Case Files of the New York City Poison Control Center: Antidotal strategies for the Management of Methotrexate toxicity

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CASE PRESENTATION

A 10-year-old boy (37.5 kg; body surface area 1.26 m^2) with osteosarcoma of the right humerus received a planned 4-hour infusion of high-dose methotrexate (16 g, 12.7 g/m^2). His previous medical history was notable for an implanted central venous catheter placement complicated by Horner's syndrome. Renal and hepatic functions were normal at baseline. A postinfusion methotrexate concentration was uninterpretable, but the significance of this result was not initially appreciated by the treating clinicians. Over the next 48 hours, the child developed blurry vision, painful mucositis, stomatitis, and facial blistering. Reported vital signs were: BP, 121/82 mm Hg; pulse, 111/minute; respirations, 16/minute. A physical examination was consistent with the reported symptoms. The 48-hour postinfusion serum methotrexate concentration at the time of poison control center (PCC) consultation was 171 μmol/L (*Figure 1*).

What is methotrexate (amethopterin) and how is it used?

Methotrexate (MTX) is a folate analogue antimetabolite commonly used in treating blood and solid organ malignancies, dermatological and rheumatic diseases, and in termination of gestation. When first introduced as chemotherapeutic agents, folic acid conjugates produced an accelerated progression in the bone marrow and viscera of children with acute leukemia, suggesting treatment options with folate antagonists. Subsequently, the antifolate aminopterin (4-aminopteroyl-glutamic acid) produced the first reported clinical success in inducing temporary remission in acute leukemia in 1948 [1]. Aminopterin's significant toxic side effects spurred a search for alternative antifolate agents with a broader therapeutic window, and led to aminopterin's substitution by MTX (amethopterin) [2–4]. MTX later provided the first medical cure of a solid cancer [5].

The FDA approved MTX for use in psoriasis in 1971, and it found additional use in the treatment of dermatomyositis, pemphigus and pemphigoid, and pityriasis rubra pilaris [6]. One of several disease-modifying antirheumatic drugs (DMARDs), MTX received an FDA indication for use in adults with severe, active rheumatoid arthritis in 1988 with extension to children with active polyarticular-course juvenile rheumatoid arthritis [7]. A 1982 report first described the use of MTX in the treatment of interstitial ectopic pregnancy [8]. Since then, MTX has become an accepted abortive medical therapy for ectopic gestations [9]. MTX is also used off-label in combination with misoprostol for elective medical termination of pregnancy [10]. MTX provides prophylaxis against graft-versus-host disease, particularly in allogeneic stem cell transplantation with peripheral-blood stem cells or bone marrow [11,12].

How is methotrexate dosed?

Methotrexate may be administered via intramuscular (IM), intrathecal (IT), intravenous (IV), or oral (PO) routes. Dosing is quite diverse due to the significant variations in MTX indication. High-dose methotrexate (HDMTX) for chemotherapy, which requires leucovorin rescue, is MTX, 1 g/m^2 IV [13]. Lower doses may be used in alternative chemotherapeutic regimens, while up to 8–12 g/m^2 or more may be given for osteosarcoma, leukemia, and lymphoma [14–16]. IT MTX is more appropriately dosed by age, as a fixed dose per m^2 was reported to result in low

