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REVIEW

What can clinicians learn from therapeutic studies about the treatment of acute oral methotrexate poisoning?

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ABSTRACT

Context: Methotrexate (MTX) is an anti-folate drug that has been utilized in both malignant and chronic inflammatory conditions. Doctors are often concerned with a potential adverse outcome when managing patients with acute oral MTX poisoning given its potential for serious adverse reactions at therapeutic doses. However, there is surprisingly little data from acute poisoning cases and more data from the therapeutic use of high-dose MTX.

Objectives: To review pharmacokinetic and pharmacological properties of MTX and systematically review series of acute MTX poisonings and therapeutic studies on high-dose MTX that provide pharmacokinetic or clinical data.

Methods: An Embase (1974–October 2016) and Medline (1946–October 2016) search was performed by combining "MTX" and "overdose/poison" or "MTX" and "toxicity" or "MTX" and "high-dose MTX" or "MTX" and "bioavailability" or "pharmacokinetics"; 25, 135, 109 and 365 articles were found, respectively, after duplicates were removed. There were 15 papers that provided clinical data on acute ingestion and toxicity that occurred with low-dose administration. Eighteen papers were on high-dose MTX (>1 g per m^2 body surface area) used as a single chemotherapy agent which provided pharmacokinetic or clinical data on MTX toxicity. Thirty papers were reviewed to determine the toxic dose, pharmacokinetics, risk factors, clinical symptoms and management of acute MTX toxicity. Given the limited acute poisoning data, a retrospective audit was performed through the consultant records of the New South Wales Poisons Information Centre from April 2004 to July 2015 to examine the clinical syndrome and toxicity of acute oral MTX poisoning.

Pharmacokinetics: Reduced MTX bioavailability is a result of saturable absorption. Although maximal bioavailable absorption occurs at a dose of ~15 mg m^{-2}, splitting the dose increases bioavailability. MTX clearance is proportional to renal function.

Acute toxicity: Oncologists prescribe doses up to 12 g m^{-2} of MTX. Patients treated with an intravenous dose of MTX <1 g m^{-2} do not require folinic acid rescue. MTX toxicity correlates better with duration and extent of exposure than peak serum concentration.

Acute oral poisoning: Acute oral MTX poisoning in 177 patients did not report any severe toxicity. In the New South Wales Poisons Information Centre audit data (2004–2015), 51 cases of acute MTX poisoning were reported, of which 15 were accidental paediatric ingestions. The median reported paediatric ingestion was 50 mg (IQR: 10–100; range: 10–150) with a median age of 2 years (IQR: 2–2; range: 1–4). Of the 36 patients with acute deliberate MTX poisoning, median age and dose were 47 years (IQR: 31–62; range: 10–85) and 325 mg (IQR: 85–500; range: 40–1000), respectively. Of the 19 patients who had serum MTX concentrations measured, all were significantly below the concentrations used in oncology and the folinic acid rescue nomogram line and no patient reported adverse sequelae.

Management of acute oral poisoning: Due to the low bioavailability of MTX, treatment is not necessary for single ingestions. Oral folinic acid may be used to lower the bioavailability further with large ingestions >1 g m^{-2}. Oral followed by intravenous folinic acid may be used in patients with staggered ingestion >36 h or patients with acute overdose and renal impairment (eGFR <45 mL/min/1.73 m^2).

Conclusions: As a consequence of saturable absorption MTXs bioavailability is so low that neither accidental paediatric MTX ingestion nor acute deliberate MTX overdose causes toxicity. An acute oral overdose will not provide a bioavailable dose even close to 1 g m^{-2} of parenteral MTX. Hence, no treatment is required in acute ingestion unless the patient has renal failure or staggered ingestion. There is also no need to monitor MTX concentrations in acute oral MTX poisoning.

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Cytotoxic; methotrexate; overdose; poisoning

Context and objectives

Methotrexate (MTX) is a folic acid antagonist, first developed in the 1950s [1]. Originally it was used as a chemotherapeutic agent, often given in large doses; MTX was later used in low doses to treat autoimmune disease and for non-surgical management of ectopic pregnancy [2–4].

