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Adverse event profiles of hypomagnesemia caused by proton pump inhibitors using the Japanese Adverse Drug Event Report (JADER) Database

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Proton pump inhibitors (PPIs) are commonly used for the prevention or treatment of gastric ulcers, but they can induce hypomagnesemia. Little is known about the onset duration and risk factors related to patient characteristics of this adverse event in Japanese patients. Therefore, we analyzed the time-to-onset of PPI-induced hypomagnesemia and evaluated the association between hypomagnesemia and PPIs using the Japanese Adverse Drug Event Report (JADER) database. We analyzed hypomagnesemia cases between 2004 and 2021. The time-to-onset analysis was performed using the Weibull distribution, and the adjusted reporting odds ratio (aROR) or 95% confidence interval (95% CI) was calculated using a multiple logistic regression analysis. The analysis database comprised 236,525 cases, with 188 cases associated with hypomagnesemia. The median onset duration (interquartile range) of PPI-induced hypomagnesemia was 99.0 (51.8–285.5) days, which is considered the random failure type. The multiple logistic regression analysis revealed that hypomagnesemia is significantly associated with male sex (aROR, 95% CI: 1.66, 1.23–2.25), age < 60 (1.59, 1.14–2.21), estimated body-mass index (eBMI) (0.94, 0.91–0.98), PPIs (1.66, 1.18–2.30), and the interaction of age (<60)*PPIs (1.58, 1.13–2.19). However, diuretics were not significantly associated with hypomagnesemia. Our results suggest that serum magnesium levels should be measured regularly regardless of the duration of PPI use, especially in patients with male sex, age < 60, or low BMI. These findings will assist health professionals in the adequate use of PPIs. These findings need to be evaluated by cohort studies and long-term clinical investigations.

1. Introduction

Hypomagnesemia can be induced by long-term use of proton pump inhibitors (PPIs) (Florentin and Elisaf 2012). PPIs and potassium-competitive acid blockers are used for the prevention of gastric ulcers caused by long-term use of corticosteroids and nonsteroidal anti-inflammatory drugs (Bardhan et al. 1991; Savarino et al. 2017; Yeomans et al. 1998), and they are commonly used over long-term periods. The relationship between PPI administration and hypomagnesemia was first reported in 2006 (Epstein et al. 2006; Swaminathan 2015), and previous studies have agreed with this finding (Boonpheng et al. 2019; Cheungpasitporn et al. 2015; Morii et al. 2022; Recart et al. 2021; Srinutta et al. 2019). PPI-induced hypomagnesemia is a rare adverse event, and it is difficult to determine the exact administration period. Although data regarding a time-to-onset profile are needed to evaluate the cause of drug-induced hypomagnesemia, few studies have investigated time-to-onset.

One possible mechanism underlying PPI-induced hypomagnesemia is PPI's impairment of intestinal magnesium absorption. PPI administration increases pH in the intestine, can change the affinity of the transient receptor potential melastatin-6 and 7 channel, and reduces active transport of magnesium ions (Bai et al. 2012; Perazella 2013). Severe hypomagnesemia is reportedly difficult to treat by magnesium injection (Fakih et al. 2006). PPI-induced hypomagnesemia can be treated by discontinuing PPI therapy and converting to a histamine-2 receptor antagonist (H_2-RA) (Hoorn et al. 2010). The concomitant use of PPIs and diuretics induces hypomagnesemia (Danziger et al. 2013) because diuretics inhibit the control of magnesium in the kidney (Dai et al. 2001). The risk of PPI-induced hypomagnesemia has been found to be higher in males and in the elderly population (Luk et al. 2013). Previous studies have suggested that PPI-induced hypomagnesemia is associated with patient characteristics such as sex, age, and concomitant drugs; however, data on the participant characteristics are limited.

The Japanese Adverse Drug Event Report (JADER) database is a spontaneous reporting system (SRS) developed by the Pharmaceuticals and Medical Devices Agency (PMDA). Although various biases can affect study outcomes with use of the JADER database (de Boissieu et al. 2014; Pariente et al. 2012), the JADER is a valuable tool that can be used to evaluate drug-associated rare and severe adverse events.

