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Retrospective Analysis of Methotrexate Elimination When Coadministered With Levetiracetam

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Abstract

Background: Delayed elimination of methotrexate was previously reported in 2 patients receiving concomitant levetiracetam. **Objective:** To explore the potential interaction between methotrexate and levetiracetam in patients receiving high-dose methotrexate. **Methods:** This retrospective study reviewed the records of 81 adults receiving 280 cycles of methotrexate to determine the effects of levetiracetam on methotrexate elimination. Institutional review board approval was obtained. **Results:** Levetiracetam was administered in 33 (12%) cycles of methotrexate. Patients receiving levetiracetam had significantly lower 24-hour methotrexate concentrations compared with those not receiving levetiracetam (2.91 vs 7.37 μmol/L, $P = 0.005$). Despite this difference, concentrations at 48 and 72 hours were similar between groups. Times to nontoxic methotrexate concentration (<0.1 μmol/L) were the same regardless of the presence of levetiracetam. The frequency of delayed elimination at 24, 48, and 72 hours was similar in both groups as was the frequency of delayed elimination at any time point. Cox regression demonstrated that levetiracetam was not a significant predictor of time to nontoxic methotrexate concentration ($P = 0.796$; HR = 1.058; 95% CI = 0.692-1.617), and logistic regression demonstrated that levetiracetam was not a significant predictor of delayed elimination at any time point. Levetiracetam use was similar between groups when comparing patients experiencing delayed elimination at any time point with those without delayed elimination (13% vs 10%, respectively, $P = 0.527$). **Conclusion:** This study does not support the previous reports of a significant interaction between levetiracetam and methotrexate. A clinically significant interaction is unlikely in those without additional risk factors for delayed elimination.

Keywords

methotrexate, drug interactions, pharmacokinetics, seizures, drug monitoring

Introduction

High-dose methotrexate protocols are utilized in the treatment of various cancers. Methotrexate is an antimetabolite that interferes with DNA synthesis by inhibiting dihydrofolate reductase, preventing the synthesis of purine nucleotides and thymidylate, and causing the subsequent death of cancer cells.[1] It was the first agent to provide a cure for cancer as monotherapy, and it has continued to remain a cornerstone of various anticancer regimens throughout the years.[2] Unfortunately, methotrexate is also well known for its many drug interactions, which require careful management during therapy. The majority of methotrexate undergoes renal elimination and can be influenced by renal function, urinary pH, and coadministration of medication competing for elimination.[3,4] Methotrexate also undergoes hepatic metabolism via cytochrome P-450 isoenzymes. Because of these issues with methotrexate pharmacokinetics, serum methotrexate concentrations are routinely monitored at 24, 48, and 72 hours after the start of the methotrexate infusion with standard goal concentrations being ≤10 to 20 μmol/L at 24 hours (depending on duration of infusion), ≤1 μmol/L at 48 hours, and ≤0.1 μmol/L at 72 hours.[3,5]

Many antiepileptic agents utilize the same metabolic pathways as methotrexate, resulting in increased or decreased serum drug concentrations of one or the other.[6] These interactions could be detrimental to patient outcomes if not properly managed because they could result in increased toxicity,

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loss of seizure control, or decreased efficacy of the oncological agent. Of particular concern is that interactions resulting in delayed methotrexate elimination may result in substantial increases in potentially life-threatening toxicity, including myelosuppression, mucositis, hepatotoxicity, and nephrotoxicity. Although it is best practice to avoid drug-drug interactions, scenarios arise in which this is not always feasible.

Levetiracetam has become one of the preferred antiepileptic agents used in patients with malignancies because of its limited potential for drug interactions.[6] Historically, no drug-drug interaction between methotrexate and levetiracetam had been identified; however, 2 cases in which levetiracetam appears to cause a delay in the elimination of methotrexate have recently been published.[7,8] Given the seriousness of any drug interaction with methotrexate, a retrospective study was completed to explore the possibility of a drug-drug interaction between methotrexate and levetiracetam.

