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Abstract

Objective: To report a case of delayed methotrexate (MTX) elimination while receiving concomitant levetiracetam. **Case Report:** A 46-year-old man with relapsed osteosarcoma of the base of the skull receiving high-dose MTX tolerated his first cycle of MTX with elimination to nontoxic MTX levels (≤0.1 µmol/L) within 90 hours. After hospital discharge, the patient experienced seizures secondary to brain metastasis and started on levetiracetam, which was continued as maintenance therapy. The patient experienced delayed MTX elimination during cycles 2, 3, and 4 while receiving levetiracetam. On average, elimination to nontoxic MTX levels took 130 hours (106-144 hours). Before the fifth cycle of MTX, lorazepam was substituted for the levetiracetam. MTX was eliminated to nontoxic levels within 95 hours. During all cycles, the patient received standard supportive care and serum creatinine remained stable. No other drugs known to interact with MTX were administered. **Discussion:** This possible drug interaction has only been reported once in the pediatric population. With a score of 6 on the Drug Interaction Probability Scale for evaluating causation of drug interactions, it is probable that the delayed MTX elimination was caused by an interaction with levetiracetam. **Conclusion:** Coadministration of levetiracetam and MTX may result in delayed elimination of MTX, increasing the likelihood of toxicity. Consideration should be given to temporarily switching from levetiracetam to another antiepileptic (ie, lorazepam) to prevent this interaction. This is particularly important in those experiencing delayed elimination with prior cycles of concomitant MTX and levetiracetam or those at greater risk for MTX toxicity.

Introduction

Patients with cancer are at a high risk for drug-drug interactions because of the complex nature of their treatment regimens. In fact, it has been reported that 12% to 63% of patients with cancer are potentially exposed to interacting medications, and 75% of these interactions may be classified as moderate or severe.[1] Chemotherapeutic agents have complex pharmacological profiles, narrow therapeutic indexes, and steep dose-toxicity curves.[2] These drug properties leave little to no room for alterations in the elimination or distribution of chemotherapeutic agents. Further complicating the use of potentially toxic chemotherapy regimens is the complex nature of the oncology patient. Many are on multiple maintenance medications to treat chronic conditions in addition to those necessary to control the symptoms of their malignancy. Patients who develop central nervous system metastases may experience seizure episodes and require long-term therapy with an antiepileptic agent; however, optimal therapy with ongoing oncological treatment has not been established.[3] When choosing an antiepileptic medication, agents with a low potential for interacting with chemotherapy and favorable safety profiles, such as levetiracetam, are preferred.[3] Here, we present a case of delayed elimination when high-dose methotrexate (MTX) was administered concomitantly with levetiracetam.

Case Report

A 46-year-old Caucasian male with relapsed osteosarcoma presented for chemotherapy with high-dose MTX alternating with ifosfamide and etoposide according to the regimen utilized in the SFOP OS94 protocol.[4] He had a past medical history of retinoblastoma that was treated with radiation at the age of 11 months, diabetes mellitus, hypertension, and hyperlipidemia. Home medications included lisinopril, simvastatin, glipizide, and aspirin. He originally presented with headaches and significant sinus complaints and was found to have radiation-induced osteosarcoma of the base of the skull. This was treated with cisplatin and doxorubicin for 6 cycles followed by surgical resection and adjuvant concurrent chemoradiation with carboplatin. The patient was disease free for approximately 1 year, when he presented with epistaxis. On magnetic resonance imaging, he was found to have a mass within the ethmoidal cells and the right orbit. On biopsy, this was confirmed to be recurrent osteosarcoma.

