Proton Pump Inhibitor use as a risk factor for Enterobacteriaceal infection: a case-control study

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BACKGROUND

Gastric acid suppressants increase the risk of gastroenteritis by allowing ingested pathogens to survive passage through the stomach. It is not known whether the same mechanism affects transmission of Enterobacteriacae. We carried out a case-control study to answer this question.

AIM

To determine whether use of Proton Pump Inhibitors (PPIs) increases the risk of infection with Enterobacteriacae in hospital patients.

METHODS

Retrospective case-control study in a teaching hospital in South West England. Cases were 126 patients infected with extended-spectrum B–Lactamase producing Enterobacteriacae (ESBL) between April 2014 and March 2015. Use of PPIs, H2 receptor antagonists or antacids at the time of admission or in the preceding six months was compared with 126 demographically matched controls infected with non-ESBL producing Enterobacteriacae and 126 uninfected controls, matched by primary diagnosis.

FINDINGS

66 of 126 ESBL cases, 62 of 126 non-ESBL controls and 34 of 126 uninfected controls were prescribed PPIs on or within 6 months of admission. Multivariable logistic regression analysis gave an Odds Ratio (95% confidence interval) of 3.37 (1.84 - 6.18) for PPI exposure versus uninfected controls and 1.15 (0.68 - 1.95) for ESBL infection versus non-ESBL infection. H2RA and antacids were not significantly associated with infection.

CONCLUSION

PPI exposure within the previous 6 months is significantly associated with infection with both ESBL and non-ESBL producing bacteria. Reducing inappropriate use of PPIs may be a novel way of reducing transmission, which might reduce antibiotic use and help control antimicrobial resistance.

Keywords

Enterobacteriacae, Proton Pump Inhibitor, Transmission, Risk factor, Case-Control Study

INTRODUCTION

Antibiotic resistance in Gram-negative bacteria is a major global cause of morbidity and mortality [1]. It has been identified as an urgent priority by the WHO, EU and US and UK Governments [2-5].

PPI use reduces gastric acidity, alters the gut microbiome [6], and increases the risk of gastroenteritis by enabling ingested pathogens to survive passage through the stomach [7]. The protective effect of gastric acid is unrelated to antibiotic resistance, so it is possible that PPI use might encourage colonisation by resistant or sensitive bacteria, with subsequent risk of systemic infection? Very little research has been carried out to investigate this, particularly in UK hospital patients.

We carried out a retrospective case-control study of PPI exposure in hospital cases infected with extended-spectrum B-lactamase producing Enterobacteriacae (ESBL) compared with two demographically matched control groups. The first group were patients infected with extended-Spectrum B-lactamase negative Enterobacteriacae (non-ESBL) and the second group were patients with no identified enterobacteriaceal infection matched by primary diagnosis (uninfected).

METHODS

STUDY COHORT

This study was carried out in Derriford Hospital, a 1000 bed university teaching hospital in South West England. All 131 patients newly identified as infected with ESBL between 1st April 2014 and 31st March 2015 (cases) were identified from laboratory records. This included inpatients and

patients undergoing day-case procedures. Five patients were excluded as their casenotes were lost and no information was available in electronic records. No screening of asymptomatic patients was performed, all samples were routine diagnostic tests. Controls were selected from the same hospital population infected with non-ESBL producing Enterobacteriacae matched by age +/- three years, date of admission +/- three months, gender, Care Group (Medicine, Surgery, Tertiary Services or Women & Children) and origin (Home, Other Hospital). A second set of controls with the same demographic features and also matched by their primary non-infectious diagnosis was similarly selected. Once a set of eligible controls was identified, one control per case was randomly selected using the Globally Unique Identifier (GUID) function in Microsoft SQL. No eligible controls could be found for 14 cases, either because of extreme age or uncommon primary diagnosis. Both genders were permitted and age matching was relaxed to +/- five years for these cases. A power calculation prior to data collection indicated that this sample size would be adequate to detect an odds ratio of 2.1 with 80% power at a 5% level of significance.

Clinical data was extracted from paper and electronic hospital casenotes, post-discharge coding records and electronic discharge summaries. The study was approved by the North West Medical Research Ethics Committee and the Plymouth Hospitals NHS Trust Research and Development Office.

EXPOSURES

Documented prescription of PPI, H2RA or simple antacids on admission or during previous episodes of care in the preceding six months was recorded. Over the counter use of gastric acid suppressants was not reliably recorded and was not analysed.

CONFOUNDING VARIABLES

A wide range of co-morbidities including those included in the Charlson Co-morbidity Score were analysed. Duration of admission prior to positive bacterial culture was recorded. Foreign travel prior to admission was not reliably recorded and was not analysed.

