Cancer Chemotherapy and Pharmacology (2019) 83:673–679
https://doi.org/10.1007/s00280-019-03772-y

ORIGINAL ARTICLE

Influence of oral magnesium-containing supplement and antacid administration on hypomagnesemia induced by panitumumab

Junya Sato[1] · **Hiroshi Ishikawa**[1] · **Rei Tanaka**[1] · **Michihiro Sino**[1]

Received: 28 August 2018 / Accepted: 6 January 2019 / Published online: 19 January 2019

Abstract

Purpose Hypomagnesemia is a common side effect of panitumumab. The effect of magnesium-containing supplement as a laxative and concomitant antacid (proton pump inhibitor and histamine H_2 antagonist) administration on panitumumab-induced hypomagnesemia was retrospectively investigated.

Methods Patients with advanced or recurrent colorectal cancer who received panitumumab were included in this study. Serum magnesium levels were extracted from the electronic medical records of 1753 administrations in 221 patients who received panitumumab. Serum magnesium levels in patients with or without oral magnesium-containing supplement and antacid treatment were compared using analysis of covariance as the number of panitumumab administration up to 16 times for covariates.

Results The mean serum magnesium levels were significantly decreased with increasing number of panitumumab administrations (2.13 mg/dL at 1st vs. 1.55 mg/dL at 16th, $p < 0.001$). The use of oral magnesium-containing supplement significantly inhibited the decline in mean serum magnesium level (1.98 mg/dL vs. 1.78 mg/dL, $p < 0.001$). However, antacid use in patients receiving oral magnesium-containing supplement significantly decreased the effectiveness of the magnesium supplement on serum magnesium level (2.02 mg/dL vs. 1.93 mg/dL, $p < 0.05$).

Conclusion The use of oral magnesium-containing supplement might function as magnesium supplement based on the finding that use of oral magnesium-containing supplement during panitumumab administration decreased hypomagnesemia. However, combination of antacid decreased the supplemental effect of oral magnesium on hypomagnesemia. These results suggest the possibility that use of antacids during anti-EGFR antibody administration may promote hypomagnesemia.

Keywords Hypomagnesemia · Panitumumab · Magnesium salt · Antacids · Proton pump inhibitor · Histamine H_2 antagonist

Introduction

Panitumumab, a recombinant human anti-epidermal growth factor receptor (EGFR) monoclonal antibody, is used for the treatment of unresectable, progressive, or recurrent colorectal cancer. The adverse effects of panitumumab include dermatopathy (acneiform rash), interstitial lung disease, infusion reaction, and hypomagnesemia. Among these, hypomagnesemia occurs frequently and is associated with the duration of treatment with panitumumab. The incidence of hypomagnesemia in the pivotal phase III trial with panitumumab was reported to be 20–28% for grade 1/2 and 6–7% for grade 3/4 [1–3]. The incidence of hypomagnesemia with cetuximab, an anti-EGFR antibody belonging to the same drug class as panitumumab, was found to be increased with its treatment duration (60–100 days) [4, 5].

✉ Junya Sato
Junya02377@nifty.com

Hiroshi Ishikawa
h.ishikawa@scchr.jp

Rei Tanaka
r.tanaka@scchr.jp

Michihiro Sino
m.shino@scchr.jp

[1] Department of Pharmacy, Shizuoka Cancer Center, 1007 Shimonagakubo, Nagaizumi-cho, Sunto-gun, Shizuoka Prefecture 411-8777, Japan

When serum magnesium level falls below 1.2 mg/dL, symptoms such as QT prolongation, convulsions, numbness, and general malaise may occur necessitating discontinuation of panitumumab and administration of intravenous magnesium supplements [6]. The mechanism by which panitumumab induces hypomagnesemia is unclear. The prevailing hypothesis relates to the anti-EGFR activity of panitumumab. EGFR is expressed in the kidney, and the reabsorption of filtered magnesium in the renal tubules is reversibly inhibited by EGFR signaling inhibition. Furthermore, the absorption of magnesium is inhibited by the disruption of EGFR signaling in the intestinal tract [7].

