

ACLIDINIUM



Abraham Lincoln's funeral procession, New York City, 25 April 1865. From his grandfather's window, seven year old, Theodore Roosevelt watched the procession go by.

"On the avenue in front of the white house were several hundred colored people, mostly women and children, weeping and wailing their loss. This crowd did not diminish through the whole of that cold, wet day. They seemed not to know what was to be their fate since their great benefactor was dead, and though strong and brave men wept when I met them, the hopeless grief of those poor colored people affected me more than almost anything else".

(Gideon Welles)

In Washington, fireworks filled the sky. A great crowd gathered around the white house and called for Lincoln. He was too weary to make a formal speech but asked the band to play Dixie.

“I have always thought it one of the best tunes I ever heard”, he said. The next day, Lincoln walked over to Alexander Gardner’s studio at the corner of Seventh and D street to sit for another portrait. Somehow, the glass-plate negative cracked while being developed.

The photographer made a single print, then threw the negative away, there would be plenty of time to make more Lincoln portraits.

Just a few blocks away, a friend found John Wilkes Booth alone in his darkened room and asked him if he wanted to get a drink.

“Yes”, said Booth, who was now drinking a quart of brandy a day, “anything to drive away the blues”

The Lincolns arrived and took their seats in the presidential box. With them were major Henry Rathbone and his fiancée, Clara Harris....

The president seemed to be enjoying the play. His wife held his hand. Booth swallowed two brandies at a nearby bar, then returned to the theatre. He waited for the laughter to rise, then slipped silently into the president’s box. He held a dagger in his left hand, a derringer pistol in his right....

Booth fired, then vaulted over the front of the box, caught his right spur in the draped flag, and landed on stage, breaking his left leg. He waved his dagger and shouted something to the stunned audience. Some thought he said, “sic semper tyrannis”- thus be it ever to tyrants, Virginia’s state motto. Others heard it as “The South is avenged!”

For a long moment, the theatre was still, then Mary Lincoln screamed. The bullet from Booth’s pistol had entered the back of Lincoln’s head, torn through his brain, and lodged behind his right eye. A surgeon from the audience pronounced the wound mortal. Soldiers carried the unconscious president from the theatre into a boarding house across 10th street.

*“We put him on the first floor and laid him on the bed. When we took him into the room we had to get out. They wouldn’t let anybody in without it was a doctor or something”.
(Private Jacob Soles).*

*“The giant sufferer lay extended diagonally across the bed, which was not long enough for him. He had been stripped of his clothes. His slow, full respiration lifted the covers with each breath he took. His features were calm and striking”.
(Gideon Welles).*

The doctors could do nothing. Mary implored her husband to speak to her and wept so inconsolably, she was finally taken into the front parlor.

Cabinet officers stood by helpless all night, doubly shocked to hear that Booth's accomplice Lewis Paine had stabbed secretary of state Seward, then run out into the street crying, "I'm mad! I'm mad!" George Atzerodt had been too frightened to carry out Booth's order to kill the Vice President.

Around 6:00 in the morning, navy secretary Welles stepped outside and found the streets filled with silent, anxious people. A little before 7:00, I went back into the room. The death struggle had begun. Robert, his son, stood at the head of the bed. He bore himself well, but on two occasions gave way and sobbed aloud, leaning on the shoulder of Senator Sumner.

At 7:22 on the morning of April 15, 1865, Abraham Lincoln died. He was 54 years old.

Secretary of war Edwin Stanton said, "Now he belongs to the ages"

*"Mother prepared breakfast and other meals as usual, but not a mouthful was eaten all day by either of us. We each drank half a cup of coffee, that was all. Little was said. We got every newspaper, morning and evening, and passed them silently to each other".
(Walt Whitman).*

The telegraph carried the news across the country in minutes. No president had ever been murdered. People would remember for the rest of their lives where they were and what they felt and what the weather was like when they heard what had happened.....