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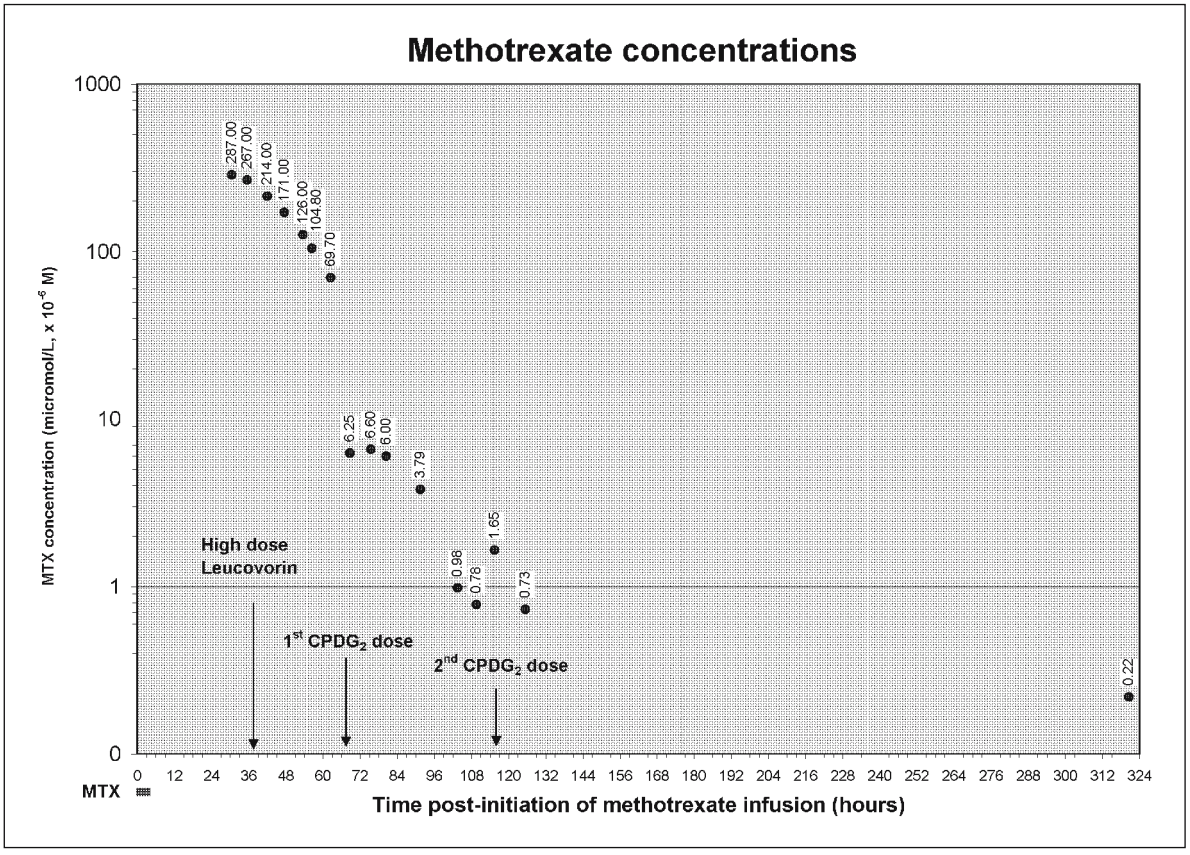


Figure 1: Methotrexate infusion (solid line), serum MTX concentrations by immunoassay (circles), and high-dose leucovorin (1500 mg/m^2) and CPDG$_2$ administration (arrows).

cerebrospinal fluid (CSF) methotrexate concentrations and reduced efficacy in children, and in high concentrations and neurotoxicity in adults [17,18]. Psoriasis patients are normally provided MTX 7.5–30 mg PO weekly [19]. Rheumatoid arthritis treatment similarly involves MTX 7.5–20 mg PO weekly [20]. Multiple fatalities and serious adverse events have resulted from prescription, dispensing, administration, and patient errors in which the intended weekly dose was incorrectly consumed daily [21,22]. For termination of ectopic pregnancy, MTX 50 mg/m^2 IM is commonly used [9]. In elective termination of pregnancy, MTX 25–75 mg/m^2 IM or 25–50 mg PO in combination with misoprostol are employed [10].

How is methotrexate metabolized?

Intracellularly, folypolyglutamyl synthase adds gamma-linked glutamate groups to MTX [23]. Polyglutamation increases the intracellular half-life of MTX, allowing it to persist despite extracellular MTX elimination or removal [24]. MTX can also be hydroxylated at the 7-position by hepatocyte aldehyde oxidase to yield 7-OH-MTX [14]. In the gut, bacterial carboxypeptidase converts MTX to 4-amino-4-deoxy-10-methylpteroic acid (DAMPA) [24].

What are the pharmacokinetics of methotrexate?

Methotrexate is a weak acid with a pK_a of 4.8–5.5, thus is ionized at physiological pH [14]. About 50% protein binding occurs, regardless of serum concentration [25]. Route of administration and dose can significantly alter MTX kinetics. With oral administration, absorption of MTX appears saturable, with a plateau achieved between 25–50 mg [19]. Thus, near-complete intestinal uptake occurs at doses $<$30 mg, while plasma MTX concentrations achieved after PO administration $\geq$80 mg are less than 10% that given IV [14]. Renal elimination of MTX occurs by passive glomerular filtration and associated active tubular reabsorption and secretion [26]. Due to individual differences in elimination, 3-fold variations in serum MTX concentrations were seen with administration of 1 g/m^2 IV [16]. Reported adult clearances of MTX and 7-OH-MTX are 99.1–156.7 ml/minute and 33.3 ml/minute [26–28]. Statistically significant differences in steady-state MTX clearance were seen in infants aged 0–6 months compared to infants 7–12 months (89 ± 32 ml/minute/m^2 versus 111 ± 40 ml/minute/m^2) [29]. Median MTX late elimination phase half-life was reported as 4.02 hours in osteosarcoma patients receiving 12 g/m^2 IV, with wide variability [27]. In contrast, pediatric patients receiving weekly low-dose oral MTX

