitalized antibiotic users suspected of *CDI*, whose stool cultures, based on real-time polymerase chain reaction (PCR) assays, were positive for *CDI*. Controls were defined as hospitalized antibiotic users suspected of *CDI* or other types of infections, whose stool cultures, based on real-time PCR assays, were negative for *CDI*. The controls were matched with the cases in terms of age, gender, and length of hospital stay.

We excluded patients whose stool culture results were not available, who were aged less than 14 years, who were admitted to ICU because of complications with suspicion of infection by many organisms, who used antacids such as ranitidine or sucralfate, and patients who used laxative medications – to prevent confusing diarrhea with *CDI*. The exclusion criteria also included patients who used systematic antibiotics for more than 30 days and patients with Crohn's disease, ulcerative colitis, short bowel syndrome, or any type of cancer. Patients who had been exposed to PPI drugs for less than 14 days were also excluded from this study.

Sample size

nQuery Advisor was used to calculate the required sample size in each group. The power analysis showed that for an odds ratio of 2.27, the anticipated probability of exposure to PPIs given a *CDI* of 65%, and an anticipated probability of exposure to PPIs given a no *CDI* of 45%, would require a sample size of 96 in each group. A total of 315 patients admitted to King Abdulaziz Medical City in Riyadh were retrieved and included in the matching process. The study included 100 patients admitted and diagnosed with *CDI* based on real-time PCR assays. Confirmed *CDI* cases were matched with the no *CDI* group on gender, age (± 5 years), and the length of hospital stay (± 7 days) on the basis of 1:1 to patients admitted who tested negative for *CDI* on real-time PCR assays. The PPIs, omeprazole, and esomeprazole were used as exposures. The final data included 200 eligible subjects (100 *CDI* cases and 100 controls).

Data collection

QuadraMed and Pharmacy computer systems as well as medical records (charts review) were reviewed retrospectively to retrieve the required variables for the controls and *CDI* cases. The following demographic data were collected: age and gender. Data on different classes of PPI drugs (including esomeprazole and omeprazole) were collected. The following clinical data were also collected: length of hospital stay, chronic diseases, diabetes (DM), hypertension (HTN), heart failure (HF), renal failure (acute or chronic), dyslipidemia, and organ transplants. Data on the type of feeding by mouth (PO) were collected (nasogastric tubes (NGT) and percutaneous endoscopic gastrostomy (PEG)). Clinical symptoms of *CDI* were collected: watery diarrhea (Yes/No), abdominal pain (Yes/No), fever (Yes/No), blood or pus in the stool (Yes/No), nausea and vomiting (Yes/No), and high white blood cell count (Yes/No).

Data analysis

We performed statistical analyses using IBM SPSS Statistics (IBM Corp. Armonk, NY, USA). Continuous data were expressed as mean and standard deviation (mean ± SD), whereas categorical data were expressed as counts (*n*) and percent (%) (Table 1). Differences in age and length of hospital stay across *CDI* cases and controls were tested using independent two-sample t-tests (Table 1). The primary analysis was to examine whether *CDI* is associated with the PPIs, esomeprazole, or omeprazole. The associations between the final diagnosis status (*CDI* cases and controls) across clinical and exposure data were assessed by a Chi-square test (Table 1). In order to identify independent risk factors for *CDI*, we assessed the relationship between *CDI* and PPIs (including esomeprazole and omeprazole), adjusting for potential confounders (Table 2). The level of significance was set at 0.05.

RESULTS

Table 1 shows that the distributions of age, gender, and length of hospital of stay were fairly similar in *CDI* cases and controls. The overall mean age (± SD) was 67.3 ± 18.2 years for both groups (67.8 ± 18.6 *CDI* cases vs. 66.8 ± 17.9 controls, $p = 0.679$) and the length of hospital stay for both groups was 19.2 ± 32.0 days (18.7 ± 23.6 *CDI* cases vs. 19.7 ± 38.8 controls, $p = 0.826$). The majority of the sample (67.5%, 135) were 65 years old or over however, no relationship between patients aged 65 years or over and *CDI* was observed. Male gender was distributed evenly between groups (42% *CDI* cases vs. 42% controls, $p = 1.0$).

