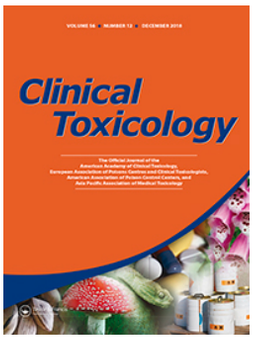

Clinical Toxicology

ISSN: 1556-3650 (Print) 1556-9519 (Online) Journal homepage: https://www.tandfonline.com/loi/ictx20

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To cite this article: Katherine Z. Isoardi, Keith Harris, Kate E. Carmichael, Goce Dimeski, Betty S. H. Chan & Colin B. Page (2018) Acute bone marrow suppression and gastrointestinal toxicity following acute oral methotrexate overdose, Clinical Toxicology, 56:12, 1204-1206, DOI: 10.1080/15563650.2018.1484128

To link to this article: https://doi.org/10.1080/15563650.2018.1484128

Published online: 05 Jul 2018.

CLINICAL TOXICOLOGY
2018, VOL. 56, NO. 12, 1204–1206
https://doi.org/10.1080/15563650.2018.1484128

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SHORT COMMUNICATION

Acute bone marrow suppression and gastrointestinal toxicity following acute oral methotrexate overdose

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ABSTRACT

Objective: Acute methotrexate overdose rarely causes systemic toxicity due to saturable absorption and rapid renal elimination. We present a case of methotrexate toxicity following acute overdose.

Case Report: A 56-year-old female presented soon after an overdose of 1250 mg of methotrexate, zopiclone and tramadol. The methotrexate was initially under-reported (500 mg) and folinic acid was not provided. Despite normal renal function, the patient developed toxicity. She represented 5 days following the overdose with mucositis, bone marrow suppression and prolonged febrile neutropenia. Treatment included folinic acid, broad-spectrum antibiotics, filgrastim, red cell and platelet transfusion. Her bone marrow began to recover 12 days following the overdose. She was discharged home on Day 17.

Discussion: Severe toxicity following an acute ingestion of a large amount of methotrexate is rarely reported. The development of toxicity was unexpected in this case given methotrexate's pharmacokinetics and the patient's normal renal function. The serum methotrexate concentrations were below the treatment threshold of the folinic acid rescue therapy nomogram suggesting that the nomogram should not be relied on in acute ingestions. Large acute oral methotrexate poisoning can result in systemic toxicity and folinic acid therapy should be provided in ingestions >1000 mg.

ARTICLE HISTORY
Received 11 April 2018
Revised 25 May 2018
Accepted 30 May 2018
Published online 4 July 2018

KEYWORDS
Methotrexate; folinic acid; toxicity

Introduction

Toxicity following an acute ingestion of a large amount of methotrexate is unlikely due to saturable gastrointestinal absorption and rapid renal elimination [1]. The oral bioavailability of methotrexate is saturable as its absorption is dependent on an active transporter to enter cells, folate carrier-1 protein [1]. Folinic acid competes with methotrexate for this transporter. Methotrexate is rapidly excreted by the kidneys through glomerular filtration and active tubular secretion with a median clearance of 100 mL/min/m^2 body surface area (BSA) [2]. Methotrexate concentrations are often undetectable within 24 h post-ingestion [3].

In an acute ingestion of <1000 mg of methotrexate the bioavailable dose is estimated to be well below the 1 g/m^2 BSA threshold for folinic acid rescue therapy used in oncology [3]. No cases of severe toxicity following acute methotrexate overdose have been reported and no specific treatment is usually required [3]. Antidote treatment with folinic acid is recommended in patients with renal impairment and in large overdoses >1000 mg (>5 mg/kg in children) [1]. Taking a serum methotrexate level to guide folinic acid therapy in these patients is also suggested [1].

Case report

A 56-year-old female, weighing 84 kg with an estimated BSA of 1.91 m^2, presented 1 h following a deliberate polypharmacy overdose. The initial risk assessment, made only from empty pill packets brought in by paramedics, was of an ingestion of 10 tablets of zopiclone 7.5 mg, 50 tablets of methotrexate 10 mg and six tablets of tramadol SR 50 mg. The patient regularly takes 30 mg of methotrexate weekly for rheumatoid arthritis.

