Accidental Methotrexate Overdose: A Case Series

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Abstract

Methotrexate is a commonly prescribed medication in clinical practice. Many dermatologists, rheumatologists and oncologists prescribe this medication. However, due to a lack of understanding of patients or in the hope of early relief of symptoms, patients tend to use higher and more frequent doses than recommended resulting in several side effects. In this case series, we report five cases of methotrexate toxicity due to accidental and over jealous use prescribed for underlying disorders. All presented with fever, skin and mucosal lesions. All the patients had deranged hematological parameters. This article discusses the presentations and management of methotrexate overdose in a resource-poor setting. Out of five admitted cases, three recovered completely with the resolution of skin and mucosal lesions and improved hematological parameters while two patients succumbed to illness. Prompt identification of symptoms and early management are required to improve overall outcomes.

Keywords: Leucovorin • Methotrexate • Psoriasis • Pancytopenia • Rheumatoid arthritis

Abbreviations: B/L: Bilateral; DMARD: Disease-Modifying Anti Rheumatic Drug; ER: Emergency Room; G-CSF: Granulocyte Colony Stimulating Factor; IV: Intravenous; JIA: Juvenile Idiopathic Arthritis; MTX: Methotrexate; NSAIDs: Non-Steroidal Anti-Inflammatory Drugs; RA: Rheumatoid Arthritis; SLE: Systemic Lupus Erythematosus

Introduction

Methotrexate (4-amino-10-methyl folic acid, MTX), a folic acid analog and antagonist, is commonly used in treating various diseases. Intended as an anticancer drug, MTX is currently a first-line DMARD in the treatment of Rheumatoid Arthritis (RA), Juvenile Idiopathic Arthritis (JIA) and psoriasis. It is also useful in Inflammatory Bowel Disease (IBD), sclerosis, vasculitis, Systemic Lupus Erythematous (SLE) and other connective tissue diseases and has used in organ transplantation too due to its beneficial anti-inflammatory and immunomodulating activities [1].

The use of MTX may have negative effects on the skin. The symptoms may range from mild to severe. Mild symptoms include itching, urticaria, ecchymosis and reversible baldness whereas severe reactions include toxic epidermal necrolysis and acute ulcerations of psoriatic plaques [2].

The main gastrointestinal symptoms are nausea, vomiting, ulcerative mucositis, stomatitis, secondary anorexia, diarrhea and occasionally pharyngitis or enteritis. Additionally, it can cause pneumonitis and hepatitis. Other symptoms include weariness, headache and vertigo. Fever and a rise in the frequency of infections are caused by immune dysregulation by MTX. Pancytopenia is brought on by bone marrow toxicity at higher MTX dosages.

Particularly tissues with a high proliferative capacity, such as the mucosal layer, the digestive system and bone marrow, are susceptible to methotrexate toxicity [3].

Case Presentation

In a study by Gutierrez, et al. twelve of the 70 instances reported case fatality due to the effects of methotrexate toxicity. The majority of them had hypoalbuminemia, concurrent infection, decreased renal function and/or concurrent therapy with multiple medications. In one of their cases, the lowest cumulative MTX dose that resulted in fatal pancytopenia was 10 mg (Tables 1 and 2) [4].

Table 1. Report of 5 different cases of accidental methotrexate poisoning.

Case	Gender/Age	Comorbidities	Drug dose/duration	Presenting complaints	Examination findings/ site
1	54/F	RA	MTX 10 mg 3-4 times/ week double doses at times	Fever, painful lesions inside the oral cavity asymptomatic blackish skin lesion over lower limbs	Multiple ulcers and erosions inside the oral cavity. Targetoid lesions in the skin
2	51/M	RA, HTN, hypothyroidism, dyslipidemia	MTX 15 mg daily for 10 days	Fever, painful lesions inside the oral cavity, genitalia asymptomatic skin lesion over lower limbs	Multiple ulcers and erosions inside the oral cavity. multiple well-defined hyperpigmented papules, plaques, and atypical target lesions in the skin

