Analysis of Patients with Hypomagnesemia using the Japanese Adverse Drug Event Report Database

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ABSTRACT – Purpose: In order to clarify the occurrence of hypomagnesemia in Japan, we conducted a database search and analysis using the Japanese Adverse Drug Event Report database (JADER). **Methods:** Among the cases recorded in JADER between April 2004 and December 2015, we targeted "hypomagnesemia" and analyzed the patients' backgrounds, drug involvement, other adverse events reported with hypomagnesemia, the time of hypomagnesemia onset, outcomes, and year when reported. For drugs with three or more reports, the signal index was calculated using the Reporting Odds Ratio (ROR) method. In addition, the association between hypomagnesemia onset and other adverse events was investigated using association analysis. **Results:** The total number of reported hypomagnesemia cases was 201. Males accounted for 62.7%, and patients in their sixties formed a large peak. Three or more cases were reported for 23 causative drugs, among which anti-EGFR antibody, calcineurin inhibitor, platinum antitumor agent and proton pump inhibitor accounted for the majority. ROR analysis detected signals for 18 drugs, and an association was found between hypomagnesemia and other electrolyte abnormalities for those drugs. The median time until onset of hypomagnesemia was classified into three patterns: around 10 days, around 30 days, and longer. Analysis of the report year revealed an increasing tendency in recent years, although increases/decreases were evident depending on fiscal years. **Conclusion:** Our survey was able to reveal the factors associated with the occurrence of hypomagnesemia.

INTRODUCTION

Magnesium is the second most abundant intracellular cation in the body, and the fourth most abundant, playing an essential physiological role in many body functions (1).

Hypomagnesemia is a condition typically defined as a serum magnesium concentration below 1.6 mg/dL, with or without accompanying magnesium depletion from total body, and does not lead to clinically significant signs and symptoms until the serum level falls below 1.2 mg/dL (2). As such, it is often overlooked in a clinical setting. Hypomagnesemia should be monitored carefully, because it sometimes causes severe clinical symptoms such as neuropsychiatric disorders (including tremor, convulsions, and coma) and cardiac disorders (including sudden death). However, hypomagnesemia has received relatively little attention in comparison with hyponatremia, hypokalemia, and hypocalcemia (2).

In a clinical setting, hypomagnesemia has sometimes been discussed in relation to the use of proton pump inhibitors (PPIs) (3), anti-EGFR antibodies (4, 5), and calcineurin inhibitors (6, 7). However, few reports have comprehensively evaluated the occurrence of hypomagnesemia, causative drugs, or patient background.

In order to clarify the factors associated with the occurrence of hypomagnesemia in Japan, we conducted a database search and analysis of such cases using the Japanese Adverse Drug Event Report database (JADER), which has been compiled and released by the Pharmaceuticals and Medical Devices Agency (PMDA).

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MATERIALS AND METHODS

Data source and survey content

Data recorded in JADER between April 2004 and December 2015 were obtained from the PMDA website (http://www.info.pmda.go.jp/fukusayoudb/CsvDownload.jsp). Among them, we targeted cases reported as "hypomagnesemia" (including "decrease of blood magnesium") as an adverse event. We extracted such cases from all the cases recorded in JADER, and analyzed the patients' background factors (gender, age, body height, body weight, primary disease), drug involvement, other adverse events reported with hypomagnesemia, the time of hypomagnesemia onset, outcomes and the year reported. Missing data were replaced with "Unknown". In JADER, since age, body weight and body height are rounded to every 10 units, we analyzed them according to these classifications. In some cases, age was registered as within a particular age group (newborn, infant, elderly, etc.) or period of pregnancy, and data for such cases were also replaced with "Unknown". In cases of drug involvement, drugs reported as "suspect drug" and "interaction" were newly defined as "causative drug" for the purposes of this study. The time of hypomagnesemia onset was defined as the period from the start of drug administration to the onset of hypomagnesemia, and was judged as "Unknown" when data for either were lacking.

