

TERLIPRESSIN



Contemporary photograph of the site of the second day of the Battle of Chickamauga Creek, near Chattanooga, Tennessee. Apart from Gettysburg it would be the bloodiest battle of the Civil War, (Library of Congress).

....Hard against the Tennessee river, at the meeting point of two strategically crucial railroads, the city of Chattanooga guarded the gateway to the eastern Confederacy and the rebel war industries in Georgia.

For five months Union general William Rosecrans resisted Lincoln's urgent calls to drive Braxton Bragg's Confederates out of Tennessee and seize Chattanooga.

When summer came, Lincoln demanded more decisive action, and at long last Rosecrans moved, launching a series of brilliant and almost bloodless flanking maneuvers.

In ten days he drove Bragg 80 miles through a relentless Tennessee rain. "No Presbyterian rain either", a soldier remembered, "but a genuine Baptist downpour".

In September Bragg abandoned Chattanooga and kept backing away until just over the Tennessee line in Georgia, where he gathered his forces, now bolstered by Longstreet's Virginia veterans, along a meandering creek called Chickamauga

Chickamauga, is like all Indian words...interpreted... to mean "River of Death" - God knows what it really means. Chickamauga was a horrendous battle, a very lot of breakthroughs, a lot of hand to hand combat, a long ragged retreat, a glorious Southern victory which was unexploited. All the western heroes were there, from Forrest on down....(lost in thought, softly)...it's a very great battle...(Shelby Foote, Civil War Historian)

At 8.00 AM on the morning of September 18th, Nathan Bedford Forrest's cavalry ran onto a brigade of Federals heading for a little bridge over the creek. By noon, one of Forrest's officers reported, "The dead were piled upon each other like cordwood to make passage for advancing columns". By nightfall, both lines held.

On the second day of fierce fighting, Rosecrans committed a fatal mistake, ordering his troops to close a gap in the Union line that wasn't there. In the process he opened up a real one, and Longstreet's Confederates stormed through.

The Union forces broke and ran. "They have fought their last man", Longstreet said, "and even he is running"

But George Henry Thomas, a Union man from Virginia, refused to retreat and organized a stubborn last minute defense that kept the battle from becoming a rout and earned him the nickname the "Rock of Chickamauga"

The Northern army limped back into Chattanooga. Rosecrans was "confused and stunned", Lincoln said, "like a duck hit on the head". Bottled up in Chattanooga, the Union forces were miserable, cold, vermin infested, cutoff from all but a thin trickle of supplies. They demolished houses and hacked down every tree and fence in town for fuel.

The Confederates besieging the city were in no better shape.

"In the very acme of our privations and hunger, when the army was most dissatisfied and unhappy we were ordered into line to be reviewed by the honorable Jefferson Davis. When he passed us with his great retinue of staff officers at full gallop, cheers greeted him with the words, "send us something to eat Master Jeff, I'm hungry, I'm hungry!"
Sam Watkins, (Confederate Soldier)

David McCullough and Shelby Foote in Ken Burns', "The Civil War", 1990.

With the evacuation of Chattanooga in September 1863, the Confederate situation in the west had become desperate in the extreme. Southern armies began to experience desertions. "There is no use fighting any longer now", wrote one deserter from Georgia, "for we are done gon up the Spout!". Jefferson Davis privately agreed and confessed himself to be in the depths of gloom... "We are now in the darkest hour of our political existence". This was not entirely true, as the Union advance on Richmond in 1862, had been even more imminently dire, until the brilliant exploits of Robert E. Lee and Stonewall Jackson had saved the South, then even threatened Washington itself. Davis called on Lee to go out west, but Lee insisted he could not, as he was fully occupied in reorganizing and rebuilding his Army of Northern Virginia, and defending Richmond following the disaster at Gettysburg. Davis thought better of it and agreed. If Lee had saved the South from a desperate situation in 1862 by unexpectedly going onto the attack then Braxton Bragg must now do the same. Accordingly he detached two of James Longstreet's veteran divisions from Lee and sent them to assist the beleaguered western commander.