Based on the previous reports, it was unclear whether a magnesium-containing supplement has a beneficial effect on hypomagnesemia during the anti-EGFR treatment. Fakih et al. administered 400 mg of magnesium oxide tablets to up to four tablets to patients with grade 3/4 cetuximab-induced hypomagnesemia. There was, however, no beneficial effects on the serum magnesium level in any of these patients [4]. In an animal study, magnesium oxide behaves like a slow-release preparation (half-life 27 h) due to insolubility, and magnesium oxide was absorbed up to 15% of doses and was excreted in urine [8]. It was also reported that combination use of antacids, such as proton pump inhibitors or histamine H_2 antagonists, attenuates the laxative effect of magnesium oxide [9, 10]. These results suggest that an acidic environment is necessary for dissolution and absorption of orally ingested magnesium. The influence of prophylactic magnesium-containing supplement on anti-EGFR antibody-induced hypomagnesemia has not been investigated in a large cohort. Furthermore, the influence of antacid administration on the effect of oral magnesium-containing supplement has not been evaluated. In this study, we have retrospectively investigated the effect of oral magnesium-containing supplement prescribed as a laxative on panitumumab-induced hypomagnesemia. We have further evaluated the influence of antacid on the effect of treatment with oral magnesium-containing supplement on hypomagnesemia.

Methods

Study period and study patients

Patients with unresectable, progressive, or recurrent colorectal cancer treated with panitumumab (Vectibix®) infusion in the Shizuoka Cancer Center from September 2011 and June 2017 were included. The following data were extracted using electronic medical records: (1) serum magnesium level, (2) presence or absence of serum magnesium level abnormality on the same day of panitumumab administration (normal level 1.8–2.4 mg/dL; abnormal low level; < 1.8 mg/dL), and (3) history of treatment with oral magnesium-containing supplement (magnesium oxide and magnesium hydroxide), proton pump inhibitors (omeprazole, lansoprazole, rabeprazole, and esomeprazole), and histamine H_2 antagonists (famotidine and ranitidine) just before the initiation of panitumumab treatment. The data were extracted for the patients who were prescribed panitumumab continuously for 8 months. The data for the maximum 16 panitumumab administrations were analyzed. A patient for whom the serum magnesium level was not estimated on the same day of panitumumab administration was excluded from the analysis.

Statistical analysis

The effect of oral magnesium-containing supplement and antacid on serum magnesium level was evaluated by an analysis of covariance (ANCOVA) adjusted by the number of panitumumab administration as a covariate. The frequency of abnormal serum magnesium level reports in the presence or absence of treatment with oral magnesium-containing supplement and antacid was evaluated by the Fisher's exact test. The change in serum magnesium level with increasing numbers of panitumumab administration was evaluated by a one-way analysis of variance (ANOVA) with a post hoc Dunnett's test. The evaluation of the effect of number of panitumumab administration was performed by an unpaired t test. All analyses were performed by Excel statistics 2015 BellCurve for Excel. A p value of < 0.05 was considered as statistically significant.

Ethical considerations

This study was approved by the Ethical Review Board of the Shizuoka Cancer Center, Japan (Approval number 30-J20-30-1-3).

Results

A flowchart summarizing the demographic characteristic of the included patients is presented in Fig. 1. The data from 303 patients and 2919 panitumumab administration during the study period and 221 patients with 1790 administrations in whom serum magnesium levels measured on the same day of panitumumab administration were extracted. Of these, the data of 37 panitumumab administrations and 7 patients were excluded from the analysis, because of abnormal serum magnesium levels at the initiation of panitumumab treatment (2 patients), treatment discontinuation following the initial panitumumab administration (4 patients), or clinical record insufficiency due to a hospital transfer (one patient), respectively. Initially, panitumumab was mostly administered after hospitalization.