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There are two common patterns of exposure: therapeutic error from repeated oral daily dosing [5] and accidental acute ingestions. There is limited information on the management of large acute oral MTX overdose (>500 mg). This review examines case series of oral MTX overdose and therapeutic studies that contain pharmacokinetic or clinical data. The goal is to provide a better understanding of acute MTX toxicity, treatment and the utility of MTX concentration in acute ingestions.

Methods

An Embase (1974–October 2016) and Medline (1946–October 2016) search on human MTX poisoning were performed by combining the search "MTX" and "overdose/poison" or "MTX" and "toxicity" or "MTX" and "high-dose MTX" or "MTX" and "bioavailability" or "pharmacokinetics", which yielded 25, 135, 109 and 365 articles, respectively, after duplicates were removed. There were 15 papers (14 case series and 1 case report) that provided clinical data on acute low-dose ingestions and toxicities. Eighteen papers on high-dose MTX as a single chemotherapy agent (15 case series and 3 review papers; 4 papers provided data on high-dose pharmacokinetic and toxicokinetic properties of MTX) provided pharmacokinetic or toxicokinetic data as well as toxicities. Thirty papers (28 case series, 2 review papers; 17 papers provided data on pharmacokinetic properties of MTX) were reviewed to determine the toxic dose, pharmacokinetics, clinical symptoms, risk factors and management of acute MTX toxicity. Papers were excluded if they were not related to poisoning, animal studies or single case reports with no pharmacokinetic data.

To supplement the limited published data on acute poisoning, an audit was also performed on acute MTX poisoning cases managed by the New South Wales (NSW) Poisons Information Centre from April 2004 to July 2015. The NSW Poisons Information Centre is Australia's largest poisons centre, taking ~100,000 calls annually, with a subset of cases being managed by consultant toxicologists. All MTX exposures recorded by consultant reports were reviewed. Ethics approval of the study was granted by the Human Research Ethics Committee from The Children's Hospital at Westmead to cover all institutions.

Pharmacokinetics

MTX is a weak acid with limited lipid solubility and small volume of distribution of 0.7 L/kg [6,7]. Following absorption, 10% of bioavailable MTX is converted to 7-hydroxy MTX. The MTX is excreted primarily by the kidneys through glomerular filtration and active tubular secretion. Median renal clearance is 99 mL/min/m^2(body surface area) [8]. Distribution half-life is 2 h while the elimination half-life varies from 6 to 8 h [6,8]. Hence, MTX concentrations often become undetectable by 24 h post ingestion.

The oral bioavailability of MTX is saturable because the absorption is dependent on an active transporter (folate carrier-1 protein) (Figure 1) [9]. MTX competes with folinic acid for the active transporter. Folinic acid is a MTX antagonist and an active form of folate that bypasses dihydrofolate