The majority (85.5%) of the patients had a chronic disease, 62.5% had diabetes mellitus, 74% had hypertension, and 12.5% had heart failure. The most common feeding was PO (74.9%). Out of the 200 patients, 120 (60%) received PPIs, 84 (42%) received esomeprazole, and 37 (18.5%) received omeprazole. On examining the association between PPI use and *CDI*, we observed no significant association with *CDI* risk. There was a similar proportion of patients who had exposure to PPIs: 65% (65 out of 100) in the *CDI* group, relative to 55% (55 out of 100) in the control group ($p = 0.149$). There was also a similar proportion of patients who had

Table 1. CDI and its relation to demographics and the clinical data.

		CDI Cases		Controls			
		n = 100		*n* = 100			
Characteristics		Mean	± SD	Mean	± SD	P	OR (95% CI)
Age	*(15 – 102)*	67.8	18.6	66.8	17.9	0.679	1.0 (0.988 – 1.019)
Length of stay	*(1 – 360)*	18.7	23.6	19.7	38.8	0.826	1.0 (0.990 – 1.008)
Characteristics		**n**	**%**	**n**	**%**	**P**	**OR (95% CI)**
Gender	*Male*	42	42.0	42	42.0	1.000	1.0 (0.570 – 1.753)
Diabetes mellitus	*Yes*	64	64.0	61	61.0	0.661	1.1 (0.641 – 2.016)
Hypertension	*Yes*	76	76.0	72	72.0	0.519	1.2 (0.654 – 2.320)
Heart failure	*Yes*	15	15.0	10	10.0	0.285	1.6 (0.677 – 3.728)
Renal failure	*Yes*	33	33.0	31	31.0	0.762	1.1 (0.605 – 1.986)
Organ transplant	*Yes*	7	7.0	2	2.0	0.170	3.7 (0.747 – 18.211)
Dyslipidemia	*Yes*	20	20.0	12	12.0	0.123	1.8 (0.843 – 3.988)
Watery diarrhea	*Yes*	74	74.0	7	7.0	0.001*	37.8 (15.549 – 91.958)
Abdominal pain	*Yes*	28	28.0	9	9.0	0.001*	3.9 (1.745 – 8.858)
Fever	*Yes*	34	34.0	34	34.0	1.000	1.0 (0.557 – 1.795)
Blood/pus in the stool	*Yes*	8	8.0	1	1.0	0.035*	8.6 (1.056 – 70.170)
Nausea	*Yes*	37	37.0	20	20.0	0.008*	2.3 (1.243 – 4.439)
High WBC	*Yes*	30	30.0	27	27.0	0.638	1.2 (0.627 – 2.143)
Feeding	*PO*	70	70.7	79	79.0	0.361	0.7 (0.324 – 1.601)
	NGT	13	13.1	8	8.0		1.3 (0.420 – 4.149)
	PEG	16	16.2	13	13.0		1.0
PPI	*Yes*	65	65.0	55	55.0	0.149	1.5 (0.860 – 2.685)
Esomeprazol	*Yes*	41	41.0	43	43.0	0.774	0.9 (0.525 – 1.615)
Omeprazol	*Yes*	24	24.0	13	13.0	0.045*	2.1 (1.007 – 4.437)

*Significant at $\alpha = 0.05$. WBC: white blood cells; PO: feeding by mouth; NGT: nasogastric tubes; PEG: percutaneous endoscopic gastrostomy; PPI: proton pump inhibitor; *CDI: Clostridium difficile* infection; PPI: proton pump inhibitor.

exposure to esomeprazole: 41% (41 out of 100) in the *CDI* group, relative to 43% (43 out of 100) in the control group ($p = 0.774$). However, the use of omeprazole was more common, 24% (24 out of 100) in *CDI* cases compared to 13% (13 out of 100) in controls ($p = 0.045$).