Near Appomattox courthouse, Virginia, Saturday, April 15:

*"Bad news has just arrived. Corporal Thomas Parker has just said President Lincoln is dead, murdered. We cannot realize that our President is dead. May God help his family and our poor distracted country".
(Elisha Hunt Rhodes, Union soldier)*

*"I have been expecting this. I am stunned, as by a fearful personal calamity, though I can see that this thing occurring just at this time may be overruled to our great good. We shall appreciate him at last".
(George Templeton Strong).*

*"On the avenue in front of the white house were several hundred colored people, mostly women and children, weeping and wailing their loss. This crowd did not diminish through the whole of that cold, wet day. They seemed not to know what was to be their fate since their great benefactor was dead, and though strong and brave men wept when I met them, the hopeless grief of those poor colored people affected me more than almost anything else".
(Gideon Welles)*

.....Lincoln's casket lay in state, first in the east room of the White House, then in the rotunda of the capitol. He was to be buried in Springfield, Illinois, his adopted home. The small coffin of his son Willy, who had died in Washington, was disinterred to make the journey with him. Mary Lincoln was too overcome with grief to go....

"You white people are the children of Abraham Lincoln. We are at best only his stepchildren. Viewed from the genuine abolition ground, Mr. Lincoln seemed tardy, cold, dull, indifferent, but measuring him by the sentiment of his country, a sentiment he was bound as a statesman to consult, he was swift, zealous, radical, and determined. Taking him all in all, measuring the tremendous magnitude of the work before him, considering the necessary means to ends, infinite wisdom has seldom sent any man into the world better fitted for his mission than Abraham Lincoln".

(Frederick Douglass).

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

The ease of access to President Lincoln by the general public was astonishing by the standards of today. Death comes like a thief in the night, and life is often unfair. Unlike Lincoln's official photographer we must make plans for worst case scenarios. Our defence against potential disaster is to remain ever vigilant, and where possible lay in preventative measures. In the matter of our patients with COPD, one such measure is available to us in the form of long acting preventive anticholinergic agents such as Aclidinium.



A mid-Nineteenth century Philadelphia Deringer, the gun used to assassinate Abraham Lincoln, (displayed at Ford's Theatre, Washington, D.C)

ACLIDINIUM

Introduction

Acclidinium is a **long acting** synthetic inhalational anticholinergic agent, (or long acting muscarinic antagonist or **LAMA**).

It is used as preventive treatment for patients with **COPD**.

Long-acting anticholinergics inhalant agents should not be used for immediate relief of bronchospasm symptoms.

History

Acclidinium was approved for clinical use in the US in July 2012.

Chemistry

Acclidinium bromide is an anticholinergic drug similar to tiotropium in that it also has two thiophene rings and a quaternary ammonium group.

It is a single stereoisomer with a 3R configuration.

Classification

The inhalational anticholinergic agents can be classified thus:

1. **Short-acting anticholinergic inhalational agents:**
 - Ipratropium
2. **Long-acting anticholinergic inhalational agents, (otherwise known as long acting muscarinic antagonists or “LAMAs”).**
 - **Acclidinium**
 - Glycopyrronium
 - Tiotropium
 - Umeclidinium

Preparations

Acclidinium bromide as:

- **Dry Powder Inhaler (DPI)**

- ♥ 322 mcg/dose
- **Fixed-dose combination:**
 - ♥ DPI, aclidinium 340 mcg + formoterol 12 mcg/dose

Mechanism of Action

Aclidinium is a long acting, specific competitive muscarinic receptor antagonist.

Similar to tiotropium, aclidinium has selectivity for M3 receptors versus M2 receptors.

Pharmacodynamics

The bronchodilation following inhalation of aclidinium is primarily a local effect on the airways.

It antagonises M3 receptors of airway smooth muscle to induce bronchodilation.

It has *minimal* systemic effects.

The **onset of action** is significantly faster than tiotropium

Pharmacokinetics

Absorption:

- Aclidinium is administered by inhalation.

Distribution

- Lung deposition of inhaled aclidinium averages approximately 30% of the metered dose.
- Protein binding is around 87% for the carboxylic acid metabolite and 15% for the alcohol metabolite.
- It is unknown if aclidinium can cross the human placenta.
- It is unknown if aclidinium is excreted into human breast milk.

Metabolism and excretion:

- Aclidinium is rapidly and extensively hydrolysed to pharmacologically inactive alcohol and carboxylic acid derivatives in the plasma, and so systemic effects are minimal.

