



"Let Us Have Peace" , oil on canvas, Jean Léon Gérôme

1:00 came - I turned about. There behind me appeared a commanding form, superbly mounted, richly accoutered, of imposing bearing, noble countenance, with expression of deep sadness over-mastered by deeper strength. It was no other than Robert E. Lee. Not long after appeared another form - plain, unassuming, simple, and familiar to our eyes, but as awe-inspiring as Lee in his splendor and sadness. It was Grant, sitting in his saddle with the ease of a born master, taking no notice of anything, all his faculties gathered into intense thought. He seemed greater than I had ever seen him, a look as of another world about him, (Joshua Lawrence Chamberlain).

...On April 6 at Saylers Creek, Union cavalry and infantry inflicted 6,000 casualties on Lee's army and captured eight generals, including Lee's own son Custis. He now had fewer than 25,000 men. 125,000 federal troops were now closing in on Lee from three sides. Union general Phil Sheridan wired Grant, "If the thing is pressed, I think that Lee will surrender".

"Let the thing be pressed!", Grant answered.

An officer urged Lee to surrender. The general asked what the country would think of him if he failed to fight on. "The country be damned", said the officer, "there is no country! There has been no country for a year or more. You're the country to these men!"

*"The few men who still carried their muskets had hardly the appearance of soldiers, their clothes all tattered and covered with mud, their eyes sunken and lusterless, yet still they were waiting for general Lee to say where they were to face about and fight".
(Magnus Thompson, 35th Virginia Cavalry battalion).*

Lee's Confederate army was moving along one side of the Appomattox river, a willow-fringed run that any country boy could jump. His pursuers clung to the opposite bank...

*5 P.M., April 7, 1865: General Lee, The result of last week must convince you of the hopelessness of further resistance. I regard it as my duty to shift from myself the responsibility of any further effusion of blood by asking of you the surrender of that portion of the Confederate States army known as the Army of Northern Virginia".
(Ulysses S. Grant).*

On April 8, Grant again flanked Lee's army and captured two trainloads of supplies. The Confederates were now living on handfuls of parched corn. That night, Lee and his weary lieutenants gathered around a campfire near the little village of Appomattox courthouse.

*"We met in the woods at his headquarters by a low-burning bivouac fire. There was no tent, no table, no chairs, no camp stools. On blankets spread upon the ground or on saddles at the roots of trees we sat around the great commander".
(General John B. Gordon).*

They were almost entirely surrounded, outnumbered nearly 5 to 1, without hope of resupply or reinforcement.

"By sunrise, we had reached Appomattox station, where we might cut Lee's retreat. Already we heard the sharp ring of the horse artillery. There was no mistake. Sheridan was square across the enemy's front, holding at bay all that was left of the proudest army of the Confederacy. It had come at last - the supreme hour". (Joshua Lawrence Chamberlain).

April 9 was Palm Sunday. Lee ordered Gordon to make one more attempt at breaking out. At dawn, just outside Appomattox courthouse, Gordon's men drove Federal cavalry from their positions and swept forward to the crest of a hill. Below them, a solid wall of blue was advancing - the entire Union army of the James.

“There is nothing left for me to do but to go and see General Grant, and I would rather die a thousand deaths”. (Robert E Lee)

Shortly before noon Lee dispatched a letter under a white flag into the Union lines. Grant was resting in a field, nursing a blinding headache. Suddenly, a horseman galloped up at full speed, a reporter noted, waving his hat above his head and shouting at every jump. Grant opened the envelope, looked at it, then asked his friend general John Rawlins to read it aloud. Lee would surrender. Grant himself said nothing, betrayed no more emotion, a witness said, than last year’s bird nest. But his headache had instantly disappeared.

“No one looked his comrade in the face. Finally colonel Duff, chief of artillery, sprang upon a log and proposed three cheers. A feeble hurrah came from a few throats, when all broke down in tears.” (Sylvanus Cadwallader, War Correspondent)

Lee dispatched colonel Charles Marshall to Appomattox courthouse to find a suitable building in which he and Grant might meet. The streets were almost deserted. Marshall stopped the first civilian he happened to see, Wilmer McLean, who reluctantly agreed to loan the army his house for the occasion. By a singular coincidence, the meeting of Generals Lee and Grant took place in the house of Wilmer McLean, the same gentleman who, in 1861, at the battle of Bull Run, had tendered his house to general Beauregard for headquarters. He removed from Manassas after the battle with the intention of seeking some quiet nook where the alarms of war could never find him!”