Luk et al. (2013) had reported an association between PPIs and hypomagnesemia in an SRS provided by the US Food and Drug Administration. Kambara et al. (2020) reported a safety profile of vonoprazan compared with proton pump inhibitors using the JADER. However, this previous study has not evaluated the patient characteristics associated with PPI-induced hypomagnesemia, and no data exist on the association between PPIs and hypomagnesemia in the JADER. It is necessary to investigate PPI's adverse events in Japan using the JADER database to examine whether PPIs are associated with hypomagnesemia.

Data on the time-to-onset profile or risk factors for PPI-induced hypomagnesemia in Japanese patients is lacking. It is important for appropriate use of PPIs to obtain data on the time-to-onset profile and the characteristics of patients with PPI-induced hypomagnesemia. Therefore, in the present study, we analyzed the time-to-onset of PPI-induced hypomagnesemia using the Weibull distribution and we evaluated the association between hypomagnesemia and PPIs using multiple logistic regression.

2. Investigations and results

The (a) DEMO table included 678,913 cases; the (b) DRUG table included 3,819,667 cases; and the (c) REAC table included 1,072,444 cases. After excluding duplicates and cases with missing data, 236,525 cases were analyzed, and we identified 188 cases of

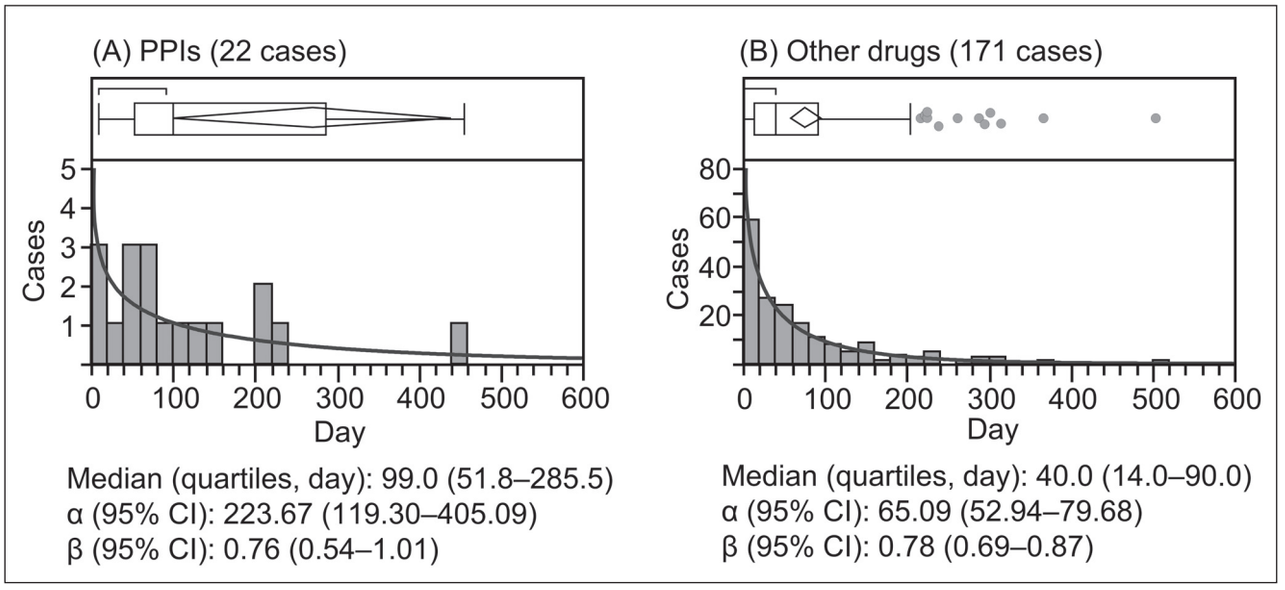

Fig. 1: Histogram and Weibull shape parameter of hypomagnesemia in (A) PPIs and (B) other drugs

hypomagnesemia. The number of hypomagnesemia cases was 122 in males and 66 in females. Similarly, the number of hypomagnesemia cases was 71 in those aged 0–59 years and 117 in those aged 60 years or older. The mean±standard deviation (minimum to maximum) of estimated BMI (eBMI) was 21.0 ± 3.7 (11.4–31.2) kg/m^2 in hypomagnesemia cases and 21.8 ± 3.9 (11.3–31.2) kg/m^2 in non-cases.

