Methotrexate poisoning: The role of glucarpidase

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Disclosures and Disclaimers

• Grants and salary support for unrelated work
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• Labeled indications of glucarpidase, if they exist, differ by country and region.

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Objectives

• Understand the indications for glucarpidase use in methotrexate (MTX) poisoning.

• Understand glucarpidase interactions with leucovorin.
Populations at risk

- **Oncology (chemotherapy)**
  - Solid organ and blood malignancies
  - MTX: ~18,000 US patients/year
  - HDMTX-induced renal dysfunction: 1.8%
    - ~200-300 US patients per year
    - ~20 UK patients per year

- **Additional uses**
  - Disease-modifying anti-rheumatic drug (DMARD)
  - Ectopic gestation
  - Elective medical termination of pregnancy (TOP)
MTX Elimination

MTX $\xrightarrow{80-90\%}$ 7-OH-MTX $\xrightarrow{\text{Aldehyde oxidase}}$ DAMPA (4-deoxy-4-amino-N10-methylpterioic acid)

$F_T$, Folate transporters: PCFT, proton-folate symporter; RFC, folate-organic phosphate (OP-) antiporter; MDRP, Multidrug resistance-associated proteins; BCRP, breast cancer-resistance protein; endocytic α,β folate receptors.

FPGS, Folylpolyglutamate synthetase.
MTX Elimination

MTX

7-OH-MTX

DAMPA

(4-deoxy-4-amino-N10-methylpteric acid)

Aldehyde oxidase

Carboxypeptidases

Folate transporters: PCFT, proton-folate symporter; RFC, folate-organic phosphate (OP') antiporter; MDRP, Multidrug resistance-associated proteins; BCRP, breast cancer-resistance protein; endocytic folate receptors.

FPGS, Folylpolyglutamate synthetase.
Chemotherapeutic Mechanisms


Not all folate pathways are depicted.

AICAR, 5- aminoimidazole-4-carboxamide ribonucleotide; AICART, AICAR transformylase; AMT, aminomethyltransferase; DHFR, dihydrofolate reductase; FAICAR, 5-formyl-AICAR; FGAR, formylglycinamide ribonucleotide; FH2, dihydrofolate; FH4, tetrahydrofolate; FTHFCL, 5-formyltetrahydrofolate cyclo-ligase (5,10-methenyltetrahydrofolate synthetase; GAR, glycaminamide ribonucleotide; GART, GAR transformylase; GFTX, glutamate formimidoyltransferase; GHMT, glycine hydroxymethyltransferase (serine hydroxymethyltransferase); MTHFR, methylene tetrahydrofolate reductase; MS, methionine synthase; MTXm, methotrexate metabolites; NMDMC, NAD-dependent methylenetetrahydrofolate dehydrogenase-cyclohydrolase; PPAT, amidophosphoribosyltransferase; PRPP, 5-phospho-beta-D-ribosylamine; TYMS, thymidylate synthase.
MTX Suppression of DNA Synthesis

Oncological Balance
Minimize toxicity **BUT** Maximize antitumor activity

![Graph showing the relationship between Leucovorin dose and plasma MTX concentration over time.](image-url)
Limitations of Existing Therapy

• Diuresis & sodium bicarbonate
  – Fluid ceiling
  – pH ceiling
  – Sodium ceiling

Methotrexate precipitation in the urine


Limitations of Existing Therapy

- **Leucovorin**
  - Inadequate at [MTX] >100 μM
  - Difficult at sustained [MTX] >10 μM
  - Intrathecal contraindication

- **Hemodialysis**
  - Plasma [MTX] rebound

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Labeled Indications (US FDA)

- VORAXAZE® (glucarpidase) is…indicated for the treatment of toxic plasma methotrexate concentrations (>1 micromole per liter) in patients with delayed methotrexate clearance due to impaired renal function.

- Limitation of use: VORAXAZE is not indicated for use in patients who exhibit the expected clearance of methotrexate (plasma methotrexate concentrations within 2 standard deviations of the mean methotrexate excretion curve specific for the dose of methotrexate administered) or those with normal or mildly impaired renal function because of the potential risk of subtherapeutic exposure to methotrexate.
Before using glucarpidase, all other supportive measures must have been optimised, such as use of fluids and folinic acid.