- Biotransformation via the CYP450 enzyme system plays only a *minor* role in the total metabolic clearance of acclidinium.
- Just 1% of the dose is excreted as unchanged acclidinium bromide in the urine.
- Elimination half-life is around 2-3 hours.

Indications

Acclidinium is indicated as a long-term maintenance bronchodilator treatment to relieve symptoms in adult patients with COPD.

Contra-indications/precautions

These include:

1. Known hypersensitivity to atropine or its derivatives or to any excipients of its preparations.
2. Like other drugs with anticholinergic activity, acclidinium should be avoided or used with caution in patients in whom atropine-like effects may precipitate or exacerbate a pre-existing clinical condition.

Patients at risk include those with narrow acute angle closure glaucoma, urinary retention or constipation.

3. Avoid powder or mist contact with the eyes (anticholinergic effects on the eyes may lead to paralysis of accommodation).

Pregnancy

Acclidinium is classed as a category B3 drug with respect to pregnancy.

Category B3 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 have shown evidence of an increased occurrence of fetal damage, the significance of which is considered uncertain in humans.

Published reports describing the use of acclidinium during pregnancy have not been located. The approved indication for the medicine, for the management of chronic obstructive pulmonary disease (COPD), would render reports of use in pregnancy rare.

However, due to low absolute bioavailability, and if the patient has been stable on acclidinium prior to conception, or if it is considered the medicine of choice, acclidinium may be considered during pregnancy.

Consultation with a respiratory physician is recommended.

Breast feeding

Published reports describing the use of aclidinium during breastfeeding have not been located.

Inhaled aclidinium is considered safe to use during breastfeeding due to the low oral bioavailability and maternal serum levels after use.

Adverse Effects

Adverse effects are usually not severe.

They may include:

1. Dry mouth, throat irritation
2. Tachycardia
3. Hypersensitivity reactions.
4. Blurred vision / acute angle-closure crisis.
5. Urinary retention
6. Constipation.

Dosing

Stop ipratropium if treatment with a long-acting anticholinergic is required for COPD. ²

Dry Powder Inhalation:

- 1 inhalation (322 micrograms) twice daily.

Fixed-dose combination with eformoterol:

- Dose is expressed as micrograms of aclidinium/formoterol.
DPI, 1 inhalation (340/12 micrograms) twice daily.



The private box of Abraham and Mary Lincoln in Ford's Theater, Washington, where President Abraham Lincoln was assassinated by John Wilkes Booth on April 14, 1865, (photograph taken c.1865, US National Archives).

Detective Corps Met. Police London April 14th 1865

1 P.M. Barry Begley (Carver Donaldson
 Roll Call Kelly and Mr. Deane present
 Noonan in charge of Office, Drill
 in charge of Department from 7th to 8
 Am.

6.12 P.M. Kelly 7 to 12 P.M.

4.8 Am. Begley 12 to 8 Am.

1 P.M. Margaret Grubber, a pauper and
 threats of bodily harm, arrested on
 a warrant issued by Justice Hillier
 35. White German Postoffice St. get
 Compt. Geo. Myers Security to keep the peace
 Begley & Kelly

1 P.M. John Neader assault on Joseph
 Hill with a Pistol 40 white w. Gambler
 married, get. Pictor for a hearing
 at 3 o'clock Apr 15, disrupted by
 Indian Police
 Charles & McNeill

1 P.M. Sergeant Johnson of Precinct delivered
 this morning to Office, Drill a Hat
 cover, buttons and three fishing lines

1 P.M. At this hour the melancholy intelligence of
 the assassination of Mr. Lincoln President
 of the U.S. at Fords Theatre was
 brought to this office, and the information
 obtained from the following persons
 goes to show that the assassin is a
 man named J. Wilks Booth
 Secretary, Howard Booth his son, Harriet
 were arrested at the same time by some of our
 Police

Washington Metropolitan
 Police Department record
 for April 14, 1865

A poignant entry at the
 bottom of the page records
 the assassination of
 President Lincoln.

“At this hour the
 melancholy intelligence of
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 Lincoln, President of the
 US, at Fords Theatre was
 brought to this office, and
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 from the following persons
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 assassin is a man named J.
 Wilks (sic) Booth”.

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Dr J. Hayes
May 2019.