“1:00 came - I turned about. There behind me appeared a commanding form, superbly mounted, richly accoutered, of imposing bearing, noble countenance, with expression of deep sadness over-mastered by deeper strength. It was no other than Robert E. Lee. Not long after appeared another form - plain, unassuming, simple, and familiar to our eyes, but as awe-inspiring as Lee in his splendor and sadness. It was Grant, sitting his saddle with the ease of a born master, taking no notice of anything, all his faculties gathered into intense thought. He seemed greater than I had ever seen him, a look as of another world about him”. (Joshua Lawrence Chamberlain).

Lee arrived at the McLean house first, magnificent in a crisp gray uniform, an engraved sword at his side. “I have probably to be General Grant’s prisoner”, he explained to an aide, “and thought I must make my best appearance”. He waited half an hour for Grant to arrive. The Union commander wore a private’s dirty jacket. His boots and trousers were splattered with mud. He had no sword. The two commanders shook hands.

“What General Lee’s feelings were, I do not know, as he was a man of much dignity with an impassible face, his feelings were entirely concealed from my observation, but my own feelings were sad and depressed. I felt like anything rather than rejoicing at the downfall of a foe who had fought so long and valiantly and had suffered so much for a cause, though that cause was, I believe, one of the worst for which people ever fought”.
(Ulysses S. Grant)

Grant reminded Lee that they had met once before during the Mexican war. Lee said he had not remembered what Grant looked like.

"Our conversation grew so pleasant that I almost forgot the object of the meeting. General Lee called my attention to the object". (Ulysses S. Grant)

"They knew each other. Grant remembered Lee very well. Lee didn't quite remember Grant. That was understandable from the time that they were acquainted back in the early days, but I think it was the sensitivity that the two men had for each other and for the moment, enormous dignity and yet the necessary informality - Grant not wanting to get to the point too quickly, Lee bringing him up shortly to the point of why they're together; Lee dressed in his last good uniform, Grant apologizing that he was rushing from the field and didn't have time to change; the scribe being unable to hold the pen steady and having it taken by another soldier. The, uh...that, from Lee's point of view, awful moment, and from Grant's point of view, glorious moment, and yet for the two of them, a sad and quiet moment; and Lee taking his leave and doffing his hat from Traveler and riding back to his troops after securing those reasonable terms. It was the beginning of the unification of the country".

(Congressman James Symington)

The terms Grant offered were simple and generous. Confederate officers could keep their side-arms and personal possessions. Officers and men who owned their own horses could keep them, too. It was planting season. Grant asked Lee how many men he had and if they needed any rations. Lee said he no longer knew the size of his army, but he was sure all his men were hungry. Grant offered 25,000 rations.

"This will have the best effect upon my men. It will be very gratifying and do much toward conciliating our people".

(Robert E. Lee)

Colonel Eli S. Parker, a Seneca Indian and a member of Grant's staff, inscribed the articles of surrender for the two commanders to sign. The two men shook hands again. Lee left the house, mounted Traveler, and started back toward his army. The Union soldiers began to cheer. Grant ordered them to stop. "The Confederates are now our prisoners", he explained, "and we do not want to exult over their downfall. The war is over. The rebels are our countrymen again".

Lee's men lined the road to his camp. "As he approached, we could see the reins hanging loose, and his head was sunk low on his breast. As the men began to cheer, he raised his head, and, hat in hand, he passed by, his face flushed, his eyes ablaze".

"As he passed, they raised their heads and looked upon him with swimming eyes. Those who could find voice said good-bye. Those who could not speak passed their hands gently over the sides of Traveler".

If one army drank the joy of victory and the other the bitter draught of defeat, it was a joy moderated by the recollection of the cost at which it had been purchased and a defeat mollified by the consciousness of many triumphs. If the victors could recall a Malvern

hill, an Antietam, a Gettysburg, a Five Forks, the vanquished could recall a Manassas, a Fredericksburg, a Chancellorsville, a Cold Harbor. A crowd of soldiers waited in front of Lee's tent.

"Boys", he told them, "I have done the best I could for you. Go home now, and if you make as good citizens as you have soldiers, you will do well, and I shall always be proud of you. Good-bye, and God bless you all". He turned and disappeared into his tent.....

The formal surrender came 3 days later. General John B. Gordon, shot through the face and wounded four more times in the service of the confederacy, led 20,000 men toward the Union lines for the last time - not to fight, but to stack their arms and surrender their battle flags. There to receive them was major general Joshua Lawrence Chamberlain, himself wounded six times for the Union. Promoted on the field at Petersburg near death, he had somehow survived.

