Proton Pump Inhibitors (PPI), H2 Blocker Use, and Risk of Inflammatory Bowel Disease (IBD) in Children

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Abstract

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Background: Previous longitudinal and cross-sectional studies have shown that changes in the composition of the gut microbiota are associated with IBD. Thus, it is plausible that drugs that alter the microbiome may increase the risk of future IBD. Previous studies have examined the association of Proton Pump Inhibitors (PPIs) and H_2-receptor antagonists (H_2 blockers) with changes in the microbiome. Some evidence suggests that use of PPIs and H_2 blockers may provoke disease flares in individuals with established IBD; however, no studies have investigated the relationship of PPIs and H_2 blockers with risk of developing IBD in children. We hypothesized that the use of acid suppression therapy in children may be associated with the development of pediatric IBD.

Methods: We conducted a nested case-control study of 285 Kaiser Permanente Northern California members, age ≤21 years who were diagnosed with IBD from 1996 to 2016. We used data from the electronic health record to identify cases and controls from inpatient and outpatient data. Four controls were matched to each case on age, race, and membership status at the case's index date. Both cases and controls had at least five years of continuous membership prior to the index date. Disease risk scores (DRS) were computed for each subject. Odds ratios (RR) and 95% confidence intervals were calculated using conditional logistic regression models adjusted for DRS.

Results: The mean age of the children was 15.1 ± 2.6 years and 49.5% were female. During the study period, 6 cases and 6 controls were prescribed PPIs and 10 cases and 28 controls were prescribed H_2 blockers (5 children were prescribed both). The odds ratios for the association of receipt of at least one prescription of PPI or H_2 blocker with risk of subsequent IBD was 3.6 (95% CI 1.1 to 11.7) for PPIs and 1.6 (95% CI 0.7 to 3.7) for H_2 blockers.

Conclusion: There appears to be a considerable difference in risk associated with PPIs compared to H_2 blockers. Many of the children in this study did not have symptoms consistent with FDA-approved indications for PPI use, highlighting need for appropriate prescribing patterns. These findings have implications for clinical treatment of children with gastrointestinal symptoms and warrants further investigation in a larger cohort. This study adds to the growing body of evidence for prudent use of PPIs by providing evidence of an association between childhood use of PPIs and future IBD diagnoses.

Introduction

From 1990 through the 2000s, the burden of pediatric inflammatory bowel disease (IBD) has increased globally.[1] In North America, more than 1.3% of the general population has IBD, amounting to over 3.1 million Americans.[2] Pediatric IBD can result in adverse consequences such as delayed puberty and growth failure.[3]

Previous longitudinal and cross-sectional studies have shown that IBD is associated with changes in the composition of the gut microbiota,[4,5] emphasizing the role of environmental factors in the development and progression of the disease. If microbiome changes influence IBD risk, then it is plausible that drugs that alter the microbiome may also alter the risk of IBD. One drug class that is known to alter the gut microbiome is acid reducing medications, such as proton pump inhibitors (PPIs) and H_2- receptor agonists (H_2 blockers), although whether it does so in a way that increases the risk of IBD is still unclear. There has been a significant upsurge in the use of PPIs and H_2 blockers among infants and children in the past decade.[6-8] Prior studies have found evidence of an association between these drugs and altered gut microbiota.[9,10] PPIs and H_2 blockers may provoke disease flares in individuals with established IBD;[11] however, no study has investigated the relationship between the use of PPIs, H_2 blockers, and incident IBD. Given the higher severity of IBD in the pediatric population, and the limited evidence from clinical trials in younger populations, this gap in knowledge is concerning. We hypothesized that the use of acid suppression therapy in children may be associated with the development of pediatric IBD.

Materials and Methods

Study Setting

Kaiser Permanente Northern California (KPNC) is a closed, prepaid, integrated health plan that serves 30% of the San Francisco Bay Area population, with over 4 million currently enrolled members.[12,13] The membership of KPNC is largely representative of the underlying population of the San Francisco Bay Area with respect to race and socioeconomic status (SES).[12] All patient encounters, prescription fills, and lab results have been recorded in a computerized database since 1996.

