

LANSOPRAZOLE



“The Declaration of Independence in Congress, at the Independence Hall, Philadelphia, July 4th, 1776”, oil on canvas, John Trumbull, 1819, US Capitol Rotunda.

The unanimous Declaration of the thirteen united States of America

“...We hold these truths to be self-evident, that all men are created equal, that they are endowed by their Creator with certain unalienable Rights, that among these are Life, Liberty and the pursuit of Happiness. — That to secure these rights, Governments are instituted among Men, deriving their just powers from the consent of the governed, — That whenever any Form of Government becomes destructive of these ends, it is the Right of the People to alter or to abolish it.... “

The Declaration of Independence, July 4th, 1776

“In thinking of America, I sometimes find myself admiring her bright blue sky, her grand old woods, her fertile fields, her beautiful rivers, her mighty lakes and star crowned mountains, but my rapture is soon checked, when I remember that all is cursed with the infernal spirit of slaveholding and wrong. When I remember that with the waters of her noblest rivers, the tears of my brethren are borne to the ocean, disregarded and forgotten, that her most fertile fields drink daily of the warm blood of my outraged sisters. I am filled with unutterable loathing”.

Frederick Douglas

“Whence shall we expect the approach of danger? Shall some transatlantic giant step the earth and crush us at a blow? Never! All the armies of Europe and Asia could not by force take a drink from the Ohio River or make a track on the Blue Ridge in the trial of a thousand years. If destruction be our lot. We must ourselves be its author and finisher. As a nation of free men, we will live forever....or die by suicide.....

As a nation we began by declaring that all men are created equal. We now practically read it, “All men are created equal, except negroes and foreigners and Catholics”. When it comes to this I should prefer emigrating to some country where they make no pretense of loving liberty, to Russia, for instance where despotism can be taken pure and without the base alloy of hypocrisy....

A house divided against itself cannot stand. I believe this government cannot endure permanently half slave, half free. I do not expect the Union to be dissolved. I do not expect the house to fall, but I do expect it will cease to be divided. It will become all one thing, or all the other.

Abraham Lincoln, 1837

“There was never a moment in our history when slavery was not a sleeping serpent, it lay coiled up under the table during the deliberations of the Constitutional Convention. Owing to the cotton gin it was more than half awake. Thereafter slavery was on everyone’s mind, though not always on his tongue”

John Jay Chapman

Any understanding of this nation has to be based, and I mean really based, on an understanding of the Civil War. I believe that firmly. It defined us. The revolution did what it did. Our involvement in the European wars, beginning with the First World War, did what it did, but the Civil War defined us as what we are, and it opened us to being what we became, uh, good and bad things. And it...it is very necessary if you’re going to understand the American character in the 20th century to learn about this enormous catastrophe of the mid-Nineteenth century. It was the...the crossroads of our being, ...and it was a hell of a crossroads.....

It was because we failed to do the thing we really have a genius for, which is compromise. Americans like to think of themselves as uncompromising. Our true genius is for compromise - our government is founded on it, and it failed.

Shelby Foote, Civil War Historian

For me the picture of the Civil War as a historic phenomenon...is not on the battlefield. Its not about weapons. It's not about soldiers, except to the extent that weapons and soldiers at that crucial moment joined the discussion about something higher, about humanity, about human dignity, about human freedom....

If there was a single event that caused the war, it was the establishment of the United States in independence from Great Britain with slavery still a part of its heritage.

Barbara Fields, Civil War Historian

By the time the nation was founded, slavery was dying in the North. There were doubts in the South too but few could conceive of any alternative. Thomas Jefferson of Virginia said maintaining slavery was like holding a wolf by the ears. You didn't like it, but you didn't dare let it go. Then in 1793, a Northerner, Eli Whitney, taught the South how to make slavery pay. Whitney's engine or gin made it easier to separate cotton from its seed. Where before it had taken one slave 10 hours to produce a single pound of lint, the cotton gin could crank out a thousand pounds a day. Production soared and with it, the demand for slaves. By 1860 the last year of peace, one out of every seven Americans belonged to another American. Four million men, women and children were slaves.

*David McCullough, Shelby Foote, Barbara Fields
in Ken Burns', "The Civil War", 1990.*

In all of history, no nation on Earth had previously called forth its own existence, on so enlightened principles. It was after all, the great Age of Reason. And yet, though the sentiments struck deep and universal human chords, a model for all future governance of nations, there remained unspoken contradictions, buried so deeply in the colonists' psyche, as for there to be no real conscious awareness of them.