"On they come with the old swinging route step and swaying battle flags. Before us in proud humiliation stood the embodiment of manhood - thin, worn, and famished, but erect and with eyes looking level into ours waking memories that bound us together as no other bond. Was not such manhood to be welcomed back into the Union so tested and assured? On our part, not a sound of trumpet more nor roll of drum, not a cheer nor word nor whisper of vain-glorying nor motion of man, but an awed stillness, rather, and breath-holding, as if it were the passing of the dead".

(Joshua Lawrence Chamberlain).

Now Chamberlain made an extraordinary gesture. "Chamberlain called his men into line, and as my men marched in front of them, the veterans in blue gave a soldierly salute to those vanquished heroes, a token of respect from Americans to Americans".

(General John B. Gordon).

"At the sound of that machinelike snap of arms general Gordon started, then wheeled his horse, facing me, touching him gently with the spur so that the animal slightly reared, and, as he wheeled, horse and rider made one motion. the horse's head swung down with a graceful bow, and General Gordon dropped his sword point to his toe in salutation".

(Joshua Lawrence Chamberlain)....

The Confederate States of America had once stretched from the Rappahannock to the Rio Grande. Its leaders had once dreamed of a tropical empire reaching ever southward to Mexico, Guatemala, Nicaragua, Brazil.

By April 1865, the dream was gone.

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

Only two things could have quickly relieved Ulysses S. Grant's blinding migraine on the morning of April 9, 1865. The 21st century fast acting triptan, zolmitriptan, was not available to him in the Nineteenth century, the surrender of Robert E. Lee and the Army of Northern Virginia, however was!

ZOLMITRIPTAN

Introduction

Zolmitriptan is a highly specific **5-HT₁** receptor **agonist** with particular affinity for the **5-HT_{1B}** and **5-HT_{1D}** receptors.

Zolmitriptan has similar **efficacy** and **adverse effects** to **sumatriptan**.

Zolmitriptan however is only available in **tablet** form in Australia.

It was developed in an attempt to provide a more lipophilic molecule that would cross the blood - brain barrier more quickly (**and so act faster**) than oral sumatriptan.

Serotonin is **5-hydroxytryptamine (5-HT)** which is a monoamine neurotransmitter that is derived from tryptophan.

Zolmitriptan is a **specific** agent for the treatment of migraine headache.

It is (along with other triptans) therefore the most specific treatment for both migraine and cluster headaches.

The triptans have a number of important advantages over many other anti-migraine medications including:

1. It is not significantly sedating, (unlike chlorpromazine)
2. It does not cause hypotension (unlike chlorpromazine)
3. It is a more efficacious agent (providing true migraine is the cause of the headache), than the simple analgesics or prochlorperazine.
4. It does not have physical or psychological addictive potential.
5. It is a **specific** treatment for migraine.
6. It alleviates the non-headache features of migraine (e.g. nausea and vomiting). (ergot does not).
7. It can be used effectively at any point in the migraine, (compared to ergot which must be used early)

History

Studies in the 1960s showed that vasoconstriction from serotonin (5-HT), ergotamine and noradrenaline could reduce migraine attacks. Research also showed that platelet 5-HT levels are reduced during migraine attacks.

As 5-HT had too many adverse effects to be used as a drug, research was commenced on the receptors of 5-HT in order to discover and develop more specific agonist agents for 5-HT receptors.

Sumatriptan was the prototype serotonin agonist and was introduced in the Netherlands in 1991 for the treatment of migraine headache.

Chemistry

Zolmitriptan is a synthetic **triptan** (i.e. tryptamine based) drug.

Tryptamine is a monoamine alkaloid that contains an indole ring structure, and is structurally similar to the amino acid tryptophan, from which it derives its name.

Zolmitriptan is a chiral molecule, which is synthesized as the S enantiomer.

It is a more lipophilic molecule than sumatriptan.

Physiology

See Appendix 1 below.

Classification

The triptan anti-migraine serotonin agonist drugs currently available in Australia include:

1. Sumatriptan
2. Eletriptan
3. Naratriptan
4. Rizatriptan
5. **Zolmitriptan**

Preparations

Zolmitriptan as:

Tablets:

- 2.5 mg.

Mechanism of Action

Triptans are specific and selective agonists for the 5-HT₁ receptors.

Zolmitriptan is a highly specific **5-HT₁** receptor **agonist** with particular affinity for the **5-HT_{1B}** and **5-HT_{1D}** receptors.

It has only modest affinity for 5HT1A receptors

Zolmitriptan has no significant affinity or pharmacological activity at 5HT2, 5HT3, 5HT4 receptors.