Study Design, Subjects, and Data Source

We conducted a nested case-control study[14,15] using data from KPNC electronic health records as described earlier for the Kaiser Permanente Autoimmune Registry.[16] We used inpatient and outpatient data to identify all children diagnosed with IBD ≤21 years of age between 1996 and 2011. We selected as cases those 285 children in the health plan with at least five years of continuous membership (with no coverage gaps longer than 60 days) prior to the date of IBD diagnosis (i.e., the index date). Four controls drawn from the general KPNC pediatric population were matched to each case on age (within 1 year), race (Asian/Pacific Islander, Black, White, Native American, Multiracial, or unknown/other), primary clinic location, and membership status at the case's index date. These data were obtained from membership data and the electronic medical record. Controls were required to have been members at least as long as their matched case, and not to have an IBD diagnosis as of the index date for the case to which they were matched.

Classification of Outcome

IBD diagnosis was defined by International Classification of Disease, Clinical Modifications 9 (ICD-9-CM) codes for IBD (555 for ulcerative colitis [UC] and 556 for Crohn's disease [CD]) and by International Classification of Disease, Clinical Modifications 10 (ICD-10-CM) codes for IBD (K50 for CD and K51 for UC) using diagnostic codes recorded during inpatient and outpatient encounters. Cases were required to have 2 or more diagnoses recorded. According to previous research, this case definition has 95% positive predictive value (95% CI 94% to 96%).[17]

Classification of Exposure

Use of PPIs and H_2 blockers was assessed from the health plan's outpatient pharmacy database that records all details of prescriptions and dispensing of medications to health plan members. This database was searched for National Drug Codes (NDC) matching PPIs and H_2 blockers. Due to the possibility that these medications were prescribed for treatment of symptoms that were due to undiagnosed IBD, we considered exposures between two and five years before the index date to be the exposure period of interest. This reduced the possibility of protopathic bias,[18] which occurs when a drug of interest is initiated to treat symptoms of the disease under study before it is diagnosed.

Chart Review

We also conducted a chart review of all children in the study who were prescribed PPIs and a sample of subjects who were prescribed H2 blockers during the period 2 to 5 years prior to index date to determine the medical indication for the prescription and to determine whether there was contemporaneous evidence of IBD (e.g., diarrhea, bloody stools, abdominal pain). The

goal was to assess the indication for which the drug was prescribed to determine if prodromal symptoms were plausible as an explanation. The note from the clinic visit preceding the first prescription during the study period was examined for patient reported symptoms, concomitant diagnostic codes, additional medications, and the primary clinical reason for the prescription

Potential Confounders

Covariates that preceded and may have been associated with both IBD and exposure to PPIs were included in our analysis as potential confounding factors. In addition to the matching factors (age at index date, race, and primary clinic location), these candidate confounders included antibiotic medication use, sex, and socioeconomic status (SES). We obtained data on antibiotic exposure using the same pharmacy databases that were used to identify PPI and H_2 blocker prescriptions. Sex was obtained from the electronic medical record. Two census tract-level measures[19] representing SES were identified using residential address geocodes: proportion of high school graduates and proportion of family households with below-poverty level income.

Because very few children were prescribed PPI or H_2 blocker medications in this database, we did not use traditional statistical adjustment methods. Instead, to control for potential differences in risk of IBD between users of PPI and H_2 blockers and non-users of either type of drug, we calculated a disease risk score (DRS) for all subjects. In general, a DRS estimates the probability of disease for each member of a study cohort in the absence of the exposure, regardless of true exposure status.[20] This method allowed us to account for medication exposure as a single measure of disease risk, which was critical because of the few children exposed to the medications of interest in this population. In addition, the method is compatible with conducting a nested case control design.[21] Both DRSs and propensity scores address

statistical problems that arise when there is a large number of covariates and a rare exposure (DRS) or outcome (propensity scores), but a DRS is preferable to propensity scores when the exposure is rare.[20] The DRS was estimated from a logistic regression analysis of sex, year of birth, number of antibiotic prescriptions in the 2 to 5 years prior to index date, and the two census-level measures described above on the odds of being an IBD case in this study.