3	62/M	RA, HTN, chronic alcoholic	MTX 10 mg daily for 2 weeks	Fever, painful lesions inside the oral cavity, reddish lesions over lower limbs	Multiple ulcers and erosions inside the oral cavity with hemorrhagic crusts over lips. multiple well-defined hyperpigmented papules, plaques, and atypical target lesions with surrounding erythema in the skin
4	61/M	RA, chronic plaque psoriasis	MTX 15 mg and 10 mg, both doses on a weekly basis indicated for two different comorbidities	Fever, painful lesions over the scrotum and inside the oral cavity, difficulty in swallowing	Blister and erosion over the scrotal region. Erosions and ulceration opposite to 2^{nd} molar, soft palate, uvula with B/L enlarged tonsils. Multiple well-defined hyperpigmented/ erythematous papules and plaques with scales over the trunks and lower limbs
5	68/F	Chronic plaque psoriasis, psoriatic arthritis, IHD, dyslipidemia, HTN	MTX 10 mg MTX 10 mg two doses from two centers, unsure about the frequency	Fever, painful lesions inside the oral cavity, skin lesions	Multiple erosions and ulceration with sloughing over the buccal mucosa, lips, soft palate, and tongue. Necrotic ulcers and erosions over the left leg and B/L groin. Multiple tender erythematous papulovesicular lesions over the B/L soles

Table 2. Five different case studies of blood count at different conditions.

Case 1	WBC	RBC	Platelet	HB	Outcome
Day 1	0.13×10^9/L	3.27×10^{12}/L	16×10^9/L	9.9 g/dl	Good and discharged on day 10
Day 3	0.06×10^9/L	2.78×10^{12}/L	10×10^9/L	8.5 g/dl	
Day 9	44×10^9/L	3.18×10^{12}	3.18×10^{12}/L	10 g/dl	
Case 2					
Day 1	1.05×10^9/L	4.1×10^{12}/L	219×10^9/L	11.7 g/dl	Death on day 7
Day 3	0.79×10^9/L	3.42×10^{12}/L	109×10^9/L	8.8 g/dl	
Day 7	0.06×10^9/L	2.91×10^{12}/L	8×10^9/L	8.6 g/dl	
Case 3					
Day 1	0.55×10^9/L	3.25×10^{12}/L	169×10^9/L	10 g/dl	Death on day 5
Day 3	0.50×10^9/L	3.03×10^{12}/L	70×10^9/L	8.7 g/dl	
Day 5	0.20×10^9/L	2.80×10^{12}/L	10×10^9/L	8.6 g/dl	
Case 4					
Day 1	2×10^9/L	3.61×10^{12}/L	41×10^9/L	9.9 g/dl	Good and discharged on day 8
Day 3	2.29×10^9/L	4.06×10^{12}/L	124×10^9/L	10 g/dl	

Day 7	5.52 × 10^9/L	4.07 × 10^{12}/L	615 × 10^9/L	9.7 g/dl	
Case 5					
Day 1	3.85 × 10^9/L	3.22 × 10^{12}/L	147 × 10^9/L	8.6 g/dl	Good and discharged on day 13
Day 2	2.1 × 10^9/L	3.67 × 10^{12}/L	91 × 10^9/L	10.9 g/dl	
Day 3	3.88 × 10^9/L	3.54 × 10^{12}/L	90 × 10^9/L	10.5 g/dl	
Day 5	1.99 × 10^9/L	3.28 × 10^{12}/L	108 × 10^9/L	9.7 g/dl	
Day 9	3.88 × 10^9/L	3.54 × 10^{12}	90 × 10^9/L	10.5 g/dl	
Day 13	6 × 10^9/L	3.41 × 10^{12}/L	327 × 10^9/L	10 g/dl	

Upon admission, patients were managed with a multidisciplinary approach. MTX was stopped immediately and high-dose leucovorin rescue with 20 mg IV every four hours was initiated for a total of 10 doses. $NaHCO_3$ infusion at 1 meq/kg daily in each liter of IV fluid every 6 hours was started for alkalization of urine. Over 2-3 L of maintenance, fluid was administered for hydration and alkalization of urine. MTX serum levels were not measured due to the unavailability of facilities. We stopped alkalinization of urine after a day. G-CSF, whole blood, and platelet-rich plasma were also administered as per hematological reports of the patients and after consultation with the department of medicine. Antibiotic and antifungal prophylactic coverage were given along with regular medications in patients with co-morbidities. The lesions were managed with emollients and topical antibiotics. Other complaints were addressed symptomatically. Despite the efforts case 2 and case 3 deteriorated within a short span of time. Even though attempts at resuscitation, were made, they could not be saved.