Methods

Study Design

A retrospective chart review was performed on qualifying patients admitted between January 1, 2008, and August 1, 2014, to a community teaching hospital. Adult patients at least 18 years old with an oncological diagnosis, who received at least 1 treatment of high-dose methotrexate (≥1000 mg/m^2 intravenously [IV] over 3-4 hours or ≥800 mg/m^2 IV over 22-24 hours) were included in the study. Patients receiving multiple cycles of high dose methotrexate were included in the study multiple times (once for each cycle). Patients were excluded from the study if they were pregnant or if methotrexate serum concentrations were not monitored. Potential participants were identified via the hospital's electronic medical record system. The study design was reviewed and approved by the local institutional review board.

Data Collection

Electronic medical records were followed until plasma concentrations of methotrexate were nontoxic (≤0.1 µmol/L). Baseline characteristics, including demographic data, were gathered for all patients. Additionally, factors related to methotrexate administration and elimination, such as leucovorin use, presence of pleural effusion or ascites, use of urinary alkalinization, urine pH, alanine transaminase (ALT), aspartate transaminase (AST), baseline serum creatinine, and methotrexate dose and infusion time were collected. The Cockroft-Gault formula was used to estimate creatinine clearance.[9] The coadministration of the following medications with the potential to interact with methotrexate elimination was noted: dantrolene, cephalosporins, aspirin, penicillins, sulfamethoxazole/trimethoprim, nonsteroidal anti-inflammatory drugs, and probenecid. Methotrexate concentrations were routinely monitored at 24, 48, and 72 hours per hospital protocol. Patients with concentrations >0.1 µmol/L at 72 hours were routinely monitored daily, thereafter. The dose and schedule of levetiracetam were also noted.

End Points

The primary end point of the study was to determine whether coadministration of levetiracetam with methotrexate resulted in more instances of delayed elimination of methotrexate at any time point after administration when compared with patients who did not receive levetiracetam. Delayed elimination was defined as plasma methotrexate concentrations of >10 µmol/L at 24 hours if receiving bolus infusion methotrexate (ie, over 3-4 hours) or >20 µmol/L at 24 hours if receiving infusional methotrexate (ie, over 22-24 hours), >1 µmol/L at 48 hours, and >0.1 µmol/L at 72 hours. Secondary end points included a comparison of the proportion with delayed elimination at 24, 48, and 72 hours; time to nontoxic methotrexate concentrations (<0.1 µmol/L); and a comparison of levetiracetam use among those with and without delayed elimination.

Statistical Analysis

Patient baseline characteristics were compared using χ^2, Fisher's exact, and Mann-Whitney *U* tests as appropriate. Analyses were completed on the entire study population as well as a subgroup of those receiving bolus methotrexate dosing to account for the differing 24-hour goals in those receiving bolus and infusional methotrexate (≤10 and ≤20 µmol/L, respectively) and the fact that all patients receiving levetiracetam received bolus infusions. Binary logistic regression was utilized to evaluate the primary end point: delayed elimination at any time point. The following variables were included: baseline creatinine clearance, number of interacting medications, baseline AST, baseline ALT, and use of levetiracetam. Cox regression was utilized to evaluate if levetiracetam was a significant predictor of time to nontoxic methotrexate concentrations, with the following variables included: baseline creatinine clearance, number of interacting medications, baseline AST, baseline ALT, and use of levetiracetam. Delayed elimination at 24, 48, and 72 hours was compared via the Mann-Whitney *U* test, and levetiracetam use among those with and without delayed elimination was compared using the χ^2 test. Data were analyzed using IBM SPSS Statistics for Windows, version 22 (IBM Corp, Armonk, NY). A P value <0.05 was considered to be statistically significant.

Table 1. Baseline Characteristics.

