Clin Kidney J (2014) 7: 590–592
doi: 10.1093/ckj/sfu093
Advance Access publication 16 September 2014

Clinical Report

CKJ

Methotrexate toxicity treated with continuous venovenous hemofiltration, leucovorin and glucarpidase

Nicholas J. Connors[1], Meghan E. Sise[2], Lewis S. Nelson[3,4], Robert S. Hoffman[3,4] and Silas W. Smith[3,4]

[1]Division of Emergency Medicine, Department of Medicine, Medical University of South Carolina, SC, USA, [2]Division of Nephrology, Department of Medicine, Columbia University Medical Center, New York, NY, USA, [3]New York City Poison Control Center, New York, NY, USA and [4]Division of Medical Toxicology, Department of Emergency Medicine, New York University School of Medicine, New York, NY, USA

Correspondence and offprint requests to: Nicholas Connors; E-mail: nicholasconnors@gmail.com

Abstract
High-dose methotrexate (MTX) can produce acute kidney injury, impairing MTX elimination. Continuous venovenous hemofiltration (CVVH) may enhance elimination in this setting, although its use is largely unstudied. A 79-year-old man received IV MTX for central nervous system lymphoma, and over a 34-h period his serum creatinine increased from 1.09 to 2.24 mg/dL. His serum MTX concentration (sMTX) at the end of this time period was 59.05 μmol/L. After urinary alkalinization and leucovorin and glucarpidase ($CPDG_2$) treatment, sMTX decreased. Fluid overload ensued and CVVH was initiated. The initial MTX extraction ratio and clearance were 0.22 and 47.0 mL/min, respectively. No MTX extraction occurred at an sMTX of 0.15 μmol/L. Continuous venovenous hemodialysis was initiated, and sMTX further declined. CVVH may help eliminate MTX and provide renal replacement at moderate sMTX.

Keywords: acute kidney injury; continuous venovenous hemofiltration; methotrexate

Background

Methotrexate (MTX) is an antimetabolite chemotherapeutic used to treat malignancies and rheumatologic conditions, such as nonHodgkin's lymphoma, osteosarcoma and rheumatoid arthritis. High-dose MTX (generally considered $\geq$500 mg/m^2) is commonly employed in regimens for leukemia, lymphoma and osteosarcoma. Unfortunately, high-dose MTX therapy may produce acute kidney injury (AKI), thereby impairing its own elimination and increasing its toxicity. The systemic toxicity of high-dose MTX regimens necessitates pretreatment urinary alkalinization, intravenous hydration and planned leucovorin rescue [1]. MTX is excreted mainly unchanged in the urine, but has low solubility in an acidic pH. Urinary alkalinization prevents precipitation of MTX and its metabolites in renal tubules and enhances their elimination. Leucovorin rescue circumvents MTX's inhibition of dihydrofolate reductase (DHFR) by providing reduced folic acid for purine nucleotide and thymidylate formation. $CPDG_2$ enzymatically cleaves MTX and significantly reduces serum MTX (sMTX), but is very expensive [2]. Additionally, avoidance of medications such as aspirin, nonsteroidal anti-inflammatory drugs and penicillins should occur prior to MTX treatment due to interactions that will increase free and active sMTX [3]. When sMTX remains elevated despite all these measures in patients with AKI, extracorporeal techniques such as hemodialysis might enhance MTX elimination. However, because MTX has a very large volume of distribution, serum concentrations are expected to rebound following a typical 4-h intermittent hemodialysis (IHD) session [4, 5]. Continuous techniques such as CVVH are logistically often easier to accomplish and may prevent rebound from redistribution. A previous case demonstrates significant reduction in sMTX with CVVH treatment [6]. We report a case of MTX toxicity where CVVH was used to reduce sMTX.

Case report

A 79-year-old, 79 kg man presented with diffuse large B-cell lymphoma with central nervous system (CNS) involvement and a history of gastroesophageal reflux disease for which he took daily omeprazole. His baseline serum creatinine was 1.08 mg/dL (95 μmol/L) when he received 12 mg of intrathecal MTX. He had not been treated with MTX previously. Three days later, he was administered 6195 mg (3.08 g/m^2) IV MTX, followed by leucovorin rescue 25 mg orally every 6 h. Approximately 34 h after the IV MTX on hospital Day 1, sMTX was 59.05 μmol/L (normal: <0.1 μmol/L), and his serum creatinine had doubled to 2.24 mg/dL (199 μmol/L). Urinary alkalinization was achieved with isotonic sodium bicarbonate 200 mL/h IV, and the leucovorin dose was increased to 100 mg IV every 6 h. The sMTX decreased to 11.06 μmol/L at 75 h. Pancytopenia developed very early, and on Day 3 the patient required

erythrocyte and platelet transfusions. Intravenous $CPDG_2$ 4000 units (50.4 units/kg) was planned after the elevated sMTX 48 h after IV MTX, but was administered within 72 h due to a delay in its acquisition. Intravenous leucovorin was further increased to 150 mg every 3 h. On Day 4, his sMTX decreased to 0.81 µmol/L, but his creatinine remained elevated at 3.59 mg/dL (317 µmol/L). The patient was given prophylactic anticoagulation with enoxaparin 40 mg subcutaneously on Days 1–2, then heparin 5000 units subcutaneously on Days 3–6. He was not treated with anticoagulation after that point.