To evaluate time-to-onset of hypomagnesemia, we included in the analysis the reports that had complete information from "All reports" regarding the date treatment was started and the date of hypomagnesemia onset. Figure 1 shows the histogram and Weibull shape parameter of hypomagnesemia. In PPIs, the median and interquartile range (IQR) of onset duration was 99.0 and 51.8–285.5 days. The minimum and maximum duration were 8 and 1392 days, respectively. Furthermore, the α and β values were 223.67 (119.30–405.09) and 0.76 (0.54–1.01), respectively. The 95% confidence interval (CI) of the β value was 1, and the onset of hypomagnesemia was considered the random failure type. In other drugs, the median onset duration was 40.0 (14.0–90.0) days, and the α and β value were 65.09 (52.94–79.68) and 0.78 (0.69–0.87), respectively. The onset of hypomagnesemia in other drugs was considered the early failure type.

Table 1 shows the number of cases and reporting odds ratios (ROR) of PPIs, diuretics, and H_2-RAs. A disproportionate occurrence of hypomagnesemia was observed in PPI users (crude ROR [cROR] 1.42, 95% CI 1.03–1.97), whereas it was not observed in H_2-RA users (cROR 1.15, 95% CI 0.73–1.81). Especially in PPIs, this disproportionality was observed in patients who used esomeprazole or vonoprazan (cROR 2.28, 95% CI 1.32–3.93 and cROR 4.03, 95% CI 2.13–7.63, respectively). A disproportional occurrence of hypomagnesemia was observed in patients who used potassium-sparing diuretic/aldosterone antagonists (PSD/AA) or carbonic anhydrase inhibitors (CAI) (cROR 2.07, 95% CI 1.20–3.58 and cROR 5.41, 95% CI 1.34–21.85, respectively), whereas it was not observed in diuretics users overall (cROR 1.34, 95% CI 0.91–2.00). The cROR with 95% CI for analogous thiazide and cimetidine could be not calculated.

Table 2 shows a multiple logistic regression analysis of hypomagnesemia using variables of drug and patient background. In all cases, the multiple logistic regression analysis revealed that hypomagnesemia is significantly associated with sex (p = 0.001), age < 60 (p = 0.006), eBMI (p = 0.002), and PPIs (p = 0.003). The adjusted ROR (aROR) (95% CI) of sex, age, eBMI, and PPIs was 1.66 (1.23–2.25), 1.59 (1.14–2.21), 0.94 (0.91–0.98), and 1.66 (1.18–2.30), respectively. The interaction of age (<60)*PPIs was also significant, and the aROR (95% CI) was 1.58 (1.13–2.19). However, diuretics were not significantly associated with hypomagnesemia. In PPI cases, the multiple logistic regression analysis revealed that PPI-induced hypomagnesemia is significantly associated with the male sex (p = 0.045), age < 60 (p = 0.001), and eBMI (p = 0.023), and these aRORs (95% CI) were 1.85 (1.03–3.44), 2.53 (1.42–4.42), and 0.92 (0.85–0.99), respectively.

Table 1: Number of cases and ROR of PPIs, diuretics, and H_2-RAs

	Hypomagnesemia			
	Cases 188	Non-cases 236,337	Crude ROR	95% CI
PPIs	50	47,925	1.42	1.03–1.97
Omeprazole	6	6,972	1.08	0.48–2.45
Lansoprazole	19	21,497	1.12	0.70–1.81
Rabeprazole	5	9,993	0.62	0.25–1.50
Esomeprazole	14	8,059	2.28	1.32–3.93
Vonoprazan	10	3,249	4.03	2.13–7.63
Diuretics	29	28,225	1.34	0.91–2.00
Thiazide	5	4,689	1.35	0.55–3.28
Thiazide analogous	0	942	N/A	N/A
Loop	20	21,755	1.17	0.74–1.87
PSD/AA	14	8,826	2.07	1.20–3.58
CAI	2	469	5.41	1.34–21.85
H_2-RAs	21	23,357	1.15	0.73–1.81
Roxatidine	1	594	2.12	0.30–15.17
Famotidine	19	19,339	1.26	0.78–2.03
Cimetidine	0	959	N/A	N/A
Lafutidine	1	1,703	0.74	0.10–5.26
Nizatidine	1	981	1.28	0.18–9.16

PPI: proton pump inhibitor; PSD/AA: potassium-sparing diuretic/aldosterone antagonist; CAI: carbonic anhydrase inhibitor; H_2-RA: histamine-2 receptor antagonist. Using all cases (236,525 cases) from the JADER dataset from April 2004 to January 2021. The reporting odds ratio (ROR) and 95% confidence intervals (95% CI) of hypomagnesemia were calculated for PPIs, diuretics, and H_2-RAs. N/A: not available.