Abraham Lincoln, the greatest President in American history, put into words in 1837, well enough the unsettling sentiments that had been on peoples' minds, yet never openly talked about - "As a nation we began by declaring that all men are created equal. We now practically read it, "All men are created equal, except negroes and foreigners and Catholics".

The Founding fathers had largely been British Protestants, and when they expressed the sentiments "that all are created equal" - what they meant was that all British Protestants are created equal - indeed the very words all "men" are created equal gave unintended emphasis to the inferior place in society of women. Suffrage was not even universal among all men, there being a wealth or property qualification, that excluded the great majority. In 1776 then it appeared that only all white, protestant males, with property and wealth were created equal.

But by the mid Nineteenth century Americans knew that the inspiring words of their Declaration of Independence had not been lived up to. Slavery had gone from the heavily

industrialized North, but it positively thrived in the agricultural South. America had grown prodigiously as a nation since 1776, and now with its 31 million people and the power of its industry that was rapidly approaching that of Great Britain, Lincoln knew that his country was finally safe from any future trans-Atlantic aggression; "All the armies of Europe and Asia" he wrote, "could not by force take a drink from the Ohio River or make a track on the Blue Ridge in the trial of a thousand years".

If the fledgling nation was to fail now it would only be because of suicide by internal division, "A house divided against itself cannot stand", Lincoln famously declared. What he and everyone else knew by mid century was that the house was indeed divided and very bitterly so. Though both North and South danced around each other over vague principles of "states rights", the unspoken issue at the heart was slavery. As new states entered the Union, decisions had to be made - would these states be slave states or free states? Lincoln was prescient, "I believe this government cannot endure permanently half slave, half free. I do not expect the Union to be dissolved. I do not expect the house to fall, but I do expect it will cease to be divided. It will become all one thing, or all the other".

The price of setting to right the founding principles of the Declaration of Independence, would be a Civil War so devastating that the toll of dead would exceed all previous and future American wars, including the two World Wars...combined.

When we prescribe empiric proton pump inhibitors for dyspepsia, we do so with the very best of intentions. However while all men may be equal, not all "dyspepsias" are! Without a definitive endoscopic diagnosis, we risk missing an underlying malignant condition at the outset, and the longer we leave this malignant condition unattended, the greater will be the battle that will ultimately need to be fought!

LANSOPRAZOLE

Introduction

Lansoprazole irreversibly inhibits the **proton pump** (i.e. the gastric **parietal cell** enzyme **H⁺/ K⁺ ATPase**), the final common step of gastric acid production thus resulting in a reduction of gastric acid secretion.

The proton pump inhibitors are the most potent inhibitors of acid secretion currently available.

All the current PPIs have similar efficacy and adverse effects, although they may differ in their potential to cause drug interactions.

Lansoprazole is only available in **oral** form.

The enteric capsules can be opened and used for **nasogastric** administration.

History

In the 1970s the newly discovered proton pump (H⁺/K⁺ ATPase) in the secretory membrane of the parietal cell was found to be the final biochemical step in stomach acid secretion

The PPIs were subsequently developed in the 1980s

Omeprazole was the first PPI to be introduced into clinical practice in 1988

Lansoprazole was introduced into clinical practice in 1991.

Chemistry

Lansoprazole, which is a substituted benzimidazole.

Classification

The proton pump inhibitor agents include:

1. Omeprazole
2. Esomeprazole (This is the S-isomer of omeprazole).
3. **Lansoprazole**
4. Pantoprazole
5. Rabeprazole.

Preparations

Lansoprazole as:

Orally disintegrating tablets:

- 15 mg
- 30 mg

Enteric coated tablets:

- 15 mg
- 30 mg

Mechanism of Action

Lansoprazole irreversibly inhibits the proton pump (i.e. the gastric enzyme H⁺/ K⁺ ATPase), at the secretory surface of the gastric parietal cell. This is **the final common step** of gastric acid production.

This results in a reduction of gastric acid secretion, (see **Appendix 1 below**).

Pharmacodynamics

A single dose of 30 mg lansoprazole inhibits stimulated acid secretion by approximately 80%.

Basal acid secretion and basal and stimulated secretion volumes are affected to a lesser degree.

After repeated dosing (for 7 days) 90 % inhibition of stimulated acid secretion is achieved.

Despite its short elimination half-life, lansoprazole has a **prolonged pharmacological action**, providing effective suppression of gastric acid secretion over **24 hours**.

When used in combination with the recommended antibiotics, lansoprazole is associated with H. pylori eradication rates of up to 90%.