During cycle 1 of chemotherapy for recurrent disease, the patient was admitted to the oncology unit and received 24 g of MTX (12 g/m^2) intravenously (IV) over 4 hours (height = 170 cm, weight = 80 kg). Supportive care included leucovorin rescue with 25 mg orally every 6 hours and urinary alkalinization with 100 mEq of sodium bicarbonate per liter of dextrose 5% in water at 125 mL/h (3 L/d). Urine pH remained above 7, and recorded input and output were well balanced throughout the hospital stay. Prior imaging in addition to history and physical exam on admission did not reveal the presence of any findings suggestive of ascites or pleural effusion. Serum MTX levels were drawn 24, 48, and 72 hours after the start of the MTX infusion, and every morning thereafter until the level was <0.1 μmol/L. Baseline serum creatinine was 0.9 mg/dL, and aspartate and alanine aminotransferases (AST/ALT) were within normal limits (10 and 39 U/L, respectively). Additional medications administered to the patient during the admission were lisinopril, simvastatin, insulin glargine, insulin aspart, oxycodone, prochlorperazine, ondansetron, and famotidine. Aspirin was held until hospital discharge. The patient tolerated the first cycle of MTX well and eliminated it to nontoxic levels (≤0.1 μmol/L) within 90 hours (Table 1). After hospital

discharge, the patient developed seizures as a result of large right-parietal/occipital lobe lesions associated with edema and shifting toward the left hemisphere. Levetiracetam was initiated and continued as maintenance therapy at 1 g orally every 12 hours, and 7 days after starting levetiracetam, chemotherapy treatments were resumed.

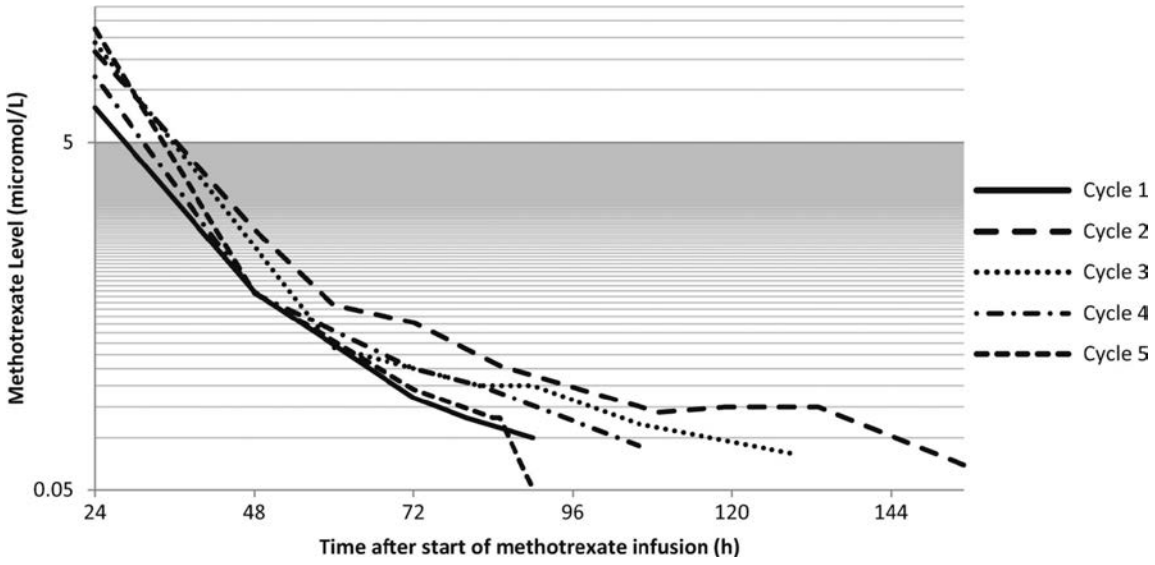
Table 1. Laboratory Values for Each Cycle of Methotrexate (MTX).

	Cycle 1	Cycle 2	Cycle 3	Cycle 4	Cycle 5
SCr (mg/dL)					
Baseline	0.9	0.8	0.87	0.81	0.78
24 hour	1.1	1.1	0.87	0.94	0.83
48 hour	1.1	1.0	0.87	0.89	0.76
72 hour	1.3	1.0	0.82	0.77	0.73
BUN (mg/dL)					
Baseline	25	15	29	20	16
24 hour	19	17	22	22	19
48 hour	19	15	22	20	17
72 hour	19	20	22	21	14
Baseline creatinine clearance (mL/min)	95	107	99	106	110
Baseline AST/ALT (U/L)	10/39	26/89	11/51	13/33	Not available
24-Hour MTX level[a] (µmol/L)	7.9	16.59	18.71	11.97	22.43
48-Hour MTX level (µmol/L)	0.69	1.58	1.26	0.68	0.68
72-Hour MTX level (µmol/L)	0.17	0.58	0.33	0.25	0.19
Time to level <0.1 µmol/L (hours)[b]	90	155	130	106	95