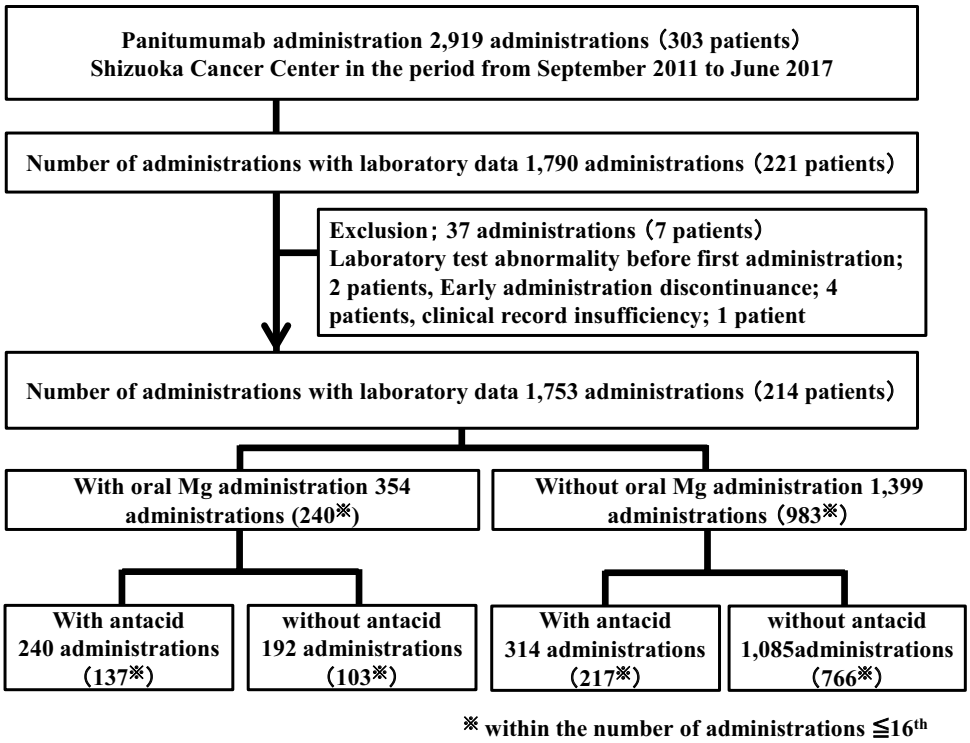

Fig. 1 Patient flowchart

The subsequent administration was done in outpatient chemotherapy unit. The magnesium-containing supplement was administered to 116 patients; 114 patients were administered magnesium oxide and 2 patients were administered magnesium hydroxide for improvement or prevention of constipation. Most of the constipation-related symptoms were controlled by the administration of irritant cathartic in addition to oral magnesium without causing severe diarrhea. The mean magnesium consumption was 904 ± 466 mg (mean ± standard deviation) per day. Therapeutic intravenous magnesium supplement was added for grades 2–3 hypomagnesemia in 57 patients (4.6%). Mean magnesium level was 1.22 ± 0.34 mg/dL at the point of the hypomagnesemia therapy. Fifty-five patients (96%) in the patients needed for therapeutic intravenous magnesium supplementation were not administered oral magnesium supplement. Antacid was administered to 169 patients; 140 patients were administered proton pump inhibitors and 21 were administered histamine H_2 antagonists. Eight patients made switching and used both drugs. The number of panitumumab administrations (mean ± standard deviation) to the study patients was 8.4 ± 4.1. The number of panitumumab administrations in the group that received oral magnesium-containing supplement was 8.3 ± 4.1 and 8.5 ± 4.1 in the group that did not receive oral magnesium-containing supplement, which did not represent a significant difference ($p = 0.568$). Among the patients who received oral magnesium-containing supplement and antacids, the number of panitumumab administrations was 8.2 ± 4.2, while, in patients who did not receive antacids, it was 8.4 ± 4.0, which did not represent a significant difference ($p = 0.708$). Similarly, among the patients who did not receive oral magnesium preparation, the number of the panitumumab administrations in the patients who received antacids and who did not receive antacids was 8.2 ± 4.2 and 8.6 ± 4.4, respectively, which did not represent a significant difference ($p = 0.395$).

The change in the serum magnesium levels is summarized in Fig. 2. The serum magnesium levels up to 16th panitumumab administrations were investigated which covered 70% of all number of administrations. Panitumumab-induced hypomagnesemia become frequent according to the number of panitumumab administrations ($p < 0.001$).

The comparison of serum magnesium levels in patients with or without receiving oral magnesium-containing supplement is summarized in Fig. 3. A supplement effect of oral magnesium may not be found, because hypomagnesemia does not occur in the early administration stage of the panitumumab. Subgroup evaluations were carried out panitumumab administration for 9–16th that hypomagnesemia became severer (Fig. 3a, 1–16th panitumumab administrations; Fig. 3b, 9–16th panitumumab administrations). For the entire period up to the 1–16th and the 9–16th administrations of panitumumab, serum magnesium levels

