

CASE REPORT

Treatment of Methotrexate Intoxication with Various Modalities of Continuous Extracorporeal Therapy and Glucarpidase

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Methotrexate, administered for treatment of pediatric and adult malignancies, is a direct renal toxin, which can lead to renal dysfunction, decreased methotrexate clearance, elevated methotrexate concentrations, and systemic toxicity. Although plasma methotrexate concentrations have been shown to decline precipitously after a single dose of glucarpidase, this drug is investigational and available only through compassionate use. Therefore, alternative treatments for methotrexate removal may be required. We describe a 13-year-old girl (body surface area 1.2 m²) with osteosarcoma who was treated with high-dose methotrexate 12 g/m² infused over 4 hours. Forty-eight hours after the infusion, her plasma methotrexate concentrations were elevated at 446 µmol/L. She exhibited severe signs of methotrexate toxicity, including encephalopathy, liver failure, and acute kidney injury, and could not tolerate conventional hemodialysis. Over the next 12 days, the patient was treated with continuous venovenous hemodialysis (CVVHD), single-pass albumin dialysis (SPAD), continuous venovenous hemodiafiltration (CVVHDF), and glucarpidase to enhance methotrexate elimination. Compared with standard CVVHD, SPAD did not significantly increase methotrexate removal as measured by elimination half-life and methotrexate saturation coefficient. The highest clearance rate among extracorporeal therapies was achieved by CVVHDF, with an effluent rate of 4950 ml/hour. The patient's clinical condition steadily improved, and all extracorporeal therapies were stopped 168 hours after methotrexate administration. The patient was discharged home and continued with chemotherapy, including methotrexate, which was dosed based on iothalamate glomerular filtration rates on the day before infusion. Although extracorporeal treatments appeared to enhance methotrexate clearance, the administration of glucarpidase resulted in the most rapid percentage decline (86%) in methotrexate concentration. Until glucarpidase is readily available, intermittent hemodialysis should be used to enhance methotrexate clearance. If the patient is unable to tolerate hemodialysis, use of CVVHDF with maximum effluent rates will enhance methotrexate clearance.

Key Words: adolescent, methotrexate, acute kidney failure, renal replacement therapy, γ -glutamyl hydrolase.
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High-dose methotrexate therapy with leucovorin rescue is used for treatment of pediatric and adult malignancies. Despite strategies to reduce

methotrexate toxicity such as leucovorin rescue, aggressive hydration, and urinary alkalization, up to 48% of patients receiving high-dose

methotrexate develop decreased methotrexate renal clearance,¹ and 2% develop severe nephropathy.² Methotrexate is a direct renal toxin, which leads to renal dysfunction, decreased methotrexate clearance, elevated methotrexate concentrations, and subsequent systemic toxicity. This can culminate in life-threatening organ damage manifested as gastrointestinal mucositis, bone marrow suppression, and liver damage.³

Glucarpidase (also known as carboxypeptidase G2 or γ -glutamyl hydrolase) is an investigational agent that hydrolyzes methotrexate to inactive metabolites. After a single dose of glucarpidase, plasma methotrexate concentrations decline precipitously.^{2, 4} Glucarpidase is not yet approved by the United States Food and Drug Administration and thus is available only through compassionate use requests. Consequently, alternative treatments to remove methotrexate from the body may be required. The physiochemical characteristics of methotrexate, including a 454-dalton molecular weight, 0.4–0.8-L/kg volume of distribution,^{5–7} and 50% plasma protein binding at therapeutic plasma concentration,^{8, 9} suggest that its removal by extracorporeal means is possible.

Several extracorporeal methods to enhance elimination have been reported,² including hemodialysis,^{10, 11} high-flux hemodialysis,¹² charcoal hemoperfusion,² plasma exchange,² and continuous renal replacement therapies.¹³ Several types of continuous renal replacement modalities are available: continuous venovenous hemofiltration (CVVH), continuous venovenous hemodialysis (CVVHD), and continuous venovenous hemodiafiltration (CVVHDF). Depending on the modality, solute clearance is achieved through convection and/or diffusion. Solute clearance during CVVH occurs through convection, during CVVHD by diffusion, and during CVVHDF through both convection and diffusion. Single-pass albumin dialysis (SPAD)

has also been reported to enhance methotrexate clearance.¹⁴ The SPAD method is accomplished by adding albumin to the dialysate in a CVVHD circuit. Ostensibly, the dialysate albumin may enhance elimination of highly protein-bound drugs. As the non-protein-bound (free) drug crosses the hemodialyzer membrane, it binds to the albumin in the dialysate, causing a gradient whereby more drug can dissociate from plasma proteins and be eliminated. This method has been used to enhance removal of highly protein-bound drugs such as carbamazepine,¹⁵ acetaminophen,¹⁶ and diltiazem.¹⁷ A case report demonstrated that, compared with standard CVVHD, the addition of albumin to the dialysis fluid improved methotrexate clearance by 20%.¹⁴

We describe a case of methotrexate clearance by different continuous extracorporeal methods in an adolescent patient experiencing methotrexate toxicity and evaluated the outcome to determine the methotrexate removal capacity of each therapy.