	Entire Population (n = 280)			Population Receiving Bolus Infusions (n = 166)		
	No LEV (n = 247)	LEV (n = 33)	*P*	No LEV (n = 133)	LEV (n = 33)	*P*
Baseline characteristic						
Male, n (%)	175 (71)	14 (42)	0.001	83 (62)	14 (42)	0.037
Age, years, median (IQR)	52 (24)	57 (21)	0.003	54 (23)	57 (21)	0.004
Body surface area, m^2, median (IQR)	1.99 (0.36)	1.92 (0.57)	0.267	2.0 (0.37)	1.92 (0.57)	0.352
Baseline creatinine clearance, mL/min, median (IQR)	91 (55)	89 (57)	0.301	82 (44)	89 (57)	0.711
Baseline AST, U/L, median (IQR)	20 (15)	23 (8)	0.382	19 (16)	23 (8)	0.247
Baseline ALT, U/L, median (IQR)	39 (21)	53 (22)	0.003	39 (36)	53 (22)	0.034
Diagnosis, n (%)						
ALL	30 (12)			2 (2)		
Burkitt's lymphoma	41 (17)			2 (2)		
CNS lymphoma	93 (38)	28 (85)		85 (64)	28 (85)	
Leptomeningeal carcinomatosis	1 (<1)			1 (<1)		
Mantle cell lymphoma	16 (7)			1 (<1)		
NHL	33 (13)	2 (6)		23 (17)	2 (6)	
NHL (testicular)	3 (1)					
Osteosarcoma	17 (7)	3 (9)		17 (13)	3 (9)	
T-cell lymphoma	13 (5)			2 (2)		
Total methotrexate dose, mg, median (IQR)	6000 (5100)	6800 (1895)	0.012	7000 (1700)	6800 (1895)	0.362
Long methotrexate infusion time (22-24 hours), n (%)	114 (46)	0 (0)	<0.001			
Number of interacting medications, n (%)			0.931			
0	199 (81)	27 (82)		108 (81)	27 (82)	
1	37 (15)	5 (15)		19 (14)	5 (15)	
2	11 (4)	1 (3)		6 (5)	1 (3)	
Pleural effusion, n (%)	1 (<1)	0 (0)	1.0	0 (0)	0 (0)	1
Ascites, n (%)	1 (<1)	0 (0)	1.0	1 (<1)	0 (0)	1

Abbreviations: ALL, acute lymphoblastic leukemia; ALT, alanine transaminase; AST, aspartate transaminase; CNS, central nervous system; IQR, interquartile range; LEV, levetiracetam; NHL, non-Hodgkin's lymphoma.

Results

Patient Characteristics

A total of 81 patients were identified and included, which represented 280 unique cycles of high-dose methotrexate. Levetiracetam was administered concurrently in 13 patients receiving a total of 33 cycles. Based on the number of patients, the study had 90% power to detect a 20% increase in the incidence of delayed elimination at any time point after administration. Baseline characteristics were well balanced among the 2 groups, except for more cycles occurring in slightly younger males in the group not receiving levetiracetam (Table 1). Additional differences in baseline characteristics of the entire population included baseline ALT and differences in methotrexate dosing because those receiving levetiracetam were likely to receive higher doses via a bolus infusion, which is consistent with the fact that the majority of the patients in the levetiracetam group had central nervous system malignancies. When the subgroup of cycles that utilized bolus infusions (≤4 hours in duration) was analyzed, it represented 59% of the methotrexate cycles (n = 166), and the baseline characteristics largely mirrored the entire population (Table 1). Disparities in methotrexate dosing between groups that were present in the entire population were not present in the subgroup receiving bolus infusions. Levetiracetam dosing ranged from 500 mg daily to 1500 mg twice daily, with the majority receiving 500 mg twice daily, and all patients were either receiving levetiracetam prior to admission or stabilized on it prior to the start of methotrexate.