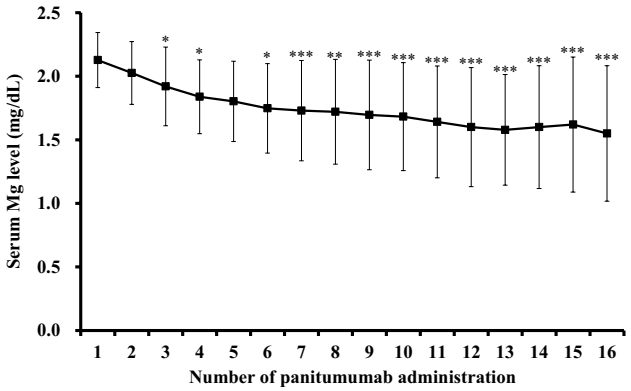

Fig. 2 Change of serum Mg level in the panitumumab administered patient. The bar shows mean ± standard deviation. *$p < 0.05$, **$p < 0.01$, ***$p < 0.001$ vs. first administration by Dunnett's test. $p < 0.001$ by one-way analysis of variance (ANOVA)

were significantly higher when oral magnesium-containing supplement was administered (Fig. 3a, 1.98 ± 0.32 vs. 1.78 ± 0.41, $p < 0.001$; Fig. 3b, 1.95 ± 0.35 vs. 1.67 ± 0.43, $p < 0.001$).

The comparison of the serum magnesium levels in the patients receiving oral magnesium-containing supplement with or without antacid administration is summarized in Fig. 4 (Fig. 4a, 1–16th panitumumab administrations; Fig. 4b, 9–16th panitumumab administrations). In the entire period up to 16th and 9–16th administrations of panitumumab, serum magnesium levels were significantly lower by antacid administration (Fig. 4a, 2.01 ± 0.34 vs. 1.93 ± 0.30, $p < 0.05$; Fig. 4b, 2.04 ± 0.35 vs. 1.81 ± 0.30, $p < 0.001$).

The comparison of the serum magnesium levels in patients who received antacids without using oral magnesium-containing supplement is summarized in Fig. 5

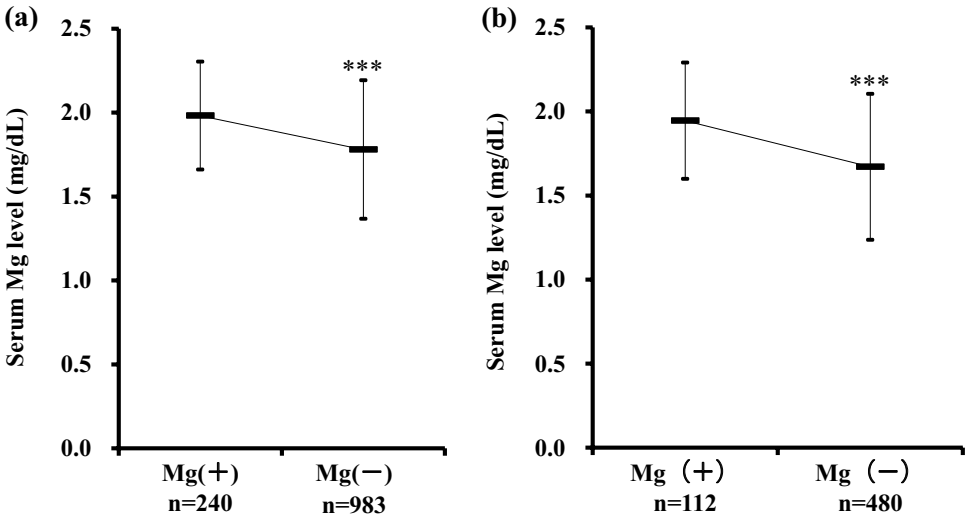

Fig. 3 Comparison of the serum Mg level in patients with or without oral Mg administration, **a** number of administration 1–16th and **b** 9–16th. The bar shows mean ± standard deviation. ***$p < 0.001$ vs. oral Mg administration(+) by the analysis of covariance (ANCOVA) with the number of administration as a covariate

