THE NORTHERN HOSPITAL

METHOTREXATE TOXICITY

Dunkirk Beach, June 1940 ("Dunkirk", Warner Bros. 2017)

We continued towards Malo-les-Bains, crossing the railway, and marching through the ruined street of Roosendaal whose skeleton walls stood around us like the ruins of some bygone civilization. The only sound was the crunching of broken glass under our boots, as if we were marching over hard ice crystals on a winter's day. Mysterious shadows flittered about the streets, in and out of broken doorways, and disappearing silently around corners. They were stray inhabitants who had been cut off by the swift march of events and were living in cellars. And a few looters. And, probably, a few spies. The

German gunfire was now incessant, the flash of the explosions continually lighting up the scene for a second or two on every side of us….

We were now in the region of the dunes, which rose like humps of a deeper darkness. And these in their turn were dotted with the still blacker shapes of abandoned vehicles, half sunk in the sand, fantastic twisted shapes of burned out skeletons, and crazy looking wreckage that had been heaped up in extraordinary piles by the explosions of bombs. All these black shapes were silhouetted against the angry red glare in the sky, which reflected down on us the agony of Dunkirk.

Slowly we picked our way between the wreckage, sinking ankle deep in loose sand, until we reached the gaunt skeletons of what had once been the houses on the promenade. The whole front was one long continuous line of blazing buildings, a high wall of fire, roaring and darting in tongues of flame, with the smoke pouring upwards and disappearing in the blackness of the sky above the rooftops. Out seawards the darkness was as thick and smooth as black velvet, except for now and again when the shape of a sunken destroyer or paddle-steamer made a slight thickening on the impenetrable surface. Facing us, the great black wall of the Mole stretched from the beach far out into the sea, the end of it almost invisible to us. The Mole had an outstanding, terrifying background of giant flames leaping a hundred feet into the air from blazing oil tanks. At the shore end of the Mole stood an obelisk, and the high explosive shells burst around it with monotonous regularity.

Along the promenade, in parties of fifty, the remnants of practically all the last regiments were wearingly trudging along. There was no singing, very little talk. Everyone was far too exhausted to waste breath. Occasionally out of the darkness came a sudden shout:

"A Company, Green Howards…."

"C Company, East Yorks….."

These shouts came either from stragglers, trying to find lost units, or guides on the lookout for the parties they were to lead on to the mole for evacuation…

From the margin of the sea, at fairly wide intervals, three long thin black lines protruded into the water, conveying the effect of low wooden breakwaters. These lines of men, standing in pairs behind one another far out into the water, waiting in queues till boats arrived to transport them, a score or so at a time, to the steamers and warships, that were filling up with the last survivors. The queues stood there, fixed and almost regular as if ruled. No bunching, no pushing….much more orderly, even, than a waiting theater queue…

A group of dead and dying soldiers on the path in front of us quickened our desire to quit the promenade. Stepping over bodies we marched down the slope on to the dark beach. Dunkirk from was now a lurid study in red and black; flames, smoke, and the night itself all mingling together to compose a frightful panorama of death and destruction. Red and black, all the time, except for an occasional flash of white now low in the sky miles away

to the left and right where big shells from coastal defense guns at Calais and Nieuport were being hurled into the town.

Down on the beach you immediately felt yourself surrounded by a deadly evil atmosphere. A horrible stench of blood and mutilated flesh pervaded the place. There was no escape from it. Not a breath of air was blowing to dissipate the appalling odour that arose from the dead bodies that had been lying on the sand, in some cases for several days. We might have been walking through a slaughter-house on a hot day. The darkness, which his some of the heights of horror from our eyes, seemed to thicken this dreadful stench. It created the impression that death was hovering around, very near at hand.

We set our faces in the direction of the sea, quickening our pace to pass through the belt of this nauseating miasma as soon as possible.

"Water…water…" whispered a voice from the ground in front of us.

