

CASE REPORT

Co-administration of High-Dose Methotrexate with a Proton Pump Inhibitor in Primary Central Nervous System Lymphoma with Recent Upper Gastrointestinal Bleed: A Case Report and Literature Review.

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DOI: <https://doi.org/10.70672/w2763k67>

Received: 11/06/2026; Revised: 07/10/2026; Accepted: 10/10/26; Published online: 01/11/2026.

Abstract

Concomitant use of interacting drugs with high-dose methotrexate (HD-MTX) may cause delay in methotrexate (MTX) clearance. Prolonged exposure to toxic MTX concentrations increases the risk of adverse events. A 28-year-old man with primary central nervous system lymphoma and recent upper gastrointestinal bleed received HD-MTX (2,500 mg/m²) as part of the DeAngelis protocol. Early intervention by discontinuing a precipitating drug (piperacillin-tazobactam) and substituting it with cefepime minimised the risk of delayed clearance. Serum MTX monitoring at 24 hours was performed for early optimisation of leucovorin rescue dose. In cycle 1, serum MTX was 3.6 µmol/L at 24 hours, <0.3 µmol/L at 48 hours, and <0.3 µmol/L at 72 hours; in cycle 2, it was 1.5 µmol/L, 0.5 µmol/L, and <0.3 µmol/L, respectively. The 72-hour result was below the reportable limit of the assay (0.3 µmol/L), so the target of <0.1 µmol/L could not be verified. No MTX toxicity of Common Terminology Criteria for Adverse Events (CTCAE) grade 3 or above was documented. Several studies report a significant drug-drug interaction between MTX and proton pump inhibitors. However, this single case does not establish the safety of co-administration. The outcome may reflect preserved renal function, hydration, urine alkalisation, leucovorin rescue, and close monitoring rather than the absence of interaction. When concurrent administration is considered necessary, earlier preventive strategies and monitoring may be instituted for early detection of delayed MTX clearance.

Keywords: Clearance, drug-drug interaction, gastrointestinal bleed, methotrexate, proton pump inhibitor, toxicity.



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Introduction

Methotrexate (MTX) is an antifolate agent used in various autoimmune diseases and cancers. High-dose methotrexate (HD-MTX) with doses of $> 500\text{mg/m}^2$ was used in some protocols of haematological cancers. Crystallisation of MTX parent drug and its metabolite within renal tubules may cause acute kidney injury (AKI), which subsequently causes delay in MTX clearance. Prolonged exposure to toxic MTX concentrations increases the risk of adverse events [1, 2].

Toxicity related to HD-MTX is severe and life-threatening. AKI may exacerbate adverse events such as myelosuppression, mucositis, dermatologic toxicity, neurotoxicity and hepatotoxicity, these events may lead to multiorgan failure. Supportive measures such as urine alkalinization, adequate hydration, and administration of leucovorin rescue as per protocol have been practised to minimise these events. Scheduled serum concentrations at 24 hours, 48 hours, and 72 hours after starting MTX infusion are crucial for optimising the leucovorin dose [2].

In addition to these preventive measures, assessment of possible risk factors for developing delayed MTX clearance is warranted prior to initiation of HD-MTX. Nephrotoxic drugs and drugs that reduce renal excretion should be avoided. Concomitant use of drugs that hypothetically cause delay in MTX clearance, such as tyrosine kinase inhibitors and proton pump inhibitors (PPIs); should be used with caution. Acidic beverages such as fruit juices and carbonated drinks may acidify the urine, promoting crystal formation in renal tubules [1]. Continuation of a potentially interacting medication is warranted only if the benefit outweighs the risk or no other alternatives are available.

Several drug-drug interactions (DDIs) that needs to be considered when high-dose MTX is planned. These include non-steroidal anti-inflammatory drugs (NSAIDs), penicillin antibiotics, salicylates, trimethoprim-sulfamethoxazole (TMP-SMX), nephrotoxic drugs such as aminoglycosides and

amphotericin B, PPIs, and p-glycoprotein inhibitors [2]. Each of the drugs that potentially interact with MTX has a different mechanism of interaction. In this review, we focus on the drug-drug interaction (DDI) between MTX and PPIs.

The proposed mechanism of interaction is through inhibition of renal H^+/K^+ -ATPase by the PPI. This pump enzyme is involved in the tubular secretion of MTX; therefore, inhibition of this pump may cause a delay in MTX elimination [3]. In this case, PPI was administered at a higher dose than usual dose for stress ulcer prophylaxis due to upper gastrointestinal bleed (UGIB). Mechanistically, a higher dose of PPI may pose a higher risk of delayed MTX clearance, postulated by enhancing the likelihood of covalent bond formation between PPI and H^+/K^+ -ATPase. Pharmacodynamically, the inhibitory activity of H^+/K^+ -ATPase depends on several factors, including accumulation of PPI in the parietal cells or renal tubule, the proportion and synthesis of the pump enzyme, and the stability of covalent binding between the PPI and the pump [4].