(2.1–22.3 mg/m^2) had a median elimination half-life of 1.7 hours. Nonsteroidal anti-inflammatory drugs, barbiturates, salicylates, sulfonamides, penicillin, benzimidazoles, and probenecid can all increase MTX concentrations, and glomerular impairment is a main factor in increasing the MTX elimination time [19, 26,30]. Of note, IT MTX can enter the systemic circulation from bulk flow CSF absorption and possibly by active transport to produce a systemic exposure 1.7 times that of an equivalent oral dose [31].

What is methotrexate's mechanism of action?

Folate (vitamin B_9) must be activated prior to its extensive utilization in the 1-carbon metabolic pathways necessary for DNA and RNA synthesis (*Figure 2*). Folate is first reduced by dihydrofolate reductase to dihydrofolate (FH_2), and then again by dihydrofolate reductase to yield "active" tetrahydrofolate (FH_4). FH_4 obtains one carbon from serine to form 5,10-methylene-FH_4. Thymidylate synthase then utilizes 5,10-methylene-FH_4 to produce deoxythymidine monophosphate (dTMP) for DNA synthesis from deoxyuridine monophosphate (dUMP). In the process, 5,10-methylene-FH_4 is converted back to FH_2 for reuse. 5,10-methylene-FH_4 or FH_4 can be converted to 10-formyl-FH_4 to drive two independent steps in purine ring synthesis (conversion of glycinamide ribonucleotide [GAR] to formylglycinamide ribonucleotide [FGAR] and conversion of 5-aminoimidazole-4-carboxamide ribonucleotide [AICAR] to 5-formyl-AICAR [FAICAR]) [32]. 5-formyl-FH_4 (leucovorin, folinic acid) is least susceptible to oxidative degradation and is the most stable natural form of reduced folate [33].

MTX antagonizes folate along multiple intracellular pathways (*Figure 2*). MTX enters the cell either by folate transmembrane transporters or in high doses by passive diffusion [24]. Subsequently, MTX and its polyglutamated metabolites competitively inhibit dihydrofolate reductase such that neither FH_2 nor active FH_4 can be generated from folate, nor can existing FH_2 be recycled. Purine ring synthesis is impaired by several means. MTX and polyglutamated MTX block the participating enzymes amidophospho-ribosyltransferase (PPAT) and 5-aminoimidazole-4-carboxamide ribonucleotide transformylase (AICART) [24,34]. Substrate depletion of 10-formyl-FH_4 as a consequence of depleted FH_4 would impair the GAR-FGAR and AICAR-FAICAR conversion. Additionally, the inhibition by MTX and its polyglutamated metabolites of thymidylate synthase (TYMS—the same enzyme target of the antimetabolite fluorouracil) further compromises thymidine synthesis [23,35]. Furthermore, MTX has complex dose-dependent effects on deoxycytidine kinase, a separate nucleoside salvage-pathway enzyme, with inhibition at low nucleoside concentrations and enhancement at high nucleoside concentrations [36].