STATISTICAL ANALYSIS

Demographic characteristics of the cases and controls were presented using descriptive statistics. Continuous variables such as age and Charlson co-morbidity index were categorized into groups for the purpose of comparison with existing literature. Conditional logistic regression model was used to investigate the relationship between an outcome of being infected with extended-spectrum β-lactamase (ESBL) positive and a set of prognostic factors such as exposure to PPI, H2RA, antacids and Charlson co-morbidity index. This was done for each of the control groups. Both univariable (adjusted for the matching variables) and multivariable logistic regression models were considered and the corresponding results presented. Possible interaction of the factors (such as PPI) with some of the matching variables (such as age) was tested by including an interaction term in the model. Results of the regression models were presented as odds ratio (OR) along with their 95% confidence intervals (CIs). A factor was considered statistically significant if the 95% CI of the corresponding OR did not contain 1. Whenever appropriate, a 5% level of significance was considered. Data analysis was performed using IBM SPSS Statistics 23 and STATA 14.

PATIENT INVOLVEMENT

No patients were involved in the design or implementation of the study, or writing up of results.

RESULTS

Characteristics of case and control patients are summarised in Table I. The median (IQR) time between admission and sample collection was 2 (11.3) days for ESBL cases and 1 (5.5) days for non-

ESBL controls. This suggests that colonisation occurred prior to admission in most cases, rather than being hospital acquired. The median (IQR) duration of admission of uninfected controls was shorter than either of the infected groups at two (11) days versus 12 (20) days for cases and 9 (16) days for non-ESBL controls. The Charlson co-morbidity score for cases ranged from 0 to 12 and that of controls ranged from 0 to 14. This was not significantly different between cases and controls.

The results of exposure to gastric acid suppressants are summarised in Table II. 66 ESBL cases (59 on admission and 7 in the previous six months) were exposed to PPIs, compared with 34 (31 on admission, 3 in the previous six months) of the uninfected controls and 62 (55 on admission, 7 in the previous 6 months) of the non-ESBL controls. After multivariable analysis the OR (95% CI) for PPI exposure in cases compared to uninfected controls was found to be 3.37 (1.84 to 6.18). No significant difference was found for PPI exposure in ESBL cases and non ESBL controls.

6 ESBL cases were taking H2RA on admission, compared with 9 of the uninfected controls and 7 of the non-ESBL controls. 4 ESBL cases were taking antacids on admission, compared with 2 of the uninfected controls and 3 of the non-ESBL controls. No significant association was found between cases and either control group for H2RA or antacids.

DISCUSSION

We found that exposure to PPIs is a significant risk factor for infection with both ESBL producing and non-ESBL producing Enterobacteriacae. This is a novel and important finding, as PPIs are widely overused, antibiotic resistance is a major threat, and conventional control measures will require an unprecedented level of global cooperation [8, 9]. Increased transmission of susceptible organisms following reduction in gastric acidity is just as important as the effect on resistant ones, as treatment of subsequent infections will increase antibiotic consumption and drive development of resistance. New antibiotic classes are unlikely to be a realistic solution. Resistance to these may already exist, as bacteria from ancient soil and mummified human remains contained genes coding for resistance

thousands of years before antibiotics were developed[10,11]. Global spread of resistance is inevitable, carried by healthy travellers [12], and in foods from endemic areas [13].

Gram-positive pathogens like meticillin-resistant *Staphylococcus aureus* are mainly spread by direct contact and are controllable with simple measures like hand washing and skin disinfection. Most transmission of Gram-negative bacteria is by ingestion, and bowel decolonisation is rarely successful. They cause no symptoms when they first colonise the bowel. Unless the patient is actively screened they remain undetected until infection occurs in the future [14].

Gastric acid is a vital host defence. It kills a wide range of bacteria, fungi and parasites. It acts synergistically with salivary nitrite, generating highly reactive nitrogen species at low pH. These are rapidly bactericidal, even killing acid tolerant organisms such as *Clostridium difficile* spores [15]. Gastric acidity is reduced in the elderly, patients with pernicious anaemia, and patients taking PPIs. The risk of infection with gastrointestinal pathogens is increased in all these groups [7], our results suggest that the same mechanism encourages transmission of Enterobacteriacae.

PPIs are vital for treating peptic ulcers, gastroesophageal reflux and other serious conditions exacerbated by gastric acidity. Rapid efficacy and the misperception that they are free of significant adverse effects has encouraged overuse. Studies show that 40%-60% of acute hospital inpatients are prescribed a PPI, often outside evidence-based guidelines [16,17]. In contrast to the complex strategies to control antimicrobial resistance recommended in the O'Neill report [8], reducing inappropriate PPI use is a simple intervention which can be initiated by any prescriber or empowered patient. Like hand washing between patient contacts, it is simply good practice, but could have a disproportionate impact on the spread of bacterial resistance?

