

FOLINIC ACID



“The Battle of Chattanooga - Missionary Ridge”, oil on canvas, c. 1880, Thure de Thulstrup. Ulysses S. Grant directs an assault on Confederate positions on Missionary Ridge.

In October, Ulysses S. Grant, now in command of all Union armies from the Appalachians to the Mississippi, hurried to Chattanooga and immediately replaced Rosecrans with Thomas.

Braxton Bragg’s Confederate Army now occupied the 6 miles crest of Missionary Ridge east of the city. Confederate guns were massed on the 2,000 foot summit of nearby Lookout Mountain south of the town.

Grant, down in Chattanooga, resolved to drive them off.

The Battle of Chattanooga began on November 24th. Union troops stormed Lookout Mountain, fighting through such dense fog that it was remembered as the "Battle Above the Clouds"

During the night a besieged Bragg withdrew from the summit of Lookout Mountain to nearby Missionary Ridge.

Just before dawn the next morning, Federals stepped out onto an overhanging rock, and as the sun rose, unfurled their flag. Thousands of Union men in the valley below broke into a thunderous cheer. The Union had won.

The next Union task was to take Missionary Ridge. In command at the bottom of the hill was 115 pound General Phil Sheridan, who pulled a flask from his pocket and toasted the Confederate gunners above him.

"Here's at you", he said. The rebels opened fire, spattering him and his officers with dirt. "That was ungenerous", Sheridan said, "I'll take your guns for that!"

"Who ordered those men up the hill?", Grant asked.

"No one", an aide replied. "They started up without orders. When those fellows get started, all hell can't stop them"

"Those defending the heights, became more and more desperate. As our men approached the top, they shouted Chickamauga as though the word itself were a weapon. They thrust cartridges into guns by the handful. They lighted the fuses of shells and rolled them down, but nothing could stop the force of the charge"
(Union soldier)

Under Grant's leadership, the Union army had broken the Confederate siege at Chattanooga. It was another triumph for Grant.

"It was a great victory", Sherman said, "the neatest and cleanest battle I was ever in, and Grant deserves the credit of it all"

In the weeks that followed, everybody posed on Lookout Mountain

General Thomas ordered a Union cemetery laid out on a hill called Orchard Nob, that had seen savage fighting. A chaplain asked if the burials should be by state.

"Hell, no! Mix 'em all up", Thomas said, "I'm sick to death of states' rights!"

Ken Burns', "The Civil War", 1990.

Following the devastating Union defeat at Chickamauga Creek, the second bloodiest battle of the American Civil War, General Rosecrans, had withdrawn to Chattanooga with what was left of his army, isolated and without supplies, where he resigned himself to the inevitable final assault by Confederate General Braxton Bragg. But astonishingly Bragg hesitated, despite the desperate urgings of his divisional commanders. It would have been the Western Confederacy's best chance since Shiloh. Just as Union commanders George Meade lost his nerve following the Battle of Gettysburg, and George B. McClellan his following Antietam, so did Bragg lose his. Despite the victory he was badly shaken by the scale and ferocity of the killing at Chickamauga.

As soon as it became apparent that Bragg was holding back, Lincoln sent every possible reinforcement he could to Chattanooga, a vitally important strategic city. It had to be held at all costs. He dismissed the broken Rosecrans and replaced him with George Henry Thomas, the Union commander who had shown the most fight at Chickamauga. Then to Thomas's aid he sent his two biggest guns in the west, Ulysses S. Grant, now in command of all Union armies from the Appalachians to the Mississippi, and his right hand man William Tecumseh Sherman with his divisions from the Army of Tennessee. He also detached Joseph Hooker with his divisions from the Army of the Potomac, and sent him to Grant as well. Bragg then regained his nerve and moved on Chattanooga taking up what seemed like impregnable positions on Lookout Mountain and Missionary Ridge just outside the city. But his delay had been long enough for a huge force under Grant to have arrived for the relief of the siege.