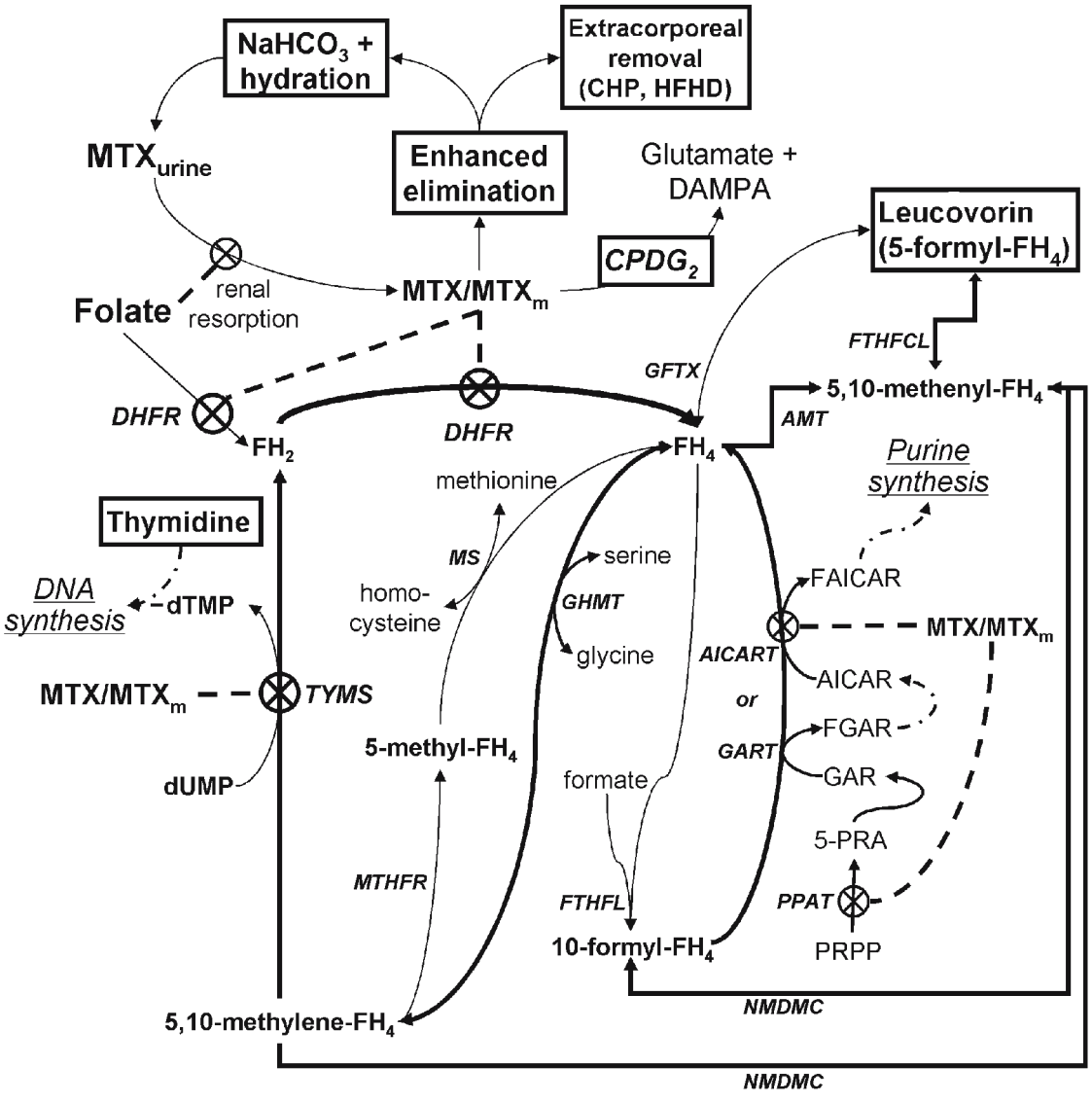
As a consequence of these multiple mechanisms, MTX affects rapidly proliferating cells (e.g., malignancies and those in the gastrointestinal tract, bone marrow or skin) that rely heavily on *de novo* nucleotide creation for DNA replication and RNA synthesis. Because of its ability to impair cellular replication, MTX use expanded beyond conventional chemotherapy regimens (e.g., breast carcinoma, choriocarcinoma, lymphoma, and osteosarcoma) to include treatment of nonneoplastic conditions with significant cellular proliferative such as psoriasis, rheumatoid arthritis, and ectopic pregnancy. In the lower doses used in rheumatic disease, increased adenosine concentrations as a consequence of AICART inhibition may underlie MTX's anti-inflammatory and antiproliferative effects on activated lymphocytes [20].

How does methotrexate poisoning with "therapeutic dosing" occur?

Methotrexate's primary route of elimination is renal. Patients with impaired renal function are therefore at increased risk of developing MTX poisoning, although elevated concentrations can occur in the absence of preexisting renal disease. Concurrent administration of nephrotoxic agents, including intravenous contrast, can also induce MTX toxicity [37]. A literature and clinical trials review of high-dose MTX for osteosarcoma reported nephrotoxicity (creatinine ≥1.5 mg/dL [132.6 μmol/L]) in 1.8% of patients (68/3887) with a range of 0–12% across the studies examined [13]. Mortality was 4.4% (4/68) in those with nephrotoxicity. Similarly, in 264 children receiving MTX 5 or 8 g/m^2, 3.8% had delayed elimination of MTX greater than 120 hours [30]. DAMPA and 7-OH-MTX are 10 times and 4 times less soluble than MTX in urine, respectively [13,14]. Precipitation of these metabolites or MTX itself in the renal tubules may cause acute renal failure and tubular necrosis, further impairing MTX excretion and prolonging MTX exposure [15]. Additionally, individual genetic polymorphisms of folate-dependent enzymes AICART, glycine hydroxymethyl-transferase (GHMT), methylene tetrahydrofolate reductase (MTHFR), and TYMS are associated with neurological, gastrointestinal, and dermatological side effects [38].