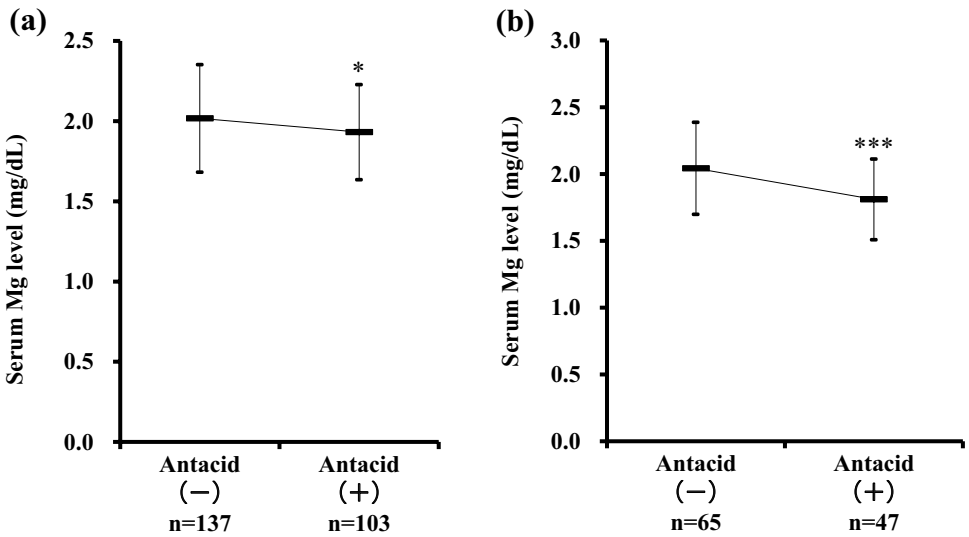

Fig. 4 Influence of antacid on serum Mg level in patients with oral Mg administration, **a** number of administrations 1–16th and **b** 9–16th. The bar shows mean ± standard deviation. *$p < 0.05$, ***$p < 0.001$ vs. oral Mg administration(+) by the analysis of covariance (ANCOVA) with the number of administration as a covariate

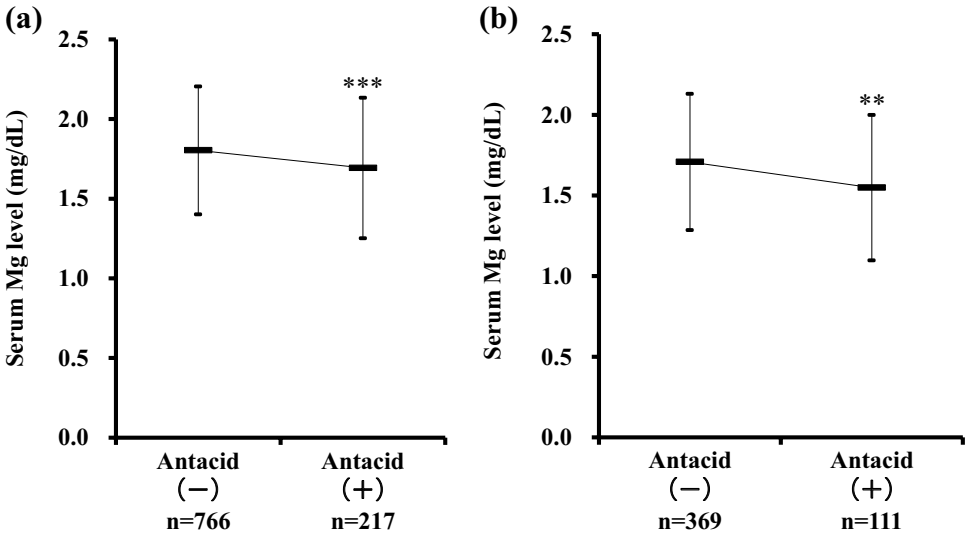

Fig. 5 Influence of antacids on serum Mg level in patients without oral Mg administration, **a** number of panitumumab administrations 1–16th and **b** 9–16th. The bar shows mean ± standard deviation. *$p < 0.05$, ***$p < 0.001$ vs. oral Mg administration(+) by the analysis of covariance (ANCOVA) with the number of administration as a covariate

(Fig. 5a, 1–16th; Fig. 5b, 9–16th panitumumab administration). During the entire period (up to 16th and 9–16th) of panitumumab administrations, the serum magnesium levels were significantly lower by antacid administration (Fig. 5a, 1.80 ± 0.40 vs. 1.69 ± 0.44, $p < 0.001$; Fig. 5b, 1.71 ± 0.42 vs. 1.55 ± 0.45, $p < 0.01$).

Incidences of serum magnesium level abnormality (< 1.8 mg/dL) coincided with the oral magnesium-containing supplement or antacid use during the 9–16th administrations of panitumumab are summarized in Fig. 6. The incidence of abnormally low magnesium level was significantly decreased in the patients administered with oral magnesium-containing supplement (Fig. 6a, 52% vs. 21%, $p < 0.001$). The use of antacids by the patients using oral magnesium-containing supplement significantly increased the incidence of abnormal low magnesium levels (Fig. 6b, 14% vs. 32%, $p < 0.05$). Similarly, the use of antacids by the patients who did not use oral magnesium-containing supplement showed a tendency of increasing the incidence of abnormal low magnesium levels (Fig. 6c, 49% vs. 59%, $p = 0.067$).