On arrival to the Emergency Department, she was sedated with a Glasgow Coma Score (GCS) of 8 (E1V2M5) and mildly hypoxic with oxygen saturations of 91% on room air. Other bedside observations were normal. She had clinical signs consistent with an aspiration pneumonitis. A full blood count (FBC) revealed a haemoglobin (Hb) of 12.3 g/dL [reference range (RR 11.5–16.0), white blood cell (WBC) count of 14.9×10^9/L (RR 4.0–11.0) and platelets of 317×10^9/L (RR 140–400)]. Her liver function tests were normal, as was her renal function with a creatinine of 64 μmol/L (RR 45–90). A chest X-ray confirmed aspiration. Because her initial risk assessment suggested a non-toxic methotrexate ingestion, she was managed with supportive care. Her GCS and oxygen saturations normalised and she was discharged home 44 h

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following presentation. Unfortunately her risk assessment was not confirmed once her consciousness improved during the initial presentation.

On Day 5 post-ingestion, she represented with abdominal pain, diarrhoea and mucosal ulcerations. Her temperature was 37.7 °C with otherwise normal bedside observations including an oxygen saturation of 97% on room air. There were no clinical signs of dehydration. A FBC confirmed a new anemia (Hb 11.0 g/dL) and a WBC of 1.1×10^9/L with a neutrophil count of 0.60×10^9/L (RR 2.00–8.00). Liver enzymes were mildly elevated with a bilirubin of 30 μmol/L (RR < 20), alkaline phosphatase of 184 U/L (RR 30–110), γ-glutamyl transferase of 176 U/L (RR < 38), alanine aminotransferase 54 U/L (RR < 34), aspartate aminotransferase 39 U/L (RR < 31) and lactate dehydrogenase of 500 U/L (RR 120–250). Renal function was unchanged. She was commenced on 15 mg of intravenous (IV) folinic acid sixth hourly for presumed methotrexate toxicity. On repeat questioning, the patient admitted to taking a single ingestion of 125 tablets of methotrexate 10 mg (1250 mg) 1 h prior to the initial presentation. When specifically questioned, she denied taking a staggered ingestion.

Over subsequent days she developed worsening bone marrow suppression with a nadir 10–12 days following the overdose consisting of a Hb of 7.5 g/dL, WBC count of 0.7×10^9/L, neutrophils of 0.01×10^9/L and platelets of 3×10^9/L (Figure 1). She developed a fever on Day 6 and was commenced on piperacillin–tazobactam and gentamicin which was later augmented with valaciclovir and fluconazole following consultation with the haematology service. She received daily filgrastim (human granulocyte colony stimulating factor) until her neutrophil count was above 0.5×10^9/L. She also received platelet and red cell transfusions on Days 11 and 12, respectively. Her platelet and WBC counts began to recover 12 days post-overdose with red cell recovery by Day 15. She was discharged home on Day 17.

Retrospective methotrexate levels were added on to the available serums from the original presentation yielding levels of 1.6 μmol/L and 0.50 μmol/L at 10 and 15 h following the ingestion, respectively. Both these concentrations are below the nomogram line (Figure 2) for folinic acid rescue therapy used in oncology following high dose IV methotrexate administration [4]. The methotrexate concentration was <0.01 μmol/L on representation to hospital (140 h post-ingestion).

Discussion

Severe poisoning following an acute oral overdose of methotrexate is rarely reported. There is limited published data regarding acute oral methotrexate overdose, and, in particular, there are no reported ingestions of >1000 mg. The dose of the original ingestion was under-reported in this case. The patient would have received folinic acid therapy had the

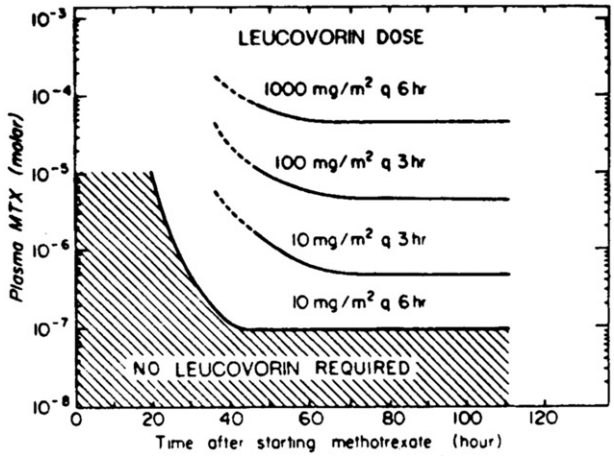

Figure 2. Folinic acid rescue nomogram [4].