Now with roughly equal forces of around 60,000 men each, Bragg commanding the Army of Tennessee finally felt confident enough to attack William S. Rosecrans' Union Army of the Cumberland. On September 18, the two armies clashed at Chickamauga Creek sparked by a fierce skirmish between Confederate General Nathan Bedford Forrest and Union troops at Reed's Bridge. It would be by far the greatest battle in the west, and indeed would be the bloodiest battle, bar Gettysburg, of the entire Civil War. There would be over 34,000 casualties in total, (16,000 Union and 18,000 Confederate). Going totally against the general run of Union victories in the west, the Battle of Chickamauga Creek would be a stunning and crushing Confederate victory, by far their greatest in the western theater.

But the Battle would be marked by serious blunders from the commanding generals of both sides. On the second day of ferocious fighting, Rosecrans committed a fatal mistake, ordering his troops to close a gap in the Union line that wasn't there. In the process he opened up a real one, and Longstreet's Confederates stormed through, scattering the panicked Union soldiers. The only thing that stopped a total Northern route was Union General, George Henry Thomas, who like Stonewall Jackson at first Bull Run, held firm against an overwhelming onslaught. Thomas' holding action, unlike Jackson's did not win the day, however it did allow Rosecrans' battered divisions to limp back into the relative safety of Chattanooga. If Jackson had been a stonewall, then Thomas had been a rock - he became known hereafter as the "Rock of Chickamauga".

Eventually however Thomas too had to fall back. Now Rosecrans was trapped in Chattanooga with his demoralized army, virtually without supplies. All Bragg had to do was to follow-up and deliver the coup de grace. But as McClellan had failed to follow-up after Antietam and Meade had failed to follow-up after Gettysburg, now it was the Confederate commander, unnerved by the ferocity and scale of the battle who failed to follow-up by attacking Rosecrans in Chattanooga. The fiery blooded Nathan Bedford Forrest, who had let his displeasure be known at Donelson at the surrender of that fort to Grant, now confronted Bragg, and exploded, "I have stood your meanness as long as I intend to. You have played the part of a dammed scoundrel....If you ever again try to interfere with me or cross my path, it will be at the peril of your life!" As at Donelson, he

then stormed off with his men, as an independent commander! James Longstreet was so disgusted he wrote to the secretary of war that, “nothing but the hand of God can save us or help us as long as we have our present commander!”. Still Bragg refused to move on Chattanooga. Worse still, Jefferson Davis, did nothing. As soon as Lincoln realized that there would be no immediate attack on Chattanooga, he dismissed Rosecrans and replaced him with Thomas. Next he called out his two biggest guns in the west - Ulysses S. Grant and William Tecumseh Sherman, both were to move immediately to reinforce Chattanooga. Though Chickamauga was a great victory, the Confederacy failed to exploit it, just as Union commanders had failed to exploit victory at Gettysburg and the stalemate at Antietam. The western Confederates had lost their best chance since Shiloh.

When we are presented with a patient with variceal bleeding of the esophagus, we may face a very bloody battle indeed. Our first strategy may include the urgent administration of IV terlipressin. By this agent we may have a significant victory, yet this alone will not ensure ultimate victory. We need recall the lessons of the great Battle at Chickamauga Creek, there must be no hesitation. In all cases timely follow-up with endoscopy must ensue, if there is to be any chance of ultimate victory.



Confederates soldiers advancing at Chickamauga, contemporary pen and ink sketch, Alfred Waud, Library of Congress, Washington D.C

TERLIPRESSIN

Introduction

Terlipressin is a synthetic analogue of vasopressin which in turn is a synthetic form of the normal human hormone arginine vasopressin (or **antidiuretic hormone**, or **ADH**).

It has **less adverse effects** than vasopressin.

It is indicated for **bleeding oesophageal varices**

History

The American biochemist **Vincent du Vigneaud** (1901 - 1978) won the 1955 Nobel Prize in Chemistry for his work on elucidating and synthesizing the posterior pituitary hormones, oxytocin and vasopressin.

Chemistry

Terlipressin is a synthetic analogue of vasopressin.

Physiology

Arginine vasopressin (or **antidiuretic hormone**, or **ADH**) is a hormone produced by the posterior lobe of the pituitary gland.

It plays an important role the homeostasis of blood pressure and blood volume, (see **Appendix 1 below**).

Classification

Terlipressin belongs to the pharmaco-therapeutic group of posterior pituitary lobe hormones (i.e vasopressin and its analogues)

Vasopressin analogues include:

1. Desmopressin (1-**desamino-8-D-arginine vasopressin** - DDAVP)
2. **Terlipressin** (L-lysine vasopressin)

Preparations

Strengths are expressed as terlipressin base.

