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Time-dependent changes in serum magnesium levels in patients receiving cetuximab with low baseline serum sodium levels

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Cetuximab causes electrolyte abnormalities, such as hypomagnesemia, hypokalemia, and hypocalcemia. However, little is known about the relationships between the onset of hypomagnesemia, patient background before administration, and time-dependent changes in serum magnesium levels. Therefore, we examined the patient backgrounds that influenced the onset of hypomagnesemia and the time-dependent changes in serum magnesium levels in patients receiving cetuximab. A retrospective study was performed to investigate patients with advanced or recurrent colorectal cancer or head and neck cancer, treated with a cetuximab regimen from 2012 to 2020 at Kindai University Nara Hospital. In total, 52 patients who met the inclusion criteria were enrolled in this study. The serum magnesium level was significantly lower in the hyponatremia before the administration group than in the non-hyponatremia group ($p < 0.001$). Univariate logistic regression analysis revealed that the baseline serum sodium levels (odds ratio [OR]: 0.741, 95% confidence interval [CI]: 0.588–0.934) and the combination of magnesium oxide tablet (OR: 0.997, 95% CI: 0.995–0.999) were one of the independent factors for hypomagnesemia. These results indicated that hyponatremia before administration may be an indicator of serum magnesium levels after administration of cetuximab. Cetuximab-induced hypomagnesemia may be predicted using baseline serum sodium levels, and hypomagnesemia may be prevented by administration of magnesium oxide tablets. Our findings provided new evidence for the management of serum magnesium levels in patients receiving cetuximab.

1. Introduction

Cetuximab is a monoclonal antibody that targets epidermal growth factor (EGFR) (Ciardiello and Tortora 2002) and is used for the treatment of unresectable advanced or recurrent colorectal cancer, and head and neck cancer. Cetuximab causes hypomagnesemia because of suppression of magnesium reabsorption mediated by EGFR-dependent transient receptor potential member 6 (TRPM6) (Groenestege et al. 2007). The percentages of hypomagnesemia, hypokalemia, and hypocalcemia in patients receiving cetuximab were 34.9%, 8.0–12.6%, and 16.8%, respectively (Cao et al. 2010; Wang et al. 2015). The median number of administrations at the onset of hypomagnesemia was 7 and 13 (Nakamoto et al. 2011; Tano et al. 2018); however, this remains controversial. Previous studies have focused on the incidence and related factors of cetuximab-induced hypomagnesemia. However, little is known about the relationship between the onset of hypomagnesemia and patient background, including electrolyte abnormalities before cetuximab administration and time-dependent changes of the serum magnesium levels. These findings are needed to appropriately monitor serum electrolyte levels after cetuximab administration.

Magnesium is an essential element, the fourth most abundant cation in humans, and plays important roles in many biological processes. The United States Food and Nutrition Board recommends a daily magnesium intake of 420 mg for males and 320 mg for females (Baaij et al. 2015). Magnesium absorption (30–50%) occurs in the small intestine (Baaij et al. 2015). Most of the filtered magnesium in the kidney is reabsorbed in the thick ascending limb of Henle (60%) (Curry and Yu 2018). Fine control of magnesium is performed in the distal tubule (Van Laecke 2019), and reabsorption in the kidney is assumed to be important for magnesium balance in the body. Hypomagnesemia is generally defined as serum magnesium levels < 1.8 mg/dL. Mild hypomagnesemia is often symptomless, but severe hypomagnesemia may induce fatal complications, such as cardiac arrhythmias if not treated (Soliman et al. 2003). A previous study reported that severe hypomagnesemia is difficult to treat by magnesium supplementation either orally or via injection (Fakih et al. 2006). It is important to prevent severe hypomagnesemia by monitoring serum magnesium levels over time. Magnesium is associated with other electrolytes, including sodium, potassium, and calcium. Magnesium is extruded into the blood compartment *via* a sodium-magnesium exchanger (Franken et al. 2021). In the kidney, magnesium deficiency inhibits the renal outer medullary potassium channel and may cause hypokalemia (Huang and Kuo 2007). Low intracellular magnesium causes hypocalcemia because of being impaired parathyroid hormone secretion (Fatemi et al. 1991; Tsujii et al. 2016).

Reportedly, significant correlations were observed between potassium, magnesium, and calcium in the non-hypomagnesemia group receiving cetuximab, whereas not observed in the hypomagnesemia group (Yamashiro et al. 2021). We hypothesized that the onset of cetuximab-induced hypomagnesemia is associated with the other serum electrolyte levels before administration. Therefore, the relationships between serum magnesium levels and baseline serum electrolyte levels such as sodium, potassium, calcium, and magnesium were investigated. This study aims to provide new information regarding serum magnesium levels in patients receiving cetuximab and examine how patient backgrounds influence the onset of hypomagnesemia and time-dependent changes in serum magnesium levels.