Supportive Management of Methotrexate Therapy

No differences were observed in the supportive care patients received in either the entire population or those receiving bolus infusions only. All patients received urinary alkalinization and leucovorin rescue. Urine pH was 7 or higher in at least 96% of patients at 24, 48, and 72 hours after the start of the methotrexate infusion, and there were no differences

Table 2. Methotrexate Management and Monitoring.

		Creatinine Clearance, mg/dL; median (IQR)			Urine pH ≥7, n (Percentage of Those With Result Available)		
Entire population							
Time after start of MTX infusion (hours)		24	48	72	24	48	72
No LEV	Number with result available	184	191	150	223	236	177
	Result	86 (57)	86 (63)	81 (58)	213 (96)	231 (98)	170 (96)
LEV	Number with result available	30	30	22	33	33	24
	Result	84 (49)	85 (47)	66 (54)	33 (100)	32 (97)	24 (100)
P value		0.568	0.278	0.232	0.369	0.548	1.0
Bolus infusion subgroup							
No LEV	Number with result available	110	104	83	129	127	102
	Result	82 (43)	82 (42)	78 (61)	125 (97)	127 (100)	102 (100)
LEV	Number with result available	30	30	22	33	33	24
	Result	84 (49)	85 (47)	66 (54)	33 (100)	32 (97)	24 (100)
P value		0.571	0.909	0.389	0.583	0.206	1.0

Abbreviations: IQR, interquartile range; LEV, levetiracetam; MTX, methotrexate.

between groups in the proportion of patients with a pH ≥7 (Table 2). Renal function, as represented by creatinine clearance, was also similar between groups at 24, 48, and 72 hours after the start of the methotrexate infusion. These characteristics were similar in the population receiving bolus infusions (Table 2).

Methotrexate Concentrations and Elimination

In the entire population, methotrexate concentrations were similar at 48 and 72 hours after the start of methotrexate; however, median concentrations were higher at 24 hours in those not receiving levetiracetam (7.37 vs 2.91 μmol/L, $P = 0.005$; Table 3). Despite this difference in concentrations at 24 hours, there was no difference in the proportion of patients with delayed elimination at 24, 48, or 72 hours after the start of methotrexate, nor was there a difference in the proportion of patients experiencing delayed elimination at any time point. Logistic regression demonstrated that the only significant predictor of delayed elimination at any time point was baseline creatinine clearance ($P = 0.012$), whereas all other parameters were nonsignificant, including receipt of levetiracetam ($P = 0.887$). Median time to a nontoxic methotrexate concentration (methotrexate concentration < 0.1 μmol/L) was also similar among groups (72 hours in those receiving no levetiracetam vs 78 hours in those receiving levetiracetam, $P = 0.229$). When data were analyzed utilizing Cox regression, receipt of levetiracetam was not a significant predictor of time to nontoxic methotrexate concentrations ($P = 0.796$; HR = 1.058; 95% CI = 0.692-1.617; Figure 1). The only significant predictor was baseline creatinine clearance ($P = 0.017$; HR = 1.004; 95% CI = 1.001-1.008).

In the population receiving only bolus infusions, the difference in the median 24-hour methotrexate concentration observed in the entire population was not present (4.06 μmol/L in those receiving no levetiracetam vs 2.91 in those receiving levetiracetam; $P = 0.864$; Table 3). All other parameters were similar to the entire population, including the proportion of those with delayed elimination and the median time to nontoxic methotrexate concentrations (Table 3). Logistic regression was also similar, in that baseline creatinine clearance was the only significant predictor of delayed elimination at any time ($P < 0.001$). Likewise, Cox regression in this population demonstrated that levetiracetam was not a significant predictor of time to nontoxic methotrexate concentration ($P = 0.342$; HR = 1.258; 95% CI = 0.784-2.019). Similar to the entire population, baseline creatinine clearance was the only significant predictor of time to nontoxic concentration in this subgroup ($P = 0.014$; HR = 1.008; 95% CI = 1.002-1.014).

