Accumulating Evidence for a Drug–Drug Interaction Between Methotrexate and Proton Pump Inhibitors

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Key Words. Methotrexate • Proton pump inhibitor • Drug interaction

Disclosures: The author(s) indicated no financial relationships.

ABSTRACT

Background. A number of medications are known to interact with methotrexate through various mechanisms. The aim of this article is to apprise practitioners of a new labeling change based on the accumulating evidence for a possible drug–drug interaction between methotrexate (primarily at high doses) and proton pump inhibitors (PPIs).

Methods. The U.S. Food and Drug Administration (FDA) Adverse Event Reporting System (AERS) database of spontaneous adverse event reports and the published literature were searched for cases reporting an interaction between methotrexate and PPIs.

Results. A search of the AERS database and existing literature found several individual case reports of drug–drug interactions and three additional supportive studies that suggest potential underlying mechanisms for the interaction.

Conclusion. There is evidence to suggest that concomitant use of methotrexate (primarily at high doses) with PPIs such as omeprazole, esomeprazole, and pantoprazole may decrease methotrexate clearance, leading to elevated serum levels of methotrexate and/or its metabolite hydroxymethotrexate, possibly leading to methotrexate toxicities. In several case reports, no methotrexate toxicity was found when a histamine H₂ blocker was substituted for a PPI. Based on the reviewed data, the FDA updated the methotrexate label to include the possible drug–drug interaction between high-dose methotrexate and PPIs. Physicians should be alerted to this potential drug–drug interaction in patients receiving concomitant high-dose methotrexate and PPIs. *The Oncologist* 2012;17:550–554

INTRODUCTION

Methotrexate was first approved by the U.S. Food and Drug Administration (FDA) in December 1953. It inhibits dihydrofolic acid reductase and thus interferes with DNA synthesis, repair, and cellular replication [1]. Methotrexate is used in a wide range of doses for the treatment of certain neoplastic diseases, severe psoriasis, and rheumatoid arthritis [1]. High-dose methotrexate is used for the treatment of malignancies such as high-grade lymphoma, osteosarcoma, and acute leukemia in doses of 300 mg/m² to 12 g/m². At higher dose levels, monitoring of serum methotrexate elimination is performed because delayed elimination can result in serious and potentially life-threatening toxicities. The FDA label for methotrexate contains a number of boxed warnings for proper administration and monitoring, for various adverse events, and for potential

drug–drug interactions. Besides methotrexate, its major metabolite 7-hydroxymethotrexate may also contribute to toxicities [2].

A number of medications are known to interact with methotrexate therapy through various mechanisms, and the drug is labeled for these drug–drug interactions [1]. Nonsteroidal anti-inflammatory drugs (NSAIDs) have been reported to elevate and prolong serum methotrexate levels by reducing tubular secretion. Other drugs, such as salicylates, phenylbutazone, phenytoin, and sulfonamides, may increase methotrexate toxicity by displacing albumin-bound methotrexate. Probenecid inhibits renal tubular transport, which can result in higher serum concentrations of methotrexate. Oral antibiotics such as tetracycline, chloramphenicol, and nonabsorbable broad spectrum antibiotics may decrease intestinal absorption of methotrexate

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or interfere with the enterohepatic circulation by inhibiting bowel flora and suppressing metabolism of the drug by bacteria. Finally, penicillin may reduce the renal clearance of methotrexate.

Proton pump inhibitors (PPIs) belong to the benzimidazole chemical family. Omeprazole (Prilosec®, AstraZeneca, Wilmington, DE) was approved by the FDA in 1989 as the first PPI; other approved PPIs include lansoprazole (Prevacid®, Takeda Pharmaceuticals U.S.A. Inc., Deerfield, IL), pantoprazole (Protonix®, Wyeth Pharmaceuticals Inc., Philadelphia, PA), rabeprazole (Aciphex®, Eisai Inc., Woodcliff Lake, NJ), esomeprazole (Nexium®, AstraZeneca, Wilmington, DE), omeprazole/bicarbonate (Zegerid®, Santarus Inc., San Diego, CA), esomeprazole/naproxen (Vimovo®, AstraZeneca, Wilmington, DE), and dexlansoprazole (Dexilant®, Takeda Pharmaceuticals U.S.A. Inc., Deerfield, IL). These agents inhibit $H^+/K^+-ATPase$ and decrease the secretion of gastric acid [3]. Some of the approved indications for PPIs include the treatment of symptoms of gastroesophageal reflux disease, the treatment of erosive esophagitis, the treatment of gastric ulcer, *Helicobacter pylori* eradication, and the reduction of NSAID-associated gastric ulcers.

