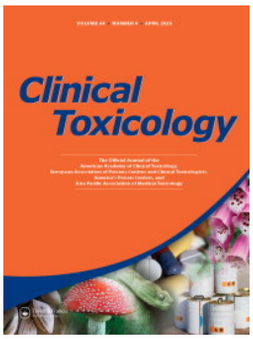

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POISON CENTRE RESEARCH

Methotrexate toxicity in the setting of oral therapeutic errors: a multicenter retrospective study

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ABSTRACT

Introduction: Methotrexate, a dihydrofolate reductase inhibitor with immunosuppressive and disease-modifying effects, is typically dosed orally once weekly. Misunderstanding instructions can lead to daily instead of weekly dosing. This study characterizes thresholds for toxicity from unintentional daily ingestion in adults.

Methods: This was a multi-center retrospective cohort study using records from six regional poison centers between January 1, 2000 and January 24, 2023. Inclusion criteria were adults ≥18 years of age with a therapeutic error of oral methotrexate administration more frequently than weekly. We defined organ system dysfunction as any cytopenia, severe mucositis/stomatitis, severe dermatologic manifestations, renal dysfunction, or elevated aminotransferase activity. The primary outcome was the threshold cumulative dose and duration associated with any organ system dysfunction.

Results: We screened 139 cases and after exclusion, 54 cases remained. Median age was 64 years (IQR 57-70) and 70% of cases were female. There were 51 cases (95%) prescribed methotrexate weekly, and 50 (93%) instead took methotrexate daily. Median duration and dose of methotrexate was six days (IQR 4-9 days) and 66 mg (IQR 45-108 mg), respectively. End organ dysfunction occurred in 31 (57%) cases, 29 (94%) of which had mucositis and 16 (52%) had any cytopenia. There were two deaths. No patient developed organ system dysfunction if methotrexate was taken for less than three consecutive days, or a total dose of <37.5 mg.

Discussion: Despite relatively low doses and duration of methotrexate exposure, patients commonly developed significant end organ toxicity. These thresholds provide additional data to develop triage and management guidelines. Healthcare providers should counsel patients on appropriate dosing. Limitations include use of voluntarily reported poison center data.

Conclusions: Daily methotrexate administration may result in severe organ dysfunction after relatively low dose and duration therapeutic errors.

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Calcium folinate; methotrexate; therapeutic error; toxicity; mucositis; cytopenia

Introduction

Methotrexate is a dihydrofolate reductase inhibitor that is commonly used orally to treat a variety of conditions including rheumatoid arthritis, vasculitis, acute lymphoid leukemia, and psoriasis for its immunosuppressive effects and as a disease-modifying agent [1]. Methotrexate inhibits the conversion of folate to tetrahydrofolate by blocking the enzyme dihydrofolate reductase, and also inhibits thymidylate synthetase leading to decreased thymidylate production. With decreased availability of purines and thymidylate, DNA and RNA synthesis are impaired.

The most common adverse effects caused by methotrexate are consequences of cytotoxic damage to rapidly dividing cells, including dermatologic, gastrointestinal, and bone marrow toxicity [2]. However, methotrexate can also cause other adverse effects including renal, hepatic, neurologic, pulmonary, and infectious complications, including patients receiving chronic low dose therapy [3].

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Acute oral single accidental overdoses are widely considered benign largely secondary to saturable intestinal absorption [4]. Serial ingestion of methotrexate, such as daily instead of weekly dosing, can cause toxicity if performed for >36 h, or if renal impairment exists. Serum or plasma methotrexate concentrations do not reliably predict adverse events, limiting their clinical utility [5,6]. Regardless, hematologic effects during supratherapeutic dosing can occur within days to weeks. One series of 22 cases summarized toxicity from oral methotrexate and found impaired renal function and daily dosing were associated with toxicity, including three deaths [7].