Case Report

A 13-year-old girl (body surface area 1.2 m²) with nonmetastatic osteosarcoma of the right humerus was prescribed high-dose methotrexate as part of her treatment regimen. She received her first dose of methotrexate 12 g/m² over 4 hours with standard prehydration and alkalization. Her plasma methotrexate concentration at 24 hours after the infusion was 1478 μ mol/L as measured by fluorescence polarization immunoassay. At 48 hours after infusion, her plasma methotrexate concentration was 446 μ mol/L (target methotrexate concentration < 0.5 μ mol/L at 48 hrs). The patient was exhibiting clinical signs of severe methotrexate toxicity, including encephalopathy, liver failure, and renal failure without oliguria (serum creatinine concentration 0.7 mg/dl at baseline and 3.6 mg/dl at 48 hrs). The nephrology service was consulted for methotrexate-induced nephropathy.

A request for compassionate-use glucarpidase was made to the Pharmaceutical Management Branch at the Cancer Therapy Evaluation Program of the National Institutes of Health, but the drug would not be available for several days. Because of the patient's unstable condition, CVVHD was begun in order to enhance methotrexate elimination. A temporary 12-French double-lumen hemodialysis catheter was inserted into the patient's right internal jugular vein, and CVVHD was administered by using a

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Prisma continuous renal replacement therapy M100 circuit (surface area 0.9 m², ultrafiltration coefficient 22 ml/hr/mm Hg; Gambro Renal Products, Inc., Lakewood, CO). The blood-pump and dialysate flow rates were 180 ml/minute and 2100 ml/hour (3000 ml/min/1.73 m²). Regional citrate anticoagulation was performed based on previously published protocols.¹⁸ After 9 hours of CVVHD, plasma methotrexate concentrations remained elevated at 123 μmol/L. Therefore, SPAD was instituted and was performed for the next 23.9 hours with identical settings as the previous CVVHD session except that albumin was added to the dialysate to yield a final dialysate albumin concentration of 1.85 g/dl (prepared by adding 400 ml of 25% albumin to a 5-L bag of Priskasate [Gambro Renal Products, Inc.]). After noting only small elimination rate differences between CVVHD and SPAD, the patient was switched back to CVVHD without albumin, at the same rates.

At 103 hours after the methotrexate dose, glucarpidase 2000 units was infused intravenously; CVVHD was stopped for 3 hours to avoid removing the glucarpidase. Although a drastic reduction (86%) in methotrexate concentration was seen (Figure 1), the methotrexate concentrations remained in the toxic range (0.85 μmol/L); thus CVVHDF with 2950 ml/hour of ultrafiltration in addition to a dialysate flow rate of 2000 ml/hour was started. Over the next 36 hours, no significant reduction in the plasma methotrexate concentration occurred, and the CVVHDF circuit

clotted. Methotrexate concentrations were monitored over the next 7 hours, and a significant rebound was seen with methotrexate levels reaching 1.83 μmol/L. Because methotrexate concentrations were measured by fluorescence polarization immunoassay, it is possible that the rebound methotrexate levels may have represented primarily methotrexate metabolites.

As the patient remained critically ill and continued to have elevated methotrexate levels, the medical team hypothesized that the free drug:protein-bound drug ratio was likely substantially lower at this junction than at the previous attempt of SPAD, and SPAD was restarted. The SPAD ran for 17 hours with the same operating characteristics as those of the previous SPAD session. No substantial change in methotrexate concentration was observed. The clinical condition of the patient steadily improved, so all extracorporeal therapies were stopped 168 hours after methotrexate administration. During the patient's entire course of hospitalization, her urine output ranged from 2–2.5 L/day, but urinary methotrexate assays were never performed.

The patient ultimately was discharged home and continued to be treated with chemotherapy including methotrexate, which was dosed based on iothalamate glomerular filtration rates on the day before infusion. She had an otherwise unremarkable course and no apparent long-term ill effects from methotrexate.

Pharmacokinetic Analysis

For each extracorporeal therapy used, methotrexate's elimination rate constant and half-life during that therapy were determined from the slope of the regression line. Area under the concentration-time curve (AUC) was determined by using the linear trapezoidal method. During periods of methotrexate rebound, it was impossible to determine an elimination rate. The terminal elimination rate was calculated once extracorporeal therapies were stopped and rebound was complete using the final seven data points. The AUC after the last measured drug concentration was extrapolated to infinity.

