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Safety profile of vonoprazan compared with proton pump inhibitors: insight from a pharmacovigilance study

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Proton pump inhibitors (PPIs) are used to treat acid-related disorders such as peptic ulcer and gastroesophageal reflux disease. Recently, vonoprazan, a novel potassium-competitive acid blocker (P-CAB), has been introduced as more effective treatment option. The purpose of this study was to clarify the adverse events associated with vonoprazan compared to PPIs using a spontaneous reporting system database. We performed a retrospective pharmacovigilance disproportionality analysis using the Japanese Adverse Drug Event Report (JADER) database. Adverse event reports submitted to the Pharmaceuticals and Medical Devices Agency between 2004 and 2017 were analyzed, and the reporting odds ratio (ROR) and 95% confidence interval (CI) for each adverse event were calculated. The database comprised 11,433 reports associated with PPIs, and 636 reports with vonoprazan. Hepatic and skin disorders were commonly detected in both PPIs and vonoprazan. There was a significant association of interstitial lung disease with PPIs as a class (ROR: 1.61, 95%CI: 1.47-1.77), but not with vonoprazan. Vonoprazan was strongly associated with haemorrhagic enterocolitis (ROR, 86.5; 95%CI, 59.7-125). Among the PPIs, the signal score of microscopic colitis was noteworthy in the case of lansoprazole (ROR, 405; 95%CI, 348-472). It is suggested that there is a diversity in the strength of the association between PPIs and vonoprazan with adverse events. Our results may provide useful information for the treatment of acid-related disorders, but further research with more data is needed to finally clarify this.

1. Introduction

Peptic ulcer disease is a chronic acid-related disease that affects up to 20% of the adult Asian population (Lau et al. 2013). Usually, ulcers in the stomach or duodenum, if left untreated, can recur or result in acute gastrointestinal bleeding (Tang and Wu 2013) and *Helicobacter pylori* infection (Sung et al. 2009). The treatment strategy for peptic ulcers is to minimize damage to gastrointestinal mucosa by reducing acid secretion. Currently, most patients with gastric ulcer or duodenal ulcer are treated with proton pump inhibitors (PPIs) such as omeprazole, lansoprazole, esomeprazole, and rabeprazole, which are available in Japan. PPIs are inhibiting the gastric H^+/K^+-ATPase, the so-called proton pump, by forming a covalent bond which, in turn, inhibits gastric acid secretion (Hori et al. 2010). Although PPIs are generally effective in the suppression of gastric acid, there are shortcomings that PPIs require approximately 2–3 days to exert maximum acid-inhibitory effects (Simon et al. 2007). Recently, potassium-competitive acid blockers (P-CABs) such as vonoprazan, have been developed and shown potential efficacy for the treatment of acid-related diseases (Rawla et al. 2018). P-CABs bind competitively and reversibly to the potassium-binding site of the ATPase (Echizen 2016). PPIs are converted to be active drugs by acid; whereas P-CABs do not need acid in order to inhibit the proton pump, which make it possible to raise gastric pH more highly and effectively at the first administration than with PPIs. Compared with PPIs, vonoprazan provides a longer acid-inhibitory effect with an elimination half-life of up to 9 h, whereas that of PPIs is 1 to 2 h. Despite of differential efficacy between PPIs and P-CAB, adverse events associated between them have not been fully evaluated.

Spontaneous reporting systems are used as tools of of post-marketing drug safety surveillance for the detection of adverse drug events (Mendes et al. 2014; Mahe et al. 2018). The Japanese Adverse Drug Event Report (JADER) database is a large published database managed by the Pharmaceuticals and Medical Devices Agency (PMDA) for pharmacovigilance (Kose 2018; Oyama et al. 2018; Hosohata et al. 2019a,b; Inada et al. 2019). The objective of this study was to clarify the profile of adverse events caused by by vonoprazan compared to that of PPIs using the JADER database.

Table 1: Number of AEs by PPI or P-CAB in JADER database between 2004 and 2017

Class	Drug	Number of AEs
PPI		
	Omeprazole	2510
	Lansoprazole	5620
	Rabeprazole	1914
	Esomeprazole	1389
P-CAB		
	Vonprazan	636

AEs, adverse events; JADER, Japanese Adverse Drug Event Report; P-CAB, potassium-competitive acid blocker; PPI, proton pump inhibitor.

