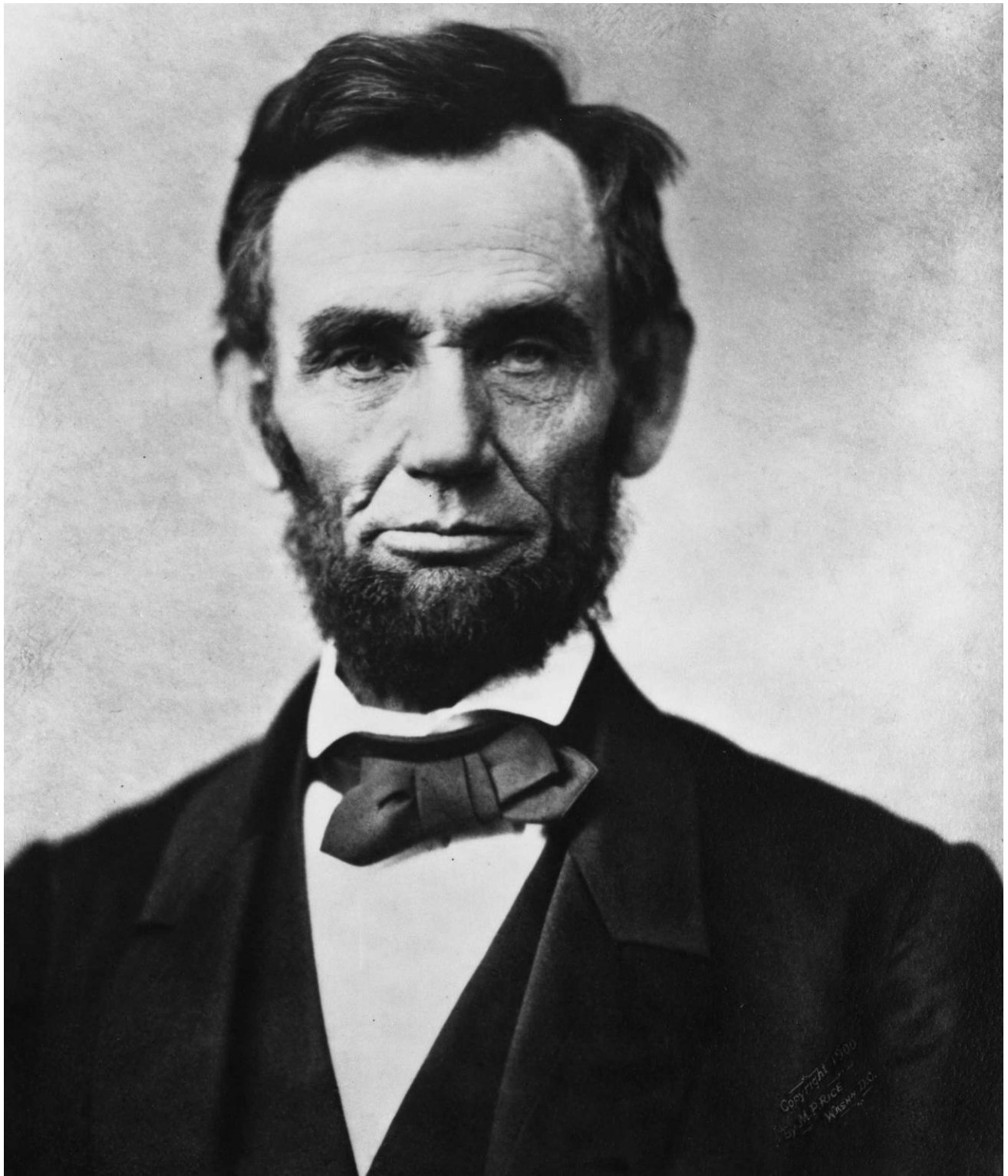


NEOSTIGMINE



Abraham Lincoln, 1863.