At several points, effluent (spent dialysate and/or ultrafiltrate) was collected and assayed for methotrexate content in order to assess methotrexate transmembrane clearance (Cl_{tm}), which was determined as follows:

$$MSA = EMC/PMS \text{ and } Cl_{tm} = MSA \times EFR$$

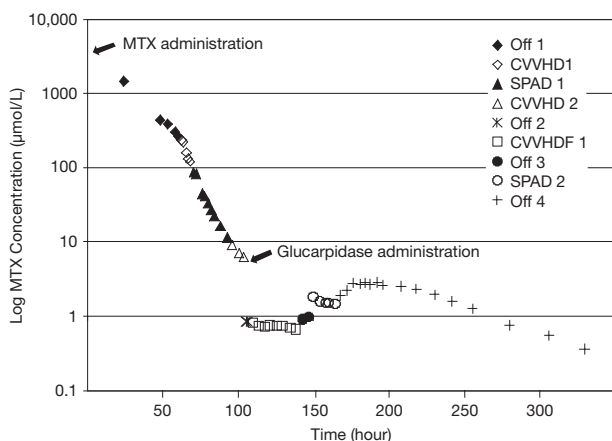


Figure 1. Plasma methotrexate (MTX) concentration at various time points without extracorporeal therapy (Off) or during continuous extracorporeal treatment sessions by various modalities. CVVHD = continuous venovenous hemodialysis; SPAD = single-pass albumin dialysis; CVVHDF = continuous venovenous hemodiafiltration.

Table 1. Summary of Extracorporeal Therapy Operating Characteristics and Methotrexate Pharmacokinetic Parameters During Each Treatment Session

Modality and Session No.	Flow Rate		Production Rate		Session Duration (hrs)	Elimination Half-Life (hrs)	Saturation Coefficient
	Blood (ml/min)	Dialysate (ml/hr)	Ultrafiltration (ml/hr)	Effluent (ml/hr)			
Off 1	—	—	—	—	59.7	14.8	—
CVVHD 1	180	2100	450	2550	9.0	6.5	0.67
SPAD 1	180	2100	450	2550	23.9	7.4	0.86
CVVHD 2	180	2100	450	2550	11.3	12.4	0.81
Off 2	—	—	—	—	3.0	NA	—
CVVHDF 1	180	2000	2950	4950	36.0	151.6	0.78
Off 3	—	—	—	—	6.9	NA	—
SPAD 2	180	2100	450	2550	17.1	49.5	—
Off 4	—	—	—	—	162.8	41.0	—

AUC = area under the concentration-time curve; Off = no extracorporeal therapy; CVVHD = continuous venovenous hemodialysis; SPAD = single-pass albumin dialysis; CVVHDF = continuous venovenous hemodiafiltration; NA = not available.

^aOff 1 AUC calculated from first data point (24 hrs) to CVVHD 1 initiation (60 hrs).

^bAUC after the last measured methotrexate concentration extrapolated to infinity.

where MSA = methotrexate saturation coefficient, EMC = effluent methotrexate concentration, PMS = prefilter methotrexate concentration, and EFR = effluent flow rate.

The amount of drug removed was calculated by using a treatment midpoint concentration (determined using the concentration-time profile regression line equation for each modality) according to the following formula:

$$\text{Amount removed} = (\text{midpoint concentration}) \times (\text{Cl}_{\text{m}}) \times (\text{duration of therapy})$$

A summary of the calculated pharmacokinetic parameters for each treatment session is presented in Table 1. The saturation coefficient and calculated amount of methotrexate removed are listed for the sequential therapies. The plasma concentration-time curve of methotrexate and all extracorporeal therapies appear in Figure 1, which illustrates that plasma methotrexate concentrations rebounded every time an extracorporeal therapy was discontinued. The highest clearance rate achieved by any of the continuous extracorporeal therapies was with CVVHDF with an effluent rate of 4950 ml/hour. The highest quantity of methotrexate removed occurred early in the course of treatment when plasma concentrations were highest. Although extracorporeal treatments appeared to enhance methotrexate clearance, the administration of glucarpidase resulted in the most rapid percentage decline in methotrexate concentrations.

Discussion

Intermittent extracorporeal therapies effectively

enhance methotrexate elimination,² but in patients too critically ill to tolerate intermittent therapies, continuous extracorporeal therapies may be necessary. To our knowledge, this case report is the first to directly compare the efficacy of different continuous extracorporeal treatments in a crossover manner. One group of authors reported on the use of CVVHD and CVVH for the treatment of methotrexate overdose in two pediatric patients.¹³ Another group suggested that SPAD accelerated methotrexate clearance in a critically ill patient.¹⁴ In our case, we used several continuous therapies and compared methotrexate clearances to determine which best removed methotrexate.