In this paper, we report the results of a literature and Adverse Events Reporting System (AERS) database review of a potential drug–drug interaction between methotrexate and PPIs. These potential interactions were noted for a number of different PPIs, including omeprazole, esomeprazole, and pantoprazole.

METHODS

The FDA maintains a database of adverse event reports associated with drugs and biologic products used by humans. Drug manufacturers are required by law to submit such reports that come to their attention. Health care professionals and consumers can voluntarily report via FDA's MedWatch program [4]. The adverse drug event reports are collected, maintained, and retrieved through the AERS database [5].

The AERS database was searched using the drug name methotrexate and the individual PPIs (omeprazole, lansoprazole, pantoprazole, rabeprazole, esomeprazole, dexlansoprazole) for drug–drug interactions from the initiation of marketing to July 31, 2011. The identified reports were then reviewed for suspected drug–drug interactions between methotrexate and PPIs. In addition, the PubMed database was searched on July 31, 2011 for articles on methotrexate and PPI-associated drug–drug interactions and for articles on possible drug–drug interaction–related toxicity.

RESULTS

AERS Database

A search of the AERS database identified several cases in which the reporters suspected an interaction between methotrexate and a number of PPIs leading to methotrexate toxicity. The identified cases include omeprazole ($n = 7$), esomeprazole ($n = 5$), and pantoprazole ($n = 2$). No cases of suspected methotrexate interaction were identified for lansoprazole, rabeprazole, or dexlansoprazole in the AERS database. When re-

ported, clinical and laboratory outcomes included renal toxicity, hematologic events, and myopathy. Two reports suggested a mechanism of PPI interference with methotrexate elimination. However, most reporters did not provide blood levels or dechallenge/rechallenge information. Of the 14 cases, 13 cases were reported from foreign sources. Eleven patients were receiving methotrexate as part of cancer chemotherapy; the other indications for use included psoriatic arthropathy ($n = 1$), pulmonary fibrosis ($n = 1$), and rheumatoid arthritis ($n = 1$). Two cases of a positive dechallenge were reported in 2009–2010 from foreign sources, and are described below.

A pharmacist reported that a 47-year-old male patient being treated for Burkitt's lymphoma experienced decreased methotrexate clearance (drug levels were recorded but not provided in the report) when esomeprazole was added to the patient's chemotherapy regimen. The patient was hospitalized (the adverse clinical event associated with the decreased renal clearance was not reported). His methotrexate clearance normalized after esomeprazole was omitted during his second chemotherapy course.

A physician reported that a 15-year-old male patient being treated for large cell lymphoma experienced decreased elimination of methotrexate while on concomitant omeprazole. The report stated that methotrexate elimination was normal during the first two cycles, but elimination lasted 1 week instead of 2 days (blood levels were provided) after omeprazole was added to the third cycle. The patient experienced no manifestations of toxicity associated with the delayed methotrexate elimination. During the subsequent two methotrexate cycles, omeprazole was discontinued and methotrexate elimination was reportedly normal.

Literature

A search of the existing literature identified four case reports describing a possible interaction between methotrexate and PPIs.

The first case of a possible interaction between omeprazole and high-dose methotrexate was reported by Reid et al. [6] in 1993 in a patient with osteosarcoma. The patient received high-dose methotrexate with leucovorin rescue while receiving omeprazole and other drugs. During the first course of therapy, his serum methotrexate levels remained elevated for several days, prompting prolonged administration of hydration, urine alkalinization, and leucovorin therapy for 8 days. After omeprazole was discontinued, the patient's serum methotrexate levels rapidly declined, with normal kinetics for the next three cycles of methotrexate therapy.

Beorlegui et al. [7] reported a case of delayed elimination of high-dose methotrexate associated with concomitant omeprazole administration. An 11-year-old male patient experienced delayed methotrexate elimination after receiving methotrexate to treat osteoblastic osteosarcoma with concomitant omeprazole (40 mg a day), megestrol, and sucralfate. Delayed elimination was determined via methotrexate plasma concentrations. The clinicians suspected an interaction with omeprazole leading to altered methotrexate levels and substituted ranitidine. Methotrexate elimination was normal in sub-

sequent cycles administered with concomitant ranitidine in place of omeprazole.