2. Investigations and results

2.1. Patient characteristics and treatment details

Table 1 shows the patient backgrounds. We identified 52 patients (40 males and 12 females) who received cetuximab during the study period. The mean age of the patients was 67.9 ± 10.3 years. Cetuximab was administrated for the treatment of colorectal cancer and head and neck cancer in 11 and 41 patients, respectively. The proportion of patients who had a history of anti-cancer therapy before cetuximab administration was 53.8% (28/52). The mean laboratory data were within the normal range. Table 2 shows the patient treatment details. The average treatment period was 50.5 ± 30.9 d. Regarding the list of regimens, the proportion of patients who received monotherapy and combination therapy group was 67.3% (35/52) and 32.7% (17/52), respectively. Patients were administered one of the following regimens: cetuximab monotherapy; CDDP+5-FU+cetuximab, which included cisplatin, 5-fluorouracil, and cetuximab; PCE therapy, which included paclitaxel, carboplatin, and cetuximab; CPT-11+cetuximab, which included irinotecan and cetuximab; DTX+cetuximab, which included docetaxel and cetuximab; CBDCA+5-FU+cetuximab, which included carboplatin, 5-fluorouracil, and cetuximab; SOX+cetuximab therapy, which included S-1, oxaliplatin, and cetuximab; and sLV5FU2+cetuximab, which included levofolinate, 5-FU, and cetuximab. Platinum-containing drugs were administered to 12 patients and eight patients received CDDP+5-FU+cetuximab, which were the most frequent regimens. The proportion of patients who additionally received magnesium oxide (MgO) tablet and magnesium sulfate ($MgSO_4$) injection was 57.7% (30/52) and 15.4% (8/52), respectively. The mean dose of MgO tablet and $MgSO_4$ injection in the treatment period were 572.46 mg/d and 1.95 mEq/d, respectively.

Table 1: Patient backgrounds

Total number	52
Male/Female	40 / 12
Age (year)	67.9 ± 10.3
Body Height (m)	1.64 ± 0.07
Body Weight (kg)	60.0 ± 11.5
BMI (kg/m^2)	22.4 ± 3.9
Type of cancer	
Colorectal	11
Head and neck	41
History of anti-cancer therapy	28
Baseline Alb (g/dL)	3.4 ± 0.5
Baseline Scr (mg/dL)	0.8 ± 0.3
Baseline Ccr (mL/min)	74.1 ± 29.0
Baseline AST (U/L)	25.7 ± 19.5
Baseline ALT (U/L)	20.6 ± 19.3
Baseline Na (mmol/L)	138.9 ± 3.3
Baseline K (mmol/L)	4.3 ± 0.5
Baseline Mg (mg/dL)	2.1 ± 0.2
Baseline Ca (mg/dL)	9.4 ± 0.5

Mean ± Standard deviation. BMI: body mass index, Alb: albumin, Scr: serum creatinine, Ccr: creatinine clearance, AST: aspartate aminotransferase, ALT: alanine aminotransferase, Na: sodium, K: potassium, Mg: magnesium, Ca: calcium.

Table 2: Patient treatment details

List of regimens	n
Monotherapy (cetuximab only)	35
Combination therapy	17
CDDP+5-FU+cetuximab	8
PCE	2
CPT-11+cetuximab	2
High dose DTX+cetuximab	2
CBDCA+5-FU+cetuximab	1
SOX+cetuximab	1
sLV5FU2+cetuximab	1
Combined therapy	n
Radiation therapy	41
Platinum-containing drugs	12
MgO tablet	30
$MgSO_4$ injection	8

Mean ± standard deviation. CDDP: cisplatin, 5-FU: 5-fluorouracil, PCE: paclitaxel+ carboplatin+cetuximab, CPT-11: irinotecan, DTX: docetaxel, CBDCA: carboplatin, SOX: S-1+oxaliplatin, sLV5FU2: levofolinate+5-FU.

2.2. Effect of patient factors on the serum magnesium levels in patients

Table 3 shows relationships between the onset of hypomagnesemia and patient characteristics during cetuximab administration. The onset of hypomagnesemia was associated with the baseline serum sodium levels [odds ratio (OR): 0.741, 95% CI (confidence interval): 0.588–0.934, p = 0.003], and a combination of MgO tablet (OR: 0.997, 95% CI: 0.995–0.999, p = 0.002). However, the onset of hypomagnesemia was not associated with the baseline serum potassium, magnesium, or calcium levels because these electrolyte levels in the most of patients were within the normal range. Furthermore, no significant difference was observed between the onset of hypomagnesemia and the combined of platinum-containing drugs (OR: 2.333, 95% CI: 0.624–8.719, p = 0.209) and $MgSO_4$ injection (OR: 3.974, 95% CI: 0.826–19.123, p = 0.079).