Zolmitriptan, Rizatriptan, Naratriptan, Almotriptan, and Frovatriptan bind to 5-HT_{1B} and 5-HT_{1D} receptors and Eletriptan binds to 5-HT_{1B}, 5-HT_{1D} and 5-HT_{1F} receptors.

The vascular 5HT₁ receptor is found predominantly in cranial blood vessels and mediates vasoconstriction. The carotid arterial circulation supplies blood to the extra-cranial and intra-cranial tissues such as the meninges. Dilatation in these vessels is thought to be the underlying mechanism of migraine. Initial aura has been attributed to an initial vasoconstriction phase, that precedes the vasodilation or headache, phase.

Triptans are believed to exert their effects through vasoconstriction of cranial vessels by acting selectively at the 5HT_{1B/1D} receptors.

They are also thought to inhibit the abnormal activation of trigeminal nociceptors.

Pharmacodynamics

With the exception of naratriptan, the oral triptans relieve headache within **30 - 60 minutes**.

Zolmitriptan (and eletriptan) have similar **efficacy** and **adverse effects** to **sumatriptan**.

Zolmitriptan was developed in an attempt to provide a more lipophilic molecule that would cross the blood - brain barrier more quickly (and so act faster) than oral sumatriptan.

It is more effective the earlier it is given following the onset of headache, however it can still have good efficacy if given late.

Eletriptan, naratriptan, rizatriptan and zolmitriptan have better oral bioavailability than sumatriptan, however this difference may not be clinically significant if adequate doses are given.¹

The response to each agent can vary considerably between individual patients.

The same individual may also respond quite differently to different triptans, and so if one agent is ineffective, a trial of a different triptan is worthwhile.

Pharmacokinetics

Absorption:

- Zolmitriptan is administered orally.
It is rapidly absorbed following ingestion.
- The mean absolute bioavailability of zolmitriptan is approximately 40% however there is a degree of intersubject variability.

Distribution

- Protein binding is modest at around 25 %.
- The volume of distribution for zolmitriptan following IV administration is 2.4 L/kg.
- It is unknown if zolmitriptan crosses the human placenta
- It is likely that zolmitriptan is excreted into human breast milk.

Metabolism and excretion:

- Zolmitriptan is eliminated largely by hepatic metabolism.

It has an active N-desmethyl metabolite (183C91).

This metabolite has higher in vitro agonist affinity for 5HT1B/1D receptors than zolmitriptan (it also has modest affinity for 5HT1A receptors).

The N-desmethyl metabolite is 2 - 6 times more potent, in animal models, than zolmitriptan.

- The plasma half-life of zolmitriptan was 4.7 hours in healthy volunteers, 7.3 hours in patients with moderate liver disease and 12 hours in those with severe liver disease.

The corresponding half-life values for the 183C91 metabolite are 5.7 hours, 7.5 hours and 7.8 hours respectively.

Indications

The triptans as a class are indicated for:

1. The acute relief of migraine headache (with or without aura).
2. The acute relief of cluster headache

They are not effective for other forms of headache.

Contra-indications/precautions

Contraindications / precautions to the triptans as a group include:

1. CVS disease:

Triptans should not be used in:

- Ischaemic heart disease
- Prinzmetal's angina
- Uncontrolled hypertension.

2. Cerebrovascular disease:

- TIA
- Stroke

3. Hemiplegic migraine:

- Although there is no good information on the use of triptans in hemiplegic migraine, current convention is that in true hemiplegic migraine (i.e attacks of organic hemiplegia), they are avoided.

Note that it is safe to use if there is just sensory deficit or mild "heaviness" of limbs on one side, as opposed to true hemiplegia.

4. Drug interactions:

- Use with, or within **14 days** of stopping, a **MAOI**:
 - ♥ These inhibit the metabolism of sumatriptan, and so may increase toxicity.

Eletriptan and **naratriptan** are the only triptans that are **not** substrates of MAO-A so these are the best options in patients taking MAOIs.
- Use with, or within **24 hours** of stopping, **ergometrine** or **methysergide**:
 - ♥ Ergometrine may increase risk of vasospasm.
 - ♥ Methysergide (an ergot alkaloid derivative) may increase the risk of vasospasm with triptans
- Use with ondansetron/ granisetron

On theoretical grounds it may be expected that ondansetron (or similar) as a serotonin antagonist could reduce the effects of triptans, which are serotonin agonists.

While - strictly speaking - they act on different serotonin receptors; ondansetron being a highly selective **5-HT₃** serotonin receptor **antagonist**, whilst triptans are highly specific **5-HT₁** receptor **agonist**, receptor specificity is probably not completely exclusive to these receptors groups.

