Omeprazole- and Esomeprazole-associated Hypomagnesaemia: Data Mining of the Public Version of the FDA Adverse Event Reporting System

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Abstract

Objective: Case reports showing that proton-pump inhibitors (PPIs), omeprazole and esomeprazole, can cause hypomagnesaemia have been accumulating since 2006. In this study, the reports submitted to the Adverse Event Reporting System (AERS) of the US Food and Drug Administration (FDA) were evaluated to assess omeprazole and esomeprazole in terms of susceptibility to hypomagnesaemia.

Methods: After a revision of arbitrary drug names and the deletion of duplicated submissions, the reports involving omeprazole and esomeprazole were analyzed. Standardized official pharmacovigilance tools were used for the quantitative detection of a signal, i.e., an association between a drug and an adverse drug event, including the proportional reporting ratio, the reporting odds ratio, the information component given by a Bayesian confidence propagation neural network, and the empirical Bayes geometric mean.

Results: A total of 22,017,956 co-occurrences were found in 1,644,220 reports from 2004 to 2009, where a co-occurrence was a pair of a drug and an adverse drug event. In total, 818 and 743 adverse drug events were listed as omeprazole- and esomeprazole-associated, with hypomagnesaemia ranking 85th and 135th, respectively. Although both PPIs were associated with hypomagnesaemia, the statistical metrics suggested that the association was more noteworthy for omeprazole.

Conclusion: The data obtained in this study do not provide sufficient evidence to recommend systematic monitoring of magnesium levels in plasma, but chronic exposure to a PPI can lead to severe hypomagnesaemia.

Key words: adverse drug events, proton pump inhibitors, data mining, pharmacovigilance.

Introduction

In 2006, Epstein et al. reported that hypomagnesaemic hypoparathyroidism could be caused by long-term use of a proton-pump inhibitor (PPI), omeprazole [1]. Thereafter, case reports accumulated, in which PPIs were shown to be associated with hypomagnesaemia [2-11], and in 2011, the US Food and
Drug Administration (FDA) published a safety announcement that long-term use of PPIs can lead to hypomagnesaemia [12]. Although recognized as a rare side effect of PPIs, hypomagnesaemia is a serious condition that can be complicated by life-threatening arrhythmias and neurologic manifestations [10, 11].

Most reports on PPI-induced hypomagnesaemia concern omeprazole or esomeprazole, the S-isomer of omeprazole, but the recurrence after substitution by other PPIs suggests that this is a class effect commonly found for PPIs. The present study was performed to assess omeprazole and esomeprazole in terms of susceptibility to hypomagnesaemia, and to this end, more than a million case reports on adverse drug events submitted to the FDA database were reviewed.

Methods

Data sources

Input data for this study were taken from the public release of the data in the FDA’s Adverse Event Reporting System (AERS), which covers the period from the first quarter of 2004 through the end of 2009. The total number of reports used was 2,231,029. This database relies on spontaneous reports of adverse drug events by health professionals, consumers, and manufacturers. The data structure of AERS is in compliance with international safety reporting guidance ICH E2B issued by the International Conference on Harmonisation, consisting of 7 data sets: patient demographic and administrative information (DEMO), drug/biologic information (DRUG), adverse drug events (REAC), patient outcomes (OUTC), report sources (RPSR), drug therapy start and end dates (THER), and indications for use/diagnosis (INDI). The adverse drug events in REAC are coded using preferred terms (PTs) in the Medical Dictionary for Regulatory Activities (MedDRA) terminology. MedDRA ver.13.0 was used in this study.

Prior to analysis, all drug names were unified into generic names by a text-mining approach, because AERS permits the registering of arbitrary drug names, including trade names and abbreviations. Spelling errors were detected by a spell checker software, GNU Aspell, and carefully confirmed by working pharmacists. The total number of errors was 223,239. Foods, beverages, treatments (e.g. X-ray radiation), and unspecified names (e.g. beta-blockers) were omitted for this study, and the total number of omissions was 164,384. Finally, duplicated reports were deleted according to the FDA’s recommendation of adopting the most recent CASE number, resulting in a reduction in the number of reports from 2,231,029 to 1,644,220. A total of 22,017,956 co-occurrences were found in 1,644,220 reports, where a co-occurrence was a pair of a drug and an adverse drug event.