2. Investigations and results

The total number of adverse events associated with the use of PPIs and P-CAB between April 2004 and January 2017 was 11,433 and 636, respectively. Among PPI, 2510, 5620, 1914, and 1389 were reported with omeprazole, lansoprazole, rabeprazole, and esomeprazole, respectively (Table 1). Omeprazole has been available for the longest period among the four PPIs.

Table 2: Top ten adverse drug events associated with PPI as a class

Adverse events	PPI as a class			Omeprazole			Lansoprazole			Esomeprazole			Rabeprazole		
	n	ROR	95%CI	n	ROR	95%CI	n	ROR	95%CI	n	ROR	95%CI	n	ROR	95%CI
Hepatic function abnormal	559	2.8	2.57-3.05*	111	2.5	2.07-3.03*	256	2.59	2.28-2.93*	70	2.87	2.25-3.65*	122	3.68	3.06-4.42*
Interstitial lung disease	498	1.61	1.47-1.77*	94	1.37	1.12-1.69*	244	1.61	1.41-1.83*	59	1.57	1.21-2.03*	101	1.97	1.61-2.41*
Colitis microscopic	404	254	218-296*	11	12.9	7.09-23.4*	357	405	348-472*	9	19	9.84-36.8*	27	42.9	29.1-63.2*
Agranulocytosis	348	8.17	7.33-9.11*	56	5.74	4.4-7.49*	196	9.25	8-10.7*	22	4.04	2.65-6.15*	74	10.1	8.04-12.8*
Platelet count decreased	304	0.99	0.88-1.11	79	1.18	0.94-1.47	138	0.91	0.77-1.08	43	1.16	0.86-1.57	44	0.85	0.63-1.15
Liver disorder	291	2.39	2.13-2.69*	67	2.5	1.96-3.18*	138	2.3	1.94-2.72*	16	1.06	0.65-1.73	70	3.46	2.72-4.39*
Toxic epidermal necrolysis	287	7.27	6.45-8.2*	93	10.6	8.62-131*	157	7.99	6.81-9.38*	24	4.81	3.21-7.21*	13	1.87	1.08-3.22*
Drug eruption	276	3.28	2.91-3.7*	61	3.27	2.53-4.21*	139	3.34	2.82-3.95*	27	2.6	1.77-3.8*	49	3.44	2.59-4.58*
Erythema multiforme	235	4.6	4.03-5.24*	29	2.51	1.74-3.63*	118	4.65	3.87-5.59*	38	6.06	4.39-8.37*	50	5.78	4.36-7.66*
Pancytopenia	223	3.11	2.72-3.56*	66	4.19	3.28-5.35*	92	2.56	2.08-3.15*	27	3.07	2.09-4.49*	38	3.14	2.27-4.33*

CI, confidence interval; PPI, proton pump inhibitor; ROR, reporting odds ratio. *, signal detected.

Table 2 shows the disproportionality analysis with reporting odds ratio (ROR) and 95% confidence (CI) based on the top 10 adverse events associated with PPIs as a class. The most frequently reported adverse events associated with PPI as a class was abnormal hepatic function (ROR, 2.8; 95%CI, 2.57-3.05), followed by interstitial lung disease (ROR, 1.61, 95%CI, 1.47-1.77), microscopic colitis (ROR, 254, 95%CI, 218-296), and agranulocytosis (ROR, 8.17; 95%CI, 7.33-9.11). The profiles of adverse events associated with individual PPIs varied. Notably, lansoprazole was identified as most potential cause of microscopic colitis (n = 357) with ROR of 405 (95%CI, 348-472).

Table 3: Top ten adverse drug events associated with vonoprazan

Adverse events	Vonoprazan		
	n	ROR	95%CI
Drug eruption	48	10.7	7.98-14.4*
Hepatic function abnormal	46	4.21	3.12-5.68*
Enterocolitis haemorrhagic	30	86.5	59.7-125*
Rash	16	3.34	2.03-5.49*
Platelet count decreased	13	0.76	0.44-1.31
Erythema multiforme	13	4.48	2.59-7.77*
Liver disorder	12	1.75	0.99-3.1
Pyrexia	12	1.33	0.75-2.36
Pancytopenia	11	2.72	1.5-4.94*
Toxic epidermal necrolysis	9	3.92	2.03-7.57*

CI, confidence interval; ROR, reporting odds ratio. *, signal detected.