Terlipressin base 0.85 mg is equivalent to terlipressin acetate 1 mg.

Terlipressin acetate as:

Ampoules:

- 0.1 mg/mL, 8.5 mL (solution)
- 0.85 mg (powder for reconstitution)

Mechanism of Action

Terlipressin acts on **V1a receptors** on vascular smooth muscle in the splanchnic and portal circulation to produce:

1. Vasoconstriction primarily of the **splanchnic bed**.
 - This leads to a reduction of splanchnic blood flow and pressure.
2. An increase in systemic mean arterial pressure (which can lead to a secondary reflex reduction in heart rate).
3. There is some weak V2 mediated antidiuretic effect (around 3% of native vasopressin).

Pharmacodynamics

The lowering of portal venous pressure and azygos blood flow is dose dependent.

The time to peak effects is around 60 - 120 minutes

Duration of effect is around **4 hours**.

In bleeding oesophageal varices, terlipressin **reduces mortality** compared to placebo; however it should be used in *combination* with **endoscopic techniques** such as variceal ligation

Pharmacokinetics

Absorption:

- Terlipressin is administered intravenously.

Terlipressin acts as a prodrug and is converted via enzymatic cleavage of its three glycyl residues to the biologically active **lysine vasopressin**.

Terlipressin → lysine vasopressin.

Distribution

- The degree of protein binding is unknown.

- The volume of distribution is 0.5 L/kg.
- It is unknown if terlipressin is excreted into breast milk.
- It is unknown if human placental transfer occurs.

Metabolism and excretion:

- There is almost complete metabolism by peptidases.
- The half-life is around 10 - 40 minutes.

Indications

Terlipressin is indicated for:

1. Bleeding oesophageal varices
2. Hepatorenal syndrome (type 1):
 - Who are actively being considered for liver transplant.

Contra-indications/precautions

These include:

1. Severe asthma or COPD:
 - May worsen these conditions
2. Unstable angina or recent MI
 - Contraindicated in unstable angina or recent MI (terlipressin causes vasoconstriction and fluid retention).
3. Cardiac disease in general:

Use with *caution* in:

- Cardiac disease
- Arrhythmias
- Coronary artery disease
- Cerebral or peripheral vascular disease
- Uncontrolled hypertension.

4. Pregnancy (see below)

Pregnancy

Terlipressin is classified as a category D drug with respect to pregnancy.

Category D drugs are those drugs which have caused, are suspected to have caused or may be expected to cause an increased incidence of human fetal malformations or irreversible damage. These drugs may also have adverse pharmacological effects. Specialised texts should be consulted for further details.

Published information describing the use of terlipressin during pregnancy has not been located.

However, as terlipressin can cause uterine contraction, increase intrauterine pressure in early pregnancy and decrease uterine blood flow.

Consider an alternative medicine during pregnancy if possible.

Breast feeding

Published information describing the use of terlipressin during breastfeeding has not been located.

Transfer of terlipressin into the breast milk would be limited by the high molecular weight of the medicine.

Also, as terlipressin has poor oral absorption and is easily inactivated by the gastrointestinal tract, infants exposed to the medicine via breast milk are unlikely to experience adverse effects.

However, consider an alternative medicine to terlipressin in breastfeeding women due to the lack of safety information.

Adverse Effects

These include:

1. Headache
2. GIT
 - Abdominal cramps
 - GIT ischaemia
3. CVS:

- Increased blood pressure
 - Cardiac Ischaemia
 - Arrhythmia (rarely torsades de pointes)
4. Pulmonary:
- Bronchospasm (due to smooth muscle contraction).
 - Pulmonary oedema
5. Injection site necrosis if given IM
6. Hyponatraemia:
- Terlipressin some weak V2 mediated antidiuretic effect (around 3% of native vasopressin).