This case report describes the co-administration of HD-MTX with a PPI in primary central nervous system lymphoma with recent UGIB and reviews the existing literature on this interaction.

Case presentation

A 28-year-old Malay man with underlying diabetes mellitus initially presented to a primary health clinic with shortness of breath and coffee-ground vomiting for one day. The symptoms were preceded by lethargy and reduced oral intake for a week. He denied any symptoms of abdominal pain, upper respiratory tract infection, or urinary tract infection. He had underlying diabetes mellitus and had defaulted to clinic follow-up for 3 years. He had also been investigated for a brain tumour 3 months ago, with a history of recent occipital craniectomy and tumour debulking surgery for the past 2 months. A biopsy of the occipital region showed diffuse large B-cell lymphoma of the central nervous system (CNS).

His past medication history includes dexamethasone 2 milligrams (mg) daily (q.d.) for the past 2 months, pantoprazole 40 mg q.d., and levetiracetam 1 gram (g) twice daily (b.i.d.).

Upon examination, the patient had tachypnoea and tachycardia, with a heart rate of 138 beats per minute and a respiratory rate of 36 breaths per minute. Glasgow Coma Scale was 14/15 and blood sugar reading was high, out of detection range. Rapid-acting insulin was given twice with ongoing intravenous fluid to correct the hyperglycaemia. He was subsequently referred to a tertiary care hospital. Upon arrival at the emergency department, the patient was alert, tachypnoeic, and tachycardic with persistent hyperglycaemia. Cardiovascular examination was unremarkable. Blood pressure was normal, and oxygen saturation was 99% under room air. However, fresh melaena was noted during a rectal examination. Bedside ultrasound showed a kissing sign on the inferior vena cava. Arterial blood gases (ABG) showed evidence of severe metabolic acidosis, and the patient was then intubated given impending respiratory collapse. Echocardiogram showed sinus tachycardia, chest X-ray was clear, and no cardiomegaly was seen. Full blood count showed total white blood cell (TWBC) of 23×10^9 /L, haemoglobin (Hb) of 14 g/dL, and platelet of 473×10^9 /L. Subsequent ABG showed resolving metabolic acidosis. The patient was diagnosed with diabetic ketoacidosis (DKA) and possible steroid-induced UGIB. A total of 4 litres of fluid was given in the emergency department (ED). He was admitted to the intensive care unit (ICU) for further monitoring and stabilisation. Intravenous pantoprazole 8 mg per hour was started for his UGIB. Oesophagogastroduodenoscopy (OGDS) revealed Forrest 2C ulcer at the prepyloric region with UGIB. Pantoprazole infusion was continued for 72 hours, then changed to 40 mg b.i.d. At that point, he had no more melaena or coffee-ground aspirate. The DKA was resolved with fixed-dose insulin and fluid therapy. Patient was stabilised after day 4 of ICU admission and transferred out to the haematology unit for the management of

primary central nervous system lymphoma (PCNSL). The baseline estimated glomerular filtration rate (EGFR) was 109 mL/min/1.73 m². He was planned for DeAngelis protocol, which consists of HD-MTX 2,500 mg/m² on odd weeks alternating with intrathecal MTX 15 mg on even weeks, cytarabine 3,000 mg/m² on weeks 16 and 19, dexamethasone tapering dose over 6 weeks, and procarbazine 150 mg/m² on weeks 1, 5, and 9. Urine alkalinisation commenced with 100 milliequivalents per litre (mEq/L) of sodium bicarbonate with a maintenance fluid of 3 litres per day. Apart from that, oral sodium bicarbonate 2.52 g four times daily (q.i.d.) was given to enhance urinary alkalinisation. Upon clinical pharmacist review, it was noted that piperacillin-tazobactam was onboard for hospital-acquired infection. Co-administration of piperacillin-tazobactam with HD-MTX may cause delayed MTX clearance, which will be discussed further. After discussion with the specialist, piperacillin-tazobactam was substituted with cefepime. Another potential drug-drug interaction (DDI) was identified between MTX and pantoprazole; however, the patient had just recovered from UGIB, and there were no alternatives available to manage his current condition; hence pantoprazole was continued. After urine pH reached 8, the DeAngelis protocol was carefully commenced with pantoprazole onboard. The HD-MTX was diluted in 500 mL dextrose 5% and infused over 3 hours. Given the anticipation of delayed MTX due to DDI, clinical pharmacokinetic monitoring for MTX was done earlier; 24-hour monitoring was performed besides the routine monitoring of 48- and 72-hour serum MTX concentrations. In addition, leucovorin dose optimisation was planned; from 20 mg q.i.d to 50 mg q.i.d. at 24 hours of starting MTX for 4 doses, followed by 25 mg q.i.d. The DeAngelis protocol was administered, and the patient tolerated the chemotherapy infusions. Pre-chemotherapy TWBC was 5.26×10^9 /L, Hb 10.3 g/dL, platelet 300×10^9 /L, and absolute neutrophil count (ANC) of 5.26×10^9 /L.