Discussion

The results of this study demonstrated that serum magnesium level decreases with increasing number panitumumab administrations. The patients who received oral magnesium-containing supplement had a significantly higher serum magnesium levels those who did not receive. These results suggest the possibility that panitumumab-induced

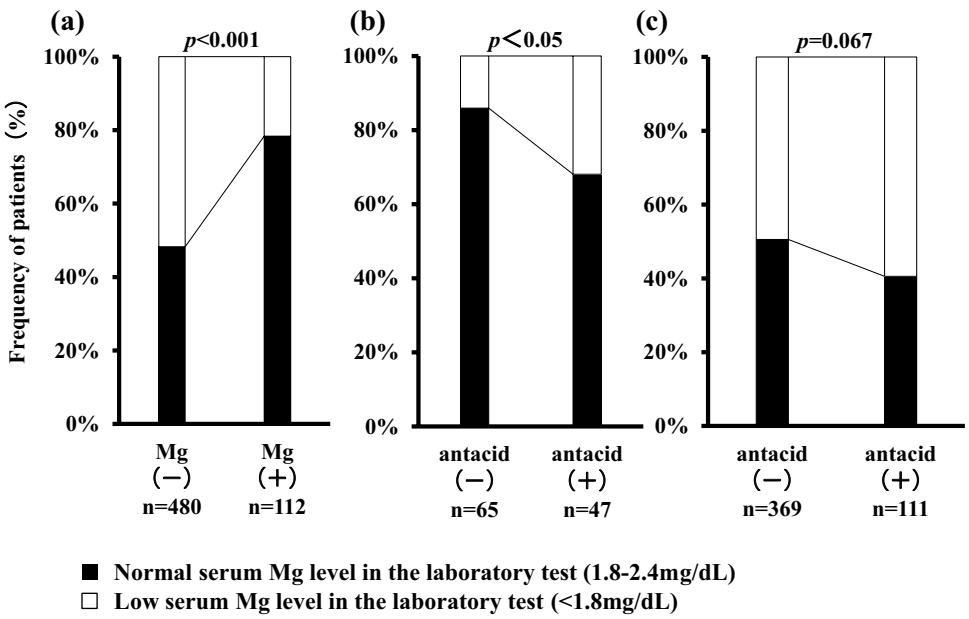

Fig. 6 Influence of oral Mg and antacid administration on serum Mg laboratory test results at number of panitumumab administrations 9–16th, **a** with or without oral Mg administration, **b** with or without antacid in patients with oral Mg administration, and **c** with or without antacid in patients without oral Mg administration

hypomagnesemia may be relieved by oral magnesium-containing supplements (magnesium supplement effect). With the exception of the observation by Fakih et al. [4] demonstrating that oral magnesium-containing supplement was not effective, the effect of the magnesium-containing supplement on hypomagnesemia induced by anti-EGFR antibodies has not been fully investigated. There are some possible explanations for this difference with the previous report of Fakih et al. There was difference in therapeutic use and the prophylactic use of oral magnesium-containing supplement. In this study, magnesium was administered before panitumumab administration. Therefore, oral magnesium-containing supplement was used for hypomagnesemia prophylactically. As other differences, this study was an investigation of panitumumab, which administered at intervals of 2 weeks unlike cetuximab. Furthermore, there was much number of patients.