Oral treatment regimens for rheumatoid arthritis, psoriasis, and other indications typically utilize 5 to 25 mg once-weekly dosing. Since these treatments are usually self-administered at home, patients may misunderstand labeled prescription information and take methotrexate daily instead of weekly. There is little evidence evaluating the threshold of toxicity when methotrexate is taken orally in repeated doses. Prior studies were small and did not specifically define thresholds for dose and duration of treatment that resulted in toxicity [8,9]. The primary objective of this study was to characterize a threshold for cumulative dose and duration for developing toxicity from unintentional, therapeutic error methotrexate ingestion in adults.

Methods

This multi-center retrospective cohort study used electronic records from regional poison centers and hospital data between January 1, 2000 and November 30, 2023. Participating sites included poison centers and/or their affiliated medical facilities from the District of Columbia, Maryland, Missouri, Minnesota, North Dakota, South Dakota, Utah, and Virginia (two sites). This study was approved by all individual participating institutional review boards.

Inclusion/exclusion criteria

We identified cases by searching poison center databases for closed human exposures to methotrexate with reason for exposure coded as therapeutic error. We searched toxicology consult service records for patients with a diagnosis of methotrexate toxicity (International Classification of Diseases codes 995.29 and T45.X5A). We included adults ≥18 years of age who took methotrexate orally more often than weekly. We excluded cases of pregnant patients, documentation of other cytotoxic or myelosuppressing coingestants, or incomplete data without at least some laboratory evaluation of organ dysfunction. When poison center cases included patients located at the investigator's home institution, we used additional data from the hospital electronic health record.

Definitions

We defined end organ dysfunction as described by the Common Terminology Criteria for Adverse Events v5.0 [10]. We defined stomatitis/mucositis as any painful oral lesion or dysphagia; acute kidney injury as a creatinine increase of ≥0.3 mg/dL (≥26.5 µmol/L) from baseline if known, or ≥1.5 times the upper limit of normal; cytopenias as an absolute neutrophil count (ANC) <500 cells/µL (0.5 x 10^9/L), hemoglobin of less than 10 g/dL (100 g/L) or platelet count less than 75,000/µL (75 x 10^9/L); hepatotoxicity as aspartate aminotransferase or alanine aminotransferase activity ≥150 IU/L; severe dermatologic manifestation as dermatitis, epidermal necrosis, significant ulceration, or alopecia. Infectious complications were defined as positive blood culture, positive urine culture, chest radiograph consistent with pneumonia, cellulitis, or other infectious complications. Recovery from cytopenia was defined as ANC >1000 cells/µL (ANC >0.100 x 10e^9/L) or white blood cell count >1,000 cells/µL (>1.0 x 10e^9/L).

Data collection

Demographic data included age, gender, height, weight, and length of hospital stay. Clinical data included the total cumulative dose of methotrexate including the dosing duration, indication for methotrexate, presence of organ system dysfunction, presence of neutropenic fever, infectious complications, treatments administered (calcium folinate, granulocyte colony-stimulating factor, antibiotics, glucarpidase, hemodialysis), and clinical outcome including length of hospitalization, intensive care unit (ICU) days, and mortality. Laboratory data collected included initial methotrexate concentration (µmol/L), complete blood count (initial and nadir for leukocytes, hemoglobin, and platelets), creatinine (initial and peak), and serum aminotransferases. Cases were identified by collaborators from each institution and de-identified information was abstracted onto a spreadsheet. Data was then transmitted via secure email.

Outcomes

The primary outcome was to evaluate cumulative methotrexate dose and duration with the presence of a composite outcome of any end organ dysfunction including presence of stomatitis/mucositis, renal

dysfunction, hepatotoxicity, dermatologic manifestations, and/or presence of cytopenia.

Data analysis

The number of patients with organ system toxicity were summarized using proportions.

Among patients experiencing each abnormality, medians were calculated. A cumulative dose and duration threshold for organ toxicity/death was calculated along with sensitivity, specificity, positive predictive value, and negative predictive value.

