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Summary of MID-NET® study: No. 2019-006

January 17, 2023

Study title

Database study using MID-NET® on risk assessment of hypocalcaemia in patients with renal impairment prescribed bisphosphonate preparations

Products investigated

The following 6 ingredients of bisphosphonate preparations indicated for osteoporosis

Alendronate sodium hydrate, ibandronate sodium hydrate, etidronate disodium, zoledronic acid hydrate, minodronic acid hydrate, and sodium risedronate hydrate

Background

- Bisphosphonate preparations are widely used as the first-line drugs for osteoporosis other than early postmenopausal osteoporosis, and the use in patients with renal impairment is alerted in the "CONTRAINDICATIONS" and "Careful Administration" sections in Information on Precautions, etc. because they have not been used in patients with renal impairment and bisphosphonate preparations are excreted renally.
- On the other hand, in drug use-results surveys and adverse drug reaction reports, hypocalcaemia occurred when bisphosphonate preparations were administered to patients with renal impairment. Hypocalcaemia is assumed to be an adverse drug reaction common to bisphosphonate preparations based on their pharmacological mechanism of action.
- In this study, the safety of bisphosphonate preparations in patients with renal impairment was examined using the onset of hypocalcaemia as an index.

Purpose of the study

To evaluate the safety of bisphosphonate preparations in patients with renal impairment by comparing the incidence of hypocalcaemia according to the severity of renal impairment in patients with osteoporosis for whom bisphosphonate preparations were prescribed

Reason to select MID-NET® for the study and Data period

Reason to select: To perform an evaluation with laboratory test results as an index
Data from all healthcare organizations cooperating with MID-NET® (22 hospitals at 10 healthcare organizations) whose data were available throughout the target data period

Data period: January 1, 2009 to March 31, 2019

Outline of method

In patients with a diagnosis of osteoporosis who were newly prescribed bisphosphonate preparations, the incidence of hypocalcaemia during the prescription period was evaluated by renal function category. In addition, subgroup analyses by each ingredient of bisphosphonate preparations and age category, sensitivity analyses with modified outcome definitions, etc. were performed.

<Definition of new prescription>

A new prescription is defined as the earliest prescription of bisphosphonate preparations during the data period. In order to appropriately identify a new prescription, only patients who had medical records at least 90 days before the start date (t_0) of a new prescription of bisphosphonate preparations were included in the study population.

<Definition of renal function categories>

As for renal function categories, the baseline estimated glomerular filtration rate (eGFR, mL/min/1.73 m^2) was calculated from the eGFR during the period from 90 days before t_0 to the day before t_0 (baseline period), and the following categories were set based on the baseline eGFR: Normal (≥ 90), mild (≥ 60 to < 90), moderate (≥ 30 to < 60), and severe (< 30). The baseline eGFR was defined as the mean of the 2 values in the baseline period closest to t_0. If multiple eGFR values were recorded on the same day, each

3-3-2 Kasumigaseki, Chiyoda-ku, Tokyo 100-0013 Japan
E-mail: safety.info@pmda.go.jp

value was replaced with the mean of the values on the same day. If only 1 test was performed during the baseline period, the value was used as the baseline eGFR.

<Definitions of prescription period and follow-up period>

The period for each prescription was adjusted in consideration of the number of days for a prescription that could be covered by health insurance, etc. If the later prescription of the same ingredient started within the grace period (14 to 90 days) in consideration of the interval of administration for each ingredient, the difference in the timing of hospital visits, etc., the prescription period was counted as a single period. The end date of the prescription period was defined as the date after the grace period from the end date of the last prescription.

A follow-up period was started at t_0 and ended at the earliest day of the following: The date of completion of the prescription period, the day before the start date of the prescription of bisphosphonate preparations with ingredients different from that at t_0, the day of change in renal function category, or the end date of the data period.

The day of change in the renal function category was defined as the second day when the renal function category differed from the baseline eGFR for 2 different days based on the arrangement of chronological order for the dates of eGFR tests during the prescription period. For calculating eGFR, the mean value was used as the eGFR for that day if multiple eGFR values were recorded on the same day.