Data mining

In pharmacovigilance analyses, data mining algorithms have been developed to identify an association between a drug and an adverse drug event or a drug-associated adverse drug event as a signal that is reported more frequently than expected by estimating expected reporting frequencies on the basis of information on all drugs and all adverse drug events in a database [14-20]. For example, the proportional reporting ratio (PRR) [14], the reporting odds ratio (ROR) [15], the information component (IC) [16], and the empirical Bayes geometric mean (EBGM) [17] are widely used. Indeed, the PRR is currently used by the UK Medicines and Healthcare products Regulatory Agency (MHRA), the ROR by the Netherlands Pharmacovigilance Centre, the IC by the World Health Organization (WHO), and the EBGM by the FDA.

All of these algorithms extract decision rules for signal detection and/or calculate scores to measure an association between a drug and an adverse drug event from a two-by-two frequency table of counts that involve the presence or absence of a particular drug and a particular adverse drug event occurring in case reports. These algorithms, however, differ from one another in that the PRR and ROR are frequentist (non-Bayesian) ones, whereas the IC and EBGM are Bayesian ones. In this section, only the scoring thresholds used in the present study are given, and the reader is referred to review articles for more extensive details of each statistical test [18-20].

In this section, we define how the association between a drug and an adverse drug event is classified as a signal, when using each statistical test. Using the PRR, a signal is detected if the count of co-occurrences is 3 or more, and the PRR is 2 or more with an associated χ² value of 4 or more [14]. For the ROR, a signal is detected if the lower bound of the 95% two-sided confidence interval of ROR exceeds 1 [15]. Signal detection using the IC is done using the IC025 metric, a criterion indicating the lower bound of the 95% two-sided confidence interval of the IC, and a signal is detected if the IC025 value exceeds 0 [16].
Finally, the EB05 metric, a lower one-sided 95% confidence limit of EBGM [17], is used and a signal is detected when EB05 is greater than or equal to the threshold value 2. In this study, the adverse drug events coded by PT numbers were listed as omeprazole- and esomeprazole-associated, when at least 1 of 4 indices met the criteria indicated above, and subsequently hypomagnesaemia was identified by the PT code number 10021027.

**Results**

The total number of co-occurrences with omeprazole and esomeprazole was 178,766 and 121,506, representing 0.812% and 0.552% of all co-occurrences in the database, respectively. In total, 818 and 743 adverse drug events were listed as omeprazole- and esomeprazole-associated with 55,904 and 48,481 co-occurrences, respectively.

Hypomagnesaemia ranked 85th among 818 omeprazole-associated adverse drug events, and 135th among 743 for esomeprazole. The statistical data on omeprazole- and esomeprazole-associated hypomagnesaemia are listed in Table 1. An association with hypomagnesaemia was suggested for both PPIs, but the association was more noteworthy for omeprazole.

**Discussion**

Magnesium is an essential factor implicated in many biochemical and physiological processes, and its homeostasis is sophisticatedly regulated by intestinal absorption, renal excretion and other systems in the body [10, 11]. Hypomagnesaemia or hypermagnesaemia may arise from various types of disorders [10, 11]. In 2006, a report was published by Epstein et al., in which a PPI, omeprazole, was shown to be associated with hypomagnesaemia [1]. To date, about 10 case reports have been published with respect to PPI-associated hypomagnesaemia [2-9], and their findings can be summarized as; 1) PPI long-term use was observed in patients with hypomagnesaemia, 2) symptoms did not occur until plasma concentrations were less than 0.5 mmol/L, 3) mechanisms by which the hypomagnesaemia occurred under PPI therapy remain unclear, 4) hypokalaemia often accompanied the hypomagnesaemia, 5) hypocalcaemia also frequently developed via impairment of parathyroid hormone secretion, 6) oral or parenteral supplement of magnesium was effective for temporary relief from symptoms, but unable to correct the plasma concentration of magnesium, and 7) withdrawal of PPI allowed to resolve the hypomagnesaemia [10, 11]. Hypomagnesaemia is understood to be a rare side effect of PPIs, but Epstein et al. speculated that the cases represented the tip of an iceberg [1]. Hypomagnesaemia might be underdiagnosed, in part, due to the relatively low frequency of magnesium measurements in routine clinical analysis. If hypomagnesaemia is found in PPI users, it might be attributed to co-administered diuretics or other nephrotoxic drugs. It is important to perform clinical studies to clarify the true prevalence and risk factors, and to clarify the mechanisms by which hypomagnesaemia develops.