Statistical Analysis

We used conditional logistic regression[14] to compare cases and controls with respect to PPI and H_2 blocker prescriptions filled between two and five years before the diagnosis, adjusting for the DRS as a continuous measure. Sensitivity analyses considered exposure within 1 year and 1-2 years prior to diagnosis for comparison to our *a priori* exposure period of interest. Odds ratios (OR) and 95% confidence intervals were calculated using conditional logistic regression models that included both PPIs and H_2 blockers. All analyses were conducted using SAS version 9.4 and proc logistic. This study was approved by the Kaiser Foundation Research Institute Institutional Review Board.

Results

Demographic characteristics

We identified 285 cases and 1,144 controls (Table 1). Two controls were missing data for SES measures and thus were dropped from the analysis for a total of 1,142 controls. The mean age at index date was 15 years for both cases and controls. More than half (54%) of cases and controls were white. Hispanic was the second most common race category for both cases and controls (14%), followed by multiracial (12%), Asian/Pacific Islander (11%), black (7%), and

Native American (1%). Controls were more likely to be female than cases (51% versus 43%). Cases and controls received similar numbers of antibiotic prescriptions in the 2 to 5 years prior to index date. SES measures were also similar between cases and controls. DRS values ranged from 130 to 334 with a median of 200(Table 2).

Association with PPIs and H_2 blockers

During the 2-5 years before the index date, 2.1% of cases (n = 6) and 0.5% of controls (n = 6) were prescribed PPIs and 3.5% of cases (n = 10) and 1.6% of controls (n = 18) were prescribed H_2 blockers (4 children were prescribed both [2 cases and 2 controls]). The OR for the association of receipt of at least one prescription with risk of subsequent IBD was 3.6 (95% CI 1.1 to 11.7) for PPIs and 1.6 (95% CI 0.7 to 3.7) for H_2 blockers after accounting for potential confounders and use of the other medication class.

Chart Review

Among the 12 children prescribed PPIs during the study period, all but two (one case and one control) had been diagnosed with gastrointestinal symptoms or conditions at the visit preceding the PPI prescription (Table 4). Two controls and four cases were prescribed PPIs for gastroesophageal reflux disease (GERD) or possible GERD. There were no discernible differences in PPI indication between cases and controls. Our analyses of four cases and five controls with H_2 blocker use did not identify differences between cases and controls.

Discussion

Prescription PPIs were 3.6 times more common in IBD cases than controls in the 2-5 years prior to diagnosis. The results from a chart review reveal a variety of indications for the prescription of PPIs with no discernible difference in indication for initiating the medication class between cases and controls.

Patients in our study were prescribed PPIs between 25 and 60 months prior to IBD diagnosis, while the average prodromal phase of IBD in pediatric populations is thought to be 7 to 11 months for Crohn's disease and 5 to 8 months for ulcerative colitis.[22] Despite this, there is a chance that these results reflect protopathic bias, due to treatment for early indications of IBD. However, the association between H_2 blockers and IBD was weak, even though the indications for H_2 blockers were similar to those for PPIs (Supplemental Table 1). This makes it less likely that the association between PPI use and IBD is solely due to protopathic bias and suggests other possibilities.[18]