Analysis of Levetiracetam Use in Those With/Without Delayed Methotrexate Elimination

In addition to comparing those receiving levetiracetam with those not receiving the medication, data were also compared based on the presence or absence of delayed methotrexate elimination (Table 4). Patients experiencing delayed methotrexate elimination tended to be older (49 vs 56 years old in the entire population, $P = 0.003$; 49 vs 57 years old in those receiving bolus infusions, $P = 0.005$). In those receiving bolus infusions, patients experiencing delayed elimination had a lower baseline creatinine clearance (101 vs 76 mL/min, $P < 0.001$) and a lower body surface area (2.03 vs 1.98 m^2, $P = 0.012$). Moreover, in the entire population, patients experiencing delayed elimination received higher doses of methotrexate (3500 vs 3000 mg/m^2, $P = 0.002$). The number of patients receiving levetiracetam in the group experiencing delayed elimination was similar to that in the

Table 3. Methotrexate Concentrations and Elimination.[a]

		Methotrexate Concentration, μmol/L, Median (IQR)			Delayed Elimination, n (%)			Delayed Elimination at Any Time, n (%)	Time to Methotrexate Concentration <0.1 μmol/L, hours, median (IQR)
Time after start of MTX infusion (hours)		24	48	72	24	48	72		
Entire population									
No LEV	Number with results available	219	247	228					
	Result	7.37 (15.78)	0.24 (0.57)	0.07 (0.16)	56 (23)	34 (14)	145 (59)	174 (70)	72 (29)
LEV	Number with results available	33	33	31					
	Result	2.91 (7.71)	0.33 (0.66)	0.11 (0.19)	4 (12)	6 (18)	23 (70)	25 (76)	78 (48)
P value		0.005	0.771	0.896	0.095	0.496	0.344	0.527	0.229
Bolus infusion subgroup									
No LEV	Number with results available	132	133	126					
	Result	4.06 (6.57)	0.24 (0.52)	0.07 (0.15)	25 (19)	18 (14)	80 (60)	91 (68)	72 (24)
LEV	Number with results available	33	33	31					
	Result	2.91 (7.71)	0.33 (0.60)	0.11 (0.19)	4 (12)	6 (18)	23 (70)	25 (76)	78 (48)
P value		0.864	0.502	0.695	0.357	0.580	0.411	0.411	0.123

Abbreviations: IQR, interquartile range; LEV, levetiracetam; MTX, methotrexate.
[a]Percentages for delayed elimination and delayed elimination at any time are based on the total population included in each group.

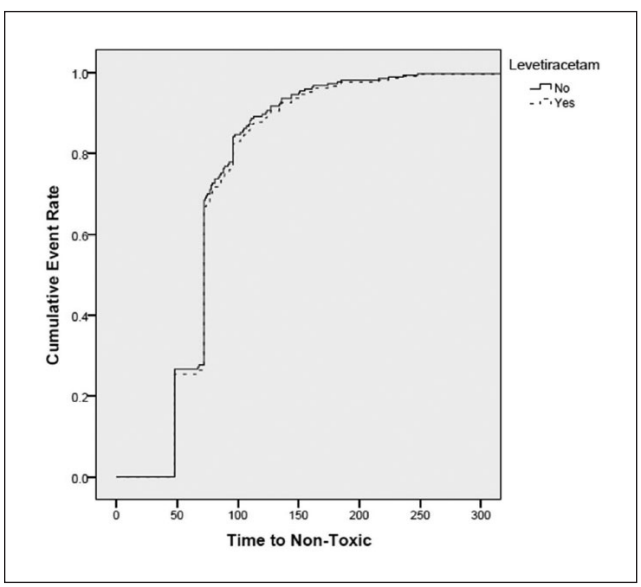

Figure 1. One minus cumulative event rate (time to nontoxic methotrexate concentration).

group not experiencing delayed elimination, as was the number of other interacting medications received by patients (Table 4).