STATISTICAL ANALYSIS

1) Signal detection

For cases where 3 or more drugs were reportedly involved, signal index were calculated using the Reporting Odds Ratio (ROR) method (Figure 1) (8). We defined signals as positive when the estimated ROR and lower limit of the corresponding 95% Confidence Interval (CI) was greater than 1. Because empirically the "rule of three" is used in the field of pharmacovigilance, causative drugs for which 3 or more cases had been reported were analyzed in this study.

2) Association analysis (Figure 2) (9)

In order to evaluate possible associations between hypomagnesemia and other related adverse events, association analysis was performed on drugs for which signals were detected by the ROR method. "Support" is the ratio of transactions that contain both X and Y, "Confidence" is the ratio of how often Y appears in transactions that contain X, and "Lift" is an index indicating the relative magnitude of the probability that Y will appear under the condition of X as compared with the probability that Y actually appears. A "Lift" value greater than 1 indicates that X and Y appear more often together than would be expected; this means that the occurrence of X has a positive effect on the occurrence of Y, or that X is positively correlated with Y.

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

$$\mathrm{ROR} = \frac{\mathrm{A/C}}{\mathrm{B/D}}$$

$$95\%\mathrm{CI} = \exp\left\{\log(\mathrm{ROR}) \pm 1.96\sqrt{\frac{1}{\mathrm{A}} + \frac{1}{\mathrm{B}} + \frac{1}{\mathrm{C}} + \frac{1}{\mathrm{D}}}\right\}$$

Figure 1. Calculation of the Reporting Odds Ratio (ROR) and 95% Confidence Interval (CI).

		X		
		Yes	No	Total
Y	Yes	a	b	a + b
	No	c	d	c + d
	Total	a + c	b + d	a + b + c + d

$$\text{Support} = \frac{a}{a+b+c+d}$$

$$\text{Confidence} = \frac{a}{a+c}$$

$$\text{Lift} = \frac{\{a/(a+c)\}}{\{(a+b)/(a+b+c+d)\}}$$

Figure 2. Assessment of association between X and Y by association analysis.

Table 1. Patient background factors for cases of hypomagnesemia.

Gender	Cases	Age (years old)	Cases	Body height (cm)	Cases	Body weight (kg)	Cases	Primary disease	Cases
Male	126	Under 10	5	70≤, <80	1	<10	1	Colorectal Cancer	67
Female	69	10-19	12	100≤, <110	1	10≤, <20	1	Gastrointestinal disorders	16
Unknown	6	20-29	9	130≤, <140	2	20≤, <30	2	Renal dysfunction	13
		30-39	15	140≤, <150	10	30≤, <40	7	Nephrotic syndrome	10
		40-49	22	150≤, <160	36	40≤, <50	31	Transplantation	9
		50-59	39	160≤, <170	41	50≤, <60	32	Others	…
		60-69	50	170≤, <180	13	60≤, <70	25		
		70-79	32	180≤, <190	2	70≤, <80	11		
		80-89	8	Unknown	95	80≤, <90	2		
		90-99	1			110≤, <120	1		
		Unknown	8			Unknown	88		

RESULTS

1. Patient background factors in cases of hypomagnesemia

The total number of cases reported in JADER between April 2004 and December 2015 was 387,162. Among them, the number of cases of hypomagnesemia reported as adverse events was 201. In terms of gender, males accounted for 62.7% (126 cases). There was a small peak for individuals in their teens and a large peak for those in their 60s. In terms of body height or weight, there were no specific characteristics, but “Unknown” accounted for a majority. Among primary diseases, colorectal cancer was reported in 67 cases. In addition, gastrointestinal disorders (16 cases), renal disorder (13 cases), nephrotic syndrome (10 cases) and transplantation (9 cases) accounted for a relatively large proportion of cases (Table 1).

2. Causative drugs of hypomagnesemia and their signal index

Among 201 cases, a total of 320 causative drugs (81 kinds; classified as "suspect drug" or "interaction") were reported. For 23 drugs with 3 or more reported cases, signal index was calculated using the ROR method, and these results are shown in Table 2. A signal was detected for 18 causative drugs except for oxaliplatin, bevacizumab, etoposide, tegafur / gimeracil / oteracil potassium compound, and docetaxel hydrate.

