

SHORT COMMUNICATION

Successful Elimination of Methotrexate by Continuous Veno-venous Haemofiltration in a Psoriatic Patient with Methotrexate Intoxication

Chien-Chih Wu^{1#}, Chih-Fen Huang^{1,2#}, Li-Jiuan Shen¹⁻³ and Fe-Lin Lin Wu^{1-3*}¹Department of Pharmacy, National Taiwan University Hospital, College of Medicine, National Taiwan University; ²School of Pharmacy, and ³Graduate Institute of Clinical Pharmacy, College of Medicine, National Taiwan University, 33 Linsen South Road, Taipei 10050, Taiwan. *E-mail: fhwu@ntu.edu.tw These authors contributed equally and should be considered as first authors.

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Methotrexate (MTX) is a folate antagonist with cytotoxic and immunosuppressant activity. Low-dose MTX is widely used for psoriasis and usually does not cause severe toxicities unless patient's renal function is poor. MTX is mainly excreted by glomerular filtration and tubular secretion. If renal function deteriorates, MTX will accumulate in the body and cause toxicity (1, 2). Glucarpidase, a carboxypeptidase G2, can rapidly reduce MTX concentrations independent of renal function, but it is not available in every country (3). High-flux haemodialysis (HD) can remove MTX successfully in patients receiving high-dose MTX (4). Although MTX has a high clearance rate during HD, it is difficult to use HD in patients with unstable haemodynamic. We reported a case with unstable vital sign who received continuous veno-venous haemofiltration (CVVH) to treat MTX intoxication.

CASE REPORT

A 48-year-old man had hypertension, diabetes mellitus, chronic kidney disease and psoriasis for many years, and medications were used chronically for underlying disease. Psoriasis was diagnosed at the age 35, and was treated with topical corticosteroids and oral acitretin initially. Due to the exacerbation of psoriasis, he started oral MTX 7.5 mg every week. Serum creatinine (S_{Cr}) was 1.8 mg/dl at that time. The patient chose to discontinue the medication and was lost to follow-up thereafter due to clinically significant improvement. However, generalised itchiness gradu-

ally developed after MTX discontinuation and he visit our clinic again. This time, the physician prescribed 10 mg MTX weekly. Generalised itching with erythema and diarrhoea developed 2 days after the first dose of MTX. He took another dose one week later and oral erosions and ulcers were noticed the following day. He came to our clinic immediately and MTX intoxication was suspected. Blood examination on the same day revealed leucopenia, hypoalbuminaemia and renal failure (S_{Cr} : 6.2 mg/dl). Decreased urine output, poor oral intake and severe diarrhoea were also noticed. His vital signs were normal except for tachycardia. MTX plasma concentration on admission (about 48 h after the last dose of MTX) was 0.14 $\mu\text{mol/l}$. Leucovorin injection and hydration with urine alkalisation was given immediately. The next day, the lab data revealed pancytopenia and further deteriorated renal function (S_{Cr} : 7.9 mg/dl). Granulocyte-colony stimulating factor and famotidine were given for leucopenia and anaemia. However, shock occurred later. Lab data still showed leucopenia, deteriorated renal function (S_{Cr} : 8.7 mg/dl) and high MTX levels (0.15 $\mu\text{mol/l}$). In addition, respiratory distress occurred, and he was intubated with mechanical ventilator support. After transfer to the intensive care unit, antibiotics were used for febrile neutropaenia. *Pseudomonas aeruginosa* was found in blood culture. Due to shock and MTX intoxication, emergency CVVH was applied. The haemofilter was Gambro HF-1400 with polyarylethersulphone hollow fibre and a surface area of 1.4 m². The ultrafiltration rate and blood pump flow rate of CVVH were 35 ml/kg/h and 150 ml/min, respectively. After CVVH, MTX level declined gradually (Fig. 1), and leucopenia recovered 6 days after admission. However, ST elevation myocardial injury and ventricular arrhythmia (VT) occurred during the intensive care treatment. His family refused further aggressive treatment and inquired palliative care. Eventually, the patient passed away after a VT episode.