Grant's plan now involved massive assaults on both flanks of the Confederate entrenchments. Hooker would attack Lookout Mountain on the right flank, while Sherman would attack the extreme left flank of Missionary Ridge. Grant considered a direct frontal assault on the central triple lines of Confederate trenches of the ridge to be suicide and so he placed Thomas' troops at the center merely to hold the line, believing that his men were still too shell shocked to be of much use in an all out assault. By this plan Grant had unwittingly applied a goad to Thomas' troops, who took this passive role as an affront to their valour. This goad, however would prove to be the stimulus for a spectacular, if somewhat serendipitous breakthrough.

The Battle of Chattanooga opened on 23 November 1863. Hooker's men stormed Lookout Mountain with an overwhelming force of three divisions against just three Confederate Brigades. The Yankee bluecoats scrambled up the steep slopes taking only relatively light casualties, over boulders and felled trees through a fog so dense that in later years the action became romanticized as the "Battle Above the Clouds". Having taken the hill they hoisted the Union flag to the thunderous cheering of the Union lines below. The Confederates drew back to strong defensive positions on the ridge however, and Hooker's advance stalled. Meanwhile on the left flank Sherman had run into serious resistance where Irish-born Confederate Commander Patrick Cleburne's division, the biggest and best in Bragg's army was repulsing repeated Union attacks. Sherman's four divisions had also stalled.

Frustrated at the lack of progress on the flanks, Grant now ordered Thomas to launch a limited assault on the first line of trenches of the Confederate center, in order to prevent Bragg from sending reinforcements to Cleburne. Thomas, humiliated at his secondary

role, needed no encouragement now....nor did his men. He sent his full four divisions directly toward the Confederate center, on a charge that seemed to be as hopeless as Picket's at Gettysburg. But the result would be the exact opposite. Helped by some confused and conflicting orders from Bragg to his front line troops the Unionists took full advantage, sweeping over the first line of trenches with astonishing ease. But then having accomplished what Grant had asked, flushed with adrenaline and momentum Thomas' men kept on charging directly into the second and then third lines of trenches. Unionists were so close on the heels of the fleeing first line of Confederates the those in the second line held their fire for fear of hitting their own men. Unsure of their orders and afraid to fire the Confederate lines suddenly disintegrated in chaos. Union regimental flags began appearing at the top of the ridge!

At his command post a mile in the rear Grant watched through his field glasses in total bewilderment. "Thomas!" he bellowed in rage, "who ordered those men up the ridge!" "I don't know General", he meekly replied, "it wasn't me!" Grant clamped his teeth hard down on his cigar and fumed, "Someone will catch hell if this turns out badly!" But he need not have worried. Thomas' men frantic for atonement and revenge for their fallen comrades took the ridge on the back of their own unstoppable momentum with shouts of "Chickamauga!" following the fleeing rebels. By sundown Union commanders were calling the action the "miracle of Missionary Ridge". Once again Ulysses S. Grant had come to the rescue of the Union, but on this occasion, perhaps by more by dumb luck than brilliant leadership!

When we are confronted with a patient with serious methotrexate toxicity, we need recall the quick action of Abraham Lincoln at the siege of Chattanooga! We must send our last best hope to the immediate rescue. In the case of methotrexate toxicity, this will be folinic acid.



"The Battle Above the Clouds", oil on canvas, 1874, James Walker

FOLINIC ACID

Introduction

Leucovorin, (folinic acid or 5-formyltetrahydrofolic acid) is routinely used for “folinic acid rescue” therapy following administration of parenteral methotrexate to oncology patients.

It has a *limited* role in toxicology therapeutics.

Note that folic acid (i.e. “folate” or vitamin B9) is NOT an effective *antidote* for methotrexate toxicity - the effective antidote for methotrexate toxicity is folinic acid, (5-formyl tetrahydrofolate).

Folinic acid is a metabolically active reduced form of folate that *bypasses* dihydrofolate reductase. It is a **stronger methotrexate antagonist** than folic acid, as folic acid must be enzymatically converted to a fully reduced form.³

However folinic acid seems to have no greater effect than folic acid in the **prevention** of methotrexate-related adverse effects. As folinic acid may reduce the effectiveness of methotrexate and is more expensive, its routine use is not recommended.³

Folinic acid has an important role in the treatment of methotrexate overdose and acute bone marrow toxicity, due to its **faster action** and **independence of dihydrofolate reductase**.³

History

Folinic acid was discovered in 1948, by H.E Sauberlich and C. A Baumann

Preparations

Folinic acid preparations include:

Tablets:

- Calcium folinate: 15 mg tablets.