3. Other adverse events in cases of hypomagnesemia

Among the 201 hypomagnesemia cases, the total number of other adverse events was 381. The most frequently reported other adverse event was electrolyte abnormality other than hypomagnesemia (122 cases), followed by neuropsychiatric disorders (49 cases) and cardiac disorders (28 cases).

The association between hypomagnesemia and electrolyte abnormalities other than hypomagnesemia was examined by association analysis, and the results are shown in Table 3. The "Lift" value was 1.0 or more for all 18 items whose signals were detected by the ROR method. Therefore, the association between hypomagnesemia and other electrolyte abnormalities was confirmed.

4. Time until onset of hypomagnesemia

The median time until hypomagnesemia onset was calculated for the top 23 causative drugs (Table 4). Onset was early (about 10 days) in cases involving tacrolimus hydrate and anti-human thymocyte rabbit immunoglobulin, about 30 days in cases involving zoledronic acid hydrate, amphotericin B, oxaliplatin and bevacizumab, and relatively late (70 - 150 days) in cases involving panitumumab, cetuximab, cisplatin, irinotecan hydrochloride hydrate, fluorouracil, levofolinate calcium and docetaxel hydrate. The median time until hypomagnesemia onset could not be calculated for 10 drugs.

Table 2. Causative drugs of hypomagnesemia and their signal index.

Causative drug	Cases	ROR	95% CI
Panitumumab	57	211.5	154.3 - 289.8
Cetuximab	37	51.10	35.65 - 73.23
Cyclosporine	26	10.58	7.002 - 15.99
Cisplatin	14	4.452	2.585 - 7.668
Tacrolimus hydrate	14	3.627	2.106 - 6.246
Irinotecan hydrochloride hydrate	12	5.466	3.048 - 9.805
Fluorouracil	12	4.207	2.346 - 7.545
Zoledronic acid hydrate	8	7.391	3.640 - 15.01
Lansoprazole	8	5.394	2.657 - 10.95
Levofolinate calcium	7	4.300	2.021 - 9.148
Amphotericin B	6	11.55	5.115 - 26.09
Oxaliplatin	6	1.831	0.8122 - 4.127
Furosemide	6	5.699	2.526 - 12.86
Carboplatin	5	2.520	1.037 - 6.126
Bevacizumab	5	1.643	0.6760 - 3.993
Rabeprazole sodium	5	8.277	3.401 - 20.14
Anti-human thymocyte rabbit immunoglobulin	5	7.233	2.972 - 17.60
Esomeprazole magnesium hydrate	4	12.41	4.598 - 33.50
Mycophenolate mofetil	4	2.814	1.045 - 7.578
Etoposide	3	2.560	0.818 - 8.011
Tegafur / gimeracil / oteracil potassium compound	3	1.047	0.3348 - 3.276
Docetaxel hydrate	3	1.337	0.4273 - 4.183
Sodium polystyrene sulfonate	3	110.6	34.28 - 356.9
Other 58 drugs [a)]	Each 1 - 2	-	-
Total	320	-	-

[a)] including Omeprazole (PPI), Ibandronate sodium hydrate (bisphosphonate), Minodronic acid (bisphosphonate)

Table 3. Association between hypomagnesemia and other electrolyte abnormalities.

