Working Through the Paradox of Methotrexate Toxicity

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0196-0644/$-see front matter
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https://doi.org/10.1016/j.annemergmed.2018.06.011

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[Ann Emerg Med. 2018;72:129-132.]

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ANNALS CASE

A 65-year-old woman presents with a diffuse necrotic rash, mucositis, and pancytopenia, which blooms into a neutropenic fever and lands her in the hospital for almost 2 weeks.[1] The cause of her syndrome may appear to be an autoimmune process, but in fact it's a complication of the very medication that was prescribed for her rheumatoid arthritis: methotrexate (MTX).

INTRODUCTION: MTX=WTF

Although it won't be the most common "meth" toxicity that you manage in your emergency department (ED), MTX-related complaints are common, affecting 16% of patients who receive it for rheumatoid arthritis.[2] Although single acute overdoses of MTX are well tolerated,[3-5] long-term overdoses, or accidental misadventures because of dosing errors, are frequent. It is these exposures that commonly cause severe toxicity,[6-8] as illustrated in the case above.

MTX seems to fit perfectly the paradox of clinical medicine: every problem has a solution, but every solution comes with its own set of problems. More specifically, the same pharmacologic properties make MTX both very useful and also quite dangerous. It is beneficial in a broad variety of illnesses, and yet it can damage almost any organ in the body when things run afoul. To cloud things a bit more, MTX toxicity in one patient presentation may not at all resemble that in the next, and toxicity with long-term dosing can be unpredictable even under the best circumstances[9] Recognizing the many varieties of MTX-related complications is vital for the emergency physician because early interventions can help mitigate the severity of later complications.

BACKGROUND: MTX=ADR

To begin with, the dosing of MTX sets the stage for a lot of different adverse drug reactions. In the oncology setting, high-dose MTX protocols use potentially fatal infusions of the drug for its antitumor effects, followed by "rescue" therapy with the antidote to save the patient's own tissues before these take a hit.[10] For central nervous system malignancies, they also use intrathecal MTX, in which overdosing errors can be catastrophic, as suggested by the very reassuring advice to do "cerebrospinal fluid exchange" if something untoward should occur.[11]

You probably won't see high-dose MTX or intrathecal MTX patients in your ED. More commonly, it is the subacute or long-term low oral dosing that gets people into trouble, and these are the complications that present to the ED.[9] MTX is frequently prescribed to be taken at low oral doses for anti-inflammatory effects in autoimmune diseases, which is fine and well, except that patients are told to take it weekly rather than daily.[12,13] However, many people inadvertently take it once a day instead, which leads to rapid drug buildup and subsequent toxicity. Even when taken as prescribed, adverse drug reactions can still occur, particularly if there is any decrease in renal function, as occurs with dehydration or concurrent nephrotoxic drugs.[14]

PHARMACOLOGY: MTX=FRENEMY

MTX is an antimetabolite with structural similarity to folate.[15] The mechanism of action centers on inhibition of the enzyme dihydrofolate reductase, which converts folic acid into the active form, folinic acid. Folinic acid (also called leucovorin) is an important precursor for the production of thymidine in DNA synthesis and repair. The upshot: MTX

targets rapidly proliferating cells, for better or worse; a subset of cancers, autoimmune diseases, and ectopic pregnancies can be treated by putting the kibosh on DNA manufacture. However, toxicity from MTX is related to the same mechanism, causing the most damage to rapidly dividing cells in the bone marrow, skin, mucosal membranes, and gastrointestinal tract.[16-21] MTX toxicity related to drug-drug interactions (such as levetiracetam, trimethoprim-sulfamethoxazole, or proton-pump inhibitors, to name a few) and patient factors can be unpredictable in many cases, and patients receiving this medication can develop toxicity even if receiving it as prescribed.[9,22-25]

CLINICAL PRESENTATION: MTX=MOF

A patient receiving MTX typically has some serious medical history, so you will likely have a broad differential diagnosis for whatever ails him or her at present. Remember to keep MTX (or other immunomodulating medications) toxicity on your differential, especially if multiple organ failure or a number of unrelated complaints and laboratory results begin to materialize during the evaluation.