Many studies have demonstrated that oral magnesium-containing supplement was beneficial with cisplatin administration [11]. It was also reported that oral magnesium carbonate and magnesium citrate administration were useful for maintaining normal serum magnesium level and prevention of renal impairment [12, 13]. The effectiveness of oral magnesium supplement may vary depending on the magnesium salt used. It has been reported that the absorbance of oral magnesium oxide is lower than that of other magnesium salts, such as citrate and carbonate [14]. The insolubility of magnesium oxide may be responsible for these differences. The absorbance of magnesium oxide increases in an acidic environment. Therefore, secretion of gastric acid greatly affects the absorption of magnesium from magnesium oxide [15]. Our results indicate that the beneficial effect of the oral magnesium-containing supplement was decreased by the concomitant use of antacids. These results suggest the possibility that gastric pH is a crucial factor influencing the absorption of oral magnesium. Interestingly, the use of antacids significantly reduced serum magnesium level in the patients who did not receive an oral magnesium-containing supplement. In a Drug Safety Communication, the United States Food and Drug Administration warns of an association between hypomagnesemia and proton pump inhibitors [16]. Owing to the acid-suppressive effect of proton pump inhibitors, they inhibit the gastrointestinal absorption of calcium, which is a cationic salt similar to magnesium, leading to the increased risk of bone fractures [17]. Reduced magnesium uptake may be the result of a similar process. The use of proton pump inhibitors in patients receiving anti-EGFR antibodies including panitumumab may increase the risk of hypomagnesemia. Therefore, the use of an antiulcer drug, such as proton pump inhibitor and histamine H_2 antagonists, should be avoided with an anti-EGFR antibody. The substitute use of gastric mucosa defense factor reinforcement drug without suppressing the gastric-acid secretion might be expected.

This study has some limitations. First, this study was a retrospective observation in a single institution. Totally, 303 patients and 2919 panitumumab administrations were included in the survey period. However, measurement of serum magnesium levels at the same time of panitumumab administration was not performed in 1129 administrations (38%). These data were excluded from analysis. Lack of serum magnesium levels was early in the number of panitumumab administration. It was likely that serum magnesium was not measured by the judgment of the prescription physician, because hypomagnesemia at early treatment umber will be extremely rare. There was limitation about the number of the panitumumab administration. Hypomagnesemia by panitumumab becomes frequent according to the number of administrations. The median duration that anti-EGFR antibody induces severe hypomagnesemia was 60–100 days [4, 5]. Therefore, the frequency of therapeutic magnesium supplement with intravenous infusion increased after 7–9th panitumumab administration. In the panitumumab administration up to 16th, intravenous magnesium was administered in 4.6% of patients. On one hand, 16% of patients received intravenous magnesium after 16th panitumumab administration. It was necessary to eliminate the influence of the magnesium supplement by the intravenous infusion. We analyzed up to 16th panitumumab administrations. There was bias about the selection and the observation period of the analysis patients.

Second, use of oral magnesium-containing supplement was extracted from drug prescription histories. As the main purpose that oral magnesium oxide or magnesium hydroxide was prescribed for prevention, improvement of the constipation, when the constipation-related symptoms were improved, these oral magnesium preparation use might be decreased or discontinued, though the data extracted the patients whom magnesium oxide or magnesium hydroxide was prescribed for continuously. Furthermore, doses of magnesium-containing supplement differed (906 ± 466 mg/day as magnesium). Thus, there was an inconsistency in the use of the oral magnesium-containing supplement.

Third, different antacids were prescribed among the patients. Proton pump inhibitors and histamine H_2 antagonists were considered as antacids. The potency of these drugs is different. To maintain gastric pH at 4, it was reported that ranitidine was significantly shorter than omeprazole (43–67% vs 93–96%) [18]. In spite of being the analysis of the few patients, in 163 panitumumab administration of these 21 patients, the use of the histamine H_2 antagonists also reduced serum magnesium level (2.00 ± 0.27 vs. 1.82 ± 0.40, $p < 0.05$, ANCOVA). There may be minor difference according to the type of antacid used, and a detailed study in this regard should be conducted in the future.

Fourth, oral magnesium-containing supplement and antacid significantly affected serum magnesium level in a statistically significant manner. However, the numerical difference may not be clinically significant. Generally, serum magnesium level lower than 1.0–1.2 mg/dL requires intravenous magnesium supplements or discontinuation of panitumumab [6]. The change in serum magnesium level resulted in magnesium levels much higher than the level at which an intervention is necessary. Fifth, loop diuretic and digitalis as co-medications might have induced hypomagnesemia. In addition, the lack of data on oral magnesium intake from food may also be a potential confounder.

Conclusion

Oral magnesium-containing supplement with anti-EGFR antibody treatment, including panitumumab, may be beneficial to prevent hypomagnesemia. In contrast, proton pump inhibitors or histamine H_2 antagonists may worsen hypomagnesemia with anti-EGFR antibody treatment regardless of the administration of oral magnesium-containing supplement. The use of antacids in patients receiving panitumumab may increase the risk of hypomagnesemia.