A case was reported by Tröger et al [8] involving a 59-year-old male patient who developed symptoms of myalgia with methotrexate toxicity. The patient had underlying folliculotropic cutaneous T-cell lymphoma and was receiving low-dose pulse methotrexate therapy (15 mg i.m., once a week) along with pantoprazole to treat Barrett's esophagus. This case described positive dechallenge and rechallenge results. The patient experienced myalgia that lasted several days with symptoms recurring over the following four methotrexate cycles. When pantoprazole was discontinued and ranitidine was given in its place, the symptoms of myalgia subsided and eventually disappeared. The patient was rechallenged with pantoprazole 8 weeks later with the patient's consent and the symptoms recurred. Serum concentrations of methotrexate and its metabolite 7-hydroxymethotrexate were monitored with and without pantoprazole. The investigator found that the concentration–time curves were identical for methotrexate in both periods but differed considerably for 7-hydroxymethotrexate. The area under the curve between 0 and 144 hours was ~70% higher for 7-hydroxymethotrexate when methotrexate was given with pantoprazole than without pantoprazole, and the half-life was doubled when pantoprazole was given with methotrexate.

Bauters et al. [9] described a 15-year-old male patient with underlying acute lymphocytic leukemia who experienced severe mucositis after taking methotrexate (5 g/m²) and omeprazole concomitantly. In the first cycle, he received high-dose methotrexate and ranitidine and experienced no problems. In the second cycle, omeprazole was substituted for ranitidine. During that cycle, his methotrexate clearance was delayed and his methotrexate levels remained elevated for several days (blood levels provided). He experienced severe mucositis, but his creatinine and liver function tests were normal. Omeprazole was discontinued and the mucositis resolved. He experienced normal methotrexate clearance with the third cycle of therapy, given without omeprazole.

The literature search also identified several articles, including some that assessed the potential underlying mechanism for the interaction.

Breast cancer resistant protein (BCRP) is present in the kidney [10]. It is thought that BCRP is responsible for methotrexate secretion in the kidneys during the process of renal excretion of methotrexate. Breedveld et al. [11] reported on their investigation of the mechanism of interaction *in vitro* in membrane vesicles from cells infected with a baculovirus containing human BCRP. They found that benzimidazoles differentially affect transport of methotrexate mediated by BCRP and multidrug resistance associated protein, and they concluded that competition for BCRP may explain the interaction between methotrexate and benzimidazoles.

An article by Suzuki et al. [12] reported retrospective data on plasma methotrexate concentrations for 171 cycles of high-dose methotrexate therapy in 74 patients. They conducted a multiple logistic regression analysis that supported coadministration of PPIs (i.e., omeprazole, lansoprazole, rabeprazole,

pantoprazole) as a risk factor for delayed elimination as well as renal and liver dysfunction. Although all four PPIs inhibited BCRP-mediated transport of methotrexate, the half-maximal inhibitory concentrations were higher than the plasma concentrations of PPIs. These authors concluded that the drug–drug interaction is likely not solely a result of the PPI effects on BCRP-mediated methotrexate transport.

Joerger et al. [13] reported on a 24- and 48-hour blood sample analysis from 76 patients receiving high-dose methotrexate in which the concentration–time data were subjected to population pharmacokinetic and covariate analyses. The study concluded that, in patients receiving high-dose methotrexate, concurrent administration of a benzimidazole was associated with a significant decrease in the clearance of methotrexate and its metabolite hydroxymethotrexate, resulting in higher plasma concentrations.

Santucci et al. [14] retrospectively analyzed the causes of delayed methotrexate elimination in six patients who had received glucarpidase rescue. Of those who had received a PPI (three of six), rechallenge in the absence of the PPI resulted in normal elimination. The same authors then conducted a larger retrospective cohort study in patients receiving methotrexate at doses >1 g/m² [15]. The retrospective study revealed that, of the 79 patients who were treated at their institution with a total of 197 cycles, 32 cycles (16%) displayed delayed elimination (>15 micromole/L at 24 hours, >1.5 micromole/L at 48 hours, or >0.15 micromole/L at 72 hours). Of these delayed cycles, coadministration of a PPI occurred in 17 of 32 cycles (53%) whereas co administration of a PPI occurred in only 24 of 165 or 15% of the cycles in which elimination was not delayed.