Causative drug	Support	Confidence	Lift
Panitumumab	0.024	0.704	9.63
Cetuximab	0.0040	0.250	11.7
Cyclosporine	0.00056	0.0411	8.51
Cisplatin	0.0016	0.0439	20.1
Tacrolimus hydrate	0.00051	0.0404	22.6
Irinotecan hydrochloride hydrate	0.0011	0.0807	29.9
Fluorouracil	0.00052	0.0536	25.7
Zoledronic acid hydrate	0.0037	0.0383	10.4
Lansoprazole	0.0020	0.140	51.6
Levofolinate calcium	0.00062	0.0909	41.9
Amphotericin B	0.0048	0.0129	2.22
Furosemide	0.0019	0.0136	4.71
Carboplatin	0.0013	0.0893	69.3
Rabeprazole sodium	0.0025	0.0638	15.2
Anti-human thymocyte rabbit immunoglobulin	0.0015	0.0870	23.7
Esomeprazole magnesium hydrate	0.0031	0.0919	14.5
Mycophenolate mofetil	0.00072	0.118	81.6
Sodium polystyrene sulfonate	0.054	0.167	3.11

Table 4. Time until onset of hypomagnesemia.

Causative drug	Cases	Median days [Range]
Panitumumab	39	86 [1 - 644]
Cetuximab	22	72 [11 - 393]
Cyclosporine	1	-
Cisplatin	6	123 [31 - 218]
Tacrolimus hydrate	8	13 [4 - 222]
Irinotecan hydrochloride hydrate	9	105 [1 - 504]
Fluorouracil	11	106 [1 - 504]
Zoledronic acid hydrate	4	25 [8 - 89]
Lansoprazole	1	-
Levofolinate calcium	5	106 [1 - 504]
Amphotericin B	4	36.5 [3 - 66]
Oxaliplatin	5	35 [1 - 815]
Furosemide	1	-
Carboplatin	2	-
Bevacizumab	3	29 [1 - 82]
Rabeprazole sodium	0	-
Anti-human thymocyte rabbit immunoglobulin	5	10 [3 - 10]
Esomeprazole magnesium hydrate	2	-
Mycophenolate mofetil	2	-
Etoposide	1	-
Tegafur / gimeracil / oteracil potassium compound	2	-
Docetaxel hydrate	3	147 [35 - 281]
Sodium polystyrene sulfonate	2	-

5. Outcomes of hypomagnesemia

The outcomes of hypomagnesemia cases are shown in Figure 3. “Recovery” and “Improvement” was seen in 42.3% and 25.4% of cases, respectively. On the other hand, “Unrecovered” accounted for 10.9%, and hypomagnesemia sometimes caused serious symptoms. It was noteworthy that “Unknown” accounted for 21.4% of cases, which was not a

negligible proportion.

6. Changes in the numbers of reports on hypomagnesemia

Changes in the numbers of reports on hypomagnesemia are shown in Figure 4. The number of reports in fiscal year (FY) 2009 and FY2011 were significantly higher than in preceding years. In FY 2013, the number of reports decreased temporarily, but since FY 2014 they have been increasing again.

DISCUSSION

In the present study, we tried to comprehensively analyze cases of hypomagnesemia using data from JADER. Among the affected patients, males accounted for 62.7% (126 cases). There was a small peak for individuals in their teens and a large peak for those in their 60s. We considered that these results were largely influenced by the primary disease and causative drugs that had been used. Especially, for hypomagnesemia patients in their 60s, use of chemotherapeutic agents for cancers such as colorectal cancer was widely reported. On the other hand, among patients in their teens, the use of calcineurin inhibitors appeared to be high. There were no apparent relationships with body height or weight, but "Unknown" accounted for an appreciable proportion of cases. Therefore, in this series interpretation of the results in terms of body height or weight was very difficult.

Eighty-one causative drugs were reported. Anti-EGFR antibodies, calcineurin inhibitors, platinum preparations, proton pump inhibitors, etc. have been generally recognized as agents capable of causing hypomagnesemia, and a number of such reports were confirmed in JADER. Since EGF regulates the expression of TRPM6 responsible for the reabsorption of Mg in the distal renal tubule, administration of anti-EGFR antibody suppresses TRPM6 expression in this location and induces hypomagnesemia (10). Calcineurin inhibitors reduce TRPM6 expression in the distal renal tubule via down-regulation of c-Fos expression (11, 12). Many cases of hypomagnesemia cases are reportedly caused by platinum-containing drugs, particularly cisplatin. Cisplatin treatment results in EGF / TRPM6 downregulation in renal tubules, causing renal Mg loss (13). PPI-induced hypomagnesemia has also become widely known since a report by the FDA in 2011. Although details of the mechanism involved have not been clarified, it is considered that PPIs enhance the colonic expression of TRPM6, probably resulting in inhibition of Mg absorption (14). In addition, some previous reports have confirmed that intravenous bisphosphonate (typically sodium zoledronate) (15), amphotericin B (16) and sodium polystyrene sulfonate (17) cause hypomagnesenia. In this study, five hypomagnesemia cases caused by anti-human thymocyte rabbit immunoglobulin were confirmed. As, to our knowledge, no previous study has demonstrated an association between this drug and hypomagnesemia, these results are very interesting.