Watery diarrhea was a more common symptom in *CDI* cases (74%, 74 out of 100) compared with the controls (7%, 7 out of 100) ($p = 0.001$). *CDI* patients were more likely to have abdominal pain (28%, 28 out of 100), compared to controls (9%, 9 out of 100) ($p = 0.001$). *CDI* case subjects were more likely to have blood or pus in the stool (8%, 8 out of 100) compared with the controls (1, 1 out of 100) ($p = 0.035$). The risk of nausea and vomiting increased in *CDI* cases (37%, 37 out of 100) compared to the control group (20%, 20 out of 100) ($p = 0.008$).

It was found that patients with a chronic disease were more likely to use PPIs. The use of PPIs were common in patients with a chronic disease (64.3%, 110 out of 171), compared to those without a chronic disease (34.5%, 10 out of 29) ($p = 0.002$). However, the risk of *CDI* was insignificantly low in patients with a chronic disease (48%, 82 out of 171), compared to those without a chronic disease (62.1%, 18 out of 29) ($p = 0.160$).

Table 2 shows independent risk factors for contracting *CDI* using the multivariate logistic models. Watery diarrhea (OR = 59.1, 95% confidence intervals (CI): 19.831 – 175.974) and abdominal pain (OR = 7.5, 95% CI: 2.184 – 25.445) were identified as primary factors associated with a high risk of *CDI*.

DISCUSSION

We used a retrospective matched case – control study to identify potential risk factors of *CDI* in a sample of hospitalized Saudi patients who received antibiotics during the previous 30 days. Each *CDI* case was matched with one control subject in terms of age,

Table 2. Risk factors of CDI using multivariate logistic model.

Factors	B	SE	Wald	P	OR	95% CI for OR	
						Lower	Upper
Age	0.01	0.01	1.08	0.299	1.0	0.987	1.043
Length of stay/days	0.00	0.01	0.54	0.463	1.0	0.993	1.015
Male	0.42	0.48	0.77	0.379	1.5	0.599	3.855
Diabetes mellitus	0.30	0.59	0.26	0.613	1.3	0.423	4.294
Hypertension	−0.08	0.70	0.01	0.904	0.9	0.234	3.608
Heart failure	0.99	0.67	2.17	0.140	2.7	0.722	10.024
Renal failure	0.45	0.51	0.79	0.373	1.6	0.580	4.278
Organ transplant	2.18	1.20	3.33	0.068	8.9	0.852	92.370
Dyslipidemia	0.65	0.61	1.13	0.288	1.9	0.578	6.330
Watery diarrhea	4.08	0.56	53.64	0.001*	59.1	19.831	175.974
Abdominal pain	2.01	0.63	10.29	0.001*	7.5	2.184	25.445
Fever	0.28	0.49	0.33	0.568	1.3	0.507	3.456
Blood or pus in the stool	2.64	1.44	3.36	0.067	14.0	0.834	235.512
Nausea	0.10	0.54	0.04	0.850	1.1	0.383	3.202
High WBC	−0.94	0.57	2.78	0.095	0.4	0.128	1.180
Feeding – PO vs. PEG	−0.77	0.66	1.37	0.242	0.5	0.126	1.686
Feeding – NGT vs. PEG	0.41	0.89	0.21	0.644	1.5	0.264	8.626
Esomeprazol	0.25	0.52	0.22	0.640	1.3	0.46	3.57
Omeprazol	0.67	0.70	0.94	0.330	2.0	0.50	7.66
Constant	−2.39	1.49	2.58	0.108	0.1		

*Significant at $\alpha = 0.05$. WBC: white blood cells; PO: feeding by mouth; NGT: nasogastric tubes; PEG: percutaneous endoscopic gastrostomy; PPI: proton pump inhibitor; *CDI: Clostridium difficile* infection.

gender, and length of hospital stay. We tested hypotheses to determine whether there was sufficient evidence that PPI use (including esomeprazole or omeprazole therapy) increases the risk of *CDI*.