The methotrexate half-life in our patient was 14.8 hours before starting any extracorporeal therapy (Table 1). After the first CVVHD and SPAD treatments were completed, the methotrexate half-life decreased to 6.5 and 7.4 hours, respectively. Clearly, both extracorporeal methods enhanced methotrexate clearance, but considering the similarity in methotrexate half-life and saturation coefficient between treatment modalities, one was not superior to the other.

Enhanced clearance of highly protein-bound drugs during SPAD has not been consistently observed. An in vitro investigation of SPAD demonstrated increased clearance of valproic acid and carbamazepine during albumin dialysis compared with albumin-free dialysis.¹⁹ However, in the same study, SPAD resulted in impaired phenytoin clearance.

We estimated that the addition of albumin to dialysate increased the cost of dialysate by

Table 1. (continued)

Transmembrane Clearance (ml/min)	AUC ($\mu\text{mol}\cdot\text{hr/L}$)	Calculated Amount of Methotrexate Removed (mg)
—	27,431.9 ^a	—
28.4	1625.9	1275.5
28.4	966.8	771.5
34.5	91.2	87.9
—	7.2	—
64.4	27.7	46.1
—	8.0	—
—	23.0	—
—	254.4	—
—	21.3 ^b	—

approximately \$500/L. Since we were unable to demonstrate an appreciable increase in methotrexate clearance with SPAD compared with albumin-free dialysis, it is unlikely that the added cost associated with SPAD justifies its use in methotrexate intoxications. If enhanced methotrexate clearance is needed by patients receiving continuous renal replacement therapy, increased elimination may be achieved with standard dialysate run at higher effluent flow rates, as observed during our CVVHDF treatment period (Cl_{tm} 64.4 ml/min).

Once glucarpidase was administered, all extracorporeal and endogenous methotrexate clearances decreased. Methotrexate rebound was likely occurring, as further corroborated by the increase in plasma methotrexate concentrations whenever SPAD or CVVHDF was stopped. Methotrexate rebound has been reported previously with glucarpidase.^{2, 20} Possible explanations of rebound include the following: methotrexate redistribution from sanctuary sites where glucarpidase did not act, absorption through enterohepatic recirculation, or elevated concentration of methotrexate metabolites that interfere with the method of methotrexate analysis (fluorescence polarization immunoassay).^{2, 12}

The concurrent rebound effect of methotrexate may give the appearance of decreased elimination half-life as observed with CVVHDF and the second SPAD treatment session compared with previous treatments.

Highly protein-bound drugs often have different protein-binding characteristics at supratherapeutic or toxic concentrations than they do at lower “therapeutic” plasma concentrations.²¹ We did not measure methotrexate protein binding directly, but when methotrexate

is present in toxic concentrations, protein binding may be lower than the 50% reported in healthy individuals because high plasma concentrations could saturate protein-binding sites and increase the percentage of methotrexate unbound in plasma available to be removed by extracorporeal means. We did not find evidence in our study of decreased plasma protein-binding fraction at toxic concentrations. In general, saturation coefficient for any continuous extracorporeal therapy was similar early and late in the course of this patient’s treatment.

In other cases, the authors reported methotrexate half-lives with CVVH and CVVHD as 10–26 hours.¹³ We used larger hemodiafilters and faster effluent rates than used in those patients, and consequently our methotrexate half-lives during all extracorporeal therapies given before glucarpidase administration tended to be much shorter (6.5–12.4 hrs). Not surprisingly, reported methotrexate elimination half-lives are shorter with intermittent hemodialysis therapies^{10, 11} than rates observed in this case. However, in clinically tenuous patients such as our patient, high-volume CVVHDF may provide the best option to remove methotrexate.

The administration of glucarpidase decreased methotrexate concentration by 86% in our patient. This degree of methotrexate decline is consistent with the methotrexate reductions (73–99%) published by others.^{2, 4, 20} The degree of methotrexate degradation by this therapy greatly exceeded what could be accomplished by any extracorporeal therapy. Unfortunately, access to the drug is limited to compassionate use. Until glucarpidase becomes commercially available, extracorporeal therapies remain important considerations for the treatment of methotrexate toxicity in patients with renal dysfunction.

Conclusion

Our case report provides insights about different methods to enhance methotrexate removal. Glucarpidase, an investigational drug available only through compassionate use request, provides the most rapid decline in methotrexate plasma concentrations. However, in patients with severe methotrexate toxicity in which glucarpidase is not readily available, extracorporeal therapy should be started in order to enhance methotrexate elimination. In clinically stable patients, frequent intermittent hemodialysis therapy with high permeability hemodialyzers is probably the preferred course.

However, when patients are too unstable to tolerate intermittent hemodialysis, then CVVHDF with maximal effluent volumes should be used to accelerate methotrexate clearance. In our patient, the addition of albumin to dialysate conferred no methotrexate clearance advantage and, therefore, due to its very high cost, cannot be recommended as a treatment over conventional extracorporeal therapies.

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