Original Article

Proton pump inhibitors are associated with a reduced likelihood for sexually transmitted diseases in women in the emergency department

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Abstract

Background: Proton pump inhibitors (PPIs) have been shown in cell culture to kill *Trichomonas vaginalis* (TV) at lower half maximal inhibitory concentration values than metronidazole (Flagyl), the most common medication used to treat the infection. However, there have been no previous clinical investigations to determine if PPIs are associated with reduced risk for TV. **Materials and Methods:** We examined the records of female patients who received testing in the emergency department for TV, *Neisseria gonorrhoea* (GC), and *Chlamydia trachomatis* (CT) between 2010 and 2014 at two academic medical centers to determine if PPI and histamine type 2 receptor antagonist (H2RA) drugs were associated with TV and GC/CT infections. **Results:** We found that H2RAs were associated with an increased likelihood for TV (odds ratio [OR]: 2.0, $P < 0.0001$) and GC and/or CT infections (OR: 1.49, $P < 0.0001$). PPIs were associated with a reduced likelihood for TV (OR: 0.75, $P < 0.0001$) and GC and/or CT infections (OR: 0.57, $P < 0.0001$). In patients infected with GC and/or CT, the likelihood of coinfection with TV was reduced in those taking a PPI (OR: 0.64, $P = 0.054$) and increased in those taking an H2RA (OR: 1.62, $P = 0.003$). **Conclusions:** PPIs are associated with a reduced risk for TV and GC/CT infection.

Key words: *Chlamydia trachomatis,* histamine type-2 receptor antagonist, *Neisseria gonorrhoea,* proton pump inhibitor, sexually transmitted disease, *Trichomonas vaginalis*

INTRODUCTION

Trichomonas vaginalis (TV) are motile, flagellated, protozoan parasites that inhabit the genital tracts of men and women.[1,2] Trichomoniasis is the most common curable sexually transmitted disease (STD) in women, causing 7.4 million infections in the United States and 170 million infections worldwide: more infections than chlamydia, syphilis, and gonorrhea combined.[1,3-6] Up to 30%–50% of women and 70%–75% of men have asymptomatic TV infections.[1] TV is one of the United States Centers for Disease Control and Prevention's top five neglected parasitic diseases in the United States.[7]

TV can cause pelvic inflammatory disease, increase the risk of human immunodeficiency

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virus transmission, and can cause complications during pregnancy including premature rupture of membranes, premature labor, and low birth weight babies.[1,5,8] Trichomoniasis is characterized by vaginitis, vaginal pruritus, vulvitis, dysuria, dyspareunia, and a malodorous frothy yellow or green mucopurulent vaginal discharge.[1,5]

Proton pump inhibitors (PPIs) are among the most commonly prescribed medications in the United States. There are several United States Food and Drug Administration (FDA)-approved PPIs including omeprazole (Prilosec); lansoprazole (Prevacid); rabeprazole (Aciphex); pantoprazole (Protonix); esomeprazole (Nexium); and dexlansoprazole (Kapidex). All PPIs are structurally similar weak bases that accumulate as prodrugs in acidic environments where they undergo acid-catalyzed conversion to the active drug.[9] PPIs are used to treat several conditions, including gastroesophageal reflux disease, nonsteroidal-induced gastrointestinal lesions, Zollinger–Ellison syndrome, dyspepsia, and for the elimination of *Helicobacter pylori*.[9] PPIs are well tolerated with few significant side effects. The investigators are unaware of any study that have evaluated whether PPIs affect vaginal pH, accumulate in vaginal secretions, or if there are any functional H^+/K^+ ATPase in the genital tract of women.[10,11]

PPIs are benzimidazole derivatives and are structurally similar to other drugs such as benzimidazole 2-methylcarbamates (BC), albendazole (ABZ), and mebendazole (MBZ), all of which kill the human protozoan parasites *Giardia lamblia*, *Entamoeba histolytica*, and TV in cell culture.[12-15] ABZ and MBZ kill TV by affecting β-tubulin polymerization and alteration of the TV cytoskeleton, microtubules, and microribbons.[15] Quantitative structure-activity relationship (SAR) analyses studies based on comparative molecular field analysis, molecular similarity indices in comparative analysis studies, and SAR studies based on structure-activity-similarity maps found that PPIs should be expected to have trichomonicidal activity based on previous results with BC, ABZ, and MBZ.[12] *In vitro* studies have shown that PPIs, and in particular pantoprazole, kill TV 1.9–3.1 times better than the drug metronidazole, the medication most commonly used to treat TV.[1,12] The TV 50% inhibitory concentration (IC_{50}) (μM) is 0.0756 for pantoprazole, 1.5905 for ABZ, and 0.2360 for metronidazole.[12]