Table 3: Relationships between hypomagnesemia and patient characteristics

Patient backgrounds and treatment details	Odds ratio	95% CI	p-value
Patient backgrounds			
Male / Female [a)]	3.333	0.643–17.265	0.119
Age (year)	0.952	0.899–1.008	0.080
BMI (kg/m^2)	0.960	0.825–1.117	0.466
Type of cancer			
Colorectal / Head and neck [a)]	1.102	0.275–4.415	0.891
History of anti-cancer therapy [a)]	1.571	0.492–5.022	0.443
Baseline Alb (g/dL)	0.758	0.314–1.832	0.539
Baseline Scr (mg/dL)	0.652	0.069–6.114	0.707
Baseline Ccr (mL/min)	1.010	0.991–1.031	0.299
Baseline AST (U/L)	1.022	0.982–1.065	0.190
Baseline ALT (U/L)	0.989	0.954–1.026	0.538
Baseline Na (mmol/L)	0.741	0.588–0.934	0.003**
Baseline K (mmol/L)	2.180	0.584–8.136	0.237
Baseline Mg (mg/dL)	0.127	0.003–5.528	0.268
Baseline Ca (mg/dL)	3.103	0.844–11.403	0.077
Treatment details			
Monotherapy / Combination [a)]	0.308	0.091–1.039	0.055
Radiation therapy [a)]	0.907	0.227–3.635	0.891
Platinum-containing drugs [a)]	2.333	0.624–8.719	0.209
MgO tablet (mg/d)	0.997	0.995–0.999	0.002**
$MgSO_4$ injection [a)]	3.974	0.826–19.123	0.079
Treatment period (d)	1.010	0.992–1.029	0.277

CI: confidence interval, BMI: body mass index, Alb: albumin, Scr: serum creatinine, Ccr: creatinine clearance, AST: aspartate aminotransferase, ALT: alanine aminotransferase, Na: sodium, K: potassium, Mg: magnesium, Ca: calcium, MgO: magnesium oxide, $MgSO_4$: magnesium sulfate. **p < 0.01, p: statistical significance obtained using the univariate logistic regression analysis, and [a)] the likelihood ratio test.

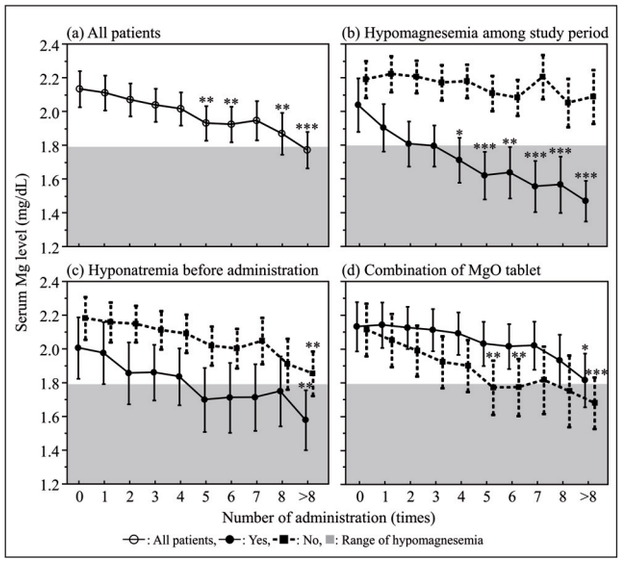

Fig.: Effects of cetuximab administration on the serum magnesium level. The data are presented as the least-square mean ± 95% confidence interval. p: statistical significance obtained using the repeated-measures ANOVA, *p<0.05, **p<0.01, ***p<0.001, vs. initial baseline.