Although MTX and creatinine concentrations trended downward with IV hydration, volume overload ensued. On Day 10, sMTX increased from 0.51 to 0.63 µmol/L and continued to rise. Considering the time from IV MTX administration, it was believed that there was a significant intracellular MTX reservoir. Because the total body clearance of MTX is known to be poor with IHD, the decision was made to initiate CVVH in an attempt to enhance MTX elimination and treat volume overload. A left internal jugular Vas-Cath™ was placed, and CVVH began on Day 13. CVVH utilized a high-flux polyethersulfone gamma sterilized filter with a membrane area of 1.5 m^2. Blood flow rate was 300 mL/min, and replacement fluid flow was 45 mL/kg/h. On Day 14, CVVH inflow and outflow MTX concentrations were 0.74 and 0.58 µmol/L, respectively, yielding an extraction ratio (ER) of 0.22, and an estimated clearance of 47.0 mL/min. On Day 16, the inflow and outflow MTX concentrations had declined to 0.15 and 0.15 µmol/L, yielding an ER of 0. CVVH was changed to continuous venovenous hemodialysis (CVVHD) modality on Day 18 for continued renal replacement therapy, given ongoing renal failure and volume overload, and not specifically for MTX clearance, as the serum concentration had been significantly reduced. Blood flow rate was 300 mL/min, and dialysate flow was 4000 mL/h. sMTX declined to 0.09 µmol/L on Day 19 and 0.06 µmol/L on Day 20. CVVHD ceased upon discovery of an expanding acute on chronic subdural hematoma with CNS lymphoma in the left frontoparietal region in rare acute leukemic phase, confirmed by flow cytometry. No other cause for the hematoma was noted. The patient elected palliative care and expired on Day 21.

Discussion

Once very elevated MTX concentrations are reached, enhanced elimination is essential, as leucovorin alone may be insufficient to overcome DHFR inhibition [4]. $CPDG_2$ carries a labeled indication for use only when sMTX exceeds 1 µmol/L and is exceedingly expensive [2]. In studies evaluating the efficacy of $CPDG_2$ in MTX toxicity, there is a broad range of time from MTX to $CPDG_2$ administration. Current recommendations call for maximizing the supportive care measures including adequate leucovorin dosage, urinary alkalinization, avoidance of medications that impair MTX excretion, and clinical evaluation for pleural effusions or ascites which can accumulate MTX and cause delayed clearance. After these issues are addressed, if the sMTX is >5 µmol/L at 42 h post MTX administration or if the sMTX is >2 SDs above the mean MTX excretion curve at 12 h post MTX administration, $CPDG_2$ should be considered [7]. In cases of MTX toxicity with AKI, $CPDG_2$ is effective in reducing sMTX and may prevent worsening toxicity and mortality.

IHD has been attempted for clearance of MTX, but because MTX has a large volume of distribution and is primarily intracellular, redistribution following IHD results in a substantial rebound in sMTX, requiring multiple sessions of IHD to reduce MTX to a nontoxic concentration [8, 9]. IHD may be helpful for renal replacement, but its effectiveness in clearance of MTX is debatable. CVVH involves a decreased blood flow rate across the dialysis filter membrane compared with IHD, but permits elimination over many hours, providing the potential benefit of constant MTX elimination as the serum and other compartments continuously equilibrate. CVVH minimizes fluid shifts and can provide clearance and renal replacement without the danger of inducing hypotension. It follows that this modality can be employed in cases of hemodynamic instability where vasopressors might be required to permit traditional IHD. No clear benefit to either IHD over CVVH exists and both should be used as adjunctive therapies to leucovorin, alkalinization and $CPDG_2$ if indicated. Because prolonged, repeated dialysis sessions are often needed given the large volume of distribution of MTX, CVVH is an option when repeated IHD sessions are not logistically possible or when the patient is hemodynamically unstable. Existing data on extracorporeal MTX removal are limited by demonstrating variable degrees of MTX clearance, but are generally unable to show benefit in the patient-centered outcomes of decreased morbidity or mortality.