What clinical effects are expected from methotrexate toxicity? How is a patient with suspected toxicity evaluated?

Organ systems with rapid cell turnover are most affected by persistently elevated serum MTX concentrations. Hematological abnormalities, particularly myelosuppression, may occur. Anemia and thrombocytopenia are also seen. Nonhematological effects commonly include stomatitis/mucositis, diarrhea, dermatitis, and hepatotoxicity [14]. Renal toxicity occurs by the mechanisms discussed previously. In one study that included adult patients aged <60 years, >60 years, and >70 years, increases in creatinine from 1.5–3.0 times normal appeared in 3%, 8% and 19%, respectively, and creatinine >3.1 times normal developed in 2%, 7%, and 5% [39]. Pulmonary findings occur in up to 10% of patients, and consist of acute interstitial pneumonitis, bronchiolitis obliterans organizing pneumonia, interstitial fibrosis, noncardiogenic pulmonary edema, pleuritis, pleural effusions, or pulmonary nodules [40,41]. Risk factors for MTX pulmonary toxicity in chemotherapy are the use of additional chemotherapeutic agents such as cyclophosphamide or bleomycin and the



Not all folate pathways are depicted.
5-PRA, 5-phosphoribosylamine
AICAR, 5-aminoimidazole-4-carboxamide ribonucleotide
AICART, AICAR transformylase (EC 2.1.2.3)
AMT, aminomethyltransferase (EC 2.1.2.10) [80]
CHP, charcoal hemoperfusion
$CPDG_2$, carboxypeptidase G_2
DAMPA, 4-amino-4-deoxy-10-methylpteroic acid
DHFR, dihydrofolate reductase (EC 1.5.1.3)
dTMP, deoxythymidine monophosphate
dUMP, deoxyuridine monophosphate
FAICAR, 5-formyl-AICAR
FGAR, formylglycinamide ribonucleotide
FH_2, dihydrofolate
FH_4, tetrahydrofolate
FTHFCL, 5-formyltetrahydrofolate cyclo-ligase (5,10-methenyltetrahydrofolate synthetase, EC 6.3.3.2) [81]
FTHFL, formate-tetrahydrofolate ligase (EC 6.3.4.3)
GAR, glycinamide ribonucleotide
GART, GAR transformylase (EC 2.1.2.2)
GFTX, glutamate formimidoyltransferase (glutamate formyltransferase, EC 2.1.2.5 formerly EC 2.1.2.6) [82]
GHMT, glycine hydroxymethyltransferase (serine hydroxymethyltransferase, EC 2.1.2.1)
HFHD, high-flux hemodialysis
MTHFR, methylene tetrahydrofolate reductase (EC 1.5.1.20)
MS, methionine synthase (EC 2.1.1.13)
MTX, methotrexate
MTX_m, methotrexate metabolites
$NaHCO_3$, sodium bicarbonate
NMDMC, NAD-dependent methylenetetrahydrofolate dehydrogenase-cyclohydrolase (comprises functions of EC 1.5.1.5 and EC 3.5.4.9)
PPAT, amidophosphoribosyltransferase (EC 2.4.2.14)
PRPP, 5-phosphoribosyl 1-pyrophosphate
TYMS, thymidylate synthase (EC 2.1.1.45)

Figure 2: Folate metabolism, methotrexate antagonism (-⊗), and antidotal strategies (boxes).

tapering of steroids; risk factors in oral low-dose therapy are older age, diabetes, previous use of DMARDs, rheumatoid pleuropulmonary involvement, and hypoalbuminemia [42,43]. Acute, subacute, and chronic neurotoxicity (after either high-dose IV or IT therapy) has been described. IT MTX can produce chemical arachnoiditis in 5–40% of patients, with headache, nausea, vomiting, fever, back pain, and dizziness being prominent symptoms [44]. Days to weeks later, paraplegia, cerebellar dysfunction, cranial nerve palsies, and seizures may occur [45]. Particularly after combined treatment with cranial irradiation, a leukoencephalopathy characterized by confusion, somnolence, ataxia, spasticity seizures, coma, or death may arise after a course of months to years [44,46,47] In patients receiving up to 4 g/m^2 IV MTX with whole-brain irradiation, 19.5% had brain MRI evidence of leukoencephalopathy and 7.1% demonstrated clinical evidence of late neurotoxicity [39].