In both the *CDI* cases and controls, a total of 120 (60%) of the patients received PPIs. The study finding suggests that PPI use was not independently associated with an increased risk of CDI in a sample of hospitalized Saudi patients. Similar results were found in a few reports assessing the independent association between PPI use and the risk of *CDI*.[5,6,16,17] The consistency in findings between our study and these reports could be due to removing the confounding effects of antibiotics as the association between PPI use and *CDI* may depend on antibiotic use.[6,16] Moreover, patients were relatively older in the cohorts of these studies, including our study.

The association between PPI use and *CDI* is still being debated, as most previous studies suggest an association between PPI use and *CDI*.[7–15] Our study revealed inconsistent findings with these reports. This could be due to methodological issues such as the characteristics of the selected cohorts (e.g., older age) and confounding effects.[6,16] In our study, we removed the confounding effects of antibiotics by including patients (*CDI* cases and controls) who received antibiotics during the previous 30 days. Moreover, when we categorized patients by age to at least over and below 65 years of age, the data failed to demonstrate an association between PPI use and *CDI* in patients 65 years of age or older. This is consistent with the findings of Lowe et al.[6]

We assessed PPIs esomeprazole and omeprazole separately for each therapy as potential risk factors of *CDI*. We found that the use of omeprazole was significantly more prevalent in the *CDI* cases than in the controls. According to our study, patients receiving omeprazole were two times more likely to develop *CDI* compared with controls. Similar findings were noted in other studies,[19,20,21] which reported that omeprazole therapy might play an important role in increasing the risk of *CDI*. Nath et al.,[19] evaluated the association between gastrointestinal drugs (omeprazole, ranitidine, cimetidine, famotidine, or sucralfate) and the risk of *CDI* in hospitalized patients. According to their study, patients receiving

gastrointestinal drugs were 3.2 times more likely to develop *CDI* compared with controls. The significance of our study is that not all previous studies have assessed the use of omeprazole separately as a risk factor of *CDI*.

Clinical symptoms show significant differences between cases and controls, especially watery diarrhea and abdominal pain, because those are the signs and symptoms of *CDI*. However, fever and a high white blood cell count were not significant because both groups had infections.

This study has several notable limitations. The observational case – control study is limited by a random sampling error of control patients. However, in order to prevent selection bias, we selected our patients (cases and controls) from the same period of time and the same population. Both groups were from a microbiology lab (which revealed *CDI* and other infections), and all patients had used antibiotics during the previous 30 days. However, in a hospital-based study, we learned that patients are more likely to be exposed to multiple antibiotic therapies, but we did not collect data on the number of antibiotics received, antibiotic class, and the timing of the antibiotics. Another limitation is that KAMC-R emergency department treats urgent medical conditions without knowing the patients' full medication history (particularly PPIs), which could have resulted in adverse drug reactions. This can lead to serious adverse events that are life-threatening or have other negative health effects. Due to the small sample size retrieved, the patients were matched 1:1 instead of one case per two controls. A large hospital-based study excluding patients taking antibiotics is needed to examine more closely the association between PPIs (omeprazole, esomeprazole) and *CDI*. To our knowledge, this study is the first in Saudi Arabia and the Middle East region to report the association between PPIs (omeprazole, esomeprazole) and the risk of *CDI*. However, more research studies on each type of PPI, route of administration, and duration of use in larger populations are needed.

CONCLUSION

The study findings suggest that PPIs were commonly used in patients admitted to the King Abdulaziz Medical City in Riyadh, as six out of ten hospital patients with infection received PPIs. PPI use was not an independent risk factor for *CDI*. The results support a possible association between the use of omeprazole and a high risk of *CDI*. To confirm causality, the link between omeprazole and CDI should be assessed in a large interventional study. Clinical symptoms such as watery diarrhea and abdominal pain were associated with a high risk of *CDI*.

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COMPETING INTERESTS

The authors declare no competing interests.

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