**Table 1. Signal detection for omeprazole- and esomeprazole-associated hypomagnesaemia.**

|        | N  | PRR (χ2) | ROR (95% two-sided CI) | IC (95% two-sided CI) | EBGM (95% one-sided CI) |
|--------|----|----------|------------------------|----------------------|------------------------|
| Omeprazole | 158 | 2.725 * (171.816) | 2.762 * (2.359, 3.165) | 1.424 * (1.197, 1.651) | 2.650 * (2.321) |
| Esomeprazole | 58  | 1.470 (8.299) | 1.474 * (1.138, 1.810) | 0.532 * (0.161, 0.903) | 1.425 (1.146) |

N: the number of co-occurrences.
PRR: the proportional reporting ratio, ROR: the reporting odds ratio, IC: the information component, EBGM: the empirical Bayes geometric mean.
CI: the confidence interval; two-sided for ROR and IC, and one-sided for EBGM.
*: signal detected, and a signal means a drug-associated adverse drug event (see “Methods” for the criteria of detection).

The hypomagnesaemia was coded as PT10021027.
To date, most case reports on PPI-associated hypomagnesaemia concern omeprazole or esomeprazole, but hypomagnesaemia is understood to be common for PPIs. Broeren et al. showed that hypomagnesaemia was resolved after the replacement of omeprazole with a H2-blocker, ranitidine, but the re-replacement of ranitidine with pantoprazole resulted in recurrence [5]. The same fluctuation was found for lansoprazole [5]. Hoorn et al. reported a case of hypomagnesaemia in which the patient was treated with pantoprazole [8]. They also documented another case in which the replacement of omeprazole with rabeprazole resulted in a further decrease in serum levels of magnesium [8]. In this study, using 1,644,220 reports from 2004 to 2009, it was suggested that hypomagnesaemia was associated with omeprazole and esomeprazole, and was more noteworthy for omeprazole, suggesting the usefulness of the AERS database and official pharmacovigilance tools. Although pantoprazole, lansoprazole and rabeprazole were also analyzed, the numbers of co-occurrences were not large enough to detect signals. The first clinical report on PPI-associated hypomagnesaemia appeared in late 2006, which was on omeprazole and esomeprazole, and the PPI-associated hypomagnesaemia entered clinical consciousness slowly. The AERS data used in this study were those from 2004 to 2009, and the latest data should be used to assess the associations with pantoprazole, lansoprazole and rabeprazole.

The AERS database is considered a valuable tool; however, some limitations inherent to spontaneous reporting have been pointed out [18]. First, the data occasionally contain misspelling and miswords, although the structure of AERS is in compliance with the international safety reporting guidance. Second, the system was started more than 10 years ago, and reporting patterns have changed over time. Third, the adverse events are coded using hierarchical terms of PTs of MedDRA, and changes in terminology over time also might affect the quality of the database. Last, there are a number of duplicate entries in the database. To overcome problems with data quality, we manually corrected mistakes in the data entities and deleted duplicates according to FDA’s recommended method, resulting in the development of a novel system to analyze an association between a drug and an adverse drug event. Previously, this system has been used to assess adverse drug events accompanying the use of platinum agents [21]. The data obtained was consistent with clinical observations, suggesting the usefulness of the system [21]. Additionally, this system was used to evaluate susceptibility to hypersensitivity reactions for 14 anticancer agents, and it was found that the number of co-occurrences was an important factor in signal detection [22, 23]. Very recently, this system was applied to the evaluation of adverse drug events induced by statins [24], capecitabine [25] and Tigecycline [26], and again the reproducibility of clinical observations was suggested, providing that the number of co-occurrences was large enough to detect a signal.

It should be noted that there is no credible counterfactual means, e.g., a randomized control group, to identify an association between a drug and an adverse drug event as a signal, and therefore disease-oriented adverse events can be extracted as signals. For example, hypomagnesaemia was extracted as an omeprazole-associated adverse drug event, but might be common in patients with acid peptic disorders irrespective of the administration of PPIs. Generally, the results obtained using this system can be biased by unmeasured confounding factors, and flawed by incomplete data; however, a comparison among PPIs possibly offsets them, resulting in a rank-order of association according to the statistical metrics. In conclusion, the data obtained in this study do not provide sufficient evidence to recommend systematic monitoring of magnesium levels in plasma, but chronic exposure to a PPI can lead to severe hypomagnesaemia.

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Competing Interests
The authors have declared that no competing interest exists.

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