Any symptoms suggestive of the above processes should prompt a clinical evaluation, a serum methotrexate concentration, and laboratory assessment of renal, hematological, and hepatic function. Further diagnostic studies such as chest radiography or brain imaging may be indicated for pulmonary or neurological complaints.

How does one interpret a reported methotrexate value?

In order to assess therapeutic or potentially toxic concentrations, serum levels of MTX are routinely monitored by automated procedures such as fluorescence polarization immunoassay or enzyme-multiplied immunoassay. Due to the presence of metabolites, these assays may overestimate the MTX concentration in 2% and 5% of 42-hour plasma samples and 3% and 31% of 66-hour plasma samples, respectively [48]. Some confusion in interpreting MTX concentrations arises from the fact that MTX may be reported variously in μmol/L or nmol/L, in μM or nM, or in exponential format (e.g., $\times 10^{-7}$ M). In patients receiving chemotherapy, 24-hour MTX concentrations $>10^{-5}$ M (10 μmol/L), 48-hour concentrations $>10^{-6}$ M (1 μmol/L), or 72-hour $>10^{-7}$ M (0.1 μmol/L or 100 nM) are considered at high risk for toxicity [49]. Values of $<10^{-8}$ M (10 nM) should be present in patients receiving MTX for other indications [19].

CASE CONTINUATION

The patient's creatinine had risen from 0.57 mg/dL (50.4 μmol/L) preinfusion to 2.76 mg/dL (244 μmol/L) at 42 hours post-methotrexate infusion. He developed abdominal pain requiring parenteral opioids. Aminotransferases rose to AST, 815 U/L and ALT, 1574 U/L with a total bilirubin of 3.5 mg/dL (59.85 μmol/L).

Would folate reverse the apparent toxicity?

Folate is not an effective antidote because methotrexate blocks the enzymes responsible for folate activation and utilization. While folate will inhibit renal resorption of methotrexate, this is inadequate therapy.

What antidotal strategies exist to treat methotrexate toxicity?

Fluids resuscitation may be required to reverse volume depletion from gastrointestinal losses. Intravenous crystalloids sufficient to maintain brisk diuresis (>60 mL/hour) are also critical to maximizing methotrexate elimination. Urine alkalinization further improves urinary elimination of MTX [50]. Methotrexate's urinary precipitation is minimized in alkaline urine: at pH 7.5 MTX is 10 times more soluble than at pH 5.5 [14,51]. The beneficial effects of alkaline diuresis are seen even in patients with preexisting renal dysfunction [52]. Therefore, intravenous sodium bicarbonate should be routinely given in addition to aggressive hydration to maximize urinary solubility [53].

Leucovorin (5-formyl-FH_4, folinic acid, citrovorum factor, calcium folinate) was first identified in 1948 as a required growth factor for deficient *Leuconostoc citrovorum* species [54]. Within 2 years it was reported to successfully reverse aminopterin and MTX toxicity, which had previously resisted folate rescue [55]. Leucovorin is a mixture of diastereoisomers of the 5-formyl derivative of tetrahydrofolic acid. The *l*-isomer is biologically and pharmacologically active, while the *d*-isomer is neither metabolized to any significant degree nor taken up in tissues [56]. Although leucovorin 20–40 mg PO is bioequivalent or superior to IV administration because of reduced absorption of the inactive form and presystemic intestinal metabolism, at doses above 40 mg PO, active intestinal transport is saturated [57,58]. Leucovorin sustains the folate cycle in bypassing the blocked dihydrofolate reductase pathways (*Figure 2*). The 10 mg/m^2 IV dose of leucovorin for normal chemotherapeutic "rescue" therapy must be increased significantly in patients with elevated MTX concentrations. Nomograms and established treatment protocols exist to guide therapy for elevated MTX concentrations at different time points [59]. Leucovorin IV doses of 100 mg/m^2 or 1000 mg/m^2 every 6 hours and as high as 10 g/day been used [60]. However, data suggest that at MTX concentrations above 100 μmol/L, adequate leucovorin concentrations cannot be achieved for competitive reversal of toxicity [15,61]. In the event that a MTX concentration is unavailable, empiric leucovorin (molecular weight 511) should be administered to achieve a plasma molar concentration equal to or greater than that of the concentration estimated from the exposure to MTX (molecular weight 455). Leucovorin is continued until the serum MTX concentration is <10 nmol/L (0.01 μmol/L) in patients not receiving MTX for malignancy, or <50–100 nmol/L (0.05–0.1 μmol/L) in patients receiving MTX as chemotherapy [57]. Because of its calcium content (0.004 mEq calcium per mg of leucovorin), leucovorin infusion should not exceed 160 mg/minute. Intrathecal administration of leucovorin is contraindicated and may be fatal [62,63]. When doses >10 mg/m^2 are administered, leucovorin should be reconstituted with sterile water.