Discussion

Methotrexate is an essential component in several cancer regimens, including in those patients with primary central nervous system lymphoma, who often require treatment for seizures. Levetiracetam for the treatment and prevention of seizures in those receiving chemotherapy has been utilized largely because of the relative lack of drug interactions compared with other antiepileptic medications, such as phenytoin. However, 2 case reports have called into question the safety of this combination. In the first case report, a 15-year-old male patient with B-cell acute lymphoblastic leukemia experienced methotrexate toxicity when it was administered at a dose of 5 g/m^2 concomitantly with levetiracetam.[7] The patient had no risk factors for methotrexate toxicity; however, during his third infusion of high-dose methotrexate, after starting oral levetiracetam 7.5 mg/kg twice daily, he experienced elevated methotrexate concentrations, hypertension, renal failure, and uncontrollable vomiting. The patient required treatment with carboxypeptidase G2 for the elevated methotrexate concentrations and renal failure. The second case reported in the literature included a 46-year-old male patient receiving methotrexate 12 g/m^2 for relapsed osteosarcoma.[8] Prior to his second cycle of methotrexate, he was started on levetiracetam to control seizures caused by brain metastases. Although methotrexate elimination was slightly delayed during cycle 1 (time to methotrexate concentration <0.1 μmol/L = 90 hours), it was delayed even further during cycles 2 to 4, during which levetiracetam was concomitantly administered (time to methotrexate concentration <0.1 μmol/L = 106-144 hours). During cycle 5, lorazepam was substituted for levetiracetam, and methotrexate elimination was similar to that in cycle 1 (time to methotrexate concentration <0.1 μmol/L = 95 hours).

The mechanism by which levetiracetam is thought to delay methotrexate elimination is not confirmed, but it may be related to the significant renal clearance of both medications. Methotrexate is cleared via glomerular filtration and active tubular secretion, as is the metabolite of levetiracetam (ucbL057).[8] The excretion of both methotrexate and

Table 4. Comparison of Characteristics in Patients With Delayed Versus No Delayed Methotrexate Elimination.

	Entire Population (n = 280)			Population Receiving Bolus Infusions (n = 166)		
Baseline Characteristic	No Delayed Elimination (n = 81)	Delayed Elimination (n = 199)	*P*	No Delayed Elimination (n = 50)	Delayed Elimination (n = 116)	*P*
Male, n (%)	57 (70)	132 (66)	0.513	34 (68)	63 (54)	0.101
Age, years, median (IQR)	49 (26)	56 (23)	0.003	49 (22)	57 (25)	0.005
Body surface area, m^2, median (IQR)	1.99 (0.36)	1.92 (0.57)	0.267	2.03 (0.4)	1.98 (0.4)	0.012
Baseline creatinine clearance, mL/min, median (IQR)	97 (52)	85 (53)	0.301	101 (47)	77 (46)	<0.001
Baseline AST, U/L, median (IQR)	19 (14)	21 (13)	0.382	15 (12)	21 (16)	0.140
Baseline ALT, U/L, median (IQR)	38 (24)	40 (26)	0.22	38 (27)	46 (46)	0.133
Diagnosis						
ALL	12 (15)	18 (9)		2 (4)		
Burkitt's lymphoma	11 (14)	30 (15)		2 (4)		
CNS lymphoma	25 (31)	96 (48)		24 (48)	89 (77)	
Leptomeningeal carcinomatosis	1 (1)	13 (7)		1 (2)		
Mantle cell lymphoma	3 (4)	18 (9)			1 (1)	
NHL	17 (21)	2 (1)		13 (26)	12 (10)	
NHL (testicular)	1 (1)	14 (7)		6 (12)	14 (12)	
Osteosarcoma	6 (7)	8 (4)		2 (4)		
T-cell lymphoma	5 (6)					
Total methotrexate dose, mg, median (IQR)	5900 (5500)	6300 (5200)	0.012	7000 (2063)	7000 (1775)	0.855
Long methotrexate infusion time (22-24 hours), n (%)	31 (38)	83 (41)	0.569			
Number of interacting medications, n (%)			0.280			0.453
0	70 (86)	156 (78)		42 (84)	93 (80)	
1	8 (10)	34 (17)		5 (10)	19 (16)	
2	3 (4)	9 (5)		3 (6)	4 (3)	
Pleural effusion, n (%)	0 (0)	1 (<1)	1	0 (0)	0 (0)	1
Ascites, n (%)	0 (0)	1 (<1)	1	0 (0)	1 (1)	1
Receiving levetiracetam, n (%)	8 (10)	25 (13)	0.527	8 (16)	25 (22)	0.411