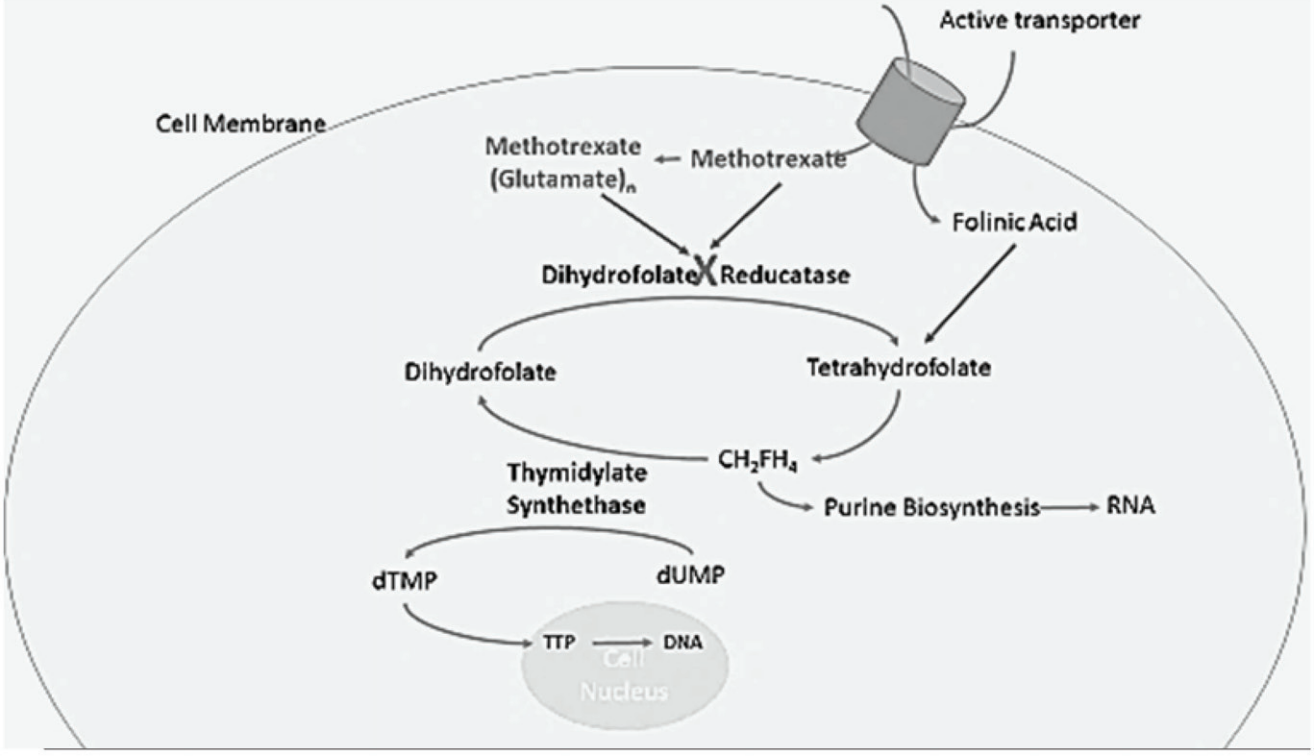

Figure 1. The mechanism of MTX toxicity. MTX primarily inhibits dihydrofolate reductase (DHFR). This results in the depletion of tetrahydrofolate, which is required for the synthesis of purine and deoxythymidine monophosphate (dTMP) from deoxyuridine monophosphate (dUMP). Folinic acid competes with MTX for the active transporter into cell and also restores the tetrahydrofolate pool, therefore circumventing the blockade by MTX.