Thymidine as a rescue agent ("thymidylate salvage") was available starting in 1978 under sponsorship of the National Cancer Institute (NCI) [64]. Thymidine does not compete with MTX for transport into the cell, and it is directly converted to

thymidine monophosphate by the salvage enzyme thymidine kinase [65,66]. Exogenously supplied thymidine negates TYMS inhibition by increasing intracellular thymidine pools for subsequent DNA synthesis by up to 6-fold [67]. MTX elimination is unaffected by thymidine. Thymidine's rapid clearance requires continuous infusion at a dose of 8 g/m^2 per day IV. However, the NCI's investigational new drug protocol is closed, and thymidine is no longer available in the United States.

Glutamate carboxypeptidase ($CPDG_2$, carboxypeptidase G_2, glucarpidase, EC 3.4.17.11) is a bacteria-derived metalloenzyme that directly cleaves methotrexate into inactive DAMPA and glutamate (*Figure 3*). Its dimerized structure contains two domains—a beta-sheet dimer interaction site and a di-zinc catalytic domain [68]. Its optimum pH is 7.0–7.5, compatible with human physiology [70]. The typical dose is 50 units/kg IV given over 5 minutes. Administration of $CPDG_2$ produces a rapid reduction of serum MTX concentrations by 95–99% within 15 minutes [13,15]. Since DAMPA is known to cross-react with most commercial MTX immunoassays, persistently elevated concentrations of MTX may be reported if an immunologically based assay is used after $CPDG_2$ administration [15]. Therefore, high-performance liquid chromatography must be employed to determine actual serum MTX concentrations. $CPDG_2$ has a 15-fold higher affinity for MTX ($K_m = 8 \times 10^{-6}$ M) than for leucovorin ($K_m = 1.2 \times 10^{-4}$ M), although affinity for folate is similar ($K_m = 4 \times 10^{-6}$ M) [69,70]. Despite this, many protocols recommend that leucovorin not be administered for 2 hours before and for up to 2 hours after $CPDG_2$ is provided. A second, identical 50 units/kg dose of $CPDG_2$ may be administered 48 hours after the first dose because $CPDG_2$ acts only on extracellular MTX, and redistribution of MTX from the intracellular compartment may occur. This slow efflux of intracellular MTX mandates continued leucovorin therapy (many protocols suggest continuing leucovorin 250 mg/m^2 IV every 6 hours until 48 hours after the second dose of carboxypeptidase). Then, leucovorin is continued until the MTX concentration is <50 nmol/L (0.05 μmol/L). Intrathecal $CPDG_2$ has been administered with complete patient recovery in cases of inadvertent IT MTX administration [71,72].

$CPDG_2$ is available in the United States on a compassionate-use basis from the NCI and under an open-label treatment protocol (ClinicalTrials.gov identifier: NCT00481559). A double-blind, placebo-controlled trial is ongoing at the M.D. Anderson Cancer Center (Houston, Texas) (ClinicalTrials.gov identifier: NCT00424645). Emergency inquiries and supply details might also be directed to AAIPharma: 866–918–1731 (intravenous emergencies) or Protherics Inc: 888–327–1027 (intrathecal emergencies). Specialty cancer centers that may have access to this antidote might also serve as a resource. Common adverse effects include