Results and Discussion

Therapeutic mistakes with an outpatient low-dose MTX regimen are a well-known issue that could have hazardous repercussions. The medical prescription is commonly misunderstood, which leads to mistakes. Uncertain doctor orders, inadequate explanations to the patients and chronic patients habituated to daily rather than weekly therapy may all be contributing factors. These explanations may lead either the patient or the dispensing pharmacist to misunderstand the prescription. MTX absorption is 90% at oral doses of less than 30 mg/m^2, whereas it is only between 10 and 20% at doses above 80 mg/m^2 which is another reason explaining why MTX intake orally in modest doses repeatedly could be riskier than taking the drug in high doses suddenly [5].

In situations when risk factors such as renal impairment, medication interactions, and advanced age are directly implicated in the development of pancytopenia, MTX therapy should be used with caution. Monitoring of renal function prior to and two weeks after the start of MTX, as well as once a month after that, is strongly advised in addition to the standard CBC with differential and platelet counts and liver function tests.

In dermatology, normal oral methotrexate starting doses range from 5 to 15 mg once a week, increasing gradually every 2 to 4 weeks to a maximum of 25 mg once a week. MTX clearance in the kidneys declines with age and concurrent use of interacting drugs (salicylates, trimethoprim, and NSAIDs.) that lower protein binding or decrease renal clearance is a major contributor to toxicity [6].

Uncertainty surrounds the mechanisms of MTX toxicity. Supplementing with folic or folinic acid helps prevent or treat several toxicities that mirror the symptoms of a folate deficiency, including cytopenia, gastrointestinal intolerance, and stomatitis. Dermatological manifestations include alopecia, rash, nodules (rare) and anaphylactic reactions; diagnostic biopsy is rarely required.

Hydration of >3 L/day along with alkalinizing the urine with oral or parenteral sodium bicarbonate can help avoid methotrexate precipitation in the acidic urine, which can cause crystalluria, and improve methotrexate elimination [7].

The most efficient initial treatment is the MTX withdrawal and intravenous folinic acid (leucovorin) delivery as soon as feasible following exposure. Patients with severe thrombocytopenia, anemia or bleeding may require a platelet and/or packed red blood cell transfusion. Intravenous fluids and bicarbonate infusions to alkalize the urine are strongly indicated. If there is severe neutropenia, colony-stimulating agents must be administered [8].

Pancytopenia may appear abruptly within 1-2 months of beginning MTX therapy, with a potential idiosyncratic reaction or years later due to a dose-dependent cumulative impact. Due to its elevated plasma levels and prolonged half-lives, MTX carries a higher risk of toxicity. MTX can be detected up to 3 weeks even after taking doses as small as 2.5 mg [9].

In various articles, there were mentions of measuring serum methotrexate levels to assess toxicity. This service was unavailable in our facility, but the clinical and hematological pictures and history strongly suggest methotrexate toxicity.

The majority of cases took methotrexate for RA. In our case 4 out of 5 patients were taking it for RA. Two of the patients had chronic plaque psoriasis.

In our case, the patients had inadvertently/over jealously taken medication with the belief of prompt resolution of their conditions. They had all presented with fever, mucosal ulcerations and skin lesions. The patients were managed accordingly with IV fluids, $NaHCO_3$ infusions, leucovorin rescue, blood and platelet transfusions, antibiotic and antifungal coverage, Granulocyte Colony-Stimulating Factors (G-CSF) and other symptomatic management. Though similar management was initiated the patients responded differently to therapy. While three of the patients were stable even with declining hematological parameters, other two developed bleeding manifestations resulting in their untimely death despite vigorous attempts at resuscitation. The patients who survived were regular in their follow ups for 2-3 months and showed no signs of toxicity thereafter. They were managed with alternatives other than methotrexate for their underlying conditions.

Conclusion

All our patients presented with fever and typical mucocutaneous manifestations of methotrexate toxicity supported by hematological parameters. Prompt identification of these symptoms and detailed drug history is important for dermatologists to exercise early management. In our case, the cause of death of two patients was presumed to be internal hemorrhage following low platelet count so it would be advisable to start platelet transfusions earlier than recommended. Pharmacists should also counsel and caution patients before dispensing medication. It is vital to prevent mishaps that could easily be avoided with proper counseling before prescribing.

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