“Fourscore and seven years ago, our fathers brought forth upon this continent a new nation, conceived in liberty and dedicated to the proposition that all men are created equal. Now we are engaged in a great Civil War, testing whether that nation or any nation so conceived and so dedicated can long endure.

We are met here on a great battlefield of that war. We have come to dedicate a portion of it as a final resting place for those who here gave their lives that their nation might live. It is altogether fitting and proper that we should do this. But in a larger sense, we cannot dedicate, we cannot consecrate, we cannot hallow this ground. The brave men living and dead, who struggled here have consecrated it far above our poor power to add or detract.

The world will little note nor long remember what we say here, but can never forget what they did here. It is for us, the living, rather, to be dedicated here to the unfinished work which they have thus far so nobly carried on. It is rather for us to be here dedicated to the great task remaining before us, that from these honoured dead we take increased devotion, to that cause for which they here gave the last full measure of devotion, that we here highly resolve that these dead shall not have died in vain, that this nation, under God, shall have a new birth of freedom, and that government of the people, by the people, for the people, shall not perish from the Earth”.

Abraham Lincoln, Gettysburg Address, 19 November 1863

“I think if I had my choice of all the moments to be present at in that period, it would be at Gettysburg during Lincoln’s delivery of his speech. Maybe to have seen him craft those beautiful words, those marvelous healing words, and then deliver them. They were for everyone to all time. They subsumed the entire war and all in it. It showed his compassion for everyone, his love for his people. That’s where I’d like to be”.

(James Symington, US Congressman)

On November 19th, Lincoln traveled to Gettysburg to dedicate the new Union cemetery. The featured speaker was Edward Everett of Massachusetts, a diplomat, clergyman and celebrated orator. The President had been invited almost as an afterthought to offer a few “appropriate” remarks.

Everett spoke for not quite two hours, then Lincoln rose.

A local photographer took his time focusing. Presumably the President could be countered on to go on for a while, he spoke just 269 words.

He started by reminding his audience that just 87 years had passed since the founding of the nation, and then he went on to embolden the Union cause with some of the most stirring words ever spoken.

Lincoln was heading back to his seat before the photographer could open the shutter.

He felt that he had failed, that it was a poor speech, that the people didn’t like it, it was so brief - less than two minutes. He felt that he had failed. Lamon, his friend Ward

Lamon, was sitting next to him on the stand. When he sat down, there was just a sprinkling of applause and he said, "Lamon, that speech won't scour". That's what you say about a plow in the prairies when the mud doesn't come off it.
(Shelby Foote, *Civil War Historian*)

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

When Abraham Lincoln said in his Gettysburg Address "The world will little note nor long remember what we say here...", he would have been very much surprised to hear that he was wrong, very wrong. Today his Gettysburg Address is rightly regarded as one of the most inspiring speeches ever made, although this was not recognized by many at the time. "The cheek of every American must tingle with shame", sniffed the Chicago Times, "as he reads the silly, flat, dish-watery utterances of the man who has to be pointed out to intelligent foreigners as the President of the United States". But there were others who recognized immediately the greatness of his words, among them the celebrated orator Edward Everett who had spoken (or rather droned on) for just on two hours before Lincoln.

Lincoln elegantly expressed in just over 269 words, just exactly why the Civil War was being fought and just exactly what it meant. All those present, despite the derogatory comments of the media were spellbound, by the President's every word. Lincoln himself felt that he had not done a good job, but Everett, generously expressed to him, what everyone at the time was thinking. "I should be glad if I could flatter myself" he told Lincoln, "that I came as near to the general idea of the occasion in hours as you did in two minutes!"

Sometimes "less is more", the famous Poet, Robert Browning, once said. The sentiment can be applied no better than to Abraham's immortal "Gettysburg Address".

When we administer the anticholinesterase agent neostigmine, we do well to keep in mind, the brilliance of Lincoln's Gettysburg address! Sometimes less is more. We may deliver up to 5 mg IV but droning on any more than this will not provide any further benefit - less is more! Above maximal recommended dosing more harm will be done than good!