In any case, anecdotally, they have often been used together with apparently good effects of both agents, (*personal communication Dr Doug Crompton 25/8/2016*).

5. Severe hepatic impairment.

6. Elderly:

- Data is limited; but use not recommended due to potential increased risk of cardiovascular adverse effects.

Pregnancy

Zolmitriptan is classified as a Category B3 drug with respect to pregnancy

Category B3 drug are those drugs which have been taken by only a limited number of pregnant women and women of childbearing age, without an increase in the frequency of malformation or other direct or indirect harmful effects on the human fetus having been observed. Studies in animals have shown evidence of an increased occurrence of fetal damage, the significance of which is considered uncertain in humans.

There is very limited information available describing the use of zolmitriptan during pregnancy.

Most of the information on triptan use during pregnancy is available specifically for sumatriptan.

Maternal use of sumatriptan for the treatment of migraines has not been associated with an increased risk of congenital malformations.

One study has suggested there may be a possible increased risk of preterm birth and low birth weight with exposure to triptans during pregnancy.

Another study has reported triptan use during the second and/or third trimesters may be associated with a slight increase in the risk of atonic uterus and haemorrhage during labour.

Analgesics such as paracetamol or opioids (e.g. codeine, morphine) are the initial medicines of choice to manage migraine attacks during pregnancy.

Breast feeding

Reports describing the use of zolmitriptan during breast feeding have not been located.

Consider an alternative medicine with greater clinical safety information during breastfeeding if possible.

If a triptan is the treatment of choice, consider sumatriptan, which has more safety information available.

Use sumatriptan at the lowest effective daily dose and observe the breastfed infant for potential adverse effects such as drowsiness, vomiting, poor feeding and restlessness.

Adverse Effects

Adverse effects are usually minor.

Possible adverse effects of the triptans, as a group include:

1. Mild dizziness
2. Mild sedation
3. A “rush” or ‘flushed’ feeling - more common with SC administration of sumatriptan
 - Also described are subjective feelings of chest “tightness” (without any documented changes in lung function or on ECG)
4. Mild elevations of blood pressure.
5. Serotonin toxicity:
 - There have been reports of triptans causing serotonin toxicity, but the risk is very low.
It may be more likely to occur when sumatriptan is combined with other serotonergic agents.
6. Coronary vasospasm.
 - Therefore is best avoided in patients with significant coronary artery disease.

Dosing

Usual adult dosing is:

- Oral **2.5 mg** as soon as possible after onset of headache.

The tablet should be swallowed whole with water.

If symptoms of migraine persist or recur within 24 hours of an initial response, a second dose may be taken. A second dose however should not be taken within **2 hours** of the initial dose.

If a patient does not achieve satisfactory relief with 2.5 mg doses, subsequent attacks can be treated with **5 mg** doses of zolmitriptan.

The maximum daily dose **10 mg**.

The maximum daily dose in severe liver failure is 5 mg.

Appendix 1

5-Hydroxy-tryptamine receptor subtypes:

5 HT Family	Receptor Type	Mechanism	Action
5 HT₁ <i>Subtypes:</i> 1A, 1B, 1D, 1E, 1F	G _i /G _o -protein coupled.	Decreasing cellular levels of cAMP.	Inhibitory
5 HT₂ <i>Subtypes:</i> 2A, 2B, 2C	G _q /G ₁₁ -protein coupled.	Increasing cellular levels of IP ₃ and DAG	Excitatory
5 HT₃	Ligand-gated Na ⁺ and K ⁺ cation channel	Depolarizing plasma membrane.	Excitatory
5 HT₄	G _s -protein coupled.	Increasing cellular levels of cAMP.	Excitatory
5 HT₅ <i>Subtypes:</i> 5A, 5B	G _i /G _o -protein coupled	Decreasing cellular levels of cAMP.	Inhibitory
5 HT₆	G _s -protein coupled.	Increasing cellular levels of cAMP.	Excitatory
5 HT₇	G _s -protein coupled.	Increasing cellular levels of cAMP.	Excitatory

There is no 5-HT_{1C} receptor, as it was reclassified as the 5-HT_{2C} receptor



Appomattox Courthouse, April 1865.

"By a singular coincidence, the meeting of Generals Lee and Grant took place in the house of Wilmer McLean, the same gentleman who, in 1861, at the battle of Bull Run, had tendered his house to general Beauregard for headquarters. He removed from Manassas after the battle with the intention of seeking some quiet nook where the alarms of war could never find him!"



The McLean house has been preserved as a memorial to the end of American Civil War. Above is a panoramic view of the parlour where Lee surrendered to Grant, as it is today.

References

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