Serum 24-hour MTX was 3.6 micromoles per litre ($\mu\text{mol/L}$), which was below the toxic range (target $<10 \mu\text{mol/L}$). Leucovorin rescue was initiated at 24-hour MTX, and urine alkalinisation was continued until the subsequent MTX concentrations were obtained. Otherwise, the patient was stable and well on subsequent days of admission. Serum MTX monitoring at 48 and 72 hours were $<0.3 \mu\text{mol/L}$, below the linearity range (target <1 and $<0.1 \mu\text{mol/L}$ for 48 and 72 hours, respectively). The patient was discharged after completing week 2 of the DeAngelis. eGFR was normal throughout admission; the rate upon discharge was $126 \text{ mL/min/1.73 m}^2$.

On week 3 of the DeAngelis protocol, the patient was scheduled for another round of HD-MTX infusion. It was noted that tablet pantoprazole was tapered down to 40 mg q.d upon his last discharge. HD-MTX commenced with pantoprazole onboard. Urine alkalinisation strategy and serum concentration monitoring were similarly done as the previous admission. Pre-chemotherapy TWBC was $6.05 \times 10^9/\text{L}$, Hb 9.9 g/dL, platelet $106 \times 10^9/\text{L}$, and absolute neutrophil count (ANC) of $5.13 \times 10^9/\text{L}$. Serum 24-hour concentration was $1.5 \mu\text{mol/L}$, while 48- and 72-hour concentrations were 0.5 and $<0.3 \mu\text{mol/L}$, respectively. His blood sugar control was improving since the steroid was tapered down. Patient was safely discharged from the ward on day 7 of admission.

Discussion

This case report highlighted the intervention strategies in managing HD-MTX administration in the presence of DDI, whereby in this case, discontinuation of drug is not possible due to the underlying condition. Several reports found significant DDI between MTX and proton pump inhibitors (PPIs). Table 1 shows a summary of reported studies on such interaction. The first case was reported in 1993 [3], followed by other studies [5, 9]. Two cases reported pancytopenia after concurrent administration of omeprazole and low-dose MTX [10]. In a retrospective study, co-administration of PPI was identified as a risk

factor for delayed MTX elimination [11]. In addition, population pharmacokinetics study showed that the use of PPI significantly increases the 24-hour and 48-hour plasma MTX concentrations, with a 27% reduction in MTX clearance [12]. A systematic review and meta-analysis also similarly reported such a DDI, as summarised in Table 1 [8].

In contrast, some studies did not find the PPI as a significant risk factor for delayed MTX clearance. A study by Wang et al. showed that co-administration of PPI was associated with elevated peak MTX concentrations at 4 hours, however, there was no association found between PPI and elevated 24-hour concentrations when given with adequate supportive therapy [8].

The DDI between piperacillin-tazobactam and MTX was reported in several articles. A case report showed an elevated 24-hour serum MTX concentration when piperacillin-tazobactam was co-administered, leading to renal failure and reversible neurotoxicity [13]. Another case reported demonstrated prolonged toxic concentrations of MTX when co-administered with piperacillin-tazobactam, suggesting a pharmacokinetic interaction between these two drugs. This effect was seen when the authors plotted a graph of serum MTX concentrations with and without piperacillin-tazobactam, and the drug clearance of MTX was only 3% of normal clearance in the presence of piperacillin-tazobactam [14]. In this case, the antibiotic was switched to cefepime, as it has low potential for DDI with MTX. Cefepime primarily utilises organic cation transport N2 for tubular secretion, which differs from MTX tubular secretion pathways [15].

It was noted that levetiracetam was continued throughout MTX administration. A case report demonstrated a delay in MTX clearance after the patient started with levetiracetam from his second cycle of chemotherapy [16]. However, a retrospective review among 430 patients found no significant association between concomitant levetiracetam with delayed MTX clearance and acute kidney injury (AKI) [17]. The proposed

mechanism for this interaction is also unknown; hence, the recommendation was to continue levetiracetam based on the latest evidence.