Previous literature has implicated PPIs as a risk factor for several health complications including gastrointestinal conditions such as *C. difficile* infection[23] and small intestinal bacterial overgrowth (SIBO).[24] Although to-date, no studies have investigated the role of PPIs in the development of IBD, there is evidence that PPI exposure increases the severity of disease when prescribed to adults with a history of IBD.[11,25] A large cohort study conducted in Canada found that patients with IBD given a new prescription for PPIs were more likely to experience IBD treatment escalation compared to patients with IBD who were not prescribed PPIs.[26] A nested case-control study conducted within the Veterans Health Affairs system found that PPI prescriptions were associated with an increased risk of IBD-related hospitalization in patients with IBD.[25]

There is a link between PPIs and intestinal dysbiosis.[27,28] In an age-sex-matched cohort study, Takagi et al. analyzed fecal samples from 36 PPI users and 36 non-users.[28] They found significant differences in the microbial composition of gut comparing users and non-users. This dysbiosis might be a mechanism by which PPIs increase risk of *C. difficile* and SIBO. Given that IBD is also associated with disturbances to the gut microbiome,[5,29] and that *C. difficile* is very common among pediatric IBD patients,[30] this adds plausibility to a potential association between PPIs and pediatric-onset IBD.

Another limitation of this study is the inability to capture PPI and H_2 blockers that may have been taken over the counter. Thus, there may be some exposure misclassification in this study, mostly in under-ascertainment of medication use. However, this bias most likely would be non-differential relative to IBD case status, because it is unlikely that over the counter PPI or H_2 blocker use differs by future disease status. It also seems unlikely that, in a population with health insurance, there would be significant self-treatment of children with these medications in the absence of medical visits. The likely net effect of this misclassification is an attenuated measure of association.

Pediatric IBD is a growing clinical concern that confers a substantial economic burden on families and healthcare systems.[31,32] In the context of increasing numbers of acid-blocker prescriptions among children,[6-8] understanding the adverse effects of these drugs is a public health priority. Short-term treatment of EOE and GERD are the only two FDA-approved indications for PPI use in children.[33] Many of the children in this study did not have symptoms consistent with these indications, highlighting the need for appropriate prescribing patterns. PPI use in childhood is also associated with allergic disease and bone loss.[24] Our study adds to the growing body of evidence for prudent use of PPIs by providing evidence of an association

between childhood use of PPIs and future IBD diagnoses. Over-prescription of PPIs is not limited to pediatric populations;[34] thus, there is a need to investigate this association in adult populations, as well. Our results have implications for clinical treatment of children with gastrointestinal symptoms and should be considered as part of the benefit/risk assessment of prescribing these medications in children.

Table 1. Demographic characteristics of IBD cases and matched controls

	Cases N = 285	Controls[1] N = 1,142
Index age (years) (mean, range)	15.1 (10-21)	15.1 (10-21)
Female, %	43.4	51.1
Race (%)		
Asian/Pacific Islander	11.0	11.0
Black	7.4	7.4
Hispanic	14.3	14.2
White	53.7	53.6
Native American	1.4	1.4
Multiracial	12.0	12.0
Unknown/Other	0.4	0.3
Missing	<1% (n=3)	<1% (n=12)
Number of antibiotic prescriptions	0.9 ± 1.5	0.8 ± 1.4
Socio-economic status[2]		
Proportion of family households with below-poverty level income	0.04 ± 0.05	0.04 ± 0.06
Proportion of high school graduates	0.2 ± 0.1	0.2 ± 0.1
Disease Risk Score	203.8 ± 29.4	198.7 ± 27.6

[1] Matched to cases on age, race, primary location, and duration of membership
[2] Based on census tract of residence

Table 2. Quartiles of calculated DRS for study subjects

Quartile	DRS
25%	174.79
50%	201.67
75%	222.51
100%	335.60

Table 3. Adjusted relative risks and 95% CI for the association between receipt of 1 or more PPI or H_2 blocker prescription 2 to 5 years before diagnosis and pediatric-onset IBD

	Cases N=285	Controls N=1,142	Odds Ratio (95% CI)*	p-value
PPIs	6 (2.1%)	6 (0.5%)	3.6 (1.1 to 11.7)	0.0321
H_2 blockers	10 (3.5%)	18 (1.6%)	1.6 (0.7 to 3.7)	0.2745