It was a horribly wounded infantry man. He had been hit so badly that there was no hope for him. Our water bottles had long been empty, but by carefully draining them all into one we managed to collect a mouthful or two. A sergeant knelt down beside the dying man and held the bottle to his lips. Then we proceeded on our way, leaving the bottle with the last few drains in it near the poor fellows' hand so he could moisten his lips from time to time".

John Charles Austin, "Return Via Dunkirk, 1940

In response to the four long years of horrific stagnant trench warfare of the First World War, French defensive strategy in the inter-war years became centered on the "Maginot Line" - a virtual city of fortified underground concrete and steel defenses armed with the biggest and most powerful guns of the day. No force on Earth would be able to penetrate this line of defense. Or so it was thought. It was constructed along the borders with Switzerland, Germany, and Luxembourg, but fatally it did not extend to the English Channel as the French government did not want to offend neutral Belgium.

But warfare strategy and military technology had progressed exponentially since the time of the Great War, and battles would now be fought by fully mechanized forces on the land, air and sea - the result was a form of lightning warfare never before seen in history, the Germans called it "blitzkrieg". The Wehrmacht imply ignored the Maginot Line - massed fighter craft flew over the top of it, huge armies rapidly flanked it in days, by invading "neutral" Belgium and Netherlands. In just 6 weeks from 10 May 1940, the German army achieved what they had not been able to archive in 4 years of the Great War. It was one of the most decisive battles in ever fought in the history warfare.

Over 400,000 British and French troops found themselves surrounded by two immense German armies and the English Channel. France was on its knees. Britain seriously considered "conditional" surrender. Then came the miracle of Dunkirk. The British War Office made the decision to attempt evacuating British forces on May 25. Recognizing

that the Royal Navy itself could not possibly evacuate this number of troops in short order, a call was put out to all merchant shipping across the nation. Over 800 hundred private sea craft of every conceivable description answered the call, picking up as many troops off the beaches of Dunkirk as each vessel could cram in, retuning them to Britain, then going back to run the German coastal artillery again and again. Under covering fire from the RAF and British Navy a staggering 340,000 British, French, Belgian and Dutch troops were successfully evacuated off the beaches in just 9 days from May 26 to June 4, though over 60,000 British and French troops would be left on the beaches and taken into captivity.

Methotrexate is an agent that carries the potential for serious toxicity. Our "Maginot" line of defence against this toxicity comes to us in the form of well spaced dosing. However in those patients who "blitzkrieg" this medication imminent disaster will be at hand. Fortunately we have at our disposal "little ships" of folinic acid, that may come to our patient's timely rescue!

Facing us, the great black wall of the Mole stretched from the beach far out into the sea, the end of it almost invisible to us…("Dunkirk", Warner Bros. 2017)

METHOTREXATE TOXICITY

Introduction

Surprisingly there are no reports of toxicity following acute single oral ingestions of methotrexate in patients with *normal renal function*.

This is due largely to its saturable absorption kinetics. [1]

Most cases of toxicity with severe effects are a result of:

- **Supratherapeutic dosing**:
  - ♥ i.e repeat-dosing errors, most commonly daily instead of weekly dosing for example. Note that **daily dosing for just 3 days** can result in toxicity.
- **High-dose intravenous** therapy with acute renal failure.
- **Intrathecal overdose.**

Acute single ingestions therefore do not need folinic acid therapy unless:

1. The patient has **significant renal failure**, i.e eGFR < 45 mL/min/1.73 m^2.
2. The ingestion is massive (where it may be considered) i.e > **1 gram per m^2 (*or about 1.7 grams for an average sized adult*).**

Specialist advice should always be sought for guidance on antidotal therapy by folinic acid rescue or the specific antidote, carboxypeptidase G2.