Glucarpidase will be routinely funded for the treatment of adults and children receiving high-dose methotrexate chemotherapy (doses > 1 g/m²) who develop a significant deterioration in renal function after the start of the high dose methotrexate, have toxic plasma methotrexate levels and, despite rescue measures, are at risk of life threatening methotrexate induced toxicities.

A significant deterioration in renal function is regarded as a serum creatinine that is at least 1.5 times the upper limit of normal and rising, or the presence of oliguria.

Defining a toxic methotrexate level is complicated by the regimen used and the time at which the level is tested. However, patients must have a dangerously high blood methotrexate level that is rising despite all standard rescue measures.”
Glucarpidase

- Pseudomonas (strain R16) zinc-dependent enzyme
- Expressed in *E. coli* K12 strain RV308
- Profile
  - Carboxypeptidase G2
  - Carboxyl-terminal glutamate residue hydrolysis
- Dose: 50 Units/kg
Mechanism

Glucarpidase PK/PD

- 83 kDa dimer with an optimal pH of 7.0 - 7.5
- Steady-state volume of distribution ($V_{ss}$)
  - Normals: 58.0 mL/kg; 42.0 mL/kg
  - Renal impairment: 67.9 mL/kg; 56.7 mL/kg
- Mean maximum serum concentration ($C_{max}$)
  - Normals: 3.1 μg/mL
  - Renal impairment: 2.9 μg/mL
- Mean pharmacokinetic half-life ($t_{1/2}$)
  - Normals: 9.0 hours
  - Renal impairment: 10.0 hours
- One Unit of glucarpidase activity
  - Catalyzes the hydrolysis of 1 µmol of MTX per minute at 37°C.
- Mean enzymatic activity half-life of glucarpidase
  - Normals: 5.6 hours
  - Renal impairment: 8.2 hours

Efficacy

1. FDA, Center for Drug Evaluation and Research. Application number: 125327Orig1s000. Medical Review(s). Review completion date 12/19/11.


