Methotrexate and Proton Pump Inhibitors

John R. Horn, PharmD, FCCP, and Philip D. Hansten, PharmD

Methotrexate (MTX) is a widely used drug for the treatment of various malignancies, including leukemia, lymphoma, and sarcoma. Both MTX and its metabolite 7-hydroxymethotrexate (7-OH-MTX) are active. MTX and 7-OH-MTX are eliminated primarily by glomerular filtration and active tubular secretion.

Several drugs, including nonsteroidal anti-inflammatory drugs (NSAIDs), penicillins, probenecid, and sulfonamides, are known to inhibit the elimination of MTX. Over the past few years, data have appeared that indicate a potential interaction between MTX and proton pump inhibitors (PPIs).

EVIDENCE OF AN INTERACTION

The first case report of a potential interaction between MTX and a PPI was noted in a patient with osteosarcoma who was receiving high-dose (15 g) MTX.[1] The authors noted a reduced clearance of MTX during concurrent PPI administration.

Subsequent case reports noted either no interaction[2] or reduced clearance of MTX during PPI administration.[3,4] The patient in one of these studies was rechallenged with and without pantoprazole. Although the patient's MTX concentrations did not change, 7-OH-MTX concentrations were increased (approximately 70%) and its half-life increased from 36 to 81 hours when pantoprazole was coadministered.[4] The substitution of ranitidine for the PPI resulted in resolution of the MTX toxicity symptoms.[3,4]

A patient with leukemia received 3 courses of MTX with omeprazole 20 mg daily administered only during the second course of therapy.[5] The coadministration of omeprazole resulted in a marked delay in MTX elimination and MTX toxicity. A study of patients being treated with low-dose (7.5-15 mg weekly) MTX for rheumatoid arthritis found no effect on MTX or 7-OH-MTX pharmacokinetics when lansoprazole 30 mg daily and naproxen 500 mg twice daily were coadministered.[6]

Seventy-six patients receiving high-dose MTX had their MTX and 7-OH-MTX concentrations measured at 24 and 48 hours after dosing.[7] Thirteen of the patients also were receiving PPIs. MTX concentrations were 2- to 3-fold higher at 24 and 48 hours after MTX infusion in patients receiving a concurrent PPI. Concentrations of 7-OH-MTX were increased by 50% to 75% in patients receiving PPIs compared with those only receiving MTX. MTX and 7-OH-MTX clearance were reduced by 27% and 39%, respectively, when PPIs were used.

In a study of 74 patients receiving MTX, 171 cycles of therapy were classified as having normal or delayed MTX elimination. PPI administration was found in 32% of the delayed versus 14% of the normal MTX elimination cases.[8] Similarly, PPI administration was more often (53%) associated with delayed MTX elimination than normal elimination (15%) in patients receiving high-dose MTX.[9]

In a retrospective study of 6 patients with MTX toxicity who were treated with glucarpidase (an enzyme that breaks down MTX in vivo), 3 of the patients had received a PPI with their MTX.[10] These patients did not experience MTX toxicity when they received MTX without a PPI.

MECHANISM OF THE INTERACTION

The elimination of MTX is primarily the unchanged drug via the kidney, with the liver eliminating both unchanged drug and 7-OH-MTX. Early reports of this interaction proposed that PPIs might inhibit renal H+-K+-ATPase, thus reducing the active tubular secretion of MTX. This would require conversion of the PPI to its active sulfenamide, an unlikely event in the kidney, because it requires an acidic (pH <4) environment.

Hepatic and renal uptake of MTX is via the organic anion transporters (OAT and OATP). Efflux from the hepatic (to bile) and renal cells (to urine) is via the breast cancer resistance protein (BCRP) and the multidrug resistance-related protein transporters.[11,12] NSAIDs and penicillins are known to inhibit the transport of MTX via the OAT. It appears that PPIs compete with MTX for transport via the BCRP efflux transporters. This would result in reduced MTX renal and biliary elimination with accumulation of MTX and increased risk of toxicity.

> Withholding PPIs for a couple of days before and after MTX administration should minimize the magnitude of the interaction.

MANAGEMENT

It appears that patients receiving high-dose MTX are particularly at risk for this interaction. The competition between MTX and PPIs for the transporters will be more important at high concentrations of MTX. For this same reason, the PPI would likely have to be administered at the same time as the MTX.

For patients taking PPIs, withholding the drug for a couple of days before and after MTX administration should minimize the magnitude of the interaction. It appears H_2-receptor blockers can be used during this period. Pending further study, these precautions should extend to patients taking low-dose MTX as well. Other drugs (NSAIDs, penicillins, etc) known to inhibit MTX elimination should be avoided. ***PT***

Drs. Horn and Hansten are both professors of pharmacy at the University of Washington School of Pharmacy. For an electronic version of this article, including references if any, visit www.hanstenandhorn.com.

› Web PharmacyTimes.com

For a list of references, go to www.PharmacyTimes.com/publications/issue/2012/April2012.