<Definition of hypocalcaemia>

Hypocalcaemia was defined as a serum Ca level of less than 8 mg/dL. If serum albumin (ALB) values were recorded within 2 weeks before and after the date of serum Ca measurement, a serum ALB value on the date of the test closest to the date of serum Ca measurement was used for correction as follows. When multiple serum Ca values were recorded on the same day, the minimum value was used as a value of the day. When multiple serum ALB values were recorded on the same day, the maximum value was used as a value of the day. When serum ALB values were not recorded within 2 weeks before and after the date of serum Ca measurement, unadjusted serum Ca values were used.

Serum ALB < 4 g/dL:	Serum Ca (mg/dL) + 4 - Serum ALB (g/dL)
Other cases (including missing data):	Serum Ca (mg/dL)

In sensitivity analyses, the incidence of hypocalcaemia defined as a decrease by 20% or

more from the baseline Ca level was evaluated. The baseline Ca level was defined as a serum Ca value on the test date closest to t_0 among serum Ca values obtained during the baseline period. The correction method of serum Ca values and handling of data on the same day for serum Ca or ALB values were the same as those described above.

Outline of results

■ Study population

- There were 20 007 patients having a new prescription for bisphosphonate preparations and diagnosis of osteoporosis in the same month with a record of serum creatinine or eGFR in the baseline period. Of those, the study population consisted of 14 551 patients excluding those with a record of serum Ca level < 8 mg/dL during the baseline period, those with a diagnosis of primary hyperparathyroidism, acute pneumonia, or septic shock, and those with a prescription of denosumab (genetical recombination), asfotase alfa (genetical recombination), cinacalcet hydrochloride, evocalcet, or etelcalcetide hydrochloride.
- In the study population, the number of patients by renal function category was 2 601 in the normal group, 7 613 in the mild group, 3 919 in the moderate group, and 418 in the severe group. The composition ratio of each ingredient in each renal function category was as follows: Alendronate sodium hydrate was 53.44 to 64.59%, minodronic acid hydrate was 14.35 to 16.77% and sodium risedronate hydrate was 19.62 to 30.03%. Ibandronate sodium hydrate, etidronate disodium, and zoledronic acid hydrate were all less than 2.39%*.

  * Data are masked so that the number of patients (less than 10) cannot be identified according to the MID-NET® publication criteria.

■ Patient background

- The proportion of females was 68.51%, 72.99%, 68.54%, and 70.33% in the normal, mild, moderate, and severe groups, respectively, with no clear difference among the groups. The mean ± standard deviation of the age (years) at t_0 was 54.9 ± 19.2 in the normal group, 67.0 ± 13.8 in the mild group, 73.6 ± 12.3 in the moderate group, and 74.1 ± 13.1 in the severe group. The mean age was higher in the groups with more severe

renal impairment. Complications and concomitant drugs during the baseline period were generally similar across renal function categories, but there were some differences in the proportion of patients with concomitant steroid use (normal group: 54.25%, mild group: 42.15%, moderate group: 39.14%, severe group: 36.12%).

■ **Association between bisphosphonate preparations and hypocalcaemia in patients with renal impairment**

- In this study, 96.4% of serum Ca values was adjusted for ALB. Point estimates of adjusted hazard ratios for hypocalcaemia compared with the normal group were 1.85, 2.30, and 22.74 in the mild, moderate, and severe groups, respectively. The point estimates increased with more severe renal impairment, and the severe group showed a marked and statistically significant increase (Table 1).

Table 1. Association between renal function categories and onset of hypocalcaemia in patients with a diagnosis of osteoporosis who were newly prescribed bisphosphonate preparations

Renal function category	Number of patients (persons)	Total follow-up period (person-year)	Number of patients who developed hypocalcaemia (persons)	Hazard ratio* (95% CI)	Adjusted hazard ratio*† (95% CI)
Normal	2 601	755.01	< 10‡	1 (reference)	1 (reference)
Mild	7 613	2 826.23	27	1.44 (0.59 - 3.49)	1.85 (0.75 - 4.57)
Moderate	3 919	1 374.43	16	1.69 (0.66 - 4.31)	2.30 (0.86 - 6.21)
Severe	418	99.57	16	18.60 (7.27 - 47.54)	22.74 (8.37 - 61.78)

* Estimated by Cox proportional-hazards model

† Adjustment factors: Sex and age at t_0 (< 65 years, ≥ 65 and < 75 years, ≥ 75 years), presence/absence of each complication (hypoparathyroidism, vitamin D deficiency, and magnesium abnormality) and presence/absence of each concomitant drug (elcatonin, steroid, calcium preparations, vitamin D preparations, sorafenib tosilate, lenvatinib mesilate, vandetanib, enviomycin sulfate, and monobasic sodium phosphate monohydrate/dibasic sodium phosphate anhydrous) at baseline

‡ Data are masked so that the number of patients (less than 10) cannot be identified according to the MID-NET® publication criteria.