Besides hyperhydration and leucovorin administration, there are two other treatment options to manage MTX toxicity: glucarpidase and high-flux haemodialysis. Glucarpidase is a synthetic enzyme that breaks down MTX molecules into inactive byproducts, which are 4-deoxy-4-amino-N10-methylpteroic acid (DAMPA) and glutamic acid. A pooled analysis of observational studies showed that glucarpidase may be beneficial when administered within 96 hours of MTX administration [18]. On the other hand, haemodialysis is a less effective option for MTX toxicity [19]. MTX has approximately 50% protein-binding capacity and a relatively high volume of distribution, hence, the strategy of high-flux dialysis may be suboptimal to manage toxic MTX concentrations [20].

The strategy to monitor serum 24-hour MTX concentration was implemented to address potential delayed MTX clearance in this case report. The justification for 24-hour serum concentration monitoring was based on a study that demonstrated the steady-state of MTX was 24 hours, regardless of infusion time. The study concluded that longer infusion time may lead to a longer drug exposure, which is beneficial for systemic cancer such as leukaemia [21]. For localised tumour such as PCNSL and osteosarcoma, shorter infusion may be a useful strategy, to minimise systemic adverse effects.

This case has several limitations. First, the 72-hour MTX level was below the assay's reportable limit (0.3 $\mu\text{mol/L}$), so the target of $<0.1 \mu\text{mol/L}$ could not be verified. This prevents definitive exclusion of delayed clearance. Second, the outcome may reflect preserved renal function, hydration, urine alkalinisation, leucovorin rescue, and close monitoring rather than the absence of interaction. Third, piperacillin-tazobactam was simultaneously substituted with cefepime, so the outcome cannot be attributed to PPI alone. Fourth, there was no cycle without PPI for comparison.

Finally, this is a single patient, and the findings cannot be generalised.

Switching to an H2-receptor antagonist without MTX toxicity has been described in case reports [2]; hence, this option may be considered in other patients.

Conclusion

In this case, MTX concentration was below the toxic range at 24 hours and below 0.3 $\mu\text{mol/L}$ at 48 and 72 hours with pantoprazole onboard. This single case does not establish the safety of co-administration of MTX and PPI. Co-administration is generally not advisable; however, in certain cases when concurrent administration is considered necessary due to underlying disease such as UGIB, earlier preventive strategies and monitoring may be instituted for early detection of delayed MTX clearance and to reduce the risk of MTX toxicity. Regular monitoring of 24-hour serum MTX concentrations may be instituted for suspected cases of delayed MTX clearance. Further exploration on the alternatives of PPI during MTX therapy is warranted.

Consent: Verbal consent was obtained from the patient for publication of this case report.

Conflict of interest

The authors declare that there are no competing interests involved.

Acknowledgement

We would like to thank the Director General of Health, Malaysia for his permission to publish this article, and it is registered under the National Medical Research Register in Malaysia with NMRR ID-24-02700-ELU.

Authors' contributions

The authors' contributions are as follows: MNY: Conceptualisation, case discussion, and final editing. SNNAJ: Literature review and discussions. ANK: Final review of manuscript as an expert panel.

Table 1. Summary of evidence on the drug-drug interaction between MTX and PPI.

Author, year	Type of study	Medical condition	Findings
May et al. 2014 [5]	Retrospective analysis	Lymphoma, sarcoma, breast carcinoma	Older age, male sex, decreased baseline CrCl, and increased PPI use were identified as risk factors of delayed MTX elimination.
Hall et al. 2017 [6]	Narrative review	Cutaneous T-cell lymphoma, RA	No clinically meaningful pharmacokinetic interaction was identified between low-dose MTX and PPI.
Steward et al. 2017 [7]	Retrospective cohort	CNS lymphoma	PPI were the most commonly co-administered. Grade ≥ 3 AKI following high-dose MTX was associated with prolonged hospital stay and reduced chemotherapy intensity.
Wang X et al. 2020 [8]	Systematic review and meta-analysis	ALL, chronic EBV, H&N cancer, NHL, osteosarcoma, plasmacytoma	Co-administration of PPI and MTX was associated with delayed high-dose MTX elimination.
Wang SF et al. 2023 [9]	Retrospective cohort	Osteosarcoma	Co-administration of MTX with PPIs, TMP-SMX, or NSAIDs may have limited effects on acute hepatotoxicity in patients receiving adequate supportive measures.

Abbreviations: AKI, acute kidney injury; ALL, acute lymphoblastic leukaemia; CNS, central nervous system; CrCl, creatinine clearance; EBV, Epstein-Barr virus; H&N, head & neck; MTX, methotrexate; NHL, non-Hodgkin's Lymphoma; NSAIDs, non-steroidal anti-inflammatory drugs; PPI, proton pump inhibitor; RA, rheumatoid arthritis; TMP-SMX, trimethoprim-sulfamethoxazole.

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