As opposed to the above described case reports and series that suggest an interaction between methotrexate and PPIs, Whelan et al. [16] reported a case of no drug interaction between methotrexate and omeprazole. The case involved a 24-year-old male patient with underlying chondroblastic osteosarcoma who was receiving methotrexate and omeprazole. The patient was receiving omeprazole for 2 months for dyspeptic symptoms. Methotrexate blood levels were elevated at 67 mmol/L at 24 hours, prompting an adjustment of the folinic acid dose. Continued monitoring of the methotrexate level demonstrated delayed elimination, with the level falling to <0.1 mmol/L by 140 hours. Omeprazole was omitted from the second cycle of methotrexate (using the same methotrexate dose, hydration, and other medications) and his serum levels measured at 24 hours revealed delayed methotrexate clearance identical to what was seen in the first course. However, there were no reported levels of the metabolite 7-hydroxymethotrexate. Additionally, a prospective evaluation of low-dose methotrexate in 28 rheumatoid arthritis patients receiving lansoprazole and naproxen for 7 days did not reveal any change in methotrexate pharmacokinetics [17].

DISCUSSION

Methotrexate is eliminated primarily via renal excretion. Methotrexate clearance rates vary widely and are generally lower at higher doses [18]. This review identified cases of decreased methotrexate clearance with some symptoms of renal

toxicity, hematologic events, mucositis, and myalgia possibly resulting from drug–drug interactions with various PPIs. The frequency of the interaction is difficult to ascertain. The AERS database cannot be used to estimate the true incidence rates of events because spontaneous reporting systems such as the AERS are subject to underreporting. In fact, it has been suggested that <10% of adverse events are reported to the FDA [19].

Two mechanisms for PPI-induced interference with methotrexate elimination have been proposed in the literature. First, there is evidence that $H^+/K^+-ATPase$ is present in renal epithelium as well as gastric parietal cells [20]. It was proposed that PPIs inhibit renal $H^+/K^+-ATPase$, which supports the active tubular secretion of methotrexate, resulting in an increased half-life of methotrexate [6]. However, it was also found that the administration of omeprazole does not change the pH of urine, suggesting the absence of a significant effect of PPIs on renal $H^+/K^+-ATPase$ [21]. Therefore, further research is needed to evaluate the validity of this hypothesis for this first proposed mechanism. A second proposed mechanism involves possible PPI inhibition of ATP-dependent efflux of methotrexate by BCRP in human kidney proximal tubules. Although it was demonstrated in vitro that PPIs inhibit BCRP-mediated transport of methotrexate, the clinical relevance of this interaction is uncertain because the half-maximal inhibitory concentrations of PPIs are significantly higher than the therapeutic unbound plasma concentration [10].

The majority of the reported cases occurred with the administration of high-dose methotrexate. Although the product label describes high-dose therapy as 12 g/m^2 as a 4-hour infusion [1], doses $\geq 500\text{ mg/m}^2$ are frequently cited as “high dose” in the literature, and the majority of the above case reports and series were reported from patients receiving doses of 300 mg/m^2 to 12 g/m^2 . It appears the risk is greatest in the high-dose setting; however, there were also cases of patients taking a PPI and experiencing toxicity at doses as low as 15 mg of methotrexate per week.

Based on reports in the literature and evidence from the

AERS, it appears that PPIs may interfere with the elimination of methotrexate (primarily at high doses), possibly leading to accumulation of methotrexate and its metabolite hydroxymethotrexate. Decreased clearance of methotrexate and its metabolite may result in an increased risk for known methotrexate toxicities, some of which can be severe and life threatening. This review cites one report of a patient who did not experience delayed elimination after receiving methotrexate and omeprazole, but the report did not mention any measurement of the metabolite hydroxymethotrexate.

CONCLUSION

There is accumulating evidence to suggest that concomitant use of methotrexate (primarily at high doses) and PPIs such as omeprazole, esomeprazole, and pantoprazole may decrease methotrexate clearance. Decreased clearance may result in elevated and prolonged serum levels of methotrexate and/or its metabolite hydroxymethotrexate, possibly leading to methotrexate toxicities. In addition, there may be a class effect because this interaction has been described for multiple PPIs.

PPIs are used extensively, and health care practitioners should be aware of this potential interaction. In several case reports, methotrexate elimination normalized and no methotrexate toxicity was found when a histamine H_2 blocker was substituted for a PPI, although no formal studies have been conducted. This possible drug–drug interaction has been added to the labels for i.v. methotrexate and PPIs. Clinicians should consider substituting H_2 blockers for PPIs when acid suppression is clinically indicated during methotrexate therapy. The FDA encourages reporting of suspected cases of drug–drug interactions to their MedWatch program (<http://www.fda.gov/medwatch>).

AUTHOR CONTRIBUTIONS

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