*Adjusted for DRS

Table 4. Clinical indications, symptoms, and additional prescriptions among 6 IBD cases and 6 controls prescribed PPIs, Kaiser Permanente Northern California, 1996-2016

Case or Control	Index Age	Timing of PPI use (age, duration)	H_2 Blocker and Antibiotic Use (age, drug type)[1]	Additional Prescriptions[2]	Diagnosis	Gastrointestinal Symptoms	Non-gastrointestinal Symptoms	Primary reason for visit
Control	14	9, 14 days	9, penicillin	Metronidazole, amoxicillin, Miralax, ondansetron, Zofran	*H. pylori*	Abdominal pain, constipation, vomiting	Decreased appetite	*H. pylori* treatment
Control	14	11, 30 days 12, 30 days	9, penicillin 10, penicillin 10, penicillin 11, penicillin 11, H_2 blocker	Amoxicillin, acetaminophen codein, dicyclomine, midrin, ranitidine, phenobarb belladonna alkaloid, sertraline	Chronic abdominal pain	Nausea, vomiting, abdominal pain	Migraine, weight loss	Abdominal pain, nausea, vomiting
Control	14	11, 30 days	None	Ondansetron, cyproheptadine, guanfacine, sertraline, mirtazapine	Anxiety disorder, oppositional defiant disorder	Diarrhea, abdominal pain (pain noted as better at visit), vomiting	Migraine	Diarrhea
Control	15	12 ,100 days	11, penicillin 11, penicillin 11, H_2 blocker 12, penicillin 13, penicillin	Amoxicillin, ranitidine	Gastritis, GERD	Upset stomach, diarrhea	Flu-like symptoms (congestion, sore throat, runny nose, fever)	GERD, not taking ranitidine as prescribed
Control	16	11, 182 days 12, 90 days 12, 90 days	None	Metoclopramide	GERD	Regurgitation, worsening GERD,	None	Worsening GERD
Control	19	16, 50 days 17, 50 days	14, tetracycline	Zofran	Suspected gastritis	Abdominal pain and nausea,	Dizziness	Abdominal pain and vomiting

						vomiting		
Case	12	8, 30 days	7, cephalosporin 8, penicillin 10, penicillin	None	Sinus infection, possible GERD	Not reported	Not reported	GERD symptoms
Case	13	8, 100 days	9, cephalosporin	Azithromycin, Cheratussin, cleocin, sulfamethoxaole; flovent	Eosinophilic esophagitis, GERD	Chronic heartburn, cough, reflux	Coughing attacks, dizziness	Eosinophilic esophagitis
Case	14	10, 30 days 10, 30 days 11, 30 days 11, 50 days 11, 75 days 11, 502 days	9, sulfonamide 9, cephalosporin 10, cephalosporin 9, H_2 blocker 10, H_2 blocker 10, H_2 blocker 10, H_2 blocker 10, sulfonamide 11, sulfonamide 11, sulfonamide	Sulfasalazine, erythromycin, ranitidine, valproate sodium	Diarrhea, acid reflux, GERD	Constipation, diarrhea, emesis	Weight loss, poor growth	Diarrhea, constipation, blood in stool and melena, gagging, vomiting
Case	15	10, 30 days 10, 30 days 12, 30 days	13, cephalosporin 13, sulfonamide	Ondansetron, clindamycin phosphate	Abdominal migraines, differential diagnosis: *H. pylori*, PUD, IBS, GERD	Abdominal pain	None	Continued abdominal pain
Case	16	12, 10 days 12, 10 days	12, penicillin	Amoxicillin, clarithromycin, desonide, azithromycin	Pharyngitis	Difficulty swallowing	Sore throat	Sore throat and difficulty swallowing, elevated *H. pylori*
Case	17	14, 60 days 14, 100 days	14, penicillin 15, H_2 blocker	Venlafaxine, neomycin polymyxin HD, anoxicillin, ondansetron, sodium chloride,	Major depression, panic disorder with agoraphobia	Constipation (severe), encopresis, abdominal pain, nausea	Weight loss, depression, anxiety	Weight loss (15 pounds over one year), abdominal pain,

				hydroxyzine HCI (atarax), citalopram, Miralax				constipation, encopresis

[1]During the 2-5 years before index date
[2]Additional prescriptions within +/- 6 months of PPI prescription

