

Technical Note

High-dose continuous venovenous hemofiltration combined with charcoal hemoperfusion for methotrexate removal

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Introduction

Methotrexate (MTX) is used to treat various disorders and can be safely administered at high doses if renal function is adequate, high urine output (UOP) is maintained, urine is alkalinized and leucovorin rescue is given. Despite those measures, toxicity (mucositis, diarrhea, renal dysfunction and myelosuppression) occurs with prolonged high serum drug concentrations [1]. Dialysis-based methods of removal are largely ineffective because MTX is highly protein bound [1]. Use of charcoal hemoperfusion has also been reported but is minimally effective. We report the first case of high-dose continuous venovenous hemofiltration (CVVH) after charcoal hemofiltration for MTX removal in a patient with toxicity following lymphoma treatment.

Case report

A 64-year-old female with diffuse large B-cell lymphoma received MTX 8 g/m² because her disease progressed despite multiple previous therapies. Although her renal and liver functions were adequate and she had received standard therapy to reduce MTX toxicity, it took 11 days for her serum MTX to reach a nontoxic level (<0.1 µmol/L). A second dose of MTX was given 30 days later. Her liver and kidney functions were again normal, and an alkaline high UOP was maintained prior to infusion to minimize toxicity. A higher than standard dose of leucovorin was also administered because of her previously prolonged serum MTX elevation. Unfortunately, 48 h after infusion, the serum MTX level was extremely high at 437.5 µmol/L. The patient developed stomatitis and thrombocytopenia, and her creatinine increased to 2 mg/dL (152.5 µmol/L) from 1.1 mg/dL (83.9 µmol/L). Besides the standard measures outlined earlier, a 4-h course of charcoal hemoperfusion was given followed by high-dose CVVH. The Prismaflex® system by Gambro was used for CVVH and run at 5 L/h (45 mL/kg/h) with half of the substitution fluid given both predilution and postdilution. The substitution fluid was high bicarbonate-containing PrismaSate® as prepackaged

by Gambro to maintain urine alkalization. To avoid alkalemia, the serum pH was monitored daily. To compensate for rapid leucovorin removal with CVVH, the patient received a 1200-mg bolus of leucovorin following charcoal hemoperfusion and a 500-mg/h maintenance infusion thereafter. The blood flow rate was 300 mL/min, and citrate was used for anticoagulation.

After hemoperfusion, the MTX level decreased to 362 µmol/L. Over the next 8 h of CVVH alone, the serum MTX level dropped to 106 µmol/L and the effluent level was 57.7 µmol/L. Because of the rapid decline in MTX with CVVH, the flow rate was increased to 7.5 L/h (67 mL/kg/h) for 24 h but was later decreased back to 5 L/h (45 mL/kg/h) because of frequent filter clotting. After ~96 h of CVVH, the MTX level was 3.55 µmol/L, but the rate of decline decreased. Another course of charcoal hemoperfusion was performed because of the decreased rate of MTX decline, but the MTX level did not decrease significantly. CVVH was reinitiated. After 7 days of CVVH, the serum MTX level decreased to 1.2 µmol/L. At that time, the effluent MTX was 0.7 µmol/L and the urinary MTX was 47.8 µmol/L. Because of the high urinary MTX as compared to the effluent, we felt that forced diuresis would be best for MTX removal and, therefore, CVVH was stopped. Her UOP increased to ~200 mL/h from 75 mL/h with diuretics. However, after CVVH discontinuation, the serum MTX increased to 1.97 µmol/L over the next 24 h.

CVVH was again reinitiated and the MTX level decreased to 0.53 µmol/L 11 days after CVVH was started. Comfort care measures were ultimately instituted because of the patient's poor prognosis from lymphoma and MTX-related complications.

Discussion

By inhibiting dihydrofolate reductase and blocking de novo nucleotide synthesis, MTX is effective at treating many conditions. Unfortunately, a high serum concentration or prolonged exposure leads to life-threatening toxicity. Toxicity depends on dose, administration schedule and

timing of leucovorin rescue. Plasma concentrations should be $<1.0 \mu\text{M}$ 48 h after high-dose infusion. Plasma concentrations $>10 \mu\text{M}$ at 48 h often leads to significant renal dysfunction and myelosuppression [1].

MTX and its metabolites are 90% renally excreted but poorly soluble at acidic pH. To enhance solubility, aggressive hydration and urine alkalinization are standard before and after high-dose infusion. Additionally, leucovorin is given, which restores the reduced folate pool and bypasses the blocked nucleotide synthesis pathway [2].

Standard therapy failed to improve MTX clearance in our case because of renal dysfunction. After prolonged and/or high-dose exposure, MTX and its metabolites precipitate in renal tubules causing direct toxicity worsening renal dysfunction and its clearance [1]. Intermittent hemodialysis, high-flux hemodialysis and peritoneal dialysis are ineffective at removing MTX because of its high protein binding (up to 80%), high volume of distribution and third-space compartment accumulation. Significant rebound of serum MTX also occurs with therapy discontinuation [1, 3, 4, 5].