<table>
<thead>
<tr>
<th>Trial</th>
<th>FDA TRIAL 001&lt;sup&gt;1&lt;/sup&gt; 2000-2003 “BERLIN”&lt;sup&gt;2&lt;/sup&gt;</th>
<th>FDA TRIAL 002&lt;sup&gt;1&lt;/sup&gt; 1993-2004 “NCI”&lt;sup&gt;3,5&lt;/sup&gt;</th>
<th>FDA TRIAL 003&lt;sup&gt;1&lt;/sup&gt; 1997-2002 “BONN”&lt;sup&gt;4&lt;/sup&gt;</th>
<th>FDA TRIAL 006&lt;sup&gt;1&lt;/sup&gt; 2004-2007 “NCI PD”&lt;sup&gt;1,5&lt;/sup&gt;</th>
<th>FDA TRIAL 016&lt;sup&gt;1&lt;/sup&gt; 2007-(2010) BTG IND 11557</th>
<th>2008-2010 “ST. JUDE”&lt;sup&gt;6&lt;/sup&gt;</th>
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<tbody>
<tr>
<td>Glucarpidase</td>
<td>CAMR</td>
<td>CAMR</td>
<td>CAMR</td>
<td>Commercial Lot</td>
<td>Commercial Lot</td>
<td>Commercial Lot</td>
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<tr>
<td>Sites</td>
<td>29</td>
<td>149</td>
<td>50</td>
<td>55</td>
<td>N.R.</td>
<td>1</td>
</tr>
<tr>
<td>N (Safety data)</td>
<td>43</td>
<td>262 (214)</td>
<td>65</td>
<td>184 (149)</td>
<td>244 (141)</td>
<td>20</td>
</tr>
<tr>
<td>Malignancies</td>
<td>ALL: 13; L: 12; +CNS: 16; OTHERS: 2</td>
<td>L/L: 111; OS/S: 75; OTHERS: 3</td>
<td>ALL: 26; NHL: 21</td>
<td>L/L: 93; OS/S: 47; OTHERS: 9</td>
<td>L/L: 88; OS/S: 46; OTHERS: 7</td>
<td>ALL: 10; OS:6;L:4</td>
</tr>
<tr>
<td>Age (Y)</td>
<td>18 – 78 (54)</td>
<td>0.4 – 82 (17)</td>
<td>0.9 – 71.8 (15.4)</td>
<td>0.08 – 85 (18)</td>
<td>0.5 – 85 (16)</td>
<td>4.1 – 20.4 (12.1)</td>
</tr>
<tr>
<td>TTT (H)</td>
<td>27 – 176 (56)</td>
<td>N.R.</td>
<td>25 – 178 (52)</td>
<td>27 – 86 (48)</td>
<td>N.R.</td>
<td>26.3 – 95 (45.9)</td>
</tr>
<tr>
<td>Dose (U/kg)</td>
<td>10 – 58 (50)</td>
<td>N.R.</td>
<td>33 – 60 (50)</td>
<td>18 – 98 (49)</td>
<td>6 – 189 (50)</td>
<td>13 – 65.6 (51.6)</td>
</tr>
<tr>
<td>[MTX] (μM)</td>
<td>1 – 1,187 (10.5)</td>
<td>1 – 849 (35)</td>
<td>0.52–901 (11.93)</td>
<td>3.9 – 708 (38.9)</td>
<td>N.R.</td>
<td>1.3-590.6 (29.1)</td>
</tr>
<tr>
<td>[MTX] &lt;sub&gt;↓&lt;/sub&gt; Baseline &lt;sub&gt;↓&lt;/sub&gt; RSCIR</td>
<td>N=24</td>
<td>N=70</td>
<td>N=25</td>
<td>N=22</td>
<td>N.R.</td>
<td>N.R.</td>
</tr>
<tr>
<td>Leucovorin</td>
<td>(mg) = [MTXS]&lt;sub&gt;5&lt;/sub&gt; (μM) x (kg); [MTXS]&lt;sub&gt;5&lt;/sub&gt; ≤ 5 μM: 15-75 mg/m&lt;sup&gt;2&lt;/sup&gt; Q 6</td>
<td>N.R.</td>
<td>None 4 H prior; post 1 H @ 100 mg/m&lt;sup&gt;2&lt;/sup&gt; Q 6 x 24 H</td>
<td>N.R.</td>
<td>N.R.</td>
<td>N.R.</td>
</tr>
<tr>
<td>Heme/ID</td>
<td>60.4% (26/43)</td>
<td>N.R.</td>
<td>12.5% (5/40)</td>
<td>N.R.</td>
<td>N.R.</td>
<td>20%+</td>
</tr>
<tr>
<td>Mucositis</td>
<td>34.9% (15/43)</td>
<td>N.R.</td>
<td>15.3% (6/39)</td>
<td>N.R.</td>
<td>N.R.</td>
<td>5%</td>
</tr>
<tr>
<td>Nephrotoxicity</td>
<td>18.6% (8/43)</td>
<td>N.R.</td>
<td>34.1% (14/41)</td>
<td>N.R.</td>
<td>N.R.</td>
<td>35%</td>
</tr>
<tr>
<td>Hepatotoxicity</td>
<td>16.2% 7/43</td>
<td>N.R.</td>
<td>32.5% (13/40)</td>
<td>N.R.</td>
<td>N.R.</td>
<td>N.R.</td>
</tr>
<tr>
<td>MTX-Death*</td>
<td>23.2% (10/43)</td>
<td>5.1% (11/214)</td>
<td>6.1% (4/65)</td>
<td>4.0% (6/149)</td>
<td>2.1% (3/141)</td>
<td>0%</td>
</tr>
</tbody>
</table>

*or not specifically malignancy-related; CAMR, Center for Applied Microbiology and Research (UK) lot 004; L/L, leukemia/lymphoma; OS/S, osteosarcoma/sarcoma; **RSCIR, rapid and sustained clinically important reduction; TTT, time to treatment.
Median plasma [MTX] decrease 98.7% within 15 min

N = 75
Efficacy

Figure 2. Rapid and sustained clinically important reduction (RSCIR) in methotrexate (MTX) concentration was achieved in 59% (95% confidence interval 51–67%) of 140 patients with preglucarpidase MTX concentrations higher than 1 μmol/L.
Glucarpidase Limitations

• Intravascular compartment restriction
  – Cannot act intracellularly
  – Cannot cross the blood-brain barrier
  – Cannot act in gastrointestinal lumen
  – Cannot treat MTX extravasation

• Does not impact urinary collecting system
  – No effect on urinary elimination
  – DAMPA has a pH-dependent urinary solubility 8-10 times less than MTX

• Immunogenicity

• Monitoring
Issues

Immunogenicity

• Hypersensitivity
  – Adverse reactions (N = 290)
    Paresthesias (2%), flushing (2%), nausea ± vomiting (2%), hypotension (1%), and headache (1%) [PI]
  – 2/4 allergic reactions in repeat dosing for escalating HDMTX

• Efficacy
  – Schwartz: 3/7 patients tested produced antiglucarpidase antibodies (AGA)
  – Summary of clinical trials [PI]
    • Single dose: 12/78 (15%) develop AGA
    • Two doses: 4/18 (22%) develop AGA (3+ @ 5-7mo)
  – Human AGA neutralizing activity: no (published) data
Issues

Immunogenicity


Smith, Silas W.