Strengths and limitations of study

The hypothesis that PPI use might be associated with ESBL infection was generated before collection or analysis of the data. When a positive association was found, a second control group of patients infected with non-ESBL bacteria was analysed. This study included 126 of 131 new cases of ESBL

infection over one year at a large UK teaching hospital. Derriford hospital provides general medical, surgical and obstetric care to an urban and rural population of 450,000, and specialist services such as neurosurgery, cardiothoracic surgery, bone marrow and solid organ transplantation to 1.7 million people. This varied case mix gives reassurance that the results are generalizable to similar centres. Patients of all ages and from all specialties were included. We reviewed all available records, including casenotes, prescription charts and electronic records. Limitations of the study are that it is retrospective and single centre. We were unable to quantify any "over the counter" use of gastric acid suppressants; however PPIs were only available on prescription at the time so would not have affected our cohort. While every effort was made to match cases and controls, unrecognised co-morbidities may have been present. Finally we chose six months prior to admission as a pragmatic cut off for review of prescriptions. PPI use more than six months prior to admission may well be a risk factor for acquisition of Enterobacteriacae, and further studies reviewing GP records for lifetime PPI use would more accurately define the risk.

Comparison with other studies

There is little published research on whether PPIs could be a risk factor for acquisition of Enterobacteriacae. A study in mice found that PPI treatment facilitated colonisation with *Klebsiella pneumonia*e and vancomycin-resistant enterococci [18]. Two studies of inpatients in Israel and the US incidentally found an association between gastric acid suppression and resistant Enterobacteriacae, but they primarily focussed on other risk factors and did not comment specifically on PPIs [19,20]. A cross-sectional study of adults registered with the Academic General Practice Network in Amsterdam in 2011 found an 8.6% prevalence of ESBL-producing enterobacteriaceae. Travel outside Europe, antibiotic use and use of gastric acid suppressants were all positively associated with carriage. Use of PPIs or H2RA had a multivariable odds ratio of 1.9 (95% CI 1.1 - 3.3) [21]. Our study found a stronger association, perhaps because the hospital population has more comorbidity and is more intensively exposed to bacteria and antibiotics. A

cross-sectional study of patients routinely screened for ESBL producing Enterobacteriacae on admission to hospital in the Netherlands found that 8.5% of PPI users were carriers versus 2.9% of non-PPI users, (adjusted odds ratio 3.89, 95% CI 1.65 - 9.19). Patients were screened within two days of admission thus excluding cross-infection within hospital, however they did not control for diagnosis or co-morbidities [22]. Søgaard *et al* in Denmark published a case-control study of community-onset ESBL E.coli UTI compared with non-ESBL E.coli UTI and population controls. They found a moderately increased risk of ESBL versus non-ESBL infection (OR 1.6, 95% CI 1.2 - 2.0) and that most risk factors also applied for non-ESBL infection [23]. Finally, two studies have looked at the possible association between carbapenemase-producing Enterobacteriacae (CPE) and PPIs, with conflicting results. Weekly screening of 31,526 inpatients in Hong Kong found that concomitant use of antibiotics and PPIs prolonged the duration of CPE carriage [24]. A study of 747 inpatients in Manchester was conducted during a CPE outbreak, with 70 CPE carriers identified. PPIs were not identified as a risk factor in this cohort, though they used PPI prescription in the 24 hours before the case finding exercise as a proxy measure of exposure. This would have underestimated any effect of previous PPI use [25].

Clinical implications and future research

We found that PPIs are much more widely used than H2RA and antacids. Studies on gastroenteritis pathogens show a dose-response effect, with less potent agents conferring a lower risk. While the number of patients taking H2RA and antacids in our population was small, we did not detect any association with ESBL or non-ESBL infection. Future studies to confirm this would be useful, as substituting these for PPIs may be easier than stopping gastric acid suppression completely.

As part of a bundle of *C.difficile* control measures, the Pharmacy and Infection Prevention and Control teams in Derriford Hospital encouraged substitution of H2RA and antacids for PPIs where possible. The initiative included an educational campaign for prescribers and prescription review by ward pharmacists. PPI use reduced from 46% to 29% of inpatients between 2012 and 2016. This

confirms that many PPI prescriptions are unnecessary and that change can be effected using existing teams and resources. Electronic prescribing and automated alert systems have also been used to reduce co-administration of PPIs and antibiotics [26]. Reducing inappropriate use of any medicine is intrinsically worthwhile, but further research is required to determine whether this will have a positive impact on transmission of Enterobacteriacae.