Clinical Uses:

Methotrexate is an increasingly used anti-metabolite agent used in a variety of conditions including:

1. Oncology, (a variety of neoplastic conditions):
   - Oncologists prescribe high doses - up to **12 grams per m^2**
   - Patients treated with an **IV dose < 1 gram per m^2** do **not** require folinic acid rescue.
2. Dermatological, (psoriasis)
3. Rheumatologic, (rheumatoid arthritis).

Preparation

Methotrexate as:

Tablets:

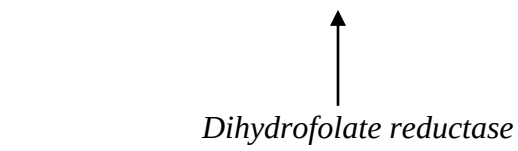
- 2.5 mg, 10 mg.

Ampoules:

- 2.5 mg/ml (2 mls)
- 25 mg/ml (2 ml, 20 mls)
- 100 mg/ml (10 ml, 50 ml)

Toxicity

Normal folate metabolism occurs as follows:



Tetrahydrofolate is essential for normal purine and hence DNA and RNA synthesis.

Methotrexate is a structural analogue of folate and hence can act as a false substrate for dihydrofolate reductase, thus leading to impaired DNA and RNA synthesis. This leads to inhibition of cell division.

See also Appendix 1 below.

Tissues with high cell turnover are therefore most affected, including:

1. Bone marrow
2. Gastrointestinal tract
3. Hair

But there can also be significant toxicity to:

4. Liver
5. Skin

6. Respiratory tract

7. Kidneys:

- In high dose methotrexate therapy, renal failure may be caused by the formation of intrarenal methotrexate crystals. Renal damage reduces methotrexate clearance, resulting in persistent elevation of MTX concentrations.

  Renal injury may therefore be the cause or result of methotrexate toxicity.

Once **inside** cells, **methotrexate** is metabolized to polyglutamate derivatives with a long median half-life of **1 - 4 weeks.** The polyglutamate derivatives cause cytotoxicity through the inhibition of dihydrofolate reductase.

This blocks the production of tetrahydrofolate, an essential co-factor in purine nucleotide synthesis inside the cells, which in turn inhibits DNA and RNA synthesis.

The low bioavailability and rapid intracellular uptake of methotrexate coupled with its short distribution half-life are the reasons why serum methotrexate concentrations are **not** useful in either **acute** *or* **chronic** ingestions.

The toxicity is therefore dependent on intracellular methotrexate concentrations, which correlate:

- Directly with bioavailable dose

And

- Inversely with renal function.

Pharmacokinetics

Absorption:

Methotrexate can be administered **orally, IV** and **intra-thecally.**

Peak levels occur within 1-2 hours of ingestion.

Oral bioavailability of methotrexate is low due to *saturable* absorption kinetics, dependent on the action of an active transporter protein (folate carrier-1 protein)

In fact it is so low that neither accidental pediatric ingestion or acute deliberate overdose in adults results in toxicity.

An **acute oral overdose** will not provide a bioavailable dose even close to 1 gram per m^2 of parenteral MTX.

Distribution:

- The volume of distribution is small at around 0.4 - 0.8 L/kg
- There is 50% protein binding.

Metabolism and excretion:

- Around 10% is metabolized to a nephrotoxic metabolite, 7-hydroxy-methotrexate.

  This metabolite can accumulate when high doses are of methotrexate are given.
- Around 90 % is excreted **renally** through both glomerular filtration and tubular secretion.
- The elimination half-life increases with the dose. With daily dosing, this can result in severe toxicity.

Risk Assessment

Acute overdose:

- There are no reports of toxicity following acute single oral ingestions in cases of deliberate self-poisoning, in patients with normal renal function.

Repeated supratherapeutic ingestions:

- Potentially **lethal bone marrow** suppression may develop if the weekly therapeutic oral dose is taken on as few as **3 consecutive days.**
- **Renal impairment** will *significantly* increase the risk of toxicity.