Not for commercial distribution
Issues
Monitoring

• DAMPA cross-reacts with radioimmunoassays (RIA) and competitive DHFR binding assays
• DAMPA and 7-OH-MTX interfere with newer fluorescence polarization immunoassay (FPIA) and enzyme multiplied immunoassay technique (EMIT) assays
• Must use high performance liquid chromatography (HPLC) to determine [MTX]

Glucarpidase Limitations II

Leucovorin

- Compartment issues
  - Persistent intracellular MTX or third-space fluid shifts (e.g., ascites or pleural effusions) mandate continued leucovorin

- Antidotal effectiveness

\[
\text{Methotrexate} \xrightarrow{\text{glucarpidase}} \text{DAMPA} + \text{Glutamate}
\]

\[
\text{Leucovorin} \xrightarrow{\text{glucarpidase}} 5\text{-formylpterioic acid} + \text{Glutamate}
\]
Antidotal Effectiveness

• Glucarpidase affinities (K_m)
  – MTX: 8.0 x 10^{-6} M; Leucovorin: 120 x 10^{-6} M; Folate: 4.0 x 10^{-6} M

• Glucarpidase cleaves active levo-(6S)-leucovorin ~50% faster

• Glucarpidase cleaves 5-methyl-tetrahydrofolate (5-mTHF)
  – ↓ 98.6% @ 15 minutes post administration

• Leucovorin at 2 hours post glucarpidase
  – Leucovorin_{max}: ↓ 54%; leucovorin_{AUC}: ↓ 33%
  – (6S)-5-mTHF_{max}: ↓ 93%; l-5-mTHF_{AUC}: ↓ 92%

• Leucovorin at 2 and 26 hours post glucarpidase
  – Leucovorin: ↓ 50% and ↓ 20%
  – (6S)-5-mTHF: ↓ 100% and ↓ 75%


Not for commercial distribution.
Leucovorin

• Do not administer (levo)leucovorin within 2 hours before or after glucarpidase administration

• Continue pre-treatment (levo)leucovorin x 48 hours
  – Then dose (levo)leucovorin based on [MTX]

• Continue (levo)leucovorin until [MTX] < leucovorin treatment threshold for a minimum of 3 days.
Summary

Figure 2. Considerations for glucarpidase use compiled from the published literature. Abbreviations: sMTX, serum methotrexate concentration; SCr, serum creatinine; CrCl, creatinine clearance; UOP, urine output; HDMTX, high-dose methotrexate; SD, standard deviation.
## Pharmacoeconomic considerations