Think of MTX in any patient with cancer, rheumatoid arthritis, psoriasis, or recent ectopic pregnancy who presents with multiple organ failure. Toxicity develops in organs with the most rapid cell turnover first, causing dermatitis, stomatitis, mucositis, gastrointestinal bleeding, diarrhea, anemia, neutropenia, or straight-up pancytopenia. Secondary effects include neutropenic fever, ischemia, hemorrhage, electrolyte and fluid losses, hepatotoxicity, and pulmonary toxicity.[26,27] Renal injury either as a complication or precipitating cause of MTX building up[10] is noteworthy because MTX and its metabolites can precipitate in the renal tubules under acidic conditions, leading to acute tubular necrosis.[14]

MTX levels can be obtained in some centers, but for most this will likely be a send-out laboratory test, rendering it less valuable in the ED.[28] Fortunately, you can make a fairly accurate assessment by using excellent history-taking and physical examination skills to estimate the patient's risk. This will permit you to start treatment empirically. Furthermore, the initial interventions to treat MTX toxicity are relatively straightforward, safe, and accessible in almost all hospitals.

TREATMENT: MTX=KFC

There are 3 key strategies to treating MTX toxicity: enhance renal elimination by giving intravenous fluids and alkalinizing the urine, bypass the blocked dihydrofolate reductase enzyme to restart the DNA synthesis process by giving folinic acid (leucovorin), and add glucarpidase to the mix to cleave and inactivate the MTX molecules. Or, as we like to say here in Fresno, MTX=KFC (kidneys, folinic acid, chainsaws).

Step 1

The first step in treatment is to get the kidneys back online, starting with fluid hydration and moving soon to urine alkalinization.[10,15,29] Optimize urine output, with the goal of making at least 60 mL/hour. Urinary alkalinization can also enhance elimination because MTX tends to deposit in the renal tubules when the pH is acidic. You can administer sodium bicarbonate by the intravenous route (the usual cocktail is 100 to 150 mEq in a liter of dextrose 5% in water) or orally (1,300 mg every 4 hours) to increase the urine pH to a target of 7.0 or higher.[30] At that pH, MTX solubility, and hence its elimination, is increased 10-fold compared with that with a urine pH of 5.5.[31] Hemodialysis or hemoperfusion can also be considered to replace renal function and remove MTX, especially in patients with persistent renal impairment.[32,33]

Step 2

The next important step is to restart the thymidine pipeline and DNA synthesis by restoring the folate-dependent pathways blocked by MTX.[16,34] We do this by providing intravenous folinic acid (aka tetrahydrofolate, citrovorum factor, or leucovorin).[35] Folate itself is not as effective because this unreduced form requires activation by the dihydrofolate reductase enzyme, which has become incapacitated by MTX. Thymidine has also been used to rescue patients out of MTX toxicity, but it is not currently used.[36]

Step 3

Approved in 2012, carboxypeptidase G2 (or glucarpidase) is the newest antidote that has been developed for MTX toxicity. It is a recombinant enzyme derived from a strain of pseudomonas, RS-16.[37] Finally, pseudomonas is doing something good! Glucarpidase is a chemical chainsaw; it cleaves MTX and renders it inactive.[38] For the pharmacology nerds, it works synergistically with leucovorin because its mechanism of action is to cleave MTX in the extracellular compartment while the leucovorin continues to function inside the cell. It's new, it's expensive, and it's not stocked at many hospitals, so it has not yet replaced leucovorin as the first-line agent for MTX toxicity. When MTX levels remain elevated despite urinary alkalinization and the administration of leucovorin, glucarpidase can be added to the regimen.[39,40]

Management of many of the other complications observed in MTX toxicity is typically the major goal of inpatient care.[9,10,13,14] For example, treatment with granulocyte-macrophage colony stimulating factor (or

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