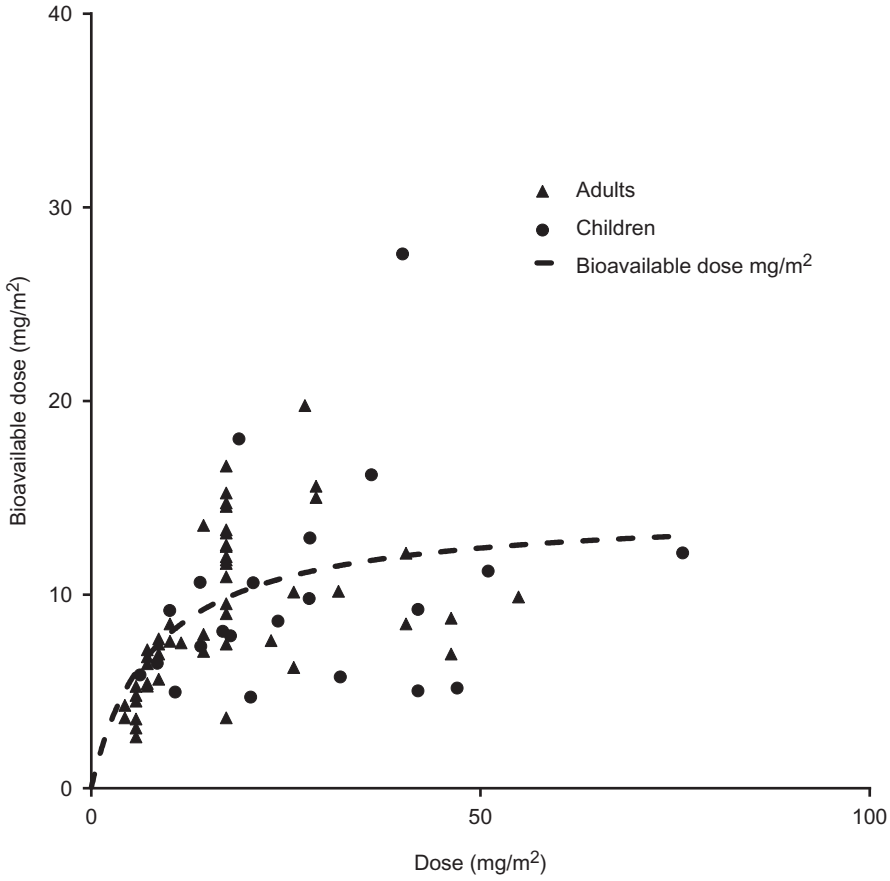

Figure 2. Bioavailable dose versus single ingested MTX dose. This graph compiles a number of paediatric [8,55,56] and adult [11,57–60] pharmacokinetic therapeutic studies on MTX. Where necessary, the adult ingested dose is divided by 1.73 to obtain ingested dose per body surface area. The bioavailable dose appears to be saturable at 14.4 ± 1.64 mg/m^2 (SEM) (95% CI: 11.2–17.7) regardless of the ingested dose. [Equation Y = 14.4X/(8.1 + X)].

reductase. In contrast, concomitant administration of folate with MTX does not decrease the bioavailability of MTX, suggesting that folate may have a separate transporter from that of MTX [10,11].

Pharmacokinetic studies confirm MTX has saturable bioavailability in single or staggered ingestions. With low-dose MTX ingestion (25–35 mg), the oral bioavailability is 70–80% [4]. In children, food reduced bioavailability of MTX from a mean (± SD) of 1.1 (± 0.51) to 0.88 (± 0.35) [12]. There is evidence to support MTX moves into cells via an active rate limited transport mechanism. The bioavailability of 30 mg weekly dose of MTX taken as a single dose is 0.76, when this weekly dose is divided into two doses taken 8 h apart the bioavailability increases to 0.9 [13].

The data (Figure 2) from pharmacokinetic studies showed that: in single acute ingestion, the bioavailable dose does not exceed 15 mg m^{-2} (hyperbolic curve fitted to the published data with Graph Pad Prism). The dose of 15 mg m^{-2} would be equivalent to about 25 mg for an average size adult (body surface area 1.7 m^2).

The evidence for saturable bioavailability is further demonstrated in two studies. When intravenous MTX was compared with oral administration of four doses of 200 mg m^{-2} given at 6 h intervals, the bioavailability of MTX was only 20% [14]. In another study, the bioavailability of MTX was 28% when 200 mg m^{-2} was administered over a 4 h period [15]. Even if ingestion is staggered over a few hours, the maximal absorbed dose will be under 56 mg m^{-2}.

Once inside cells, MTX is metabolized to polyglutamate derivatives with a median half-life of 1–4 weeks [16]. The polyglutamate derivatives cause cytotoxicity through the inhibition of dihydrofolate reductase (Figure 1) [16]. This blocks the production of tetrahydrofolate, an essential co-factor in purine nucleotide synthesis inside the cells. This in turn inhibits DNA and RNA syntheses. The low bioavailability and rapid intracellular uptake of MTX coupled with its short distribution half-life are the reasons for serum MTX concentrations being not useful in either acute or chronic ingestion [8,17].

Acute toxicity

MTX is potentially toxic to multiple organs, including bone marrow, liver, gastrointestinal tract, renal, respiratory, dermatological and haematological systems. Signs and symptoms include severe myelosuppression, nausea, vomiting, stomatitis, mucositis, hepatotoxicity and renal failure. The toxicity is dependent on intracellular MTX concentration, which correlates with bioavailable dose and is inversely proportional to renal function. In high-dose MTX therapy, renal failure may be caused by the formation of intrarenal MTX crystals. Renal damage reduces MTX clearance, resulting in persistent elevation of MTX concentrations. Renal injury may be the cause or result of MTX toxicity [18–20].

There is an increased risk of lymphoproliferative malignancies amongst rheumatoid arthritis patients who are on

long-term low-dose MTX [7,21,22]. There is no evidence to suggest an increased risk in mutagenesis with a single ingestion in the paediatric or adult aged group.

In oncology practice, high-dose MTX is usually administered as an intravenous infusion in doses of 1–33 g m^{-2} [23]. Such high-dose MTX regimens are administered either as a bolus, or over 4–6 h (to target the poorly perfused tumour cells), or as an infusion over 20–40 h (to cover the entire cycle of the tumour cells) [24] (Table 1). High-dose MTX dose varied from 1 to 12 g m^{-2}. With a median dose of 12 g m^{-2}, the peak MTX concentration reaches 1100–1500 μmol/L [25,26].