Results

The initial search identified 139 cases and after exclusion, 54 cases remained for final analysis. Among excluded cases, four involved other myelosuppressing agents and 81 had incomplete data. Forty subjects were female (74%). The median age (IQR) of included subjects was 64 years (57-70). Data sources were poison center chart only (78%), hospital chart only (9%), and both poison center and hospital chart (13%). Of the cohort, 51 (95%) were prescribed methotrexate weekly, with the most common dosing error being daily administration in 50 patients (93%). Three patients had an intended frequency other than weekly: one patient had an unknown specified dosing interval, another was prescribed methotrexate twice daily for three days but took it for five days, and the final patient had a dispensing error of methotrexate instead of metolazone 2.5 mg once daily. One patient took 40 mg total over one week, but exact dosing interval was not specified. Indication for methotrexate was rheumatoid arthritis (17, 31%), psoriasis (6, 11%), other (7, 13%), with specific indication not reported in 24 (44%).

The median duration and cumulative dose of methotrexate was six days (IQR 4-9 days, range 2-21 days) and 66 mg (IQR 45-108 mg, range 17.5-260 mg). In the 27 patients with a reported weight, the median weight based dose was 0.73 mg/kg (IQR 0.59-1.38 mg/kg). Height was rarely reported so we did not calculate a body surface area based dose.

A methotrexate concentration was obtained in 30 cases with a median concentration of 0.005 µmol/L (IQR 0-0.04 mcmol/L, range 0-1.8 mcmol/L). All cases had a methotrexate concentration <1 µmol/L with the exception of a single patient who ingested 45 mg over 3 days with an initial concentration of 1.80 µmol/L. In patients with an undetectable methotrexate concentration at presentation ($n = 15$), organ system dysfunction was present in 11 (73%) with one death. In patients with a detectable methotrexate concentration at presentation ($n = 15$), organ system dysfunction was present in 13 (87%) with one death.

Organ system dysfunction was observed in 31 (57%) patients, with specific organ system dysfunction for the cohort listed in Table 1. Mucositis was present in the majority of patients with organ dysfunction. Of the two patients without mucositis that had organ dysfunction, one patient had cytopenia after taking 40 mg over seven days and the other developed a dermatologic manifestation taking 120 mg over six days. Both patients were admitted to the hospital and received calcium folinate, but neither died. For patients with cytopenias present, the ANC nadir occurred at a median of four days (IQR 1-7 days) and recovery day by 8.5 (IQR 3.75-11.25 days). Two subjects died and therefore had no recovery. Infectious complications were observed in nine (17%) patients. Treatments performed are shown in Table 2. Hemodialysis was performed in one patient, who had end stage renal disease requiring hemodialysis at baseline.

Median hospital length of stay was 2.5 days (IQR 1-7 days) for the entire cohort and four days (IQR 2-9 days) for subjects that had organ system dysfunction present. Three patients were admitted to ICU during their hospitalization. There were two deaths reported. A 75-year-old female with end stage renal disease on hemodialysis received methotrexate 2.5 mg daily instead of metolazone 2.5 mg daily for 13 days due to a dispensing error. She continued to receive routine hemodialysis during this time before the error was recognized, and not specifically for methotrexate removal. She presented to the emergency department with gastrointestinal bleeding and pneumonia. Initial laboratory values included: hemoglobin 6 g/dL (60 g/L), platelets 8 K/µL (8 x $10e^9$/L), ANC 0 cells/µL (ANC 0 cells/L), and methotrexate concentration 0.09 µmol/L. The treating team recognized the medication error after noting the

Table 1. Specific organ systems involved.

Organ system dysfunction	$n = 31$
Stomatitis/mucositis	29 (94%)
Any cytopenia	16 (52%)
Dermatologic manifestation	18 (58%)
Liver injury	3 (10%)
Renal injury	6 (19%)

Table 2. Treatments performed.

	Whole cohort	Patients with any organ system dysfunction present
Leucovorin	31 (57%)	28 (90%)
gCSF	6 (11%)	6 (19%)
Antibiotics	14 (26%)	13 (42%)
Hemodialysis	1 (2%)	1 (3%)
Glucarpidase	0 (0%)	0 (0%)

gCSF: granulocyte colony-stimulating factor.