Dosing

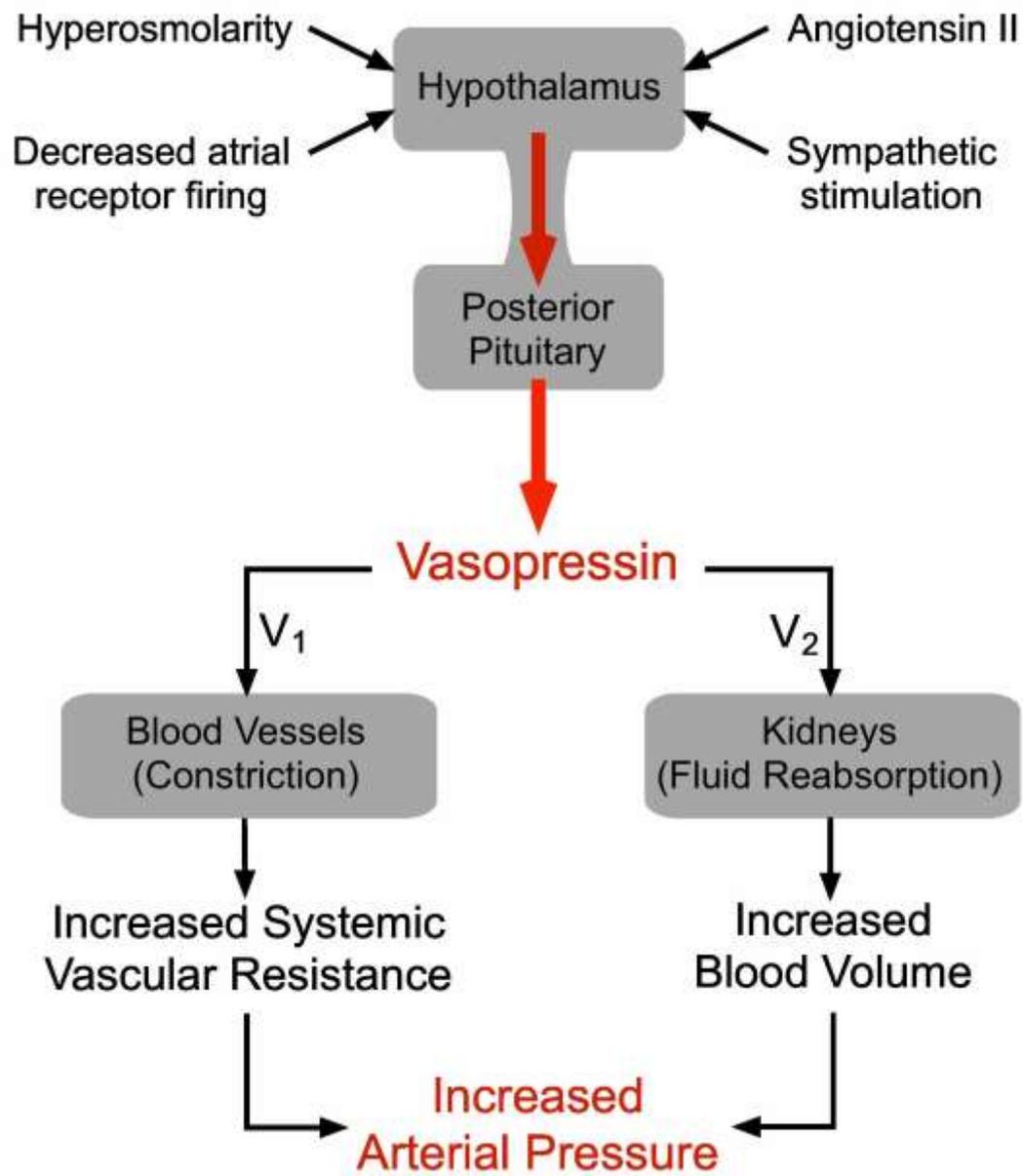
Usual dosing for bleeding oesophageal varices is:

- **Terlipressin acetate 2.0 mg IV, 6 hourly for 2 - 3 days**
(2 mg terlipressin acetate = 1.7 mg terlipressin base)

Give by **slow IV injection**.

Appendix 1

The action of vasopressin (or ADH) in the body:





Crawfish Springs 1863, where the Battle of Chickamauga began

References

1. eTG - March 2018
2. Terlipressin in Australian Medicines Handbook Website, Accessed May 2018.
3. Terlipressin in MIMs Website 1 October 2016
4. Terlipressin in RWH Pregnancy & Breast feeding Guidelines, 18 May 2016.

Dr J. Hayes
Reviewed 2 October 2018