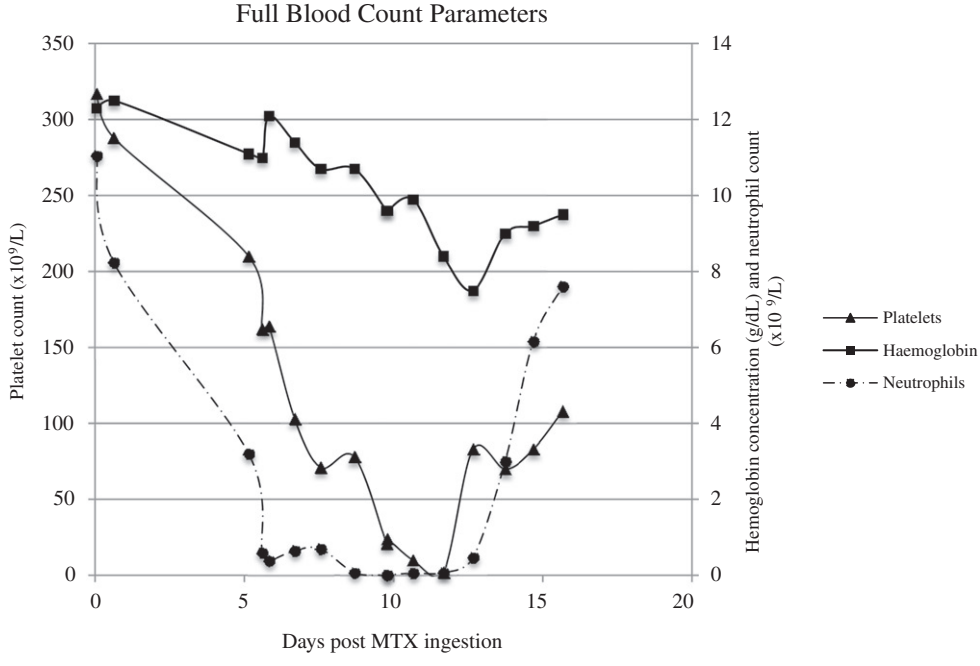

Figure 1. Time chart of full blood count results during admission to hospital.

actual dose of 1250 mg been known, as our threshold for treatment with folinic acid is >1000 mg in adults [1]. In large acute ingestions, oral folinic acid may be given for 24 h to reduce absorption as it shares the same transport system as methotrexate. Folinic acid also bypasses the effects of methotrexate on dihydrofolate reductase by providing reduced folate. It is cheap and simple to administer. Even so, the development of toxicity was unexpected in this case for a number of reasons. Firstly, the patient had normal renal function. Furthermore, this was a single, not a staggered, ingestion. Lastly, the dose ingested was calculated to be 0.65 g/m^2, which is below the 1 g/m^2 BSA threshold used for folinic acid therapy in oncological practice.

Plotting the serum methotrexate concentrations in this case on the folinic acid rescue nomogram did not identify the potential for toxicity. The nomogram was developed to guide folinic acid rescue therapy in patients receiving high dose IV methotrexate therapy [5]. In a Poisons Information Centre study of 36 patients who deliberately took an overdose of methotrexate (dose ranging from 40 to 1000 mg), none developed severe toxicity. Serum methotrexate concentrations measured in 19 patients were all below the folinic acid rescue nomogram [3]. Our case suggests that serum methotrexate concentrations should not be used to guide the provision of folinic acid therapy in acute poisoning.

Methotrexate toxicity correlates better with the duration of the exposure rather than peak concentration [3] which may explain the development of toxicity in this case. Unfortunately, serum samples beyond 24 h were not taken during the initial presentation to confirm a prolonged exposure. Methotrexate pharmacogenomics may have also contributed to toxicity in this case. There are a number of single nucleotide polymorphisms in the intracellular methotrexate pathway that influence inter-individual differences in toxicity [6]. Many of these polymorphisms are specific to patients with rheumatoid arthritis [6].

Development of toxicity in this overdose supports the recommendation to provide oral folinic acid for 24 h in large overdoses >1000 mg, even in patients with normal renal function [1]. The folinic acid rescue nomogram would not have predicted toxicity in this case of acute overdose.

Disclosure statement

No potential conflict of interest was reported by the authors.

Funding

CB Page is supported by a research fellowship from the Queensland Emergency Medicine Research Foundation.

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