Folinic acid rescue is not recommended if the MTX dose is <1 g m^{-2} or the plasma MTX concentration is <10 μmol/L at 24 h and <0.1 μmol/L ≥ 48 h post treatment (Figure 3) [27–30]. In general, MTX toxicity is not expected unless there is a sustained elevation of plasma MTX concentration >10 μM at 24 h, >1 μM at 48 h and >0.1 μM at 72 h following exposure [23,27].

MTX toxicity is directly proportional to the duration of exposure and less dependent on MTX concentration [31]. MTX infusions which produced a peak plasma concentration of 500 μmol/L did not cause myelosuppression if folinic acid was commenced within 36 h. On the other hand, significant myelosuppression was observed with prolonged MTX infusions lasting for >36 h, irrespective of the total dose used [31]. Serious toxicity correlates better with area under the curve rather than peak serum MTX concentrations [25]. In addition, the same MTX dose infused over a longer period of time could lead to greater MTX exposure and toxic effects than if it is administered over a shorter time frame due to its rapid clearance by the kidney. For example, an intravenous infusion of MTX 3 g m^{-2} given over 7 and 24 h would produce a MTX concentration of 0.7 and 33.7 μM at 24 h, respectively [32]. In addition, prolonged elimination of MTX and higher serum MTX concentrations are associated with higher serum creatinine and lower creatinine clearance [32,33]. Hence, patients with abnormal renal function or prolonged exposures to MTX >36 h are at most risk from MTX toxicity.

Acute oral poisoning

Published data are very limited. Most acute MTX overdose series were published in abstract format only and come from Poisons Information Centres. There were three studies with 101 deliberate poisonings and 1 study with 76 accidental paediatric MTX ingestions (Table 2) [34–37]. A few patients were reported to have developed abdominal pain, mucositis, nausea, dizziness or headache. However, no patient developed renal failure or bone marrow suppression, and there were no fatalities. None of these studies reported serum MTX concentration.

Patients with renal impairment have increased risk of severe toxicity from low-dose exposures to MTX [38,39]. With an eGFR <45 mL/min/1.73 m^2, the risk of toxicity is significantly elevated (OR = 5.7, 95% CI = 1.4, 23.6) [39]. Fourteen dialysis-dependent renal failure patients developed severe myelosuppression, fever and stomatitis from low-dose oral MTX. Five of these patients died with three of them receiving a single dose of MTX 2.5–50 mg m^{-2} [38]. A haemodialysis-dependent patient developed life-threatening myelosuppression and mucositis after receiving a single dose of MTX (100 mg intramuscularly) and tramadol for the management of ectopic pregnancy [40].

Our audit of NSW Poisons Information Centre cases had 51 acute oral MTX poisonings managed by consultant toxicologists (2004–2015) [41]. There were 36 patients who had taken a deliberate oral MTX overdose, the median age and dose were 47 years (IQR: 31–62; range: 10–85) and 325 mg (IQR: 85–500; range: 40–1000), respectively. Fifteen were accidental paediatric ingestions and the median age and dose were 2 years (IQR: 2–2; range: 1–4) and 50 mg (IQR: 10–100; range: 10–150), respectively. In the 19 patients whose serum concentrations were reported, all non-toxic and the concentrations were at least 10-fold below the folinic acid rescue and chemotherapy toxicity nomogram lines (Figure 3).

No patient was reported to have adverse outcomes. There are limitations to Poisons Information data. Data were collected in a non-systematic fashion and many cases did not report MTX concentration and lack follow up.

In summary, in accidental or deliberate acute MTX ingestion, the bioavailable dose will be less than 50 mg m^{-2}. As the bioavailable dose is well short of the 1 g m^{-2} intravenous dose used in oncology when the nomogram is designed to be applied, serum concentrations will also never exceed the nomogram line [24,42]. Even with high-dose intravenous MTX therapy, plasma MTX concentration is not a reliable predictor for adverse events [43]. In addition, the nomogram was developed to manage high-dose MTX therapy in oncology patients [30]. Hence, in acute oral MTX overdose, there is no reason to monitor MTX concentration. The only groups demonstrated to be at significant risk are patients who have staggered ingestion >36 h [31] or renal impairment (eGFR <45 mL/min/1.73m^2) [20].