The Figure shows the effects of cetuximab administration on the serum magnesium level in all patients, patients with hypomagnesemia among study period, patients administered MgO tablet, and patients with pre-hyponatremia. Serum magnesium levels tended to decline with an increasing number of administrations. Serum magnesium levels were significantly reduced in the hypomagnesemia group than in the non-hypomagnesemia group (least-square (LS) mean, 95% CI: 1.7 mg/dL, 1.6–1.8 mg/dL vs. 2.1 mg/dL, 2.1–2.2 mg/dL, $p < 0.001$). The serum magnesium level before administration was not significantly different between the hypomagnesemia group and the non-hypomagnesemia group (LS mean, 95% CI: 2.0 mg/dL, 1.9–2.2 mg/dL vs. 2.2 mg/dL, 2.1–2.3 mg/dL). However, the serum magnesium level after the two administrations was significantly different between the two groups (LS mean, 95% CI: 1.8 mg/dL, 1.7–1.9 mg/dL vs. 2.2 mg/dL, 2.1–2.3 mg/dL). The serum magnesium level was significantly lower in the patient who had pre-hyponatremia (LS mean, 95% CI: 1.8, 1.7–1.9 mg/dL vs. 2.1, 2.0–2.1 mg/dL, $p = 0.003$). In the patient who developed pre-hyponatremia, the LS mean of serum magnesium level was less than 1.8 mg/dL after the five administrations. Additionally, the serum magnesium levels were significantly higher in the patients receiving combined MgO tablets (LS mean, 95% CI: 2.0, 1.9–2.1 mg/dL vs. 1.9, 1.8–2.0 mg/dL, $p = 0.041$).

3. Discussion

In this study, we showed that serum magnesium levels are reduced in a time-dependent manner, and the onset of hypomagnesemia is affected by patient characteristics, including pre-hyponatremia and the combination of MgO tabs. In our study, the onset of hypomagnesemia was associated with the baseline serum sodium levels, but not with the baseline serum potassium, magnesium, or calcium levels. Because the baseline serum potassium, magnesium, or calcium levels in the most of patients were within the normal range. In distal tubules, the expression of EGFR-dependent TRPM6 is the greatest, and TRPM6 initiates fine control of magnesium excretion (Hoenderop and Bindels 2005). Reportedly, cetuximab inhibits TRPM6 in the distal tubules, which may result in magnesium deficiency in patients receiving cetuximab (Groenestege et al. 2007). Franken et al. (2021) reported that magnesium is reabsorbed into the cell by TRPM6 and is extruded into the blood compartment via a sodium-magnesium exchanger (SLC41A1) in exchange for sodium. Therefore, it is assumed that the serum magnesium level in patients was associated with the baseline serum sodium levels in our study. Although the onset of hypomagnesemia was not significantly associated with the combination of platinum-containing drugs, serum magnesium levels trended to be lower in patients who received platinum-containing drugs. Reportedly, cisplatin reduces mRNA expression of TRPM6 in rat kidneys (Ledeganck et al. 2013) and induces the onset of hypomagnesemia (Inose et al. 2015; Tano et al. 2018). However, Stintzing et al. (2013) reported that a significant difference was not observed between platinum and non-platinum receiving patients in terms of the course of serum magnesium levels. Furthermore, Tanaka et al. (2018) reported that the median time until onset of hypomagnesemia was 72 d (11–393 d) with cetuximab and 123 d (31–218 d) with cisplatin. The treatment period in our study was 50.5 d, which was shorter than that of Tanaka's study. This may be why a difference in the incidence of hypomagnesemia during the treatment period was not observed between platinum and non-platinum receiving patients in our study. While the doses may affect the incidence of hypomagnesemia, but the previous study has not reported the administration doses. Nevertheless, it is important for patients who are treated with platinum-containing drugs to monitor serum magnesium levels because cisplatin affects the onset of hypomagnesemia. In summary, our results suggest that patients with hyponatremia before cetuximab administration should be carefully monitored for serum magnesium levels, and early magnesium supplementation may be needed to maintain serum electrolyte levels.

Serum magnesium levels were significantly reduced after five administrations, and the median day to the onset of hypomagnesemia was 22 d. Magnesium in the body is stored in bone and muscle, and serum magnesium levels reflect only 1% of the body's magnesium content (Elin 1994). Hence, magnesium deficiencies in the body may be caused even if the serum magnesium levels are within the normal range. In our study, despite the serum magnesium levels being within the normal range, the body magnesium may be deficient after two administrations of cetuximab. Serum magnesium levels in patients receiving cetuximab were significantly reduced in the hypomagnesemia group compared with that of the non-hypomagnesemia group. A previous study necessitates treatment of hypomagnesemia when the patient displayed the presence of clinical symptoms and/or severe hypomagnesemia (<1.25 mg/dL) (Van Laecke 2019). Fakih et al. (2006) reported that patients with grade 3/4 hypomagnesemia did not achieve their target serum magnesium level despite multiple magnesium infusions a week. These previous studies have shown that correction of serum magnesium levels is needed before severe hypomagnesemia occurs. Mild hypomagnesemia with no or only mild symptoms can be treated with oral magnesium supplementation (± 360 mg/d) (Baaij et al. 2015; Yamamoto and Yamaguchi 2007).

