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Proton pump inhibitors and risk of Clostridium difficile infection: a multi-country study using sequence symmetry analysis.

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Running title: PPIs and C. difficile multinational results

Key words: Proton pump inhibitors, Clostridium difficile, adverse event, Asia, sequence symmetry analysis.

Structured summary:

Background: Research showing an association between proton pump inhibitors (PPIs) and Clostridium difficile infections has largely been undertaken in Europe and North America. Clostridium difficile strains vary by region and may influence risk estimates across regions.

Aim: To determine the association between incident proton pump inhibitor (PPI) use and Clostridium difficile infections across multiple countries

Method: National data covering the total population in Australia and Korea, the Canadian population over 65 years and a 3 million person random sample data set from Taiwan were assessed, as were data from a worker insurance population and a hospital inpatient/ outpatient population in Japan. Sequence symmetry analysis was used to assess the association with oral vancomycin dispensing as the outcome of interest.

Results: 54,957 patients were included. Positive associations were observed in Australia; adjusted sequence ratio (ASR) 2.48 (95% CI 1.90, 3.12), Korea ASR 2.15 (95%CI 2.11, 2.19), Canada ASR 1.45 (95% CI 1.16, 1.79), Japan hospital dataset ASR 3.21 (95%CI 2.12, 4.55) and Japan worker insurance dataset ASR 5.40 (95% CI 2.73, 8.75). The pooled result was ASR 2.40 (95%CI 1.88, 3.05) and 3.16 (95%CI 1.95, 5.10) when limited to Asian countries. Results did not vary by individual PPI. The temporal analysis showed effects within the first two weeks of PPI initiation.

Conclusion: When analysis was limited to the Asian countries, pooled risk estimates were higher than those which had been observed in European and North American populations. Research to identify reasons underpinning any risk difference in the Asian region is required.

Introduction

There is a significant body of research showing an association between use of proton pump inhibitors and Clostridium difficile infections,[1-5] however, limited research has been undertaken in Asia-Pacific populations. A 2012 meta-analysis assessing the association between Clostridium difficile infections and proton pump inhibitor use included 51 studies and reported a pooled odds ratio of 1.65 (95% CI 1.47, 1.85), however, only 3 observations were from the Asia region.[1] When analysis was limited to the Asian observations, and the pooled result was higher at OR 3.26, (95%CI 1.91 -5.58.).[1]

The prevalence of different strains of Clostridium difficile varies substantially by region. Ribotyping has shown that the most frequent ribotypes in Australia are 014 and 002,[6] in China it is 017, 046, and 012; in Japan 018, 014, 002, 001, Korea 018, 017, Taiwan 017, and Hong Kong it is 002.[7] This compares with Europe where the ribotypes are 027, 014,001/072, and 078.[8] This may have implications for the risk of clostridium difficile from proton pump inhibitors. In some clostridium difficile ribotypes the level of expression of toxin genes and their regulators was greater at higher pH levels and elevated even further in the presence of PPIs.[9] For Ribotype 001, PPI exposure was associated with a 120-fold higher expression of tcdA at higher pH levels, while for ribotypes 027 and 028, more than 50 fold increases were observed at higher pH levels. For tcdB and cdtB expression the relationship was less clear.[9] Whether the differing prevalence of different strains of Clostridium difficile and the potential for PPIs to affect toxin gene expression differently according to strain means that differences in risk of PPI induced Clostridium difficile can be observed across countries is unclear.

There has been only limited study of the association between proton pump inhibitors and risk of Clostridium difficile infection in the Asia Pacific region, with the majority of studies undertaken to date being from North America or Europe (48 of 51).[1] No multi-country studies have been undertaken to date. Further many studies have been single centre sites (40 of 51), have been undertaken in the

hospital setting (37 of 51, 6 involved both hospital and community and 8 involved community only) and have been case-control studies (37 of 51).[1] The majority of studies assessed any proton pump inhibitor exposure with limited analysis of the effect of incident use.

To further add to the evidence base and address some of the limitations of prior research we undertook a multi-country study, which included 4 countries (6 databases) from the Asia Pacific region. We used a self-controlled method. We had national data for four of the countries involved, thus providing the largest study sample to date to assess the association between proton pump inhibitor use and Clostridium difficile infection.