Management of acute oral poisoning

In general, neither MTX concentration monitoring nor gastrointestinal decontamination are required in acute MTX ingestion, as toxicity is not expected due to small ingested doses, short distribution half-life and saturable bioavailability (Figure 2) [41]. Even with a large staggered ingestion of 100×10 mg tablets over a few hours, the bioavailability would not exceed 20% [14,15] and the bioavailable dose would be expected to be between 25 and 200 mg. However, large ingestion >1 g m^{-2} or staggered ingestion >36 h should be managed with folinic acid as MTX toxicity is seen in oncology patients who have prolonged exposure (Table 3) [24,31]. The other group at risk is patients with renal impairment (eGFR <45 mL/min/1.73 m^2), which will prolong MTX excretion and duration of exposure. Folinic acid should be given in patients with renal failure who have an acute oral overdose of MTX.

Table 1. High-dose oncology MTX studies with clinical or pharmacokinetic data. Single high dose MTX therapy was used in these studies to treat various malignancies.

Authors	Cancer type	MTX dose	No. patients/ MTX cycles	Adverse effect No (%)	Duration of administration	MTX pharmacokinetics	Time when folinic acid given- ± other treatment
Larsen et al. [61]	Adult ALL	High dose 2–5 g m^{-2}	1125 patients	**HDMTX ($n = 1125$)** Mucositis (any) 162 (14.4%) Febrile neutropenia 57 (5.1%) Infection 138 (12.3%) Seizure 18 (1.6%) Stroke 5 (0.4%)	24 h infusion		24 h after HDMTX randomly assigned to receive dexamethasone or prednisone
Larsen et al. [61]	Adult ALL	Capizzi escalating dose 100–300 mg m^{-2} -increasing doses of MTX every 10 days, beginning at 100 mg m^{-2} and increased 50 mg m^{-2} dose as tolerated	1152 patients	**Escalating MTX ($n = 1152$)** Mucositis 162 (14.1%) Infection 141 (12.2%) Febrile Neutropenia 95 (8.3%) Seizure 21 (1.8%)	Escalating dose: multiple infusions		No folinic acid given Received L-asparaginase Randomly assigned to receive dexamethasone or prednisone
Holmboe et al. [26]	Adult and paediatric osteosarcoma	12 g m^{-2} (range: 8–16)	65/288 cycles	Hepatitis 65 (100%) Leucopenia 59 (49%) Thrombocytopenia 56 (46%) Mucositis 47 (39%) Renal impairment 11 (17%)	4 h infusion	C_{max} 1509 μM (range: 722–2512) $T_{1/2\alpha}$ 2.5 h (range: 1.7–6.5) $T_{1/2\beta}$ 8.4 h (range: 5.6–21.7)	24 h after MTX
Zelcer et al. [62]	Paediatric sarcoma	12 g m^{-2}	82/708 cycles	Neutropenia 16% Anaemia 3% Thrombocytopenia 3% Renal impairment 2%	4 h infusion	At 24 h, MTX conc 51% <10 μM 78% ≤20 μM 5% ≥50 μM At 72 h, 62% ≤0.1 μM	24 h after MTX
Xu et al. [32]	Paediatric ALL	3 g m^{-2}	404 infusions	**404 infusions** Leucopenia 66 (65%) Hepatitis 58 (40%) Mucositis 33(32%) Thrombocytopenia 27 (26%) Infection 18 (18%) Renal impairment 4 (8%) Nausea/vomiting 8 (4%)	7 h vs. 24 h infusion	Plasma conc at 24 h 7 h infusion = 0.7 μM (delayed gp = 5.8 μM) 24 h infusion = 33.7 μM (delayed gp = 47.2 μM)	36 h after MTX
Xu et al. [32]	Paediatric ALL	5 g m^{-2}	121/497 cycles	**93 infusions** Hepatitis 9 (64%) Leucopenia 13 (59%) Nausea/vomiting 8 (36%) Thrombocytopenia 6(27%) Infection 5 (23%) Mucositis 4 (18%) Renal impairment 0	24 h infusion	Plasma conc at 24 h 24 h infusion = 46 μM (delayed gp 81 μM)	36 h after MTX
Comandone et al. [25]	Adult osteosarcoma	12 g m^{-2}	25/64 cycles	Reversible haematological and renal toxicity 2 (8%)	4 h	C_{max} 1150 μM (range: 692–2200), AUC_{tot}: 6955 μmol*h/L Toxicity dependent on highest AUC values. $T_{1/2}$ 4 h (range: 2.4–11.4)	24 h after MTX
Ridolfi et al. [63] Abstract in Italian only	Paediatric ALL osteosarcoma	ALL – 5 g m^{-2} Osteosarcoma – 8 g m^{-2}	ALL 22/88 cycles Osteosarcoma 18/90 cycles	Mild renal impairment in both groups **ALL** Myelosuppression 7% Hepatotoxicity 6% **Osteosarcoma** Hepatotoxicity 32% Myelosuppression 3%	ALL 24 h infusion Osteosarcoma 6 h infusion		
Leahy et al. [64]	Adult melanoma	50–250 mg/kg (2–10 g m^{-2})	29/81 cycles	Mucositis 6 (21%) Leukopenia 6 (21%) Renal impairment 5 (18%)	6 h or 24 h infusion		4 h after the 6 h MTX infusion or Immediately after the 24 h infusion