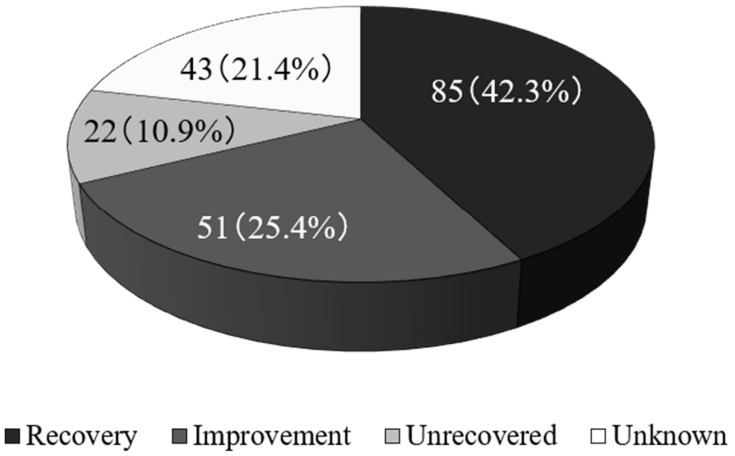

Figure 3. Outcomes of hypomagnesemia.

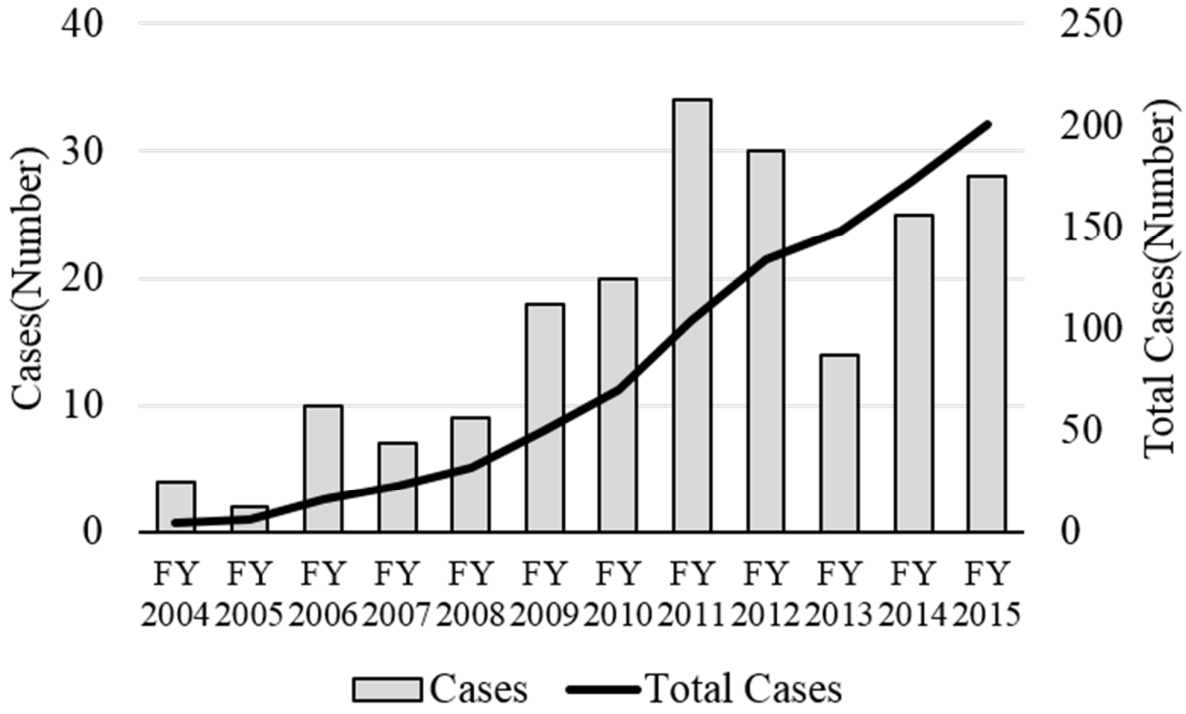

Figure 4. Changes in the numbers of reports on hypomagnesemia between FY 2004 and FY 2015.

For 23 causative drugs for which at least 3 cases of hypomagnesemia were reported, the RORs were calculated. Consequently, a signal was detected for 18 causative drugs, with the exception of oxaliplatin, bevacizumab, etoposide, tegafur / gimeracil / oteracil potassium compound, and docetaxel hydrate. Therefore, the possibility of hypomagnesemia associated with a number of reported drugs and signal detected drugs should be borne in mind.

Among 201 cases of hypomagnesemia, the total number of other adverse events was 381. The most frequently reported other adverse event was electrolyte abnormality other than hypomagnesemia (122 cases), followed by neuropsychiatric disorders (49 cases) and cardiac disorders (28 cases). Hypomagnesemia sometimes causes severe clinical symptoms such as neuropsychiatric disorders (including tremor, convulsions, and coma) and cardiac disorders (including sudden death). However, serum Mg levels are not routinely measured at many facilities, and hypomagnesemia may not be sufficiently diagnosed. Therefore, in this study, the association between hypomagnesemia and other electrolyte anomalies was evaluated using association analysis. An association was found between hypomagnesemia and other electrolyte abnormalities for all 18 drugs whose signals were detected by the ROR method. These results suggest the need to confirm the presence of hypomagnesemia when other electrolyte abnormalities are observed during administration of these drugs.

We analyzed the time until hypomagnesemia onset following the start of drug administration. Among 23 drugs, the median time until hypomagnesemia onset could not be calculated for 10 drugs. The time until onset for 13 drugs was largely classifiable into three patterns: around 10 days, around 30 days, and later. These results suggest that hypomagnesemia should be monitored according to the properties of individual drugs.