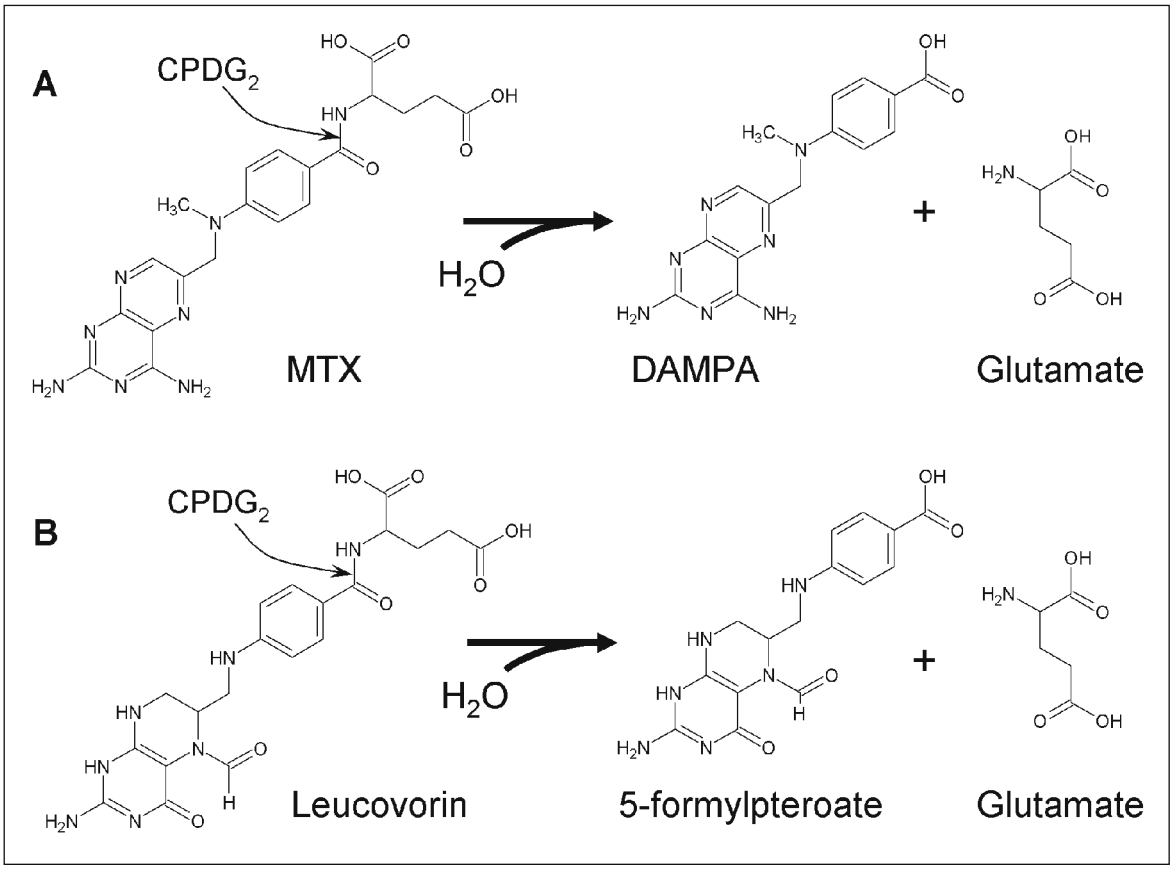


Figure 3: $CPDG_2$ hydrolysis of (A) methotrexate or (B) leucovorin to DAMPA (4-amino-4-deoxy-10-methylpteroic acid) or 5-formylpteroate plus glutamate.

feeling of warmth, tingling fingers, flushing, shaking, burning of the face and extremities, head pressure, and pruritus [15,66].

Is there a role for extracorporeal drug removal?

High-flux hemodialysis or charcoal hemoperfusion may be indicated for patients at risk for developing MTX toxicity despite leucovorin treatment, particularly those with worsening renal function. Clinically significant quantities of MTX can be removed by high-flux hemodialysis, charcoal hemoperfusion, or combination of the two [73–77]. MTX redistribution from the cellular compartment may result in a rebound from the mean 53% to 76% reductions in MTX concentrations achieved, and require repeat dialysis sessions [13]. Peritoneal dialysis is not effective, as it clears MTX only in the first hour of the exchange and has negligible effect on serum concentrations [78,79]. Carboxypeptidase (see above) is largely replacing the need for dialysis, although dialysis may be required in the setting of severe renal dysfunction, if $CPDG_2$ is unavailable, or while awaiting its delivery.

CASE CONCLUSION

The patient initially received saline hydration and leucovorin (1500 mg/m^2 every 6 hours), although urinary alkalinization with sodium bicarbonate was insufficient (pH <7). The PCC recommended enhanced urinary alkalinization and either high-flux hemodialysis or charcoal hemoperfusion pending determination of $CPDG_2$ availability and delivery. The PCC assisted in obtaining $CPDG_2$ (50 U/kg) on a compassionate-use basis, which was administered at 68 hours post-onset of MTX infusion (*Figure 1*). The MTX concentration measured by immunoassay dropped by approximately 90% (HPLC unavailable) to 6.25 μmol/L ($6.25 \times 10–^6$ M). A second identical $CPDG_2$ dose was given 48 hours later. The patient's creatinine peaked at 2.95 mg/dL (260.8 μmol/L). Within 24 hours of $CPDG_2$ administration, renal and hepatic dysfunction stabilized and began trending towards normal. Visual symptoms rapidly resolved, and his abdominal pain improved over several days. Ultimately, he was discharged 28 days after the initial MTX infusion and was able to undergo a subsequent chemotherapy cycle.

The authors have no financial interest in any commercial products mentioned nor the companies that produce them.

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