(*continued*)

Table 1. Continued

Authors	Cancer type	MTX dose	No. patients/ MTX cycles	Adverse effect No (%)	Duration of administration	MTX pharmacokinetics	Time when folinic acid given- ± other treatment
Kirkwood et al. [65]	Adult head and neck CA	Weekly 3–7.5 g m^{-2}	HDMTX = 35/254 cycles	**HDMTX** Renal impairment 34 (97%) (reversible) Myelosuppression 14 (40%) Mucositis 9(26%)			24 h after MTX
Kirkwood et al. [65]	Adult head and neck CA	Twice weekly 50 mg m^{-2}	Twice weekly dose = 20/277 cycles	**Low-dose regime** Renal impairment 13 (65%) (reversible) Mucositis 3(15%) Myelosuppression 1(5%)			24 h after MTX
Isacoff et al. [66]	Adolescent and adult solid Tumours	50–250 mg/kg (2–10 g m^{-2})	46/111 cycles	Myelosuppression 11% Vomiting 8% Stomatitis 4% Renal impairment 4%	4 h infusion	C_{max} 340–2000 µM At 24 h, 0.45–4.5 µM 11 had delayed clearance	4 h after MTX
Lucchesi et al. [67]	Infant <12 months with brain tumours	8 g m^{-2}	8 patients		6 h infusion	Steady state conc at 6 h: 486 µM Clearance: 4.24 L/h/m^2 At 24 h, 3.29 µM 3 had delayed clearance	24 h after MTX 2 had additional folinic acid, 1 had exchange transfusion

HDMTX: high-dose MTX; vs: versus; delayed gp: delayed clearance group; ALL: acute lymphocytic leukemia.
Assume adult weighs 70 kg, body surface area: 1.7 m^2; C_{max}: peak concentration; AUC_{tot}: total area under curve; conc: concentration.

Figure 3. Serum MTX concentrations of patients with acute poisoning managed by NSW Poisons Information Centre consultants from 2005 to 2015. All concentrations were below the MTX chemotherapy folinic acid rescue nomogram line. Data from three high-dose MTX oncology studies were included for comparison [25,26,32]. The doses used varied from 3 to 12 g m^{-2}. MTX concentrations above the toxicity line are expected to cause organ damage [29,41,42]. The equation for the extrapolated toxicity line is log (y) = $-0.042^{*}x + 2$.

Folinic acid

Folinic acid (Leucovorin) interferes with the absorption and transport of MTX and also bypasses the effect of MTX on dihydrofolate reductase, by directly providing reduced folate. Oral folinic acid, given for 24 h following ingestion, can compete for absorption and could be considered in single ingestions >1 g m^{-2}, staggered ingestion >36 h or patients with renal impairment (eGFR <45 mL/min/1.73 m^2). Folinic acid is inexpensive, easily administered and completely safe. Folinic acid has saturable bioavailability because it shares the same active transporter with MTX and the maximum amount that can be absorbed is around 15 mg [44].