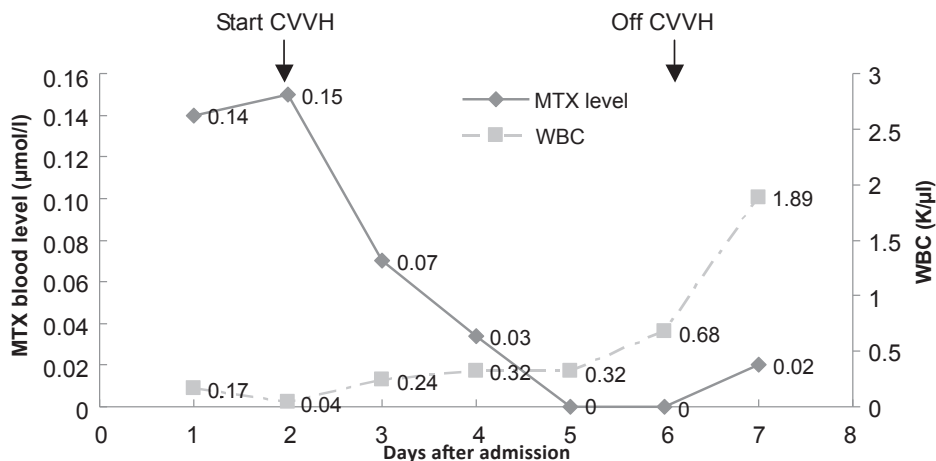


Fig. 1. Methotrexate (MTX) serum concentration and white blood cell (WBC) count before and after a continuous veno-venous haemofiltration (CVVH) use. A gradual reduction in serum MTX concentrations and recovery of WBC count was observed after CVVH use. After discontinuing CVVH, a rebound of MTX levels were observed.

DISCUSSION

The severity of MTX toxicity is related to the duration of exposure to high MTX concentrations. The MTX levels should be lower than 5, 0.1 and 0.05 $\mu\text{mol/l}$ at 24, 48 and 72 h after MTX intake, respectively. In this case, the MTX levels were 0.14 $\mu\text{mol/l}$ at 48 h. Although leucovorin rescue, hydration and urine alkalinisation were applied, MTX toxicities still exacerbated. Glucarpidase was not available (3). Extracorporeal removal, such as HD, continuous renal replacement therapy (CRRT) and haemoperfusion, is another way to remove MTX. CRRT includes 3 primary variants: CVVH, continuous venovenous haemodialysis (CVV-HD), and continuous venovenous haemodiafiltration (CVVHDF). Haemoperfusion is usually used for highly protein bound molecules (5). Haemodialysis and haemofiltration utilise diffusion and convection, respectively, to remove solute (6). Diffusion methods are usually more effective in removal of substances than convection. Therefore, dialysis should be the first choice to remove toxic substances. CRRT can remove larger molecules (20,000 Dalton) than high flux HD (up to 1000 Dalton) (7). However, high flux HD is more effective than CRRT because of higher blood and dialysate flow rate. Other determinants include blood flow rate, protein binding, properties of the membrane and volume of distribution (V_d) of solute (7). A solute with smaller molecular weight, lower V_d ($\leq 0.7\text{l/kg}$) and protein binding ($< 80\%$) is easier to remove by HD and CRRT (6). The physicochemical characteristics of MTX, including a molecular weight of 454 Dalton, a V_d of 0.4–0.8 l/kg, and a plasma protein binding of 50% at therapeutic plasma concentration, make its extracorporeal removal possible (8). The success of high flux HD and haemoperfusion to treat MTX intoxication has been published (4, 9). Three case reports showed that CRRT could help eliminating MTX (10–12). All these cases received high dose MTX for malignancy (10–12). This is the first report to treat low dose MTX-related toxicity by CVVH. Although the MTX levels in our patient were much lower than other cases, it still caused serious toxicity and resulted in death. This suggests that MTX toxicities are related to exposure time of high drug levels rather than the magnitude of peak drug levels (13).

Because of profound hypotension (despite the use of high dose inotropic agents), our patient received CVVH rather than HD. The $t_{1/2}$ of low dose MTX in patients with severe renal insufficiency without dialysis is around 42 h (14). In our patient, MTX was eliminated very slowly when CVVH was not used in this case (Fig. 1). The MTX levels were below toxic levels 3 days after CVVH use and leucopaenia gradually recovered after MTX removal. A rebound of MTX levels when CVVH was discontinued was observed, which was also found in the 3 cases mentioned above (10–12). This

phenomenon may be caused by redistribution of tissue MTX. Monitoring MTX levels for another several days is recommended to ensure that MTX levels are not within toxic range after CVVH is stopped.

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