TV is incapable of *de novo* synthesis of purine and pyrimidine rings; it relies on uridine nucleoside ribohydrolase (UNH) to cleave a bond between uracil and ribose in the uridine salvage pathway.[16] Pantoprazole was found to inhibit UNH in an *in vitro* assay with an IC_{50} of 14.5 μM; however, it is unclear if this is the mechanism responsible for PPI toxicity against TV.[16]

Tritrichomonas foetus (TF), a sexually transmitted parasitic disease, which causes trichomoniasis in cattle, is the most similar nonhuman trichomonad to TV.[6,17] The PPI omeprazole was found to kill metronidazole-resistant TF at 22 μg/mL (63 μM) in cell culture.[17] The authors suggest that omeprazole works by inhibition of pyruvate decarboxylase (PDC), which is an enzyme responsible for ethanol production. PDC was inhibited by omeprazole with an IC_{50} of 16 μg/mL.[17]

The investigators are unaware of previous clinical investigations to determine if PPI use is associated with a reduced risk for TV infection in humans. *Neisseria gonorrhoea* (GC) and *Chlamydia trachomatis* (CT) – two STDs diagnosed in the emergency department (ED) in women also at risk for TV – are not known to be affected by PPIs and were used as controls. Histamine type 2 receptor antagonists (H2RAs) were used as additional controls because they have similar clinical indications as PPIs but have no known effect on GC, CT, or TV.

MATERIALS AND METHODS

We received the Institutional Review Board approval from University Hospitals (UH) (IRB #08-14-12) and exemption from Eastern Virginia Medical School (EVMS) (IRB #15·06·NH·0123) to conduct this chart review study. The chart review data were abstracted from each institution's respective electronic medical records: UHCare for UH and Epic for Sentara Healthcare, which is affiliated with EVMS. The data were for women aged 18–40 years who received testing for TV, GC, and CT in the emergency department between 2010 and 2014. The data were provided to study investigators without protected health information in a de-identified, aggregate manner.

Subjects were considered infected with TV if they had TV reported on their wet prep or they had a positive APTIMA nucleic acid amplification test (NAAT) for TV. Subjects were considered positive for GC/CT if a NAAT was positive for either or both GC and CT. Subjects were considered to be taking a PPI (omeprazole, lansoprazole, rabeprazole, pantoprazole, esomeprazole, or dexlansoprazole)

and/or H2RA (cimetidine, famotidine, nizatidine, or ranitidine) if it was listed on their chart during the medical encounter when testing for STDs was conducted.

For the UH dataset, we determined the breakdown of how TV was diagnosed in our subjects. We found that 90% of subjects diagnosed with TV had only a wet prep performed while 10% of subjects were diagnosed by NAAT. TV was excluded as a diagnosis in our study subjects based on a negative wet prep only (i.e., no NAAT performed after a negative wet prep) in 82% of subjects. The breakdown of subjects diagnosed with TV at EVMS who had a wet prep and/or NAAT was not available to the investigators for analysis.

RESULTS

There were 654,538 women aged 18–40 years in the Sentara Epic database and 48,372 in the UH database (total 702,910). After meeting appropriate inclusion and exclusion criteria, there were 87,550 subjects from EVMS and 30,901 subjects from UH that were used in the final data set for a total of 118,451 charts reviewed. A summary of the data is provided in Table 1.

Table 2 shows the odds ratio (OR) for PPI use, H2RA use, and persons taking neither a PPI nor H2RA in relation to the results of the TV and GC/CT testing for both UHCare and the Sentara healthcare systems (EVMS)-Epic and the combined UHCare and Epic datasets. Using the combined UHCare and Epic databases, we found that PPI use, compared with no PPI or H2RA use, was associated with a reduced likelihood for both TV (OR: 0.75, 95% confidence interval [CI]: 0.65–0.86, $P < 0.0001$) and GC/CT (OR: 0.57, 95% CI: 0.50–0.64, $P < 0.0001$) infections. Using the combined UHCare and Epic databases, we also found that H2RA use, compared to no PPI or H2RA use, was associated with an increased likelihood for both TV (OR: 2.0, 95% CI: 1.77–2.36, $P < 0.0001$) and GC/CT (1.49, 95% CI: 1.30–1.71, $P < 0.0001$) infection. However, the associations between PPI and H2RA use and TV did not achieve statistical significance when only the UHCare data were analyzed but was highly statistically significant in the Epic dataset.