Methods

Data sources

This multi country study was initiated by Health Canada, with participation from the member groups of the Asian PharmacoEpidemiology Network (AsPEN).[10] AsPEN provides a mechanism to support the conduct of cross-country pharmacoepidemiological research to facilitate prompt detection and communication of emerging safety issues between countries. The data sources used are listed in table 1. All datasets held patient level dispensing data which included: a patient identifier, patient demographics, date of medicine supply, medicine dispensed, quantity and strength. Medicines were mapped from individual country specific codes to the WHO Anatomical Therapeutic Chemical (ATC) classification codes.[11]

Study design

We used sequence symmetry analysis,[12] which has been validated as an adverse event signal detection tool,[13 14] to assess the association between proton pump inhibitor use and Clostridium difficile, using oral vancomycin as the marker medicine for Clostridium difficile. Oral vancomycin use would be

expected to rise after PPI initiation if there is an association with Clostridium difficile infection as oral vancomycin is only indicated for Clostridium difficile infections and staphylococcal enterocolitis.[15] Oral vancomycin has been used as a marker of Clostridium difficile infections in previous research.[16] Vancomycin's poor absorption from the gastrointestinal tract makes it unsuitable for other types of infection so risk of misclassification bias is low.

A distributive network model [17] was employed. The co-ordinating centre for this study, the University of South Australia, developed the statistical analysis code as a stand-alone SAS program for execution by each participant in their home institution. The SAS program used global macro variables. Participants executed the SAS code and a standardised file of summary results was returned to the co-ordinating centre for collation. These standardised files included graphics of the number of people dispensed the study medicines each month (prevalent population), the number of people starting study medicines each month (incident population), and the results of the sequence symmetry analyses (SSA) results including the graphics showing temporal sequences.

The primary outcome was the first dispensing of oral vancomycin (ATC code C03CA01) as an indicator medicine for Clostridium difficile. Oral vancomycin was only used in Taiwan at the beginning of the study period, with injectable formulations of vancomycin used orally at both the beginning of the study and in subsequent years. Hong Kong used injectable forms of vancomycin orally throughout the study period, thus, Hong Kong data were not included in the results. Proton pump inhibitors assessed included omeprazole, esomeprazole, lansoprazole, pantoprazole and rabeprazole. Proton pump inhibitors dispensed as part of a helicobacter eradication therapy co-pack were excluded.

In the SSA method, the date of incident dispensing of proton pump inhibitors and oral vancomycin was determined for each individual patient. All incident dispensings that occurred within one year of each other for the same person were included in the analysis. We excluded patients who initiated any of the

study medicines in the first year of data coverage in any dataset to ensure we limited the analyses to incident users. The SSA method uses a within person design, making it robust towards confounders that are stable over time,[12] however, it is sensitive to prescribing trends over time and adjustment was made for temporal trends using thee null-effect sequence ratio as described by Tsiropolous.[18] Bootstrapped 95% confidence intervals (CI) were obtained using 500 replicates. The SSA analyses were restricted to sequences of incident dispensings within 12 months of each other to limit the effect of age and other potential time-varying covariates on the probability of exposure and outcome. Moreover, a 12-month period has better specificity and positive predictive value compared with shorter periods.[13] Pooled estimates were obtained with a random effects model, using the generic inverse variance method.[19].

Results:

In total, 54,957 patients who received oral vancomycin and proton pump inhibitors were included in the study. Positive associations were see in all countries apart from Taiwan, where due to low use of oral vancomycin, insufficient numbers were available to determine effect. (Table 2) The pooled estimate showed a 2.4 fold increased risk (figure 1). When limited to the Asian countries (Japan, Korea and Taiwan) the pooled estimate was 3.16 (95%CI 1.95, 5.10). The temporal relationship was apparent in all countries, with effects being observed within the first two weeks of treatment (See figure 2 shows results for Australia (national) and Japan Medical Data Centre (JMDC)). Results for the individual PPIs are presented in table 3 for Australia (national) and Korea, the only countries with sufficient numbers to undertake individual agent analysis, and show similar risk for each agent.

Discussion

This multi-country study found an elevated risk of Clostridium difficile infections after initiation of proton pump inhibitors. Our pooled estimate of 2.4 (95% CI 1.88-3.05) is slightly higher but consistent with prior research, with meta-analysis evidence finding an increased odds of 1.65 (95% CI 1.47-1.85). [1] All countries in the Asia Pacific region had risk estimates greater than 2.0. When our pooled analysis was limited to Asian countries we found a three-fold increased risk which is also consistent with previous meta-analysis results from Asian countries OR 3.26, (95%CI 1.91 -5.58.).[1] Analysis by individual agents showed the risk was present and of similar magnitude for each proton pump inhibitor.