Table 2: Multiple logistic regression analysis of hypomagnesemia using drug and patient background variables

Variable	All cases			PPI cases		
	aROR	95% CI	*p*-value	aROR	95% CI	*p*-value
Sex	1.66	1.23–2.25	0.001**	1.85	1.03–3.44	0.045*
Age	1.59	1.14–2.21	0.006**	2.53	1.42–4.42	0.001**
eBMI	0.94	0.91–0.98	0.002**	0.92	0.85–0.99	0.023*
PPIs	1.66	1.18–2.30	0.003**			
Diuretics						
Sex*Age						
Sex*eBMI						
Sex*PPIs						
Sex*Diuretics						
Age*eBMI						
Age*PPIs	1.58	1.13–2.19	0.007**			
Age*Diuretics						
eBMI*PPIs						
eBMI*Diuretics						
PPIs*Diuretics						

Sex: male vs. Female; age: <60 vs. ≥60, eBMI: estimated body-mass index (kg/m^2); PPI: proton pump inhibitor. Using all cases (236,525 cases) from the JADER dataset from April 2004 to January 2021. The adjusted reporting odds ratio (aROR), 95% confidence intervals (95% CI), and p-value of hypomagnesemia were calculated using a multiple logistic regression analysis. The effectiveness of explanatory variables was evaluated using the stepwise method with a significance level of 0.05 (forward, and backward).*p<0.05, **p<0.01.

3. Discussion

In the present study, we analyzed the time-to-onset of PPI-induced hypomagnesemia, and also evaluated the association between hypomagnesemia and PPIs. Our results suggest that serum magnesium levels should be measured regularly regardless of the duration of PPI use, especially in patients with male sex, age < 60, or low BMI.

Our results showed the median onset duration (IQR) of hypomagnesemia was 99.0 (51.8–285.5) days for PPIs and 40.0 (14.0–90.0) days for other drugs. The time-to-onset profile of PPIs was considered the random failure type, whereas that of other drugs was considered the early failure type in this study. The onset duration of PPI-induced hypomagnesemia has been reported to be more than 1 year (Florentin and Elisaf 2012). Hess et al. (2012) had indicated the time-to-onset of PPI-induced hypomagnesemia ranged from 14 days up to 13 years, with a mean of 5.5 years. Meanwhile, the duration of PPI use was not significantly associated with serum magnesium levels (Mikolasevic et al. 2016). These findings and our results indicate that the time-to-onset of PPI-induced hypomagnesemia is more variable than with other drugs. In these cases, it is important to evaluate the risk factors related to patient characteristics and to monitor long-term serum magnesium levels compared with other drugs.

Our findings showed a disproportionality of hypomagnesemia in PPI users especially those who used esomeprazole and vonoprazan, whereas it was not observed in the patients who used H_2-RAs or diuretics, excluding PSD/AA and CAI. The mechanism of PPI-induced hypomagnesemia has been considered to be PPI administration increasing intestinal pH, which can reduce active transport of magnesium ions (Bai et al. 2012; Perazella 2013). On the other hand, previous studies have shown that drugs that inhibit acid secretion, such as H_2-RA, do not induce hypomagnesemia (Hess et al. 2012; Zipursky et al. 2014). Reportedly, the acid-inhibitory effect of PPIs is stronger than that of H_2-RA and is poorer overnight than in the daytime (Tutuian et al. 2000; Xue et al. 2001). For this reason, PPIs might inhibit the absorption of magnesium from a meal more than H_2-RA. Additionally, tolerance to famotidine is reported to occur during continuous administration for 14 days (Komazawa et al. 2003). These findings suggest that H_2-RA does not induce hypomagnesemia. Our results showed that a disproportionality of hypomagnesemia was not observed in patients who used diuretics, excluding PSD/AA and CAI. Loop and thiazide diuretics are known to induce hypomagnesemia, which results from decreased magnesium reabsorption by inhibition of the electrical gradient in the thick ascending loop (Ahmed and Mohammed 2019; Topf and Murray 2003). We assume it is for this reason that no hypomagnesemia disproportionality was observed in the patients who used loop or