Abbreviations: SCr, serum creatinine; BUN, blood urea nitrogen; AST, aspartate aminotransferase; ALT, alanine aminotransferase.
[a]The 24-, 48-, and 72-hour MTX levels were drawn 24, 48, and 72 hours after the start of the MTX infusion, respectively.
[b]Time to level <0.1 µmol/L measured as time from drug administration to the time when MTX serum level laboratory result was <0.1 µmol/L.

During cycles 2, 3, and 4 of MTX, the patient experienced delayed elimination, with an average time to nontoxic levels of 130 hours (106-155 hours; Figure 1). The patient continued to receive the same dose of MTX as cycle 1 (12 g/m^2) along with the same supportive care. Urine pH remained above 7.0 from the start of each MTX infusion until levels were nontoxic, and recorded input and output remained well balanced. History and physical exams during each admission did not reveal the presence of any findings suggestive of ascites or pleural effusion. Changes to the patient's medications throughout cycles 2 to 4 included the addition of fluoxetine prior to cycle 3 and the discontinuation of lisinopril during cycle 4. No medications known to interact with MTX were administered during the hospital stays for cycles 2 to 5 of MTX administration. During each of these cycles, leucovorin was increased to 50-mg IV every 6 hours because of the elevated MTX levels at 24 hours and continued until levels were nontoxic.

Prior to the fifth cycle of MTX, lorazepam was substituted for levetiracetam to control the patient's seizures. MTX was administered the same as in cycles 1 to 4 with the same supportive care. Urine pH remained above 7, and recorded input and output were well balanced. Leucovorin was increased to 50-mg IV every 6 hours because of the elevated MTX levels at 24 hours. Overall, the patient eliminated MTX to nontoxic levels within 95 hours.



Discussion

It is well known that MTX interacts with multiple medications. Drugs that are highly protein bound, including many antiepileptics, have been shown to reduce renal clearance of MTX through protein-drug displacement and lead to increased serum concentrations, placing patients at risk for toxicity.[2] Additionally, active renal tubular secretion of MTX has been shown to be reduced by drugs such as probenecid and weak organic acids.[5] Delayed MTX elimination can lead to significant toxicities, such as acute renal failure, bone marrow suppression, mucositis, and hepatotoxicity. Levetiracetam displays less protein binding than other antiepileptics (<5%).[6] Additionally, levetiracetam lacks any significant effects on the metabolism of medications via hepatic enzymes (cytochrome P450, glucuronidation, etc) and is often a preferred agent because of the decreased likelihood of adverse interactions and subsequent toxicities.[7]

A possible mechanism responsible for decreased MTX elimination when coadministered with levetiracetam has not been proposed; however, it may be because of competition for tubular secretion. Though levetiracetam undergoes glomerular filtration, the metabolite ucb L057 is eliminated via active tubular secretion.[8] When levetiracetam was coadministered with probenecid, renal clearance of the metabolite ucb L057 was decreased by 60% and the Cmax doubled.[8] MTX also undergoes active tubular secretion and interacts with many medications that compete for secretion. When administered with probenecid, MTX levels doubled.[9] Given the similar interactions with probenecid, it is plausible that with the common route of elimination, MTX and levetiracetam's metabolite ucb L057 may compete with each other for tubular secretion.

A search of the literature was performed using the search term *methotrexate and levetiracetam* revealing 1 publication relating to a possible drug interaction. A pediatric case report was recently published in which a 15-year-old boy with B-cell lymphoblastic leukemia was receiving treatment with high-dose MTX.[10] During treatment, he developed seizures, was diagnosed with brain metastases, and initiated on oral levetiracetam. After the third infusion of high-dose MTX (5 g/m^2/24 hour) the patient developed vomiting, renal failure, and hypertension. He was also found

to have an elevated serum creatinine and MTX level and required treatment with carboxypeptidase G_2. It was noted that the patient had no prior risk factors for MTX toxicity and was receiving no concomitant interacting medications.