Intrathecal overdose:

- This is potentially lethal.

Clinical Features

Most patients remain asymptomatic after single acute ingestions.

Following inadvertent supratherapeutic ingestion, patients may present with:

1. Stomatitis:
   - This is an early sign of toxicity.
2. GIT upset:

- Nausea, vomiting and diarrhoea are common.

3. Bone marrow depression:

   - Anaemia is seen within 1-2 weeks.

4. Hepatic impairment.

5. Renal impairment.

Investigations

1. FBE.

2. U&Es/ glucose.

3. LFTs

Other tests are done as clinically indicated, ECG, blood alcohol level, paracetamol level.

Management

Following acute single ingestions:

1. Activated oral 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** also competes with methotrexate for oral absorption and so may also prevent absorption.

     However in patients who have been given activated charcoal or who have significant renal failure, folinic acid would have to be given **IV** in **order to antagonize the cellular toxicity of methotrexate.**

2. IV fluid rehydration, as required.

3. **Folinic acid:**

   Specialist toxicologist advice should always be sought for guidance on antidotal therapy by folinic acid rescue (or the specific antidote, carboxypeptidase G2), in particular for cases of inadvertent IV or intrathecal overdose.

   Note that folinic acid is not the same thing as folic acid.

In accidental or deliberate acute methotrexate ingestion, the bioavailable dose will be less than 50 mg ^{2}.

As the **bioavailable** dose is usually well short of the **1 gram per m ^{2}** intravenous dose used in oncology where a specific nomogram is designed to be applied, serum concentrations will not exceed this nomogram line.

Even with high dose **intravenous** methotrexate therapy, plasma methotrexate concentration is not a reliable predictor for adverse events. Hence, in acute oral methotrexate overdose, there is no reason to monitor methotrexate concentrations.

The only groups to be at significant risk who would require folinic acid therapy following acute single ingestion are

- **Very large ingestions > 1 gram per m ^{2}**
  - ♥ An average size adult body surface area is around 1.7 m^2

    So 1 gram MTX per m ^{2} = 1.7 grams of MTX - for the 10 mg tablet this would come to (the unlikely to be taken total) of **170 tablets.**
- **Renal impairment with eGFR < 45 mL/min/1.73 m ^{2}.**

Give 15 mg orally, every 6 hours.

For patients with nausea or vomiting this can be given IV in the first instance until the patient is tolerating oral tablets.

If charcoal has been given - then IV folate should be used in the first instance.

Therapy must be continued for at least 3 days

Patients should be discussed with a Clinical Toxicologist to determine the optimum duration of treatment and to define the desired end point (generally no symptoms and a normal blood count

Following chronic toxicity, (i.e. repeated supratherapeutic or staggered dosing):

- **Give 15 mg orally, every 6 hours.**

For patients with nausea or vomiting this can be given IV in the first instance until the patient is tolerating oral tablets.

Therapy must be continued for at least 3 days

Patients should be discussed with a Clinical Toxicologist to determine the optimum duration of treatment and to define the desired end point (generally no symptoms and a normal blood count).

G-CSF:

Granulocyte colony stimulating factor (G-CSF) has been used for established bone marrow depression, however the effectiveness of this treatment has not been established.

Glucarpidase:

Glucarpidase, is a recombinant form of the bacterial enzyme carboxypeptidase G2 that converts methotrexate into non-toxic metabolites.

It is used for inadvertent **intrathecal** methotrexate administration.