Pharmacokinetics

Absorption:

- Lansoprazole is administered orally.

It is well absorbed

It has around 80 - 90 % bioavailability following oral administration.

Peak plasma levels occur within 1.5 - 2 hours.

- For nasogastric tube administration.

Lansoprazole enteric capsules can be administered as follows.

- ♥ Open the enteric capsule.
- ♥ Mix the intact granules into 40 mL of apple juice (do not use any other liquids).
- ♥ Inject through the nasogastric tube into the stomach.
- ♥ Flush with additional apple juice to clear the tube.

Distribution

- After IV administration, the volume of distribution is 29 ± 4 liters
- Protein binding is high at 98%.
- It is unknown if lansoprazole crosses the human placenta.
- Lansoprazole is likely to be excreted into the breast milk

Metabolism and excretion:

- Lansoprazole is extensively metabolised. Metabolites are excreted by both the renal and biliary route.
- Half -life is around 1 -2 hours

Indications

Indications include:

1. Dyspepsia
2. Peptic ulcer:
 - Prophylaxis against peptic ulcer
 - Treatment of peptic ulcer
3. Oesophagitis:

- Due to GORD or other causes, (such as scleroderma).
4. Zollinger-Ellison syndrome
 - 5 Adjunct to H. pylori eradication:
 - PPIs do not eradicate H.pylori in their own right, but act synergistically with antibiotics to do so.
 - Optimal eradication rates are achieved when the PPI is combined with two antimicrobial agents.
 - 6 The prevention or treatment of gastric and duodenal ulcers and erosions associated with NSAIDs.
 7. Prevention of *acid* aspiration

Contra-indications/precautions

These include:

- 1 Hypersensitivity to lansoprazole
- 2 Caution should be exercised in the use of the PPIs in the presumptive diagnosis of “dyspepsia” without prior endoscopy

Important diagnoses to keep in mind include:

Possible upper GIT malignancy:

- Caution as PPIs may alleviate symptoms and thereby delay diagnosis.

Possible H. Pylori Infection:

- Infection must be treated in order to cure the underlying cause of the symptoms.

Pregnancy

Lansoprazole is a category B3 drug with respect to pregnancy.

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.

Lansoprazole use during pregnancy has not been associated with an increased risk for major malformations, spontaneous abortions or preterm delivery.

However, lifestyle **modifications (including dietary changes), antacids and histamine-2 antagonists** should be trialed before the use of a proton pump inhibitor for the treatment of heartburn and gastro-oesophageal reflux disease during pregnancy.

If a proton pump inhibitor is required, **omeprazole** is the medicine of choice, as more fetal safety data is available.

Breast feeding

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

Lansoprazole is likely to be excreted into the breast milk, but maternal use is not expected to cause adverse effects in the breastfed infant.

However, lifestyle modifications (including dietary changes), antacids and histamine-2 antagonists should be trialed before the use of a proton pump inhibitor for the treatment of heartburn and gastro-oesophageal reflux disease during breastfeeding.

If a proton pump inhibitor is required, omeprazole is the medicine of choice, as more infant safety information is available.

Adverse Effects

PPIs are generally well tolerated.

1. GIT upset may occasionally occur
2. Hypersensitivity reactions, (rare)
 - Allergic / anaphylactic.
 - Skin reactions:
 - ♥ Stevens-Johnson syndrome/ toxic epidermal necrolysis
3. Some *epidemiological* studies have suggested *possible* associations between PPI use and increased risk of:
 - Enteric infections (including Clostridium difficile-associated disease)
 - Pneumonia
 - Decreased serum vitamin B12 concentration (long-term use)

- Fracture (long-term use); for patients at risk of osteoporosis and taking PPIs long term (>1 year), consider daily calcium intake and vitamin D status.

Dosing

Peptic Ulcer Disease:

Usual adult dosing is:

- Oral, initially 30 mg once daily for 4 - 8 weeks.
- Maintenance, oral 15 mg once daily.

Gastro-oesophageal reflux disease:

Usual adult dosing is:

- Initially, oral 30 mg once daily for 4 - 8 weeks.
- If response inadequate, increase to 30 mg twice daily for a further 4 weeks.
- Maintenance, reduce to minimum required.

For Child >1 year

- < 30 kg, oral 15 mg once daily for 8 - 12 weeks.
- > 30 kg, oral 30 mg once daily for 8 - 12 weeks.

Dyspepsia:

Adult, oral, initially 15 - 30 mg once daily for 2 - 4 weeks.