We observed the highest risk in the Japanese data sets, with risk estimates increased three and five fold respectively in the two Japanese data sets, for which confidence intervals overlapped. These results are higher risk estimates than have been reported previously in Japan. The largest previous Japanese study, which was a multi-institution study involving 1025 cases and 878 controls that assessed hospital acquired CDI, did not find proton pump inhibitors were a risk factor for CDI, however, assessment of PPI use was limited to that prescribed during the hospital stay.[20] By comparison our results include outpatient proton pump inhibitor use up to one year prior to CDI infection. A small Japanese study, limited to 26 cases and 52 controls, assessed risk factors for community acquired CDI, finding no association with proton pump inhibitor use.[21] Another small study of risk of recurrent infection, involving 14 patients with recurrent infection and 62 without also did not find a significant effect of proton pump inhibitors on recurrence.[22] These latter two studies may have had insufficient sample size to demonstrate effect. Finally, a Japanese study amongst a cohort of people who had been prescribed injectable antibiotics did find proton pump inhibitors were associated with increased risk of subsequent Clostridium difficile infections.[23] Previous research in Korea has assessed the relationship between recurrent Clostridium difficile infections and PPIs, demonstrating an association.[24, 25] No prior studies from Korea examined the effect on incident infection. One small study involving 84 persons from

Taiwan found proton pump inhibitors were an independent risk factor for development of Clostridium difficile infections (OR 3.2, p=0.014)[26], while a second study found of those with Clostridium difficile colonization, use of proton pump inhibitors was more common in those who subsequently developed infection.[27]

While it has been postulated that the acid suppressions mechanism of PPIs may play a role by allowing clostridium difficile spores to survive the gastric environment, this may not be the mechanism as clostridium difficile spores can survive acid gastric contents.[28] Acid levels, though, may affect toxin expression. As we previously noted, one in-vitro study found that expression of toxin genes and their regulators were different in the presence of PPIs in some clostridium difficile ribotypes.[9] Another in vitro study also examining the effect of PPIs on expression of colonocyte genes found PPIs decreased their expression.[29] The consequence of decreased expression includes loss of maintenance of cell junction, and reduced production of proteins known to protect the intestinal epithelium, one of which is known to protect against clostridium difficile induced intestinal damage. An effect on bile acid metabolism and transport was also observed.[29] All of these effects have the potential to increase susceptibility to or worsen clostridium difficile infection.

Given one of the possible mechanisms by which PPIs may exert their influence on Clostridium difficile infection is toxin expression and that toxin expression differs by ribotype,[9] our results, highlight the importance of obtaining risk estimates, where possible, from local data as data from other countries may not be directly applicable. Our results show slightly higher risk estimates in the Asian countries, however, we did not have access to clinical records and so could not ascertain any information on whether this could be related to the strain of Clostridium difficile being treated.

Strengths of our research include the access to national data sets for Australia, Canada, Korea, and Taiwan. Our research used a common method and a common analytic approach which ensures results

are comparative with regards to method and data variables used. Limitations of our study include lack of diagnostic information at the outpatient level in the majority of countries, and hence the reliance on oral vancomycin as the proxy indicator for Clostridium difficile. Oral vancomycin, however, has been used as a marker of Clostridium difficile infection in previous research[16] and is the sole reimbursed indication for oral vancomycin in Australia[30], Canada and Korea[31]. In Japan it is indicated for "infectious enteritis (including pseudomembranous colitis)" caused by vancomycin-sensitive MRSA colitis and C. diff, and 2) "sterilization of gastrointestinal tract at bone-marrow transplantation" the other countries it may be used for either Clostridium difficile or staphylococcal enterocolitis. A limitation of the method was the inability to include results from Hong Kong and Taiwan where the injectable formulation of vancomycin is provided orally as a treatment for Clostridium difficile infections, as these dispensings could not be distinguished from vancomycin given in the injectable form for other reasons. A further limitation is that oral vancomycin is second line therapy in many countries, with metronidazole being first line therapy for Clostridium difficile infections; including in Australia, Japan and Canada. We did not use metronidazole as our indicator of Clostridium difficile infections, however, because metronidazole is also indicated for other conditions and thus may have biased the results. This limitation means that we did not include cases of Clostridium difficile treated only by metronidazole only and so will not have captured all events. Finally, we cannot exclude the possibility that some of the differences observed across countries may be due to differences in health care practice.

In conclusion, our results provide further evidence of the association between proton pump inhibitors and risk of Clostridium difficile infections. When analysis was limited to the Asian countries, pooled risk estimates were higher than those which had been observed in European and North American populations. Further research to confirm reasons underpinning any risk difference in the Asian region is required.

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Table 1: Data sources for the study

Data source	Data type	Population covered	Years of coverage	Comments
Australian Government Department of Human Services	National pharmacy claims data	23 million persons	2003-2013	Excludes inpatient use in public hospitals
Australian Government Department of Veterans' Affairs	Pharmacy claims data for Australian veterans and their dependents	300,000	2001-2012	Excludes inpatient use in public hospitals. Predominantly older population (median age 80 years)
Canadian Institute for Health Information (CIHI)'s National Prescription Drug Utilization Information System (NPDUIS) Database	National Pharmacy Claims from public drug programs	3.5 million	2001-2012	Data from 7 Canadian provinces included in this study. Includes population aged 65 years and over who are eligible for coverage by provincial public drug programs. Includes only drugs dispensed in a community-based setting.
Hong Kong Clinical Data Analysis and Reporting System	National electronic healthcare record of public hospitals and their ambulatory clinics.	7 million	2008-2012	Oral vancomycin not reimbursed. Injectable formulation given orally.
Japan Medical Data Center database	Private health insurance data set for workers	1,000,000	2008-2013	
Japan Hamamatsu Medical University Database	Hospital data set	200,000	1996-2014	
Korea Health Insurance Review and Assessment	National Health Insurance data	50 million	2009-2013	