Disposition:

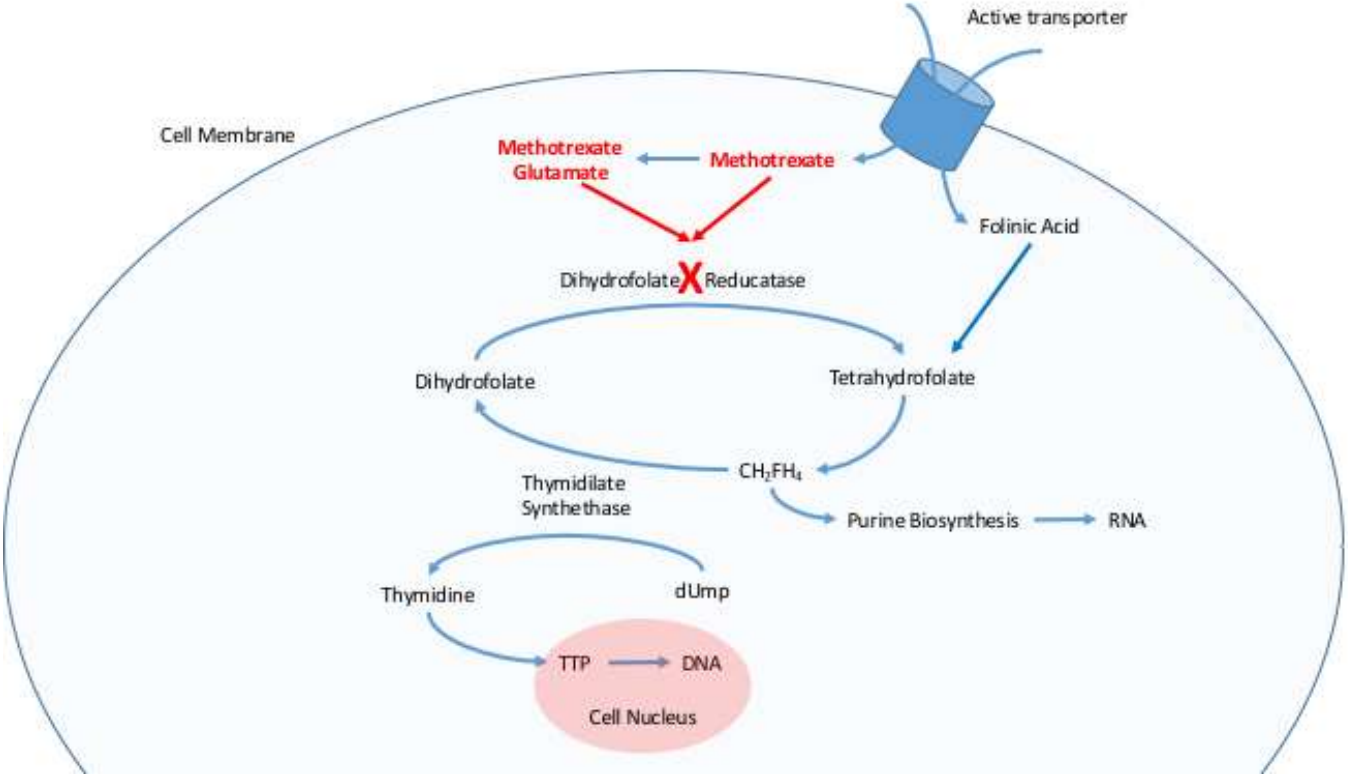
Specialist Toxicologist advice should always be sought for guidance on antidotal therapy by folinic acid rescue or the specific antidote, carboxypeptidase G2.

Patients with acute oral overdose and without renal failure will not require admission on medical grounds - but of course, may do so on psychiatric grounds.

Patients with chronic toxicity or with symptoms or abnormal investigations should be admitted to hospital. Selected asymptomatic patients with normal investigations may be suitable for management as an outpatient.

Appendix 1

The mechanism of MTX toxicity: [1]



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.

References

1. Betty S. Chan, Andrew H. Dawson & Nicholas A. Buckley. What can clinicians learn from therapeutic studies about the treatment of acute oral methotrexate poisoning? Clinical Toxicology, 2017 Vol. 55, No. 2, 88 - 96.

2. Methotrexate Toxicity in L Murray et al. Toxicology Handbook 3rd ed 2015.

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