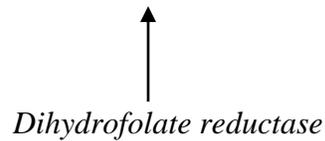
Ampoules:

- Calcium folinate: 15 mg/ 2 ml ampoules.
- Calcium folinate: 50 mg/ 5 ml ampoules.
- Calcium folinate: 100 mg/ 10 ml ampoules.

Mechanism of Action

Normal folate metabolism occurs as follows:

Folate → Dihydrofolate → Tetrahydrofolate



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.

Folinic acid is a metabolically active reduced form of folate that *bypasses* dihydrofolate reductase.

Pharmacodynamics

Folinic acid has an important role in the treatment of methotrexate overdose and acute bone marrow toxicity, due to its **faster action** and **independence of dihydrofolate reductase**

Pharmacokinetics

Administration:

- Folinic acid can be given orally, IM or IV.

Oral bioavailability is almost 100 % following a **15 mg dose**, but becomes less with higher doses.

Distribution:

- The active isomer has a Vd of 13.6 L

Metabolism:

- Elimination is predominantly by metabolism to another active metabolite, 5-methyl- tetrahydrofolate.

Indications

Toxicological indications include:

1. Supratherapeutic methotrexate ingestion:

This usually occurs in the context of accidental daily dosing rather than the usual weekly dosing regimen.

Folinic acid therapy will be indicated when:

- There are clinical signs of toxicity.
- The weekly dose has been administered daily for more than 3 consecutive days.

2. Single acute oral methotrexate overdose:

Surprisingly methotrexate toxicity has not been reported in this scenario!

- However empirical folinic acid is recommended if **more than 500 mg (5mg/kg in children)**, has been ingested, until methotrexate levels become available to more fully assess the risk of toxicity.
- If less than 500 mg of methotrexate is ingested, consider folinic acid when methotrexate levels are not available within 24 hours.

3. Adjunctive treatment for methanol poisoning:

- Folinic acid can enhance the elimination of formic acid

4. Massive overdose of:

- Pyrimethamine
- Trimethoprim

Contra-indications / Precautions

- Known severe allergic reactions.

Pregnancy:

Folinic acid is a category A drug with respect to pregnancy.

Category A drugs are those drugs which have been taken by a large number of pregnant women and women of childbearing age without any proven increase in the frequency of malformations or other direct or indirect harmful effects on the fetus having been observed.

Calcium folinate is an active metabolite of folic acid which works to counteract the effects of folic acid antagonists.

It has been used with antineoplastic agents such as 5-fluorouracil and oxaliplatin for metastatic colon cancer during the second and third trimesters of pregnancy with normal pregnancy outcomes .

Calcium folinate is safe to use during pregnancy at the recommended doses.

Breast deeding:

Folinic acid is considered to be safe in breast feeding.

Adverse Reactions

1. Allergic reactions
2. Seizures
3. Hypercalcemia, (with rapid IV administration, > 160 mg/min).

Dosing

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

For the treatment of methotrexate poisoning in adults:

Acute single ingestion overdose:

In accidental or deliberate acute methotrexate ingestion, the bioavailable dose will be less than 50 mg².

As the **bioavailable** dose is usually well short of the **1 gram per m²** 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 m²**
 - ♥ An average size adult body surface area is around 1.7 m²
So 1 gram MTX per m² = 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 m².**

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

Chronic toxicity, (i.e. repeated suprathreshold or staggered dosing):

Give 15 mg orally, every 6 hours.

Folinic acid has saturable bioavailability because it shares the same active transporter with methotrexate and the maximum amount that can be absorbed is around 15 mg

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).



Ulysses S. Grant (left) poses at Missionary Ridge following his victory at the Battle of Chattanooga, November 1863.

References

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