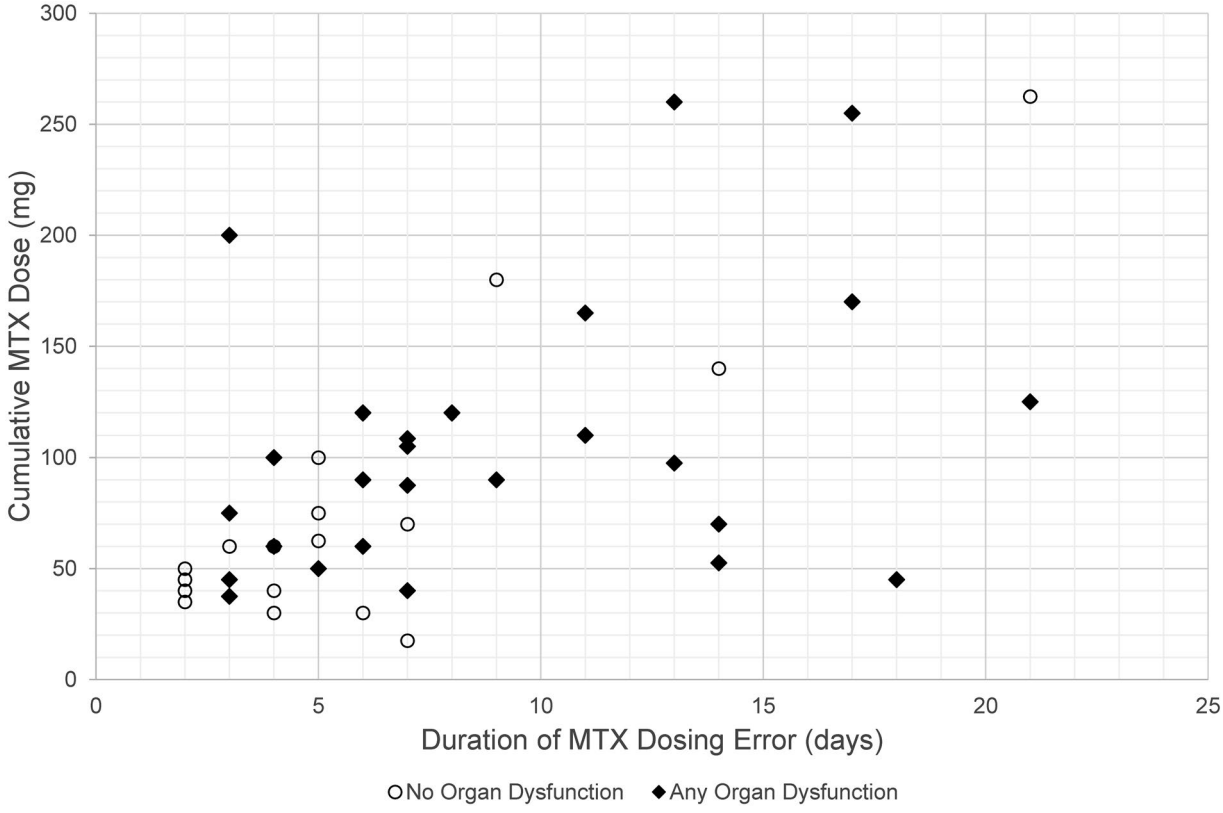

Figure 1. Cumulative methotrexate (MTX) dose and duration of dosing error shown with presence/absence of organ dysfunction.

pancytopenia and reviewing her current medications. She developed hemorrhagic and septic shock. Over the course of 17 days she was treated with antibiotics, red cell and platelet transfusions, granulocyte colony-stimulating factor, calcium folinate, and additional intermittent hemodialysis. The patient suffered a bradyasystolic cardiac arrest following an aspiration event and died. The second death was a 80 year-old female with a prior history of T-cell lymphoma and Alzheimer's disease who presented with altered mental status, extensive dermal eruptions, acute kidney injury, and pancytopenia. The patient took 15 mg daily instead of weekly for seven days (total dose 105 mg). The laboratory values included: hemoglobin nadir 0.9 g/dL (9 g/L), initial and nadir ANC 0.2 cells/μL (0.0002 cells/10e^9/L), initial WBC 1.1 cells/μL (WBC 0.0011 cells/10e^9/L), WBC nadir 0.9 cells/μL (WBC 0.0009 cells/10e^9/L), platelet nadir 16 K/μL (16 x 10e^9/L), initial creatinine of 4.1 mg/dL (362.44 μmol/L), and undetectable methotrexate concentration. Other signs included stomatitis, extensive dermal eruptions and encephalopathy. The patient developed severe sepsis, progressive encephalopathy, respiratory failure, and care was de-escalated resulting in death on hospital day five.