Among the outcomes of hypomagnesemia, “Recovery” and “Improvement” accounted for 42.3% and 25.4% of cases, respectively. On the other hand, “Unrecovered” accounted for 10.9%, suggesting that hypomagnesemia sometimes causes serious symptoms. In addition, the fact that “Unknown” accounted for 21.4% should not be overlooked. Furthermore, as stated above, since serum Mg levels are not measured routinely, hypomagnesemia may not have been reported to PMDA in some cases. In addition, neuropsychiatric

disorders and heart disorders that occurred during the use of such drugs might have been attributable to hypomagnesemia. Also, the JADER data give no indication of the severity of adverse events.

Changes in the numbers of reports of hypomagnesemia are shown in Figure 4. The number of reports in FY2009 and FY2011 showed a significant increase relative to preceding years. In FY 2013, the number of reports temporarily decreased, but since FY 2014 there has been an increasing trend. This seems to reflect the clinical use of cetuximab (from September 2008) and panitumumab (from June 2010). Also, the results may have been influenced by fact that an association between long-term use of PPIs and hypomagnesemia was reported by the FDA in March 2011.

One limitation of the present study was that the JADER has various biases, such as the lack of a denominator that would indicate the total number of patients who received the drugs of interest, as well as the lack of data on confounding factors. Therefore, various problems remain to be solved in research using JADER, requiring scrupulous attention to interpretation of the results.

In conclusion, this study has revealed part of the overall picture of hypomagnesemia in Japan. We anticipate that the present findings will help to provide guidelines for the proper use of drugs that can potentially cause hypomagnesemia.

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