CVVH has previously been employed effectively in a patient with an sMTX of 2.8 µmol/L until a concentration of 0.1 µmol/L was achieved [6]. The reported CVVH clearance ranges from 21 to 25 mL/min. CVVH was used in that case after CVVHD was initially employed, but concentrations plateaued at 1.6 µmol/L, and clearance ceased [6]. The present case illustrates the potential benefits of alkalinization, hydration and administration of leucovorin and $CPDG_2$ to reduce elevated sMTX at the onset of treatment (Days 1–9 in the Figure 1). As the patient developed fluid overload and IV fluid administration was restricted, there was a significant rebound in sMTX and consequent

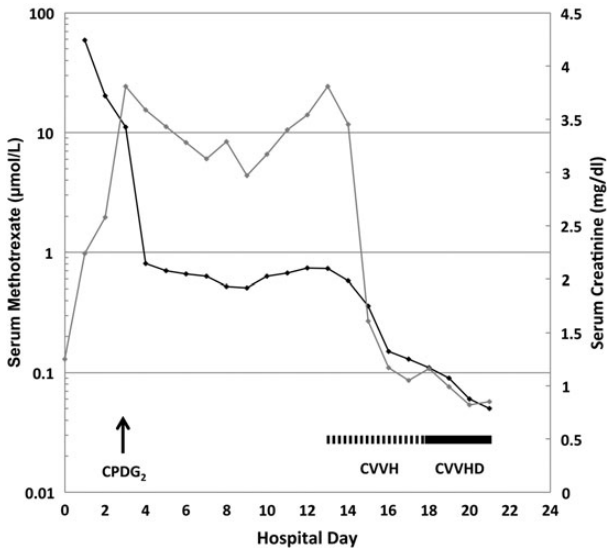

Fig. 1. Serum MTX (sMTX) concentrations (black line) trended downwards but rebounded on Day 9. This increase in sMTX concentration correlated with the worsening serum creatinine (gray line) that trended upwards starting that day. The sMTX concentrations improved following the initiation of CVVH on Day 13, and continued to improve with CVVHD initiated on Day 18. $CPDG_2$ was administered on Day 3.

deterioration of renal function. CVVH provided renal replacement and augmented MTX clearance. The effect of CVVH on this case varied depending on sMTX, with significant clearance when the concentration was high, but negligible elimination when the concentration was nearly nontoxic. One potential explanation is that low sMTX may provide an insufficient gradient for removal at the low flow rates associated with CVVH.

In summary, the initial treatment of MTX toxicity should commence early and include administration of bicarbonate, leucovorin, and, when indicated, $CPDG_2$. Renal replacement therapies may be considered for MTX toxicity, with the risks of infection and bleeding carefully weighed against the potential benefits for each individual patient. Due to the intracellular distribution of MTX, renal replacement should be a continuous modality with high blood flow rates or possibly prolonged and repeated IHD.

Conclusion

While an uncommon adjuvant treatment for MTX toxicity, CVVH may assist in MTX elimination, provide renal replacement, and potentially prevent the rebound in sMTX that follows IHD. In this case, CVVH at initiation resulted in an initial ER of 0.22 and a calculated clearance of 47.0 mL/min. The MTX clearance and ER were negligible at a sMTX of 0.15 µmol/L, suggesting the benefit of CVVH is limited to higher sMTX.

Conflict of interest statement. This case was printed in abstract form in *Clinical Toxicology* and presented as an abstract poster at the European Association of Poison Centres and Clinical Toxicologists 2013 International Conference in Copenhagen. The authors of this manuscript have no conflicts of interest to declare.

References

1. Visentin M, Zhao R, Goldman ID. The antifolates. *Hematol Oncol Clin North Am* 2012; 26: 629–648. , ix
2. Voroxaze® (glucarpidase) [prescribing information]. Brentwood, TN: BTG International Inc., 2012. http://www.accessdata.fda.gov/drugsatfda_docs/label/2012/125327lbl.pdf (1 September 2014, date last accessed)
3. Evans WE, Christensen ML. Drug interactions with methotrexate. *J Rheymatol Suppl* 1985; 12 (Suppl 12): 15–20
4. Pinedo HM, Zaharko DS, Bull JM *et al*. The reversal of methotrexate cytotoxicity to mouse bone marrow cells by leucovorin and nucleosides. *Cancer Res* 1976; 36: 4418–4424
5. Widemann BC, Balis FM, Kempf-Bielack B *et al*. High-dose methotrexate-induced nephrotoxicity in patients with osteosarcoma. *Cancer* 2004; 100: 2222–2232
6. Jambou P, Levraut J, Favier C *et al*. Removal of methotrexate by continuous venovenous hemodiafiltration. *Contrib Nephrol* 1995; 116: 48–52
7. Cavone JL, Yang D, Wang A. Glucarpidase intervention for delayed methotrexate clearance. *Ann Pharmacother* 2014; 48: 897–907
8. Grafft C, Gunderson H, Langman L *et al*. High-dose continuous venovenous hemofiltration combined with charcoal hemoperfusion for methotrexate removal. *NDT Plus* 2011; 4: 87–89
9. Bertram A, Ivanyi P, Hafer C *et al*. High cut-off dialysis as a salvage therapy option in high-dose methotrexate chemotherapy? *Ann Hematol* 2014; 93: 1053–1055

Received for publication: 24.2.14; Accepted in revised form: 15.8.14