A plot of duration of methotrexate ingestion and cumulative dose with the outcome of any organ dysfunction is shown in Figure 1. A threshold of methotrexate taken for less than three consecutive days or a total dose of <37.5 mg (equivalent to 0.54 mg/kg in a 70 kg adult) produced a sensitivity for any organ dysfunction of 100% (95% CI 88.4-100%). Specificity for developing any organ dysfunction at this 37.5 mg threshold was 21.7% (95% CI 7.5-43.7%) with a positive predictive value of 62.5% (95% CI 57.3%-67.4%) and negative predictive value of 100% (95% CI 47.8%-100%). The lowest dose to produce neutropenia was 40 mg taken over 7 days, and the shortest duration to produce neutropenia was 75 mg taken over 3 days. We excluded the case of the 75 year-old with end stage renal disease who received a total of 32.5 mg methotrexate from the threshold analyses given the highly atypical nature of the case.

Discussion

In this multi-center retrospective cohort study of subjects with unintentional oral methotrexate ingestion more frequently than once weekly, no patient developed organ system dysfunction if methotrexate was taken for less than three consecutive days or a cumulative dose of <37.5 mg. However, given the small sample size, the negative predictive value of this threshold carries a very wide confidence interval and cannot be used to definitively exclude toxicity. This study

provides additional data needed to develop guidelines regarding triage and management of supratherapeutic dosing of methotrexate.

Methotrexate poisoning is a relatively rare, but potentially catastrophic entity. Much of the available literature is derived from its use in high doses as chemotherapy where methotrexate concentrations are used to guide calcium folinate rescue. The threshold dose for toxicity outside of chemotherapy is not well understood. However, the use of methotrexate for ectopic pregnancy has some parallels to the short-term repeated oral dosing of methotrexate. For instance, methotrexate may be given without calcium folinate rescue therapy as a single 50 mg/m^2 intramuscular dose or with a second dose on day 4 [11]. However, when utilizing a multiple-dose regimen totaling 4 mg/kg (i.e., 150 mg/m^2) over 4 separate days, calcium folinate is given between methotrexate doses. Assuming a typical body surface area of 1.6 m^2 in an adult female, the single dose administered intramuscularly in ectopic pregnancy without calcium folinate rescue is about 80 mg. This is higher than the 37.5 mg threshold (0.54 mg/kg or 23.4 mg/m^2 in a 70 kg, 1.6 m^2 BSA adult female) in our study and may be due to differences in these two patient populations including age and medical co-morbidities such as renal dysfunction which would reduce methotrexate clearance compared to healthy pregnant patients. However, some adverse effects do occur in pregnant patients receiving these doses with one series reporting at least one adverse effect in 34% of patients treated with methotrexate 50 mg/m^2 [12].

Much less literature is available regarding both acute and repeated oral overdose, leaving little data available on which to develop management guidelines. A single acute oral overdose is most often benign secondary to saturable intestinal absorption [4]. In addition, acute overdose more closely mimics methotrexate use in chemotherapy where guidelines exist regarding methotrexate concentrations and the need for calcium folinate rescue therapy [13]. In unintentional repeated dosing of methotrexate, saturation of intestinal absorption is less likely to be achieved, resulting in prolonged inhibition of dihydrofolate reductase, reduced purine synthesis with impairment of DNA and RNA production and subsequent organ system dysfunction. As toxicity in this instance occurs from prolonged methotrexate exposure rather than high doses, serum concentrations are less useful in predicting toxicity [5,6,14]. Prior studies evaluating oral therapeutic errors have found significant toxicity despite low or undetectable concentrations [6,8]. This current study supports this conclusion: most patients had an undetectable methotrexate concentration and still had organ system dysfunction. Methotrexate concentrations are not useful in predicting toxicity in these patients.