In Table 3, the top ten adverse events associated with P-CAB are listed, in which drug eruption, abnormal hepatic function, haemorrhagic enterocolitis, and rash ranked highly. Of note, the signal score for haemorrhagic enterocolitis was noteworthy (ROR, 86.5; 95%CI, 59.7-125). Hepatic and skin disorders were commonly detected in both PPIs and vonoprazan; whereas, unlike PPIs, interstitial lung disease was not significantly associated with P-CAB (ROR, 0.45; 95%CI, 0.22-0.9).

3. Discussion

Using a large and nationwide study of pharmacovigilance data, we compared the safety profiles of PPIs as a class and individual agents and vonoprazan. In this study, similar to PPIs, vonoprazan was significantly associated with abnormal hepatic function, drug eruption, erythema multiforme, pancytopenia, and toxic epidermal necrolysis. On the other hand, interstitial lung disease was not listed as a highly reported adverse event for vonoprazan. In addition, there is a variability in the safety profile among the PPIs. To the best of our knowledge, this is the first study to clarify the profiles of adverse events caused by vonoprazan compared to PPIs using a spontaneous reporting database.

Our pooled analysis showed a positive association between all PPIs and abnormal hepatic function as well as with vonoprazan, and the signal scores were almost the same. Considering individual PPIs, our results revealed that the number of reports for abnormal hepatic function was the highest in lansoprazole, but the signal score was almost the same as for the other PPIs. Our results are inconsistent with the reports of Spanish Pharmacovigilance System Database, where liver and biliary disorders were more frequently reported for omeprazole and lansoprazole among the PPIs. On the other hand, users of omeprazole have been found to experience a low frequency of abnormal liver enzyme elevations (Loof et al. 1984; Solvell 1986). Further clinical studies will be needed.

In this study, we found that drug eruption, toxic epidermal necrosis (TEN), and erythema multiforme were associated with PPIs as well as with vonoprazan. PPIs have been reported to cause hypersensitivity reactions in 0.2–3% of cases (Demirkan et al. 2006). The molecular mechanism underlying the development of hypersensitivity to PPI is still unclear. In most cases, hypersensitivity reactions are IgE-mediated, which is generally called type I, and the remaining cases are T-cell-mediated delayed-type hypersensitivity reactions (Bose et al. 2013). Some studies reported PPI-related type I hypersensitivity reactions (Lobera et al. 2009; Kepil Ozdemir et al. 2016), but there were few studies about PPI-induced delayed-type hypersensitivity reactions, such as Stevens-Johnson syndrome (SJS), acute generalized exanthematous pustulosis (AGEP), toxic epidermal necrosis (TEN), and drug rash with eosinophilia and systemic symptoms (DRESS). Recently, PPI-related delayed-type hypersensitivity reactions were reported; esomeprazole-induced DRESS (Caboni et al. 2007), omeprazole-induced AGEP (Nantes Castillejo et al. 2008), esomeprazole-induced fixed-drug-eruption (Morais et al. 2010), and lansoprazole-induced TEN (Fracaroli et al. 2013). In this study, we found positive signal for individual PPI as well as vonoprazan will provide important information in clinical settings.

Although hematological adverse events have also been reported in patients receiving H_2-receptor antagonists (Aymard et al. 1988), reports of pancytopenia under PPIs as well as vonoprazan were limited. In our results, PPI as well as vonoprazan were significantly associated with pancytopenia, with almost the same signal scores. Thus, careful observation is required after the initiation of PPI and vonoprazan in clinical settings.

Our post-marketing data showed that PPIs were associated with interstitial lung disease (ROR, 498; 95%CI, 1.47-1.77), whereas it was not listed as a highly reported in connection with vonoprazan. There have been few reports about PPIs-induced interstitial lung disease. Two case reports showed lansoprazole-induced interstitial lung disease (Hwang et al. 2008; Atkins et al. 2014), but there were no reports of interstitial lung disease related to vonoprazan.