Table 1: The number of subjects with TV and GC and/or CT (GC/CT) who are taking a PPI, H2RA, or neither class of drug

TV	GC/CT	H2RA	PPI	UHCare	Sentara Epic	Total number of subjects
+	+	+	–	16	30	46
+	+	–	+	8	12	20
+	+	–	–	605	822	1,427
–	–	+	–	563	714	1,277
–	–	–	+	452	3,130	3,582
–	–	–	–	23,484	71,335	94,819
+	–	+	–	64	116	180
+	–	–	+	43	150	193
+	–	–	–	2,381	4,041	6,422
–	+	+	–	60	140	200
–	+	–	+	47	175	222
–	+	–	–	3178	6,885	10,063
	Totals			30,901	87,550	118,451

Table 3 shows the OR for TV and GC/CT use when PPI use (intervention) is compared to H2RA use (control) in the combined UHCare and Epic datasets (compared to Table 2 where PPI and H2RA use was compared to no PPI or H2RA use). We performed this analysis because PPIs and H2RAs treat many of the same clinical symptoms but have different mechanisms of action. We found a statistically significant association between PPI use and not being infected with TV (OR: 0.37, 95% CI: 0.30–0.45, $P < 0.0001$) and GC and/or CT (OR: 0.38, 95% CI: 0.31–0.46, $P < 0.0001$) compared with H2RA use.

We examined the association between TV infection in women who were also coinfected with GC and/or CT (i.e., +TV+GC-CT, +TV-GC+CT, or +TV+GC+CT) and whether they were taking PPIs or H2RAs. The results are summarized in Table 4. We found that PPI use, compared with no PPI or H2RA use, was associated with a reduced likelihood for TV infection in women who were coinfected with TV and GC/CT (i.e., +TV+GC-CT, +TV-GC+CT, or +TV+GC+CT) (OR: 0.64, 95% CI: 0.40–1.01, $P = 0.05$). We found that H2RA use, compared with no PPI or H2RA use, was associated with an increased likelihood for TV infection in women who were also coinfected with GC/CT (i.e., +TV+GC-CT, +TV-GC+CT, or +TV+GC+CT) (OR: 1.62, 95% CI: 1.17–2.25, $P = 0.004$). When controlling for GC/CT coinfection, we found that PPI use, compared with H2RA use, was associated with a reduced likelihood for TV infection in women who were coinfected with GC/CT (i.e., +TV+GC-CT, +TV-GC+CT, or +TV+GC+CT) (OR: 0.39 95% CI: 0.22–0.68, $P = 0.001$).

DISCUSSION

We report a reduced likelihood of TV and GC/CT infection in women in the ED taking a PPI and an increased likelihood of TV and GC/CT infection when taking an H2RA. The reduced likelihood

Table 2: The Odds ratios for PPI and H2RA use and TV and GC and/or CT (GC/CT) infection in female patients 18-40 years of age in the ED

UHCare + Epic	+TV	−TV	Odds Ratio: 0.7482
+PPI	213	3,804	95% CI: 0.6505-0.8606
−PPI and −H2RA	7,849	104,882	*P*<0.0001
UHCare + Epic	+TV	−TV	Odds Ratio: 2.0446
+H2RA	226	1477	95% CI: 1.7742-2.3563
−PPI and −H2RA	7,849	104,882	*P*<0.0001
UHCare + Epic	+GC/CT	−GC/CT	Odds Ratio: 0.5649
+PPI	242	3,775	95% CI: 0.4953-0.6442
−PPI and −H2RA	11,490	101,241	*P*<0.0001
UHCare + Epic	+GC/CT	−GC/CT	Odds Ratio: 1.4877
+H2RA	246	1457	95% CI: 1.2979-1.7052
−PPI and −H2RA	11,490	101,241	*P*<0.0001
UHCare	+TV	−TV	Odds Ratio: 0.9126
+PPI	51	499	95% CI: 0.6824-1.2203
−PPI and −H2RA	2,986	26,662	*P*=0.5373
UHCare	+TV	−TV	Odds Ratio: 1.1466
+H2RA	80	623	95% CI: 0.9057-1.4515
−PPI and −H2RA	2,986	26,662	*P*=0.2556
UHCare	+GC/CT	−GC/CT	Odds Ratio: 0.7597
+PPI	55	495	95% CI: 0.5738-1.0058
−PPI and −H2RA	3,783	25,865	*P*=0.0549
UHCare	+GC/CT	−GC/CT	Odds Ratio: 0.8287
+H2RA	76	627	95% CI: 0.6516-1.0541
−PPI and −H2RA	3,783	25,865	*P*=0.1258
Epic	+TV	−TV	Odds Ratio: 0.7884
+PPI	162	3,305	95% CI: 0.6716-0.9256
−PPI and −H2RA	4,863	78,220	*P*=0.0037
Epic	+TV	−TV	Odds Ratio: 2.7498
+H2RA	146	854	95% CI: 2.3017-3.2853
−PPI and −H2RA	4,863	78,220	*P*<0.0001
Epic	+GC/CT	−GC/CT	Odds Ratio: 0.5576
+PPI	187	3,280	95% CI: 0.4803-0.6473
−PPI and −H2RA	7,707	75,376	*P*<0.0001
Epic	+GC/CT	−GC/CT	Odds Ratio: 2.0032
+H2RA	170	830	95% CI: 1.6957-2.3665
−PPI and −H2RA	7,707	75,376	*P*<0.0001