Prior study of poison center cases of methotrexate therapeutic errors found results similar to ours: a predominance of older adult patients taking methotrexate daily instead of weekly. Vial and colleagues evaluated methotrexate errors reported to French poison centers and found that patients with no symptoms or only mild toxicity took a lower mean cumulative methotrexate dose of 68 mg compared to 94.8 mg in patients with severe toxicity [15]. Schicchi and colleagues evaluated methotrexate errors reported to an Italian poison center. Symptomatic patients had a mean methotrexate cumulative dose of 75 mg compared to 12.5 mg in asymptomatic patients [8]. Though these studies found that increased age and total dose were associated with the presence of symptoms, they did not evaluate a specific threshold for development of toxicity [8,9,15].

In this study, a history of taking methotrexate for less than three consecutive days, and a total dose of <37.5 mg were not associated with organ system dysfunction. While one patient did develop toxicity with a cumulative dose of 32.5 mg, this case was unusual as methotrexate use should generally be avoided altogether in end stage renal disease. There is no safe therapeutic dosing of oral methotrexate in such patients, so including such a patient in our threshold calculations would not inform management of patients taking methotrexate without such contraindications. Medical personnel, including poison centers, may use these criteria to help determine risk of toxicity and appropriate triage for at home monitoring. Those not meeting these criteria should be considered for further evaluation of organ system dysfunction. Additionally, stomatitis/mucositis was a common manifestation of toxicity, with 38/40 (95%) subjects that developed any organ system toxicity having this finding. Patients with a history suggestive of toxicity or with stomatitis/mucositis on physical exam should have laboratory evaluation of other organ system involvement, including assessment of renal function, aminotransferase activity, and a complete blood count with differential. We did not evaluate time to onset of organ system dysfunction following the dosing error, but future studies could evaluate the optimal duration of observation and timing of laboratory investigations.

Daily instead of weekly dosing was the most common error in this cohort. Healthcare providers prescribing or dispensing methotrexate should carefully counsel patients on the appropriate dosing interval, especially when first starting methotrexate [16]. Use of

blister packs could also help remind patients of weekly dosing [17]. Recommendations for system based practices to prevent methotrexate errors include default weekly dosing for methotrexate prescription orders, requiring verification of an appropriate indication for methotrexate, and requiring the patient to repeat back dosing instructions [18].

Limitations

This study has several important limitations. The retrospective design relies on chart documentation which may be incomplete or inaccurate. Seventy-eight percent of the cases relied on data collected from the poison center chart only. Poison center data relies on caller-reported information, which may be limited and confirmatory review is not often available. Some minor effects, such as mucositis and dermatologic findings, may be underreported. Additionally, data abstractors were not blinded to the study aim. Interrater reliability was not assessed due to only having a single abstractor from each study site. A substantial number of initially identified cases were excluded due to incomplete data, which could bias results either toward more severe cases requiring consultation or milder cases with straightforward and complete documentation. This may reduce the generalizability of our findings and limit the ability to detect less common presentations of toxicity. Patients with no symptoms or lab abnormalities at presentation may have developed delayed organ dysfunction, as we did not require repeated follow-up testing for inclusion. The small sample size lead to relatively large confidence intervals around sensitivity and negative predictive value, limiting utility as definitive thresholds for organ dysfunction. We included relatively few patients with a single extra dose over a two day period. Most centers involved routinely managed such cases at home without laboratory evaluation. It is possible these lower dose/shorter duration ingestions also caused toxicity. We did not collect specifics of calcium folinate dosing, which could influence development of toxicity. Finally, we could not always assess potentially important risk factors for methotrexate toxicity such as other medical comorbidities. This may limit the applicability of findings to all patient populations.

Conclusions

In this multicenter cohort, organ system dysfunction occurred in patients taking methotrexate for ≥3 days or in a cumulative dose greater than 37.5 mg. While prospective studies are needed to validate the proposed thresholds of toxicity and better characterize patient-level risk factors, poison centers can use this data to help establish referral and evaluation guidelines for accidental daily methotrexate exposures.

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Data availability statement

Study data available from corresponding author upon reasonable request.

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