Hemoperfusion has been used for MTX removal because it removes protein-bound substances from the blood [1]. The resin in the hemoperfusion cartridge has plasma proteins for drug adsorption. Unfortunately, the cartridge can become saturated and adsorption or activation of coagulation factors has been observed. Thrombocytopenia and/or leucopenia can also occur [6].

A new agent, carboxypeptidase G₂ (CPDG₂) hydrolyzes glutamate residues from natural and synthetic folate analogs like MTX. This agent rapidly degrades MTX into the inactive metabolite 2,4-diamino-*N*¹⁰-methylpteroic acid (DAMPA) [7]. In a prospective, open-label non-randomized trial, GPDG₂ was given to patients with elevated MTX levels and renal dysfunction. Serum MTX decreased up to 94%, 30 min after administration. In another study, MTX levels rapidly decreased with GPDG₂, but renal recovery and other outcomes were not improved when compared to traditional therapy [8]. Repeat dosing of CPDG₂ can be ineffective because of antibody formation; and DAMPA, the inactive metabolite of MTX, may accumulate leading to persistent renal dysfunction [7, 8]. Further study of CPDG₂ is needed.

High-flow CVVH has a theoretical advantage over intermittent hemodialysis for MTX removal because it may prevent rebound of plasma drug levels. This modality is also safe in hemodynamically unstable patients like those with life-threatening intoxications [3]. Continuous renal replacement has been used to treat lithium, carbamazepine, valproic acid, metformin, salicylate and other poisonings [3]. One case of MTX removal with continuous venovenous hemodiafiltration alone has been previously reported [9].

MTX removal with combined intermittent hemodialysis and hemoperfusion has been reported [10]. In that case, a pediatric patient with a plasma MTX level of 300–400 $\mu\text{mol/L}$ was treated with hemodialysis and hemoperfusion continuously for 16.5 h. Charcoal cartridges were replaced every 3–4 h. The MTX level decreased by 94% to 21 $\mu\text{mol/L}$ with treatment but rapidly increased after discontinuation because of rebound [10].

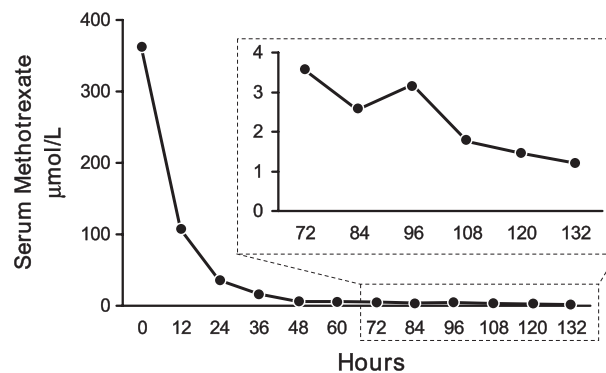


Fig. 1. Decrease in MTX over 132 h of CVVH. A 4-h course of hemoperfusion was given at Hours 1–4 and approximately Hours 96–100.

We report the use of combined charcoal hemoperfusion and CVVH for MTX removal. Although charcoal hemoperfusion has been reported to remove MTX, we did not have that experience. The decline in serum MTX was not significantly different with hemoperfusion as compared to CVVH alone (Figure 1). Specifically, after the first 12 h of treatment (the first 4 h were with hemoperfusion combined with CVVH), the MTX concentration decreased by ~75% as compared with 94% the second day of treatment without charcoal hemoperfusion. The second charcoal hemoperfusion treatment was also ineffective.

As the serum MTX level decreased, it appeared that the removal rate decreased. The dramatic decline in MTX initially may have resulted from saturated protein-binding sites leaving a high proportion of free MTX easily removed with hemofiltration. It is unclear why hemoperfusion was relatively ineffective in our case. Perhaps after starting treatment, the largest proportion of serum MTX was nonprotein bound or the high MTX serum concentration quickly saturated the charcoal cartridge leaving it ineffective.

After prolonged therapy, it seemed that minimal MTX was removed because the serum level did not significantly change. However, CVVH appeared useful because MTX was consistently in the effluent, and third-space compartments served as a constant reservoir. Furthermore, there was minimal rebound in serum MTX after CVVH discontinuation.

If CVVH is used for MTX removal, high doses of leucovorin are needed to compensate for its rapid removal, and a high bicarbonate bath is needed for urine alkalinization. Experienced nursing and dialysis staff are essential for timely treatment and for troubleshooting problems with the CVVH machine.

Despite rapid MTX removal with CVVH in our patient, the extremely high initial MTX level most likely caused irreversible damage. Although, our patient succumbed to lymphoma and MTX toxicity, high-dose CVVH was effective at removing high levels of MTX without significant complication. Our patient remained hemodynamically stable and maintained a high UOP further facilitating MTX removal.

Conflict of interest statement. None declared.

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