Among the PPIs, the signal score of microscopic colitis was noteworthy for lansoprazole (ROR, 405; 95%CI, 348-472). This is consistent with a study that lansoprazole is one of the causes of collagenous colitis (Ianiro et al. 2012). Concerning the mechanism underlying microscopic colitis caused by PPIs it has been suggested that inhibition of proton pumps in the colon mucosa may trigger an immune response (Bonderup et al. 2018). Especially, the binding sites of PPI to the proton pumps are different with lansoprazole-binding the cysteine residue, why it has been hypothesized that lansoprazole may trigger the specific changes in the colonic protein pump (Bonderup et al. 2018). In addition, the study shows that lansoprazole-related microscopic colitis depends on the chemical structure or property of lansoprazole (Bonderup et al. 2018). Lansoprazole is also a fluorine-containing compound in contrast to the other PPIs. The fluorine atom is small and highly electronegative (Shah and Westwell 2007). Selective installation of fluorine into a medicine can enhance a number of pharmacokinetic and physicochemical properties such as the improvement of stability, the improvement of lipophilicity, and an increased affinity to the enzyme by hydrogen bond etc (Shah and Westwell 2007). Therefore, it is hypothesized that the chemical structure of lansoprazole may trigger the development of microscopic colitis.

This pharmacovigilance study using the JADER database has several limitations. First, as in all pharmacovigilance studies, we were unable to calculate the true incidence rates, especially due to: 1) the lack of the total number of patients receiving the drugs of interest and 2) underreporting. Adverse events that are well-known to be due to certain drugs are less likely to be reported. Second, ROR does not provide a robust indication of the signal strength. In spontaneous reporting systems such as JADER, control populations are not included, so ROR is different from the "odds ratio" that is commonly used in epidemiological studies. In real terms, ROR indicates an increased risk of adverse event reporting, and not the risk of an adverse event itself. Third, the extent of actual exposure in the treated population is not available from the database. Finally, there might be other confounding factors related with the adverse events, but the present method did not provide us with detailed clinical information on the patients (Franciotta et al. 2009).

This is the first study to reveal that hepatic and skin disorders were commonly detected under both PPIs and vonoprazan; whereas there was a significant association of interstitial lung disease with PPIs as a class, but not with vonoprazan in a real-world setting. Physicians should be alerted in order to take precautions against the associated adverse events, and so potentially avoid them.

4. Experimental

4.1. Data

We used the JADER database of PMDA as a spontaneous reporting database (Anzai et al. 2019; Kose 2018). The JADER database is freely obtainable from the website of the PMDA and we accessed the dataset to which adverse event reports were submitted between April 2004 and January 2017. The data structure of JADER consists of 4 datasets: patient demographic information (DEMO), drug information (DRUG), adverse events (REAC), and medical history. We removed duplicated data from each table because the same case report can be received from different sources (Bate and Evans 2009). Physicians represent the most frequent source of reports, while the remaining reporters include pharmacists, other healthcare professionals, and patients. The DEMO table was then linked to the DRUG and REAC tables using the ID number. In each case, the contribution of the medication to adverse events was classified into three categories: "suspected medicine," "concomitant medicine," and "interaction." A "suspected medicine" is defined as a pharmaceutical product suspected of causing an adverse event. When the reporter suspects an interaction, he/she reports it as an "interaction." A "concomitant medicine" is defined as another pharmaceutical product used at the time of the adverse reaction. In signal detection analysis, the masking effect is defined as the condition whereby a given drug-event pair might be hidden by the presence of another product (Maignen et al. 2014). We only extracted cases that were classified as "suspected medicine."

4.2. Data analysis

Then, we analyzed reports of suspected drugs and adverse events, which we selected in the "Preferred Term (PT)" coded in the Medical Dictionary for Regulatory Activities (MedDRA) (version 20). We compiled a cross-tabulation table based on two classifications: the presence or absence of the adverse event, and the suspected medicine. Then, we calculated ROR by the following formula.

$$\mathrm{ROR} = \frac{a/b}{c/d}, 95\%\ \mathrm{CI} = \exp\left\{\log(\mathrm{ROR}) \pm 1.96\sqrt{\frac{1}{a}+\frac{1}{b}+\frac{1}{c}+\frac{1}{d}}\right\}$$

a : the number of patients developing a target event when they received a target drug

b : the number of patients developing non-target adverse events when they received a target drug

c : the number of patients developing the target event when they received non-target drugs

d : the number of patients developing non-target adverse events when they received non-target drugs

Generally, ROR is used with the spontaneous reporting database as an index of the relative risk of drug-associated adverse events. A signal was considered to be present when the lower limit of the 95% CI of the ROR was >1.

In this database, age, height, and weight information are indicated as follows: age in decades, height in centimetres, and weight in kilograms. These data are not given as continuous variables because of privacy considerations, so we could not conduct multiple analyses using them. All analyses were performed with JMP Pro 12 (SAS Institute Inc., Cary, NC, USA).

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