Our results suggest that patients who received cetuximab require oral magnesium supplementation when the serum magnesium level is less than 1.8 mg/dL. The bioavailability of MgO is 4%, which is the lowest of all magnesium supplements (Van Laecke 2019). Administration of MgO tab up to 400 mg three times a day was shown to be ineffective for grade 3/4 hypomagnesemia (Fakih et al. 2006). However, in our study, the serum magnesium level was higher in the group with a combined MgO tab than in the control group. Zarif Yeganeh et al. (2016) reported that continuous administration of the MgO tab according to the cisplatin dose reduces the decline in serum magnesium levels and the incidence of hypomagnesemia in cancer patients. Although further investigation is needed, the concomitant use of MgO tabs may contribute to delaying the onset of hypomagnesemia in patients receiving cetuximab. $MgSO_4$ injection is known to improve the hypomagnesemia. By contrast, no significant difference was observed between the onset of hypomagnesemia and the combined $MgSO_4$ injection, but the incidence of hypomagnesemia is higher in the injection group than non-injection group. This result suggests that the incidence of hypomagnesemia was high in the patients who received $MgSO_4$ injections because $MgSO_4$ injections were administered after the onset of hypomagnesemia.

Notably, our study has several potential limitations. First, this study had a retrospective design, and the number of patients with electrolyte abnormalities was small. Second, our study period was short compared with previous studies. In the future, a prospective

study is needed to evaluate the management of serum electrolyte levels using our findings. To our knowledge, this is the first study to show relationships between the onset of hypomagnesemia and patient factors including baseline serum sodium levels and the combination of MgO tabs, and between serum magnesium levels and the number of cetuximab administrations. Here, we provide new evidence that adequate management of serum electrolyte levels is necessary for maintaining chemotherapy.

4. Experimental

4.1. Patients and study design

A retrospective study was performed to investigate serum magnesium levels in patients who received cetuximab at Kindai University Nara Hospital. Clinical data for patients with unresectable advanced or recurrent colorectal cancer or head and neck cancer treated with cetuximab from March 2010 to September 2020 were retrieved from the medical records. The main eligibility criteria included measurement of serum electrolyte levels, >1 cetuximab administration, and completion of the regimen. Patient serum creatinine (Scr), sodium, potassium, magnesium, and calcium levels were investigated before and after cetuximab administration. The serum calcium level was corrected using Payne's equation (Payne et al. 1973). Creatinine clearance (Ccr) was calculated using the Cockcroft-Gault formula (Cockcroft and Gault 1976). A total of 113 patients received cetuximab during the study period. Forty-eight patients whose serum magnesium, calcium, or albumin levels were not measured during cetuximab treatment were excluded. Additionally, we excluded six patients who had only one administration of cetuximab and seven patients whose regimen was not completed.

4.2. Definition of electrolyte abnormalities

Electrolyte abnormalities were graded according to the Common Terminology Criteria for Adverse Events version 5.0, translated by the Japanese Clinical Oncology Group (CTCAE ver. 5.0 JCOG version) (Japanese Clinical Oncology Group 2019). Electrolyte abnormalities during cetuximab administration were defined as follows: hyponatremia, serum sodium level < 138.0 mmol/L; hypokalemia, serum potassium level < 3.6 mmol/L; hypomagnesemia, serum magnesium level < 1.8 mg/dL; hypocalcemia, serum corrected calcium level < 8.8 mg/dL.

4.3. Statistical analysis

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. The relationship between the onset of hypomagnesemia and patient characteristics was evaluated using the likelihood ratio test and univariate logistic regression analysis. Serum magnesium levels were compared with the initial baseline by using a repeated-measures analysis of variance (ANOVA) with Tukey's test. To reveal changes in serum magnesium levels in patients with hypomagnesemia during the study period, serum magnesium levels were compared with and without hypomagnesemia by using a repeated-measures ANOVA between the two groups with regard to the number of administrations. Similarly, serum magnesium levels were compared with and without patient characteristics using a repeated-measures ANOVA.

4.4. Ethical consideration

This study was approved by the Ethics Committee of Kindai University Nara Hospital (approval ID: 19–44) on April 20, 2020. All procedures in this study involving human participants were conducted following the ethical standards of the institutional research committee and the 1964 Declaration of Helsinki and its later amendments, or comparable ethical standards. Patients were not required to provide informed consent for study participation because this study was a retrospective study. We applied the opt-out method to obtain consent for this study. The opt-out method was approved by the Ethics Committee of Kindai University Nara Hospital.

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