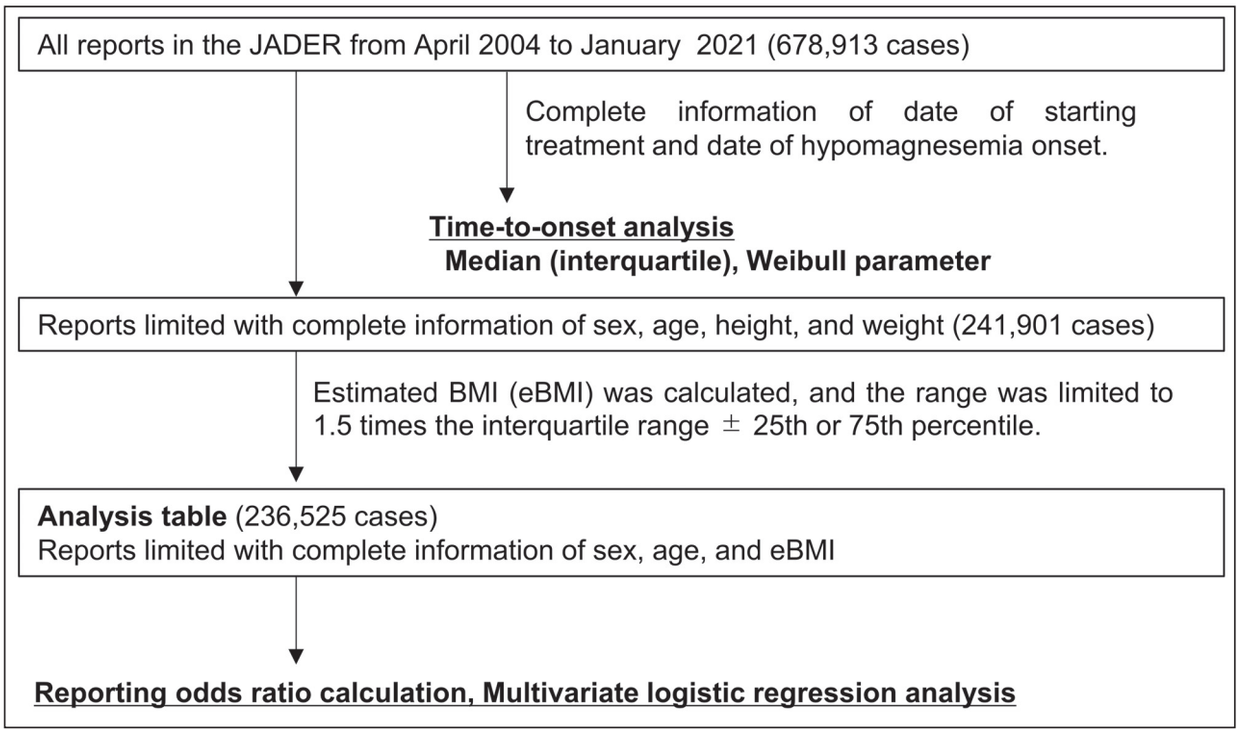

Fig. 2: Flowchart for dataset construction from the JADER

	Cases of interest	Other cases	Total
Drugs of interest	A	B	A+B
All other drugs	C	D	C+D
Total	A+C	B+D	A+B+C+D

$$\text{Reporting odds ratio (ROR)} = \frac{AD}{BC}$$

$$95\%\ \text{confidence interval (CI)} = \exp\left[\ln(ROR) \pm 1.96 \times \sqrt{\frac{1}{A}+\frac{1}{B}+\frac{1}{C}+\frac{1}{D}}\right]$$

Fig. 3: Two-by-two contingency table for calculating the ROR and 95% CI of hypomagnesemia

thiazide in this study. Although PSD/AA is considered not to induce hypomagnesemia because PSD/AA decreases magnesium excretion (Ahmed and Mohammed 2019), a disproportionality of hypomagnesemia was observed in patients who use PSD/AA in the present study. Additionally, CAI carries a light risk of hyponatremia and hypokalemia (Kataoka 2018), and the onset of hypokalemia is associated with magnesium deficiency (Baaij et al. 2015). Our results could indicate that PSD/AA and CAI are potential risk factors for hypomagnesemia. Nevertheless, the use of loop and thiazide is a risk factor for hypomagnesemia, and their concomitant use with other drugs could enhance this phenomenon.