Supplemental Table 1. Clinical indications, symptoms, and additional prescriptions among 9 study subjects prescribed H_2 blockers, Kaiser Permanente Northern California, 1996-2016

Case or Control	Additional Prescriptions[1]	Diagnosis	Gastrointestinal Symptoms	Non-gastrointestinal Symptoms	Primary reason for visit
Control	Norgestimate-Ethinyl Estradiol	Iron deficiency	Abdominal pain, nausea	Fatigue	Well-child visit
Control	Zofran, Mupirocin, Azithromycin	Vomiting, indigestion	Abdominal pain, vomiting	Congestion, cough	Abdominal pain, vomiting 1-6/day
Control	Montelukast, Miralax	GERD	Adbominal pain, constipation, hard stools	Chest pain	Nausea, chest pain
Control	Fluticasone	Hoarseness	None	Patient clears throat constantly	Reflux
Control	Sertraline (Zoloft), Abilify, Albuterol, QUEtiapine (SEROquel), Adderall, Levonorgestrel-Ethinyl Estradiol	Vomiting, GERD differential diagnosis	Vomiting	Headache, low iron	Vomiting and headache
Case	Diphenhydramine-Lido viscous-maalox oral suspension, Nonrinyl, hydrocodone-acetaminophen, Miralax	Gastroenteritis, herpangina	Diarrhea, vomiting	Fever, oral sores	Gastroenteritis
Case	Azithromycin (Zithromax)	Postinfectious gastritis/enteropathy	Diarrhea, abdominal pain, nausea, constipation at times	Leg pain	Gastritis/enteropathy
Case	Trimethoprim-sulfamethoxazole, prednisone, cephalexin, amoxicillin	Folliculitis	None	Rash around right ear, leg	Rash on right side of face, folliculitis
Case	None	Pancreatitis, anemia	Abdominal pain	None	Abdominal pain, acute pancreatitis

[1]Additional prescriptions within +/- 6 months of H_2 blocker prescription

Supplemental Table 2. Sensitivity analysis, adjusted relative risks and 95% CI for the association between receipt of 1 or more PPI or H_2 blocker prescription and pediatric-onset IBD <1 year and >1 year to 2 years prior to diagnosis

Time prior to diagnosis	Cases N=285	Controls N=1,142	Odds Ratio (95% CI)*
<1 year			
PPIs	69 (24.2%)	5 (0.4%)	89.4 (28.0 to 285.5)
H_2 blockers	24 (8.4%)	15 (1.3%)	4.8 (2.4 to 9.8)
>1 year – 2 years			
PPIs	11 (3.9%)	4 (0.4%)	12.4 (3.6 to 43.1)
H_2 blockers	4 (1.4%)	8 (0.7%)	0.8 (0.2 to 3.5)

*Adjusted for DRS

Appendix 1. Drug classes included in study exposure classifications

Exposure Classification	Included Drug Classes
PPIs	Proton-Pump Inhibitors
H_2 blockers	Histamine H_2-Antagonists
Antibiotics	Tetracyclines Penicillins Sulfonamides Quinolones Macrolides Cephalosporins

Appendix 2. Mean DRS by exposure status for PPIs and H_2 blockers

Exposure	Mean DRS	Median DRS
PPI – yes	202.7 ± 23.8	198.6
PPI – no	199.7 ± 28.1	201.9
H2B – yes	202.2 ± 31.3	198.1
H2B – no	199.7 ± 28.0	201.9

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