Table 3: The Odds ratio of PPI use, compared with H2RA use, for TV and G/CT infection

UHCare + Epic	+TV	−TV	Odds Ratio: 0.3659
+PPI	213	3,804	95% CI: 0.3006-0.4454
+H2RA	226	1,477	*P*<0.0001
UHCare + Epic	+GC/CT	−GC/CT	Odds Ratio: 0.3797
+PPI	242	3,775	95% CI: 0.3148-0.4580
+H2RA	246	1,457	*P*<0.0001

of both TV and GC/CT infection in our subjects taking a PPI may be the result of an unidentified confounder; however, when we controlled for GC/CT infection, PPI use was still associated with a reduced likelihood of TV infection.

There are limitations to this chart review study including: we used retrospective data; we did not take into account medical compliance with PPIs and H2RAs; the medical record may not accurately reflect the medications that patients have been prescribed; the medical record may not reflect over-the-counter H2RA or PPI drugs taken intermittently for symptomatic relief of gastrointestinal distress; and we did not control for the different FDA-approved PPIs or doses. Most of the subjects in our UH dataset were identified as infected or uninfected with TV based on a wet prep, known to have only moderate sensitivity, and not a NAAT that has excellent sensitivity and specificity.

Only 3.4% of subjects in our dataset were taking a PPI, and 1.4% was taking an H2RA. The increased cost of PPIs over H2RAs may be a confounder because the demographic most at risk for STD infection are young, socioeconomically disadvantaged women who may not be able to afford the relatively more expensive PPIs.

We did not observe a statistically significant reduced likelihood of TV infection in those subjects taking a PPI when only the smaller UHCare dataset was used. A statistically significant effect was only seen when evaluating the Epic and the combined Epic + UHCare datasets. It is possible that this difference in effect is the result of an unidentified confounding variable, which could include differences in the socioeconomic status of subjects at the different institutions, sample size, race (as it relates to potential drug pharmacokinetics), methods used for diagnosing TV, and the accuracy of the ED electronic medical record to reflect the drugs patients are actually taking.

The investigators are unaware of any previous investigation into whether PPIs are found in the genital secretions of women although it may be theoretically possible based on the known pharmacokinetics of the drugs. The results of this study support the need for further investigation into the pharmacokinetics of PPIs in the genital tract of women including a more rigorous evaluation to whether PPIs have any *in vivo* antitrichomonal effects.

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Conflicts of interest
There are no conflicts of interest.

Table 4: The Odds ratio for TV infection in those women infected with GC and/or CT who are taking PPIs, H2RAs, or neither drug

UHCare + Epic	+TV and +GC/CT	−TV and +GC/CT	Odds Ratio: 0.6353
+PPI	20	222	95% CI: 0.4007-1.0073
−PPI and −H2RA	1,427	10,063	*P*=0.0537
UHCare + Epic	+TV and +GC/CT	−TV and +GC/CT	Odds Rato: 1.6219
+H2RA	46	200	95% CI: 1.1716-2.2454
−PPI and −H2RA	1,427	10,063	*P*=0.0036
UHCare + Epic	+TV and +GC/CT	−TV and +GC/CT	Odds Ratio: 0.3917
+PPI	20	222	95% CI: 0.2240-0.6848
+H2RA	46	200	*P*=0.001

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