The multiple logistic regression analysis revealed that PPI-induced hypomagnesemia is significantly associated with male sex, age < 60, and eBMI. A previous meta-analysis has shown that obesity induces hypomagnesemia (Cruz et al. 2020). Hyperglycemia has also been associated with hypomagnesemia irrespective of obesity (Guerrero-Romero et al. 2016). However, our results indicated that PPI-induced hypomagnesemia is associated with a low eBMI. Although we could not determine a plausible biological mechanism, lower BMI might be a risk factor for PPI-induced hypomagnesemia but not for non-drug-induced hypomagnesemia. Previous studies have reported PPI-induced hypomagnesemia is associated with the male sex (Luk et al. 2013) and an age < 45 years (Kim et al. 2015), and our results are similar to these studies. These characteristics might enhance the likelihood of onset of hypomagnesemia caused by PPIs. Further research is needed to confirm the patient characteristics related to this adverse event.

This study has several limitations. First, the study outcome is subject to a lack of a denominator, over-or-under-reporting, and various biases such as competition bias and notoriety bias. Nevertheless, the JADER database is a valuable tool that can be used to evaluate drug-associated rare and severe adverse events. Second, the number of cases using the time-to-onset analysis is limited. It is difficult to investigate the date of starting PPIs because this treatment period is often long-term; thus, our assessment of the time-to-onset profile is useful for monitoring adverse events. To our knowledge, this is the first study to evaluate the time-to-onset profile of PPI-induced hypomagnesemia and also to evaluate the association between hypomagnesemia and PPIs using the JADER database. Here we provide new evidence for appropriate administration of PPIs.

4. Experimental

4.1. Data source and flowchart of data selection

The JADER database, which was recorded from April 2004 to January 2021, was obtained from the PMDA website (http://www.pmda.go.jp/). The JADER dataset consists of 4 tables: (a) a DEMO table, including patient information such as sex, age, body height, and weight; (b) a DRUG table, including patient drug information; (c) a REAC table, including patient adverse events and outcomes; and (d) a HIST table, including medical history and primary illness. Three tables (a, b, and c) were used for the analyses in the present study. When we accessed these tables with an ID number, duplicated data were removed and the results were combined into a single table. The combined table was defined as "All reports" (678,913 cases), and it was used for constructing a time-to-onset analysis table. Figure 2 shows a flowchart for the construction of the dataset from the JADER. We excluded cases in which data on sex, age, height, and weight were missing or unclear from the "All reports." The age classifications used in this analysis were as follows: <10, 10–19, 20–29, 30–39, 40–49, 50–59, 60–69, 70–79, 80–89, 90–99, and ≥100 years.

In the JADER dataset, height and weight were recorded for each classification. Given that it was difficult to calculate BMI, we calculated eBMI using the below formula. The intermediate value of height or weight was defined as the intermediate value in each classification. For instance, for a patient whose height and weight were 160–169 cm and 50–59 kg, the eBMI was calculated as follows:

eBMI = intermediate of weight (kg)/[intermediate of height (m)]^2 = 55 (kg)/[1.65 (m)]^2 = 20.2 kg/m^2

After calculating eBMI, an outlier of eBMI was excluded using the boxplot method (Schwertman et al. 2004). The range of eBMI in this study was limited to 1.5 times the IQR ± 25th or 75th percentile. This table was defined as an "Analysis table" (236,525 cases).