NEOSTIGMINE

Introduction

Neostigmine is an anticholinesterase agent which reversibly inhibits the hydrolysis of acetylcholine by competing with acetylcholine for attachment to acetylcholinesterase.

It is primarily used for the reversal of neuromuscular blockade induced by **non-depolarising** neuromuscular blockers.

A dose of **atropine** is usually also given to inhibit the muscarinic effects of neostigmine.

Neostigmine *does not* reverse, and may in fact prolong, the Phase I block of *depolarizing* muscle relaxants such as **succinylcholine**.

History

Neostigmine was first synthesized by Aeschlimann and Reinert in 1931.

Classification

Anticholinesterases may be classified as follows:

Reversible binding to cholinesterases:

1. Short acting:
 - Edrophonium
2. Long acting:

Do not readily cross BBB:

- **Neostigmine**
- Pyridostigmine
- Carbamate Insecticides, (aldicarb, carbendazole, carbedazim, carbazine)

Readily cross BBB:

- Physostigmine
- Tacrine

Irreversible binding to cholinesterases:

1. **Insecticides:**

- The thioates: Malathion, Parathion, Fenthion
- Coumaphos • Diazinon • Dichlorvos
- Dimethoate • Clorpyrifos. • Trichlorfon

2. Nerve gases:

- Sarin (GB) • Tabun (GA)
- Soman (GD) • VX

Preparation

Neostigmine as:

Ampoules:

- 0.5 mg/mL, 1 mL
- 2.5 mg/mL, 1 mL

Mechanism of Action

Neostigmine is an anticholinesterase agent which reversibly inhibits the hydrolysis of acetylcholine by competing with acetylcholine for attachment to acetylcholinesterase.

As a result, acetylcholine *accumulates* at cholinergic synapses and its effects are prolonged and increased.

Neostigmine is therefore capable of producing a generalised cholinergic response.

By this direct cholinomimetic effect on skeletal muscle, neostigmine is used to reverse the effects of non-depolarizing muscle relaxants.

Pharmacodynamics

Neostigmine is primarily used for the reversal of neuromuscular blockade induced by *non-depolarising* neuromuscular blockers.

When given IV for reversal of neuromuscular blockade, neostigmine acts within **1 minute** and effects last for **20 - 30 minutes**.

Pharmacokinetics

Absorption:

- Neostigmine is given **IV**, (it can be given IM, but IV is the preferred route for reversal of non-depolarizing muscle relaxants)
- When given **IV** for reversal of neuromuscular blockade, neostigmine acts in general within 1 minute and effects last for 20 - 30 minutes.

The speed of recovery from neuromuscular blockade is primarily determined by the intensity of the block at the time of antagonism. ¹

Distribution:

- Because of its quaternary ammonium structure, neostigmine, in moderate doses, does *not* cross the blood-brain barrier to produce CNS effects
- Protein binding is low - moderate at around 15 - 25 %.
- Neostigmine can cross the human placenta.
- It is unknown if neostigmine is excreted into human breast milk.

Metabolism and excretion:

- Neostigmine is metabolized partly by the hydrolysis of the ester linkage and partly by microsomal enzymes in the liver.
- Following IV administration the elimination half-life ranges from about 50 - 60 minutes.

Indications

Reversal of neuromuscular blockade induced by non-depolarising neuromuscular blockers

*Note that neostigmine is still marketed for postoperative urinary retention and intestinal atony (or ileus), but it should **not** be used for these indications.* ²

Pyridostigmine is the treatment of choice for myasthenia gravis, (not neostigmine).

Contra-indications/precautions

1. Known hypersensitivity to neostigmine
2. The following are *relative* contraindications.
 - Mechanical obstruction of the gastrointestinal tract
 - Asthma

- Bradycardia/ cardiac conduction delays

Pregnancy

Neostigmine is classified as a class B2 drug with respect to pregnancy. ^{1,2}

Class B2 drugs 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 are inadequate or may be lacking, but available data show no evidence of an increased occurrence of fetal damage.