Abbreviations: ALL, acute lymphoblastic leukemia; ALT, alanine transaminase; AST, aspartate transaminase; CNS, central nervous system; IQR, interquartile range; NHL, non-Hodgkin's lymphoma.

levetiracetam is delayed when coadministered with probenecid, and with this commonality, it is possible that the 2 drugs compete for tubular secretion.[8]

Despite the potential for this drug-drug interaction, it was not observed in the current study. The only significant predictor of time to nontoxic methotrexate concentration and delayed elimination at any time was baseline creatinine clearance. Baseline characteristics between the groups were similar, besides those receiving levetiracetam being slightly older, with a higher baseline ALT, and more likely to be female. None of these discrepancies between groups are believed to have affected the results. These characteristics would have put the levetiracetam group at a disadvantage, leading to potentially higher incidences of delayed elimination in those receiving levetiracetam, which was not observed. Another difference noted between groups was in the median methotrexate concentration at 24 hours, which was higher in those not receiving levetiracetam when the entire population was analyzed. This discrepancy between groups was likely a result of the increased number of patients receiving prolonged infusions in the group without levetiracetam, which are typically associated with higher 24-hour methotrexate concentrations.

Though the current study does not suggest the presence of an interaction, without a formal pharmacokinetic study, an interaction cannot be ruled out. It is possible that patients at risk for delayed elimination at baseline are at even higher risk when levetiracetam is present. In the adult case report described above, the patient had a slight delay in elimination in cycle 1, prior to starting levetiracetam. A slight delay in methotrexate elimination in those with other risk factors may be further enhanced in the presence of levetiracetam, which may not have been captured in the current study design. Although there was no significant difference between the groups, patients receiving levetiracetam did have a slightly higher incidence of delayed elimination at

any time (71% vs 76% in the entire population; 68% vs 76% in the bolus infusion population) and a slightly longer time to methotrexate concentration <0.1 μmol/L (72 vs 78 hours in both the entire population and the bolus infusion population). These slight differences could be significant to a patient with additional risk factors for delayed elimination. Additionally, this study did not record the incidence of adverse events; therefore, it is possible that patients receiving concomitant levetiracetam had a higher frequency of adverse events despite insignificant changes in methotrexate elimination. However, this is unlikely because of the strong correlation between methotrexate serum concentrations and the rate of adverse events.[3] This study was limited by the retrospective nature and limited number of patients receiving levetiracetam concomitantly with methotrexate.

Conclusion

This study did not detect a difference in methotrexate elimination caused by coadministration of levetiracetam and methotrexate and refutes the hypothesis generated by the 2 case reports; however, one of the cases included a dose of 12 g/m^2, whereas the other included a dose of 5 g/m^2. In this study, the median dose was 3.5 g/m^2. Delayed elimination caused by concomitant levetiracetam administration cannot be completely ruled out without a prospective, controlled, formal pharmacokinetic analysis; however, a clinically significant interaction is unlikely in those without additional risk factors for delayed elimination.

Declaration of Conflicting Interests

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