Service database (HIRA DB)	set			
Taiwan National Health Insurance Research Database	National Health insurance data set	23 million	2001-2012	3 million person random sample data set utilised. Oral vancomycin not used after 2005. Injectable formulation given orally across whole time frame.

Table 2: Sequence symmetry results for association between incident proton pump inhibitor (class) supply and incident oral vancomycin supply.

	Study Population n	**Oral vancomycin dispensed after PPI n**	**Oral vancomycin dispensed before PPI n**	**Crude Sequence Ratio**	**Null Effect Sequence ratio**	**Adjusted sequence ratio (95% confidence intervals)**
Korea	53820	37113	16707	2.22	1.03	2.15 (2.11-2.19)
Australia	351	257	94	2.734	1.10	2.48 (1.90-3.12)
Australia DVA	77	49	28	1.75	0.99	1.76 (0.97-2.71)
Japan Hamamatsu	171	128	43	2.98	0.93	3.21 (2.12-4.55)
Japan Medical Data Center	139	116	23	5.04	0.93	5.40 (2.73-8.75)
Canada	388	270	118	2.29	1.58	1.45 (1.16-1.79)
Taiwan[#]	11	8	3	2.67	0.99	2.70 (-1.60-8.91)

Low numbers for Taiwan as a result of preferential use of injectable vancomycin

Table 3: Sequence symmetry results for association between incident proton pump inhibitor (individual agent) supply and incident oral vancomycin supply.

	Study Population	Number of people with oral vancomycin dispensed after PPI	Number of people with oral vancomycin dispensed before PPI	Adjusted sequence ratio (95%confidence intervals)
Omeprazole				
Australia	113	82	31	2.41 (1.45, 3.58)
Korea	14878	9512	5366	1.67 (1.61, 1.72)
Pantoprazole				
Australia	299	209	90	2.08 (1.57, 2.65)
Korea	32070	20219	11851	1.71 (1.67, 1.75)
Lansoprazole				
Australia	18	16	2	7.66 (-1.06 18.99)
Korea	25917	15731	10186	1.53 (1.50,1.57)
Rabeprazole				
Australia	104	70	34	1.84 (1.10, 2.69)
Korea	23021	15474	7547	2.07 (2.02, 2.13)
Esomeprazole				
Australia	284	192	92	1.90 (1.44, 2.41)
Korea	20261	12000	8261	1.67 (1.62, 1.71)

Figure 1: Pooled estimate for association between incident proton pump inhibitor supply and incident oral vancomycin supply.

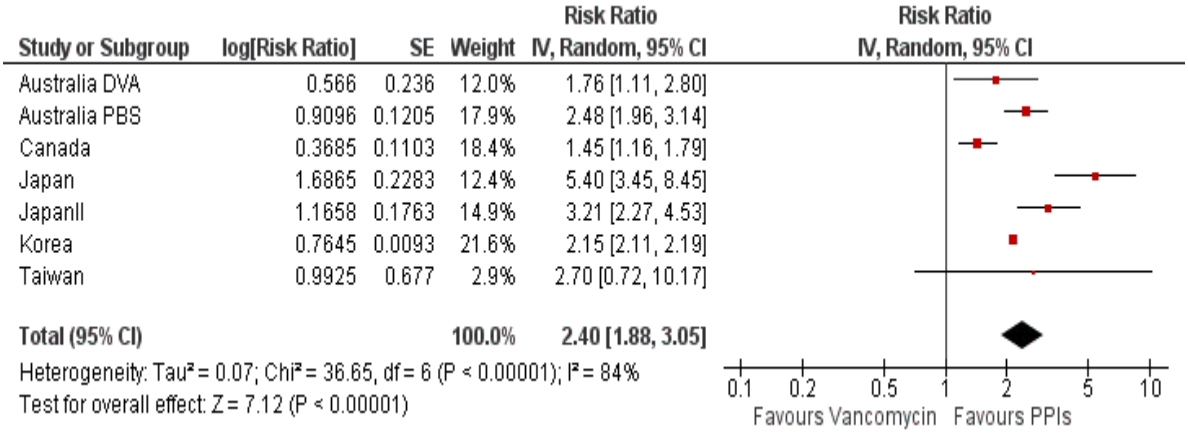

Figure 2: Temporal relationship of incident PPI supply and incident vancomycin use