4.2. Definitions of adverse events and drugs of interest

The definition of adverse events in the present study was compliant with the Medical Dictionary for Regulatory Activities/Japanese (MedDRA/J) version 24.0 (https://www.jmo.gr.jp/jmo/servlet/mdrLoginTop). We evaluated the preferred terms (PTs)

Table 3: Drug classifications

Drug classification	Drugs
PPIs	Omeprazole, lansoprazole, rabeprazole, esomeprazole, vonoprazan
Diuretics	
Thiazide	Trichlormethiazide, bentyl hydrochlorothiazide, hydrochlorothiazide
Thiazide analogous	Chlorthalidone, methyclan, indapamide, tripamide, meflusid
Loop	Furosemide, bumetanide, torasemide, azosemide, piretanide
PSD/AA	Triamterene, spironolactone, eplerenone, potassium canrenoate
CAI	Acetazolamide
H_2-RAs	Roxatidine, famotidine, cimetidine, lafutidine, nizatidine

The combination agent of each drug was also included in this study. PPI: proton pump inhibitor; PSD/AA: potassium-sparing diuretic/aldosterone antagonist; CAI: carbonic anhydrase inhibitor; H_2-RA: histamine-2 receptor antagonist.

"magnesium deficiency" (PT code: 10025433), "blood magnesium decreased" (PT code: 10005654), and "hypomagnesemia" (PT code: 10021027) for hypomagnesemia according to the MedDRA/J. The three types of drugs selected for this investigation were PPIs, diuretics, and H_2-RA; and the details are listed in Table 3.

4.3. Statistical analysis

To perform the time-to-onset analysis, "All reports" were limited to complete information on the date of treatment initiation and the date of hypomagnesemia onset. The shortest duration of onset was defined as the time-to-onset in this study. The median day, IQR day, and the Weibull shape parameters were used to clarify the time-to-onset profile of hypomagnesemia. The Weibull distribution has two parameters: the scale parameter (α) and the shape parameter (β). The shape parameter indicates the failure rate distribution over time and was assessed as follows: upper limit of 95% CI of $\beta < 1$, the incidence might decrease over time (the early failure type); 95% CI of β includes 1, the incidence might be constant over time (the random failure type); lower limit of 95% CI of $\beta > 1$, the incidence might increase over time (the wear-out failure type).

To evaluate the effect of age on hypomagnesemia, the analysis table was stratified into the following age groups: 0–59 years and 60 years or older. We compiled a two-by-two contingency table based on two classifications: the presence or absence of hypomagnesemia, and the drug of interest (PPIs, diuretics, and H_2-RAs). Then, we calculated the ROR and 95% CI based on the previous study (van Puijenbroek et al. 2002) (Fig. 3). A signal was considered positive when the lower limit of the 95% CI was >1. Furthermore, a multiple logistic regression analysis was performed to consider confounding factors that might be present in the database. Multiple logistic regression analyses have been performed in various studies based on JADER (Hosoya et al. 2017; Shimada et al. 2019). The objective variable was set to hypomagnesemia, and the explanatory variables were set to sex, age, eBMI, PPIs, and diuretics. A forward and backward stepwise selection with a significance level of 0.05 was performed to evaluate the effectiveness of the explanatory variables including all interaction terms (Shimada et al. 2019; Takeyama et al. 2017). The final multiple logistic regression model was as follows:

$\log(\text{odds}) = \beta_0 + \beta_1 S + \beta_2 A + \beta_3 B + \beta_4 P + \beta_5 A*P$

S: sex (male vs. female), A: age (<60 vs. ≥60), B: eBMI (kg/m^2), P: PPIs.

The aROR was calculated using the parameter estimates, and the results of the likelihood ratio test with *p*-values below 0.05 were considered statistically significant regarding the influence of explanatory variables. The statistical analyses were performed using JMP Pro, version 15.0.0 (SAS Institute Inc., Cary, NC, USA). A *p*-value less than 0.05 was considered significant.

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Conflicts of Interest: The authors declare no conflict of interest.

Ethics approval: No ethical approval was needed for this study.

Availability of data and material: The datasets generated during and/or analyzed during the current study are available in the JADER, http://www.pmda.go.jp/.

Authors' contributions: K.Y. and K.H. contributed to the concept and designed the study. K.Y. analyzed the data and wrote the manuscript. K.H. and S.Y. interpreted the data and helped to write the manuscript. F.O., T.N. and N.K. supervised the findings of the study and reviewed the manuscript. All authors have read and approved the final version of the manuscript.

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