If this is a causal association, there are significant implications for policymakers and clinicians managing common gastrointestinal disorders. PPIs are widely overprescribed in primary and secondary care. Heavily promoted by the pharmaceutical industry, they have replaced H2 receptor antagonists as the treatment of choice for dyspepsia, and are now available over the counter. The association between PPI use and *C.difficile* infection was first described in 2003 but it was not until 2012 that sufficient evidence accumulated to enable the FDA to mandate a warning on PPI datasheets. As antibiotic resistance is such a serious issue and PPIs are so widely overused, we suggest a similar FDA warning should be urgently considered if further research confirms our findings.

CONCLUSIONS

We found a significant association between PPI exposure and infection with both ESBL and non-ESBL producing Enterobacteriacae. This is the first time this risk factor has been identified in a UK hospital population and the magnitude is greater than in previous community based studies. Applying evidence based guidelines on appropriate use of PPIs has the potential to reduce bacterial transmission without harming those patients who genuinely need such potent gastric acid suppression.

CONFLICT OF INTEREST STATEMENT

All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf and declare: no support from any organisation for the submitted work; no financial relationships with any organisations that might have an interest in the submitted work in the previous three years; no other relationships or activities that could appear to have influenced the submitted work.

Transparency declaration

I, Dr Richard Cunningham, affirm that this manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

Study title:	**Proton Pump Inhibitor (PPI) Exposure and Antibiotic Resistance: PEAR**
REC reference:	**16/NW/0235**
IRAS project ID:	**199890**

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Table I

Baseline characteristics and outcomes for cases and matched controls. Values are numbers (percentages) unless stated otherwise.

Characteristics	ESBL Cases	Non-ESBL Controls	Uninfected Controls
Total	126	126	126
Mean (SD) age, years	70 (17.8)	71 (17.7)	70 (17.7)
Female sex	79 (62.7)	78 (61.9)	84 (66.7)
Care Group			
- Medical	75 (59.5)	74 (58.7)	74 (58.7)
- Surgical	28 (22.2)	31 (24.6)	29 (23)
- Tertiary Services	22 (17.5)	20 (15.9)	22 (17.5)
- Women and Children	1 (0.8)	1 (0.8)	1 (0.8)
Origin			
- Home	120 (95.2)	123 (97.6)	120 (95.2)
- Other hospital	6 (4.8)	3 (2.4)	6 (4.8)
Length of stay in days Median (IQR)	12 (20)	9 (16)	2 (11)

Days from admission to sample collection Median (IQR)	2 (11.25)	1 (5.5)	N/A
Exposed to PPI	66 (52.4)	62 (49.2)	34 (27)
Exposed to H2RA	6 (4.8)	7 (5.6)	9 (7.1)
Exposed to Antacids	4 (3.2)	3 (2.4)	2 (1.6)
Charlson Score			
- 0	31 (24.6)	34 (27)	31 (24.6)
- 1-2	41 (32.5)	50 (39.7)	30 (23.8)
- ≥3	54 (42.9)	42 (33.3)	65 (51.6)

Table II

Odds ratio (95% confidence interval) of risk factors for infection with extended-spectrum β-lactamase (ESBL) producers versus two sets of controls (uninfected and non-ESBL producers) based on univariable and multivariable logistic regression models

Characteristic	ESBL cases versus uninfected controls		ESBL cases versus non-ESBL controls	
	Univariable	Multivariable	Univariable	Multivariable
Exposed to PPI	2.88 (1.66- 5.00)	3.37 (1.84 - 6.18)	1.15 (0.68 - 1.95)	1.06 (0.62 - 1.82)
Exposed to H2RA	0.57 (0.17 to 1.95)	0.92 (0.24 - 3.57)	0.8 (0.21 - 2.98)	0.68 (0.18 - 2.67)
Exposed to Antacids	2.00 (0.37 - 10.92)	0.98 (0.16 - 6.06)	1.33 (0.30 - 5.96)	1.57 (0.34 - 7.29)
Charlson score*				
Medium vs low	1.26 (0.65 - 2.46)	1.16 (0.56 - 2.39)	0.90 (0.44 - 1.86)	0.89 (0.43 - 1.85)
High vs low	0.82 (0.43 - 1.57)	0.58 (0.28 - 1.20)	1.56 (0.75 - 3.26)	1.58 (0.75 - 3.32)

*Charlson score: 0=low; 1-2: medium; 3+=high

PPI:= Proton pump inhibitors; H2RA: = H2-receptor antagonist