After an initial dose of oral folinic acid, intravenous folinic acid can be administered to antagonize the cytotoxic effect of MTX in patients with staggered ingestion >36 h or acute oral overdose with renal impairment. If intravenous folinic acid is administered, it should be given early if possible, but it can be administered as late as 30–36 h [27,45].

Folinic acid is preferred over folic acid because it is an active form of folate and folate's conversion is non-competitively blocked by MTX via the inhibition of dihydrofolate reductase. It also appears to block absorption more effectively than folic acid. The optimal intravenous dose of folinic acid is not known but it is unlikely to be greater 10 mg m^{-2} every 6 h. This is because the bioavailable MTX dose is likely to be <50 mg m^{-2} and the serum MTX concentration will be below the folinic acid treatment line [24,45].

Activated charcoal

Due to saturable bioavailability and therefore limited potential for toxicity, decontamination with activated charcoal is of no benefit in reducing absorption. Oral folinic acid competes with MTX for oral absorption and is more effective than charcoal in preventing absorption.

Urine alkalinization

Urine MTX solubility is directly proportional to pH. MTX and its 7-hydroxy metabolite precipitate in acidic urine (pH <5.5)

Table 2. Studies which reported on acute ingestion of MTX.

Study	Study design	No. of patients	Dose	Symptoms of toxicity
Wieferich et al. [34]	Retrospective study of PIC data	25	Range: 1.25–60 mg	No toxicity
Bebarta et al. [35]	Retrospective study of 6 PIC data (2000–2005)	63	Median 24 mg (range 2.5–100 mg) DSP only: 47.5 mg (12.5–100 mg)	Abdominal pain, mucositis, nausea, dizziness or headache in 13 patients
LoVecchio et al. [36]	Retrospective study of PIC data (2000–2003)	13	Average: 13 mg	Nil
Thornton et al. [37]	Retrospective study of PIC data (2000–2009) Accidental antineoplastic ingestion	76	Not reported (paediatric ingestions)	None significant

PIC: Poisons Information Centre; DSP: deliberate self-poisoning.

Table 3. Management of acute MTX, staggered ingestion >36 h and acute ingestions with renal failure.

	Acute ingestion	Staggered ingestion >36 h	Acute ingestion with renal impairment (eGFR <45 mL/min/1.73 m^2)
Dosage	>1 g m^{-2}	Any	Any
Folinic acid	Oral 15 mg Q6h for 24 h	Oral dose 15 mg followed by IV 15 mg Q6h for 3 days	Oral dose 15 mg followed by IV 15 mg Q6h for 3 days

and their solubilities increase 10-fold at pH 7 [46]. Although urine alkalinization may reduce the formation of crystals in the renal tubules and increase the elimination of MTX, such high intratubular concentrations and crystalluria are not expected after oral doses. A linear relationship between urine pH and MTX clearance exists in patients with normal and impaired renal function. The C_{MTX}/C_{creat} increased from 0.9 at pH 5.5 to 2.6 at pH 8.4 in a group of oncology patients [47].

Glucarpidase

Glucarpidase is a carboxypeptidase recombinant bacterial enzyme that breaks down MTX into inactive metabolites. Glucarpidase has high affinity for folate analogs, including folinic acid and MTX. It reduces MTX concentrations rapidly, but as acute MTX ingestion does not cause toxicity, glucarpidase is not indicated in acute overdose [48–51]. The primary indication for glucarpidase is inadvertent intrathecal MTX administration [52–54].

Conclusions

Severe toxicity does not occur following acute oral overdose of MTX in patients with normal renal function due to its saturable bioavailability and short half-life. No adverse effects have been observed after intravenous administration of much larger doses than would occur in oral ingestion. If an exceptionally large oral ingestion (e.g. >1 g m^{-2}) occurred, 24 h of oral folinic acid might be considered as it is safe and will compete with the absorption of MTX. Patients with staggered ingestion (>36 h) or renal failure (eGFR <45 mL/min/1.73 m^2) are at risk for toxicity and oral followed by intravenous folinic acid should be considered in these patients. Activated charcoal and glucarpidase is not indicated following acute ingestion of MTX. Urine alkalinization may be considered in patients with renal failure. Serum MTX concentrations and the folinic acid rescue and chemotherapy nomogram are of no value in acute MTX ingestions.

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Disclosure statement

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of this paper.

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