<table>
<thead>
<tr>
<th>Antidote</th>
<th>Formulation</th>
<th>Quantity</th>
<th>AWP 2012&lt;sup&gt;2&lt;/sup&gt;</th>
<th>AWP 2016&lt;sup&gt;2&lt;/sup&gt;</th>
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</thead>
<tbody>
<tr>
<td>Acetadote® (IV)</td>
<td>200 mg/mL 30 mL</td>
<td>4</td>
<td>$994.38</td>
<td>$994.38</td>
</tr>
<tr>
<td>Anascorp®</td>
<td>1 vial</td>
<td>1</td>
<td>$4,375.00</td>
<td>$4,905.68</td>
</tr>
<tr>
<td>Deferoxamine (Fresenius)</td>
<td>2 gram vial</td>
<td>1</td>
<td>$49.90</td>
<td>$49.40</td>
</tr>
<tr>
<td>Deferoxamine (Hospira)</td>
<td>2 gram vial</td>
<td>4</td>
<td>$176.40</td>
<td>$151.58</td>
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<tr>
<td>Fomepizole (Paladin)</td>
<td>1 g/mL 1.5 mL</td>
<td>4</td>
<td>$5,454.00</td>
<td>$5,459.40</td>
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<tr>
<td>Fomepizole (Bioniche)</td>
<td>1 g/mL 1.5 mL</td>
<td>1</td>
<td>$755.00</td>
<td>$755.00</td>
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<tr>
<td>Fomepizole (Sandoz)</td>
<td>1 g/mL 1.5 mL</td>
<td>1</td>
<td>$1,312.00</td>
<td>$1,312.00</td>
</tr>
<tr>
<td>Glucarpidase (Voraxaze®)</td>
<td>1000 Units/vial</td>
<td>1</td>
<td>$27,000.00</td>
<td>$32,816.40</td>
</tr>
<tr>
<td>Hydroxocobalamin</td>
<td>2.5 gram (need 2)</td>
<td>1</td>
<td>$4,104.00</td>
<td>$4,257.48</td>
</tr>
<tr>
<td>Leucovorin</td>
<td>10 mg/ml - 10 ml</td>
<td>1</td>
<td>$11.36</td>
<td>$24.00</td>
</tr>
<tr>
<td>Leucovorin</td>
<td>200 mg vial powder</td>
<td>1</td>
<td>$48.00</td>
<td>$48.00</td>
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<tr>
<td>Levoleucovorin (Fusilev®)</td>
<td>50 mg vial powder</td>
<td>1</td>
<td>$240.00</td>
<td>$273.60</td>
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<tr>
<td>Naloxone (Hospira)</td>
<td>0.4 mg/mL</td>
<td>10</td>
<td>$45.00</td>
<td>$185.28</td>
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<tr>
<td>Phytonadione</td>
<td>10 mg/mL</td>
<td>25</td>
<td>$404.60</td>
<td>$1,133.10</td>
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<tr>
<td>Phytonadione</td>
<td>1 mg/0.5 mL</td>
<td>10</td>
<td>$51.00</td>
<td>$216.00</td>
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<tr>
<td>Succimer (Chemet®)</td>
<td>100 mg capsules</td>
<td>1 (100 caps)</td>
<td>$989.00</td>
<td>$1,700.04</td>
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<tr>
<td>Uridine Triacetate (Vistogard®)</td>
<td>10 g/packet</td>
<td>20</td>
<td>N/A</td>
<td>$90,000.00</td>
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<tr>
<td>Vitamin K (Mephyton®)</td>
<td>5 mg oral tab</td>
<td>100</td>
<td>$1283.00 in 2013</td>
<td>$7,051.21</td>
</tr>
</tbody>
</table>

“Cash generation supporting investment in future growth drivers”

“High growth Interventional Medicine portfolio supported by strong cash generation in Specialty Pharmaceuticals and Licensing”

“Many of the Group’s products are life-saving in nature, providing some protection against an uncertain economic outlook…”

Pharmacoeconomic considerations

• Treatment costs
  – 70 kg patient @ 50 Units/kg = 3,500 Units
    • 1,000 unit vial @ $32,816.40 each (AWP) = $131,265.60
  – 2 vials (1000 units/vial) @ £26,900 (incl. VAT)
    • Patients ≤ 40 kg, cost = £26,900 (NHS)
    • Patients 40-80 kg, cost = £53,800 (NHS)
• Reimbursement
  – $270.56/10 Units (NDWSI) = $94,696/$108,224
  – Centers for Medicare and Medicaid Services

Variable Glucarpidase Dosing

St. Jude Children’s Research Hospital

N = 26

A

B

“Our institution has since adopted the practice of capping individual glucarpidase doses at a maximum of 2,000 units.”
Coda: IT MTX exposure

- IT Leucovorin contraindicated
- Fixed glucarpidase dose (2000 Units) IT (off-label)


<table>
<thead>
<tr>
<th>CSF MTX Level Before CPDG2</th>
<th>CSF MTX Level After CPDG2</th>
</tr>
</thead>
<tbody>
<tr>
<td>μM</td>
<td>μM</td>
</tr>
<tr>
<td>100000</td>
<td>10000</td>
</tr>
<tr>
<td>10000</td>
<td>1000</td>
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<td>1000</td>
<td>100</td>
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<tr>
<td>100</td>
<td>10</td>
</tr>
<tr>
<td>10</td>
<td>1</td>
</tr>
<tr>
<td>1</td>
<td>0.1</td>
</tr>
</tbody>
</table>

Data are from Bradley AM et al.
Test your knowledge

• Once glucarpidase has been administered, leucovorin may be discontinued.

• **Answer: False**
Test your knowledge

• In the first 48 hours following glucarpidase administration, immunoassays provide a rapid, reliable measurement of methotrexate concentrations.

• **Answer: False**