- In the subgroup analysis by ingredient, an adjusted hazard ratio (95% CI) in each severity group for alendronate sodium hydrate (n = 7 972) prescribed to the largest number of patients was 1.66 (0.55 to 5.00) in the mild group, 2.31 (0.70 to 7.69) in the moderate group, and 16.03 (4.68 to 54.96) in the severe group, showing a similar trend

to the overall results. A similar trend was also observed with minodronic acid hydrate (n = 2 332) and sodium risedronate hydrate (n = 4 011). For the other 3 ingredients (n < 120* for each ingredient), no onset of hypocalcaemia was observed in many groups due to the small number of target patients. Therefore, adjusted hazard ratios could not be calculated.

- In the subgroup analysis by age category, adjusted hazard ratios (95% CI) in patients aged < 65 years (n = 4 954) were 2.56 (0.73 to 8.93) in the mild group, 3.87 (0.92 to 16.27) in the moderate group, and 52.76 (12.80 to 217.38) in the severe group, showing a similar trend to the overall results. In patients aged ≥ 65 and < 75 years (n = 4 286), the adjusted hazard ratio (95% CI) in each group was 0.28 (0.06 to 1.43) in the mild group, 0.42 (0.07 to 2.53) in the moderate group, and 2.84 (0.28 to 28.45) in the severe group, indicating a similar trend in which the point estimate of the adjusted hazard ratio increases with the severity of renal impairment, although it was necessary to interpret this carefully due to the small number of cases of hypocalcaemia. Among patients aged ≥ 75 years (n = 5 311), the adjusted hazard ratio could not be calculated since no onset of hypocalcaemia was observed due to the small number of target patients. However, the incidence of hypocalcaemia (95% CI) (persons/person-year)† was 0.014 (0.005 to 0.023) in the mild group, 0.013 (0.004 to 0.022) in the moderate group, and 0.131 (0.045 to 0.217) in the severe group, showing a similar trend in which the incidence of hypocalcaemia increases in the severe group.
- In examination of hypocalcaemia (decrease by 20% or more from the baseline Ca level) as a sensitivity analysis, only patients with an identified baseline Ca level were included in the study population (n = 10 111), and adjusted hazard ratios (95% CI) of hypocalcaemia to the normal group were 0.67 (0.16 to 2.86) in the mild group, 2.25 (0.57 to 8.94) in the moderate group, and 22.89 (5.87 to 89.21) in the severe group, showing the same trend as in the other analyses.

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†The number of patients and the follow-up period are not shown so that the number of patients (less than 10) cannot be identified according to the MID-NET® publication criteria.

■ **Discussion based on the results**

- Based on results of analyses of all bisphosphonate preparations included, it was considered that the risk of hypocalcaemia was higher in patients with severe renal impairment than in those with normal renal function. In addition, the adjusted hazard ratio of hypocalcaemia increased with more severe renal impairment, suggesting that the risk of hypocalcaemia may increase with more severe renal impairment.
- Similar results were obtained in the analysis of each ingredient for alendronate sodium hydrate, minodronic acid hydrate, and sodium risedronate hydrate. Since the bisphosphonate preparations have the same pharmacological mechanism, it was suggested that characteristics of the risk of onset of hypocalcaemia observed in this study may be common to bisphosphonate preparations, although it was difficult to evaluate ibandronate sodium hydrate, etidronate disodium, and zoledronic acid hydrate due to the small number of patients.
- It should be noted that hypocalcaemia observed in this study has certain limitations, including the possibility that it may be due not only to the drugs but also to decreased renal function per se, and that other potential confounding factors (e.g., severity of comorbidities other than renal impairment and other concomitant drugs) may have affected the results.