From the limited information available, neostigmine use during pregnancy has not been associated with an increased risk of adverse effects or congenital malformations. Healthy pregnancy outcomes have also been reported following neostigmine use for myasthenia gravis in pregnancy. However, women with myasthenia gravis should discuss treatment options with their neurologist before and during pregnancy.

Pyridostigmine is preferred for maintenance treatment of myasthenia gravis during pregnancy, as neostigmine has a short half-life. However, if neostigmine is the medicine of choice, monitoring of both maternal and fetal wellbeing is recommended. It is also recommended that a multidisciplinary team is informed of in utero exposure to neostigmine as supportive treatment may be required following delivery.

Breastfeeding:

Evidence indicates that only negligible amounts of neostigmine enter the breast milk; nevertheless, the possibility of adverse effects on the breastfeeding infant should always be kept in mind. ¹

Adverse Effects

1. Allergic reactions (rare).
2. CVS:
 - Bradycardia (which can be significant).
 - Asystole, especially with repeated doses and in younger children, is, (clearly), the most serious adverse effect.
3. Cholinergic crisis:
 - If used in excessive dosages, a cholinergic syndrome can occur, with typical features of this syndrome including:
 - ♥ Diaphoresis / flushing

- ♥ Increased salivation
- ♥ Hypotension and bradycardia
- ♥ Miosis
- ♥ Bronchospasm
- ♥ Increased oral, pharyngeal and bronchial secretions
- ♥ GIT upset (cramps/ nausea/ vomiting/ diarrhea/ salivation)
- ♥ Urinary frequency.
- ♥ In *severe* cases:
 - ♥♥ Seizures / coma
 - ♥♥ Increased muscle weakness leading to fasciculation and paralysis
 - ♥♥ Respiratory depression.

See also Cholinergic Syndrome (in Toxicology folder).

3. Allergic reactions (rare)
4. Worsening of a depolarizing muscle relaxant block.
 - Neostigmine *does not* reverse, and may in fact prolong, the Phase I block of *depolarizing* muscle relaxants such as succinylcholine.

Dosing

Neostigmine is primarily used for the reversal of neuromuscular blockade induced by *non-depolarising* neuromuscular blockers.

A dose of **atropine** is usually also given *simultaneously* to inhibit the muscarinic effects of neostigmine, (especially bradycardia).

When given IV for reversal of neuromuscular blockade, neostigmine acts within 1 minute and effects last for 20 - 30 minutes. ²

For reversal of non-depolarizing neuromuscular give:

Adults:

- Neostigmine: **2.5 mg IV.**

A maximum of 5 mg can be given with caution.

(0.5 mg intravenously is approximately equivalent in effect to 1.0 to 1.5 mg IM or SC.)¹

Plus

- Atropine: **1.2 mg IV**

The maximum recommended dose of neostigmine in adults is 5 mg.¹

Children:

The suggested dose is neostigmine **0.05 mg/kg (to a maximum of 2.5 mg) and atropine sulfate 0.02 mg/kg** by slow intravenous injection over one minute.¹



One of only two known photographs depicting Abraham Lincoln, at his Gettysburg Address, 19 November, 1863. (Library of Congress).

Abraham Lincoln is seen without a hat, just left of center. To Lincoln's right is his bodyguard Ward Hill Lamon, while to his left is Governor Andrew G. Curtin of Pennsylvania. The original glass plate negative was found at the National Archives where it had laid unknown until

1952 when Josephine Cobb indentified Lincoln in the image. It is thought that the photograph was taken at about noontime, just after Lincoln arrived, and before Edward Everett's arrival and about three hours before Lincoln gave his famous Gettysburg Address.

References

1. Neostigmine in MIMs Website 1 December 2004.
2. Neostigmine in AMH Website, January 2018.
3. Neostigmine in RWH Pregnancy & Breastfeeding Guidelines, 17 March 2017.

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