Funding This study was funded by a research grant of Shizuoka Cancer Center.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

References

1. Kim TW, Elme A, Kusic Z et al (2014) A phase 3 trial evaluating panitumumab plus best supportive care vs best supportive care in chemorefractory wild-type KRAS or RAS metastatic colorectal cancer. Br J Cancer 115:1206–1214
2. Price TJ, Peeters M, Kim TW et al (2014) Panitumumab versus cetuximab in patients with chemotherapy-refractory wild-type KRAS exon 2 metastatic colorectal cancer (ASPECCT): a randomised, multicentre, open-label, non-inferiority phase 3 study. Lancet Oncol 15:569–579
3. Douillard JY, Siena S, Cassidy J et al (2014) Final results from PRIME: randomized phase III study of panitumumab with FOLFOX4 for first-line treatment of metastatic colorectal cancer. Ann Oncol 25:1346–1355
4. Fakih M, Wilding G, Lombardo J (2006) Cetuximab-induced hypomagnesemia in patients with colorectal cancer. Clin Colorectal Cancer 6:152–156
5. Tejpar S, Piessevaux H, Claes K, Piront P, Hoenderop JG, Verslype C, Van Cutsem E (2007) Magnesium wasting associated with epidermal-growth-factor receptor-targeting antibodies in colorectal cancer: a prospective study. Lancet Oncol 8:387–394
6. Fakih M (2008) Management of anti-EGFR-targeting monoclonal antibody-induced hypomagnesemia. Oncology (Williston Park) 22:74–76
7. Schrag D, Chung KY, Flombaum C, Saltz L (2005) Cetuximab therapy and symptomatic hypomagnesemia. J Natl Cancer Inst 97:1221–1224
8. Yoshimura Y, Fujisaki K, Yamamoto T, Shinohara Y (2017) Pharmacokinetic studies of orally administered magnesium oxide in rats. Yakugaku Zasshi 137:581–587
9. Ibuka H, Ishihara M, Suzuki A, Kagaya H, Shimizu M, Kinosada Y, Itoh Y (2016) Antacid attenuates the laxative action of magnesia in cancer patients receiving opioid analgesic. J Pharm Pharmacol 68:1214–1221
10. Yamasaki M, Funakoshi S, Matsuda S, Imazu T, Takeda Y, Murakami T, Maeda Y (2014) Interaction of magnesium oxide with gastric acid secretion inhibitors in clinical pharmacotherapy. Eur J Clin Pharmacol 70:921–924
11. Yamamoto Y, Watanabe K, Tsukiyama I, Yabushita H, Matsuura K, Wakatsuki A (2016) Hydration with 15 mEq magnesium is effective at reducing the risk for cisplatin-induced nephrotoxicity in patients receiving cisplatin ($\geq$ 50 mg/m^2) combination chemotherapy. Anticancer Res 36:1873–1877
12. Bodnar L, Wcislo G, Gasowska-Bodnar A, Synowiec A, Szarlej-Wcisło K, Szczylik C (2008) Renal protection with magnesium subcarbonate and magnesium sulphate in patients with epithelial ovarian cancer after cisplatin and paclitaxel chemotherapy: a randomised phase II study. Eur J Cancer 44:2608–2614
13. Willox JC, McAllister EJ, Sangster G, Kaye SB (1986) Effects of magnesium supplementation in testicular cancer patients receiving cis-platin: a randomised trial. Br J Cancer 54:19–23
14. Ranade VV, Somberg JC (2001) Bioavailability and pharmacokinetics of magnesium after administration of magnesium salts to humans. Am J Ther 8:345–357
15. Lindberg JS, Zobitz MM, Poindexter JR, Pak CY (1990) Magnesium bioavailability from magnesium citrate and magnesium oxide. J Am Coll Nutr 9:48–55
16. FDA Drug Safety Communication. Low magnesium levels can be associated with long-term use of Proton Pump Inhibitor drugs (PPIs). https://www.fda.gov/drugs/drugsafety/ucm245011.htm. Accessed 7 Dec 2018 (Updated 8 Apr 2017)
17. Eom CS, Park SM, Myung SK, Yun JM, Ahn JS (2011) Use of acid-suppressive drugs and risk of fracture: a meta-analysis of observational studies. Ann Fam Med 9:257–267
18. Merki HS, Wilder-Smith CH (1994) Do continuous infusions of omeprazole and ranitidine retain their effect with prolonged dosing? Gastroenterology 106:60–64