In the present case report, the patient did not experience any toxicity; however, MTX levels were above the goal ranges at 24 (goal MTX level <10 μmol/L), 48 (goal MTX level <1 μmol/L), and 72 (goal MTX level <0.1 μmol/L) hours after the start of the MTX infusion when receiving concomitant levetiracetam (Table 1). During cycle 5, the 24-hour MTX level was above goal range; however, this may be because of the effect of residual levetiracetam present from administration prior to hospital admission. Given a half-life of approximately 8 hours, it is plausible that levetiracetam was still being eliminated and available to interact with MTX. This was not the case for the 48-hour level, which was 0.69 μmol/L, well below the goal of 1 μmol/L. Most important, the time to nontoxic MTX levels was shorter when levetiracetam was not coadministered with the high-dose MTX (Table 1). During the fourth cycle of MTX, elimination was not as delayed as during cycles 2 and 3. During all 3 of these cycles, the patient received the same care, including the coadministration of levetiracetam; however, during cycle 4, the patient's lisinopril was held during the hospital stay. Though no interaction has been reported between lisinopril and MTX, the renal vasoconstriction caused by this medication in the efferent arteriole may decrease blood flow through the glomerulus, which theoretically could decrease MTX elimination. Holding lisinopril may have slightly improved MTX clearance during cycle 4. Lisinopril was administered during cycles 1 to 3 and during cycle 5.

Unfortunately, little data exist regarding the optimal treatment of seizures in cancer patients with brain metastases. There are a multitude of drug interactions associated with many antiepileptic medications, particularly via their hepatic enzyme–inducing effects and protein-binding effects. For these reasons, agents such as phenytoin, phenobarbital, carbamazepine, oxcarbazepine, and topiramate are not recommended as first-line agents.[11] Valproate has been associated with increased hematological toxicity when combined with chemotherapy and is best avoided if possible.[12] Benzodiazepines may be recommended in the acute treatment of seizures because of their relative lack of drug interactions. For long-term treatment of seizures associated with brain metastases, it has been recommended to utilize agents relatively free of drug interactions (levetiracetam, gabapentin, lamotrigine, topiramate, and pregabalin).[11]

Until now, a potential drug interaction between MTX and levetiracetam has not been reported in adults. The Drug Interaction Probability Scale (DIPS) was used to evaluate the causation of a potential drug interaction between MTX and levetiracetam.[13] With a DIPS score of 6, it is probable that the delayed MTX elimination seen in this patient was the result of an interaction with levetiracetam as evidenced by more rapid MTX elimination during cycles 1 and 5 with no concomitant levetiracetam and delayed elimination during cycles 2, 3, and 4 with concomitant levetiracetam (Table 2). Therefore, an interaction between MTX and levetiracetam cannot be ruled out. Patients receiving concomitant levetiracetam and MTX who are experiencing delayed elimination may benefit from the substitution of levetiracetam until MTX levels are nontoxic. When possible, consideration should be given to temporarily switching from levetiracetam to another antiepileptic (ie, lorazepam) to prevent this interaction. This is particularly important in

those who experienced delayed elimination with prior cycles of concomitant MTX and levetiracetam coadministration or those felt to be at greater risk for MTX toxicity.

Table 2. Drug Interaction Probability Scale.[13]

Question	Answer	Score
Are there previous credible reports of this interaction in humans?	Yes	+1
Is the observed interaction consistent with the known interactive properties of precipitant drug?	Yes	+1
Is the observed interaction consistent with the known interactive properties of the object drug?	Yes	+1
Did the interaction remit on dechallenge of the precipitant drug with no change in the object drug?	Yes	+1
Did the interaction reappear when the precipitant drug was readministered in the presence of continued use of object drug?	Unknown	0
Are there reasonable alternative causes for the event?	No	+1
Was the object drug detected in the blood or other fluids in concentrations consistent with the proposed interaction?	Yes	+1
Was the drug interaction confirmed by any objective evidence consistent with the effects on the object drug?	No	0
Was the interaction greater when the precipitant drug dose was increased or less when the precipitant drug dose was decreased?	Unknown	0
Total DIPS score		6

Declaration of Conflicting Interests

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