H. pylori eradication:

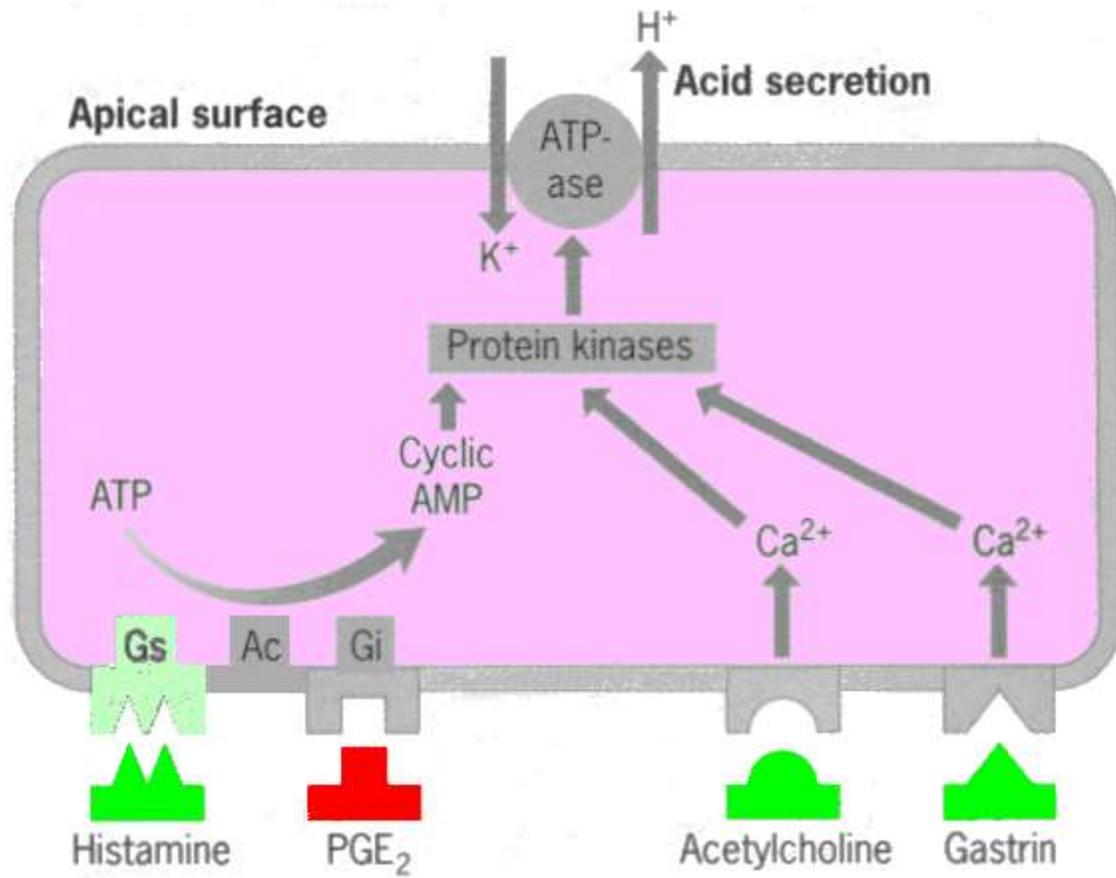
Adult, oral 30 mg twice daily, with 2 antibacterials.

Severe hepatic impairment:

Halve the daily dose.

Appendix 1

The Gastric Proton Pump:



The Proton Pump, (School of Biochemistry and Microbiology University of Leeds).

IN CONGRESS, JULY 4, 1776.

The unanimous Declaration of the thirteen united States of America

When in the course of these events, it became necessary to explain the causes and intentions of our separation from Great Britain, we have addressed the following Declaration to all mankind. We therefore, the Representatives of the united States of America, in General Congress assembled, solemnly publish and declare, that these United States are, and of right ought to be, free and independent States; that they are absolved from all allegiance to the British Crown, and that all political connections between them and that Kingdom, are and ought to be totally dissolved; and that as free and independent States, they have full power to levy war, conclude peace, contract alliances, establish commerce, and to do all other acts which States of equal power may do. In support of which Declaration, we have signed our names, and have caused the Seal of the United States to be hereunto affixed.

We therefore, the Representatives of the united States of America, in General Congress assembled, solemnly publish and declare, that these United States are, and of right ought to be, free and independent States; that they are absolved from all allegiance to the British Crown, and that all political connections between them and that Kingdom, are and ought to be totally dissolved; and that as free and independent States, they have full power to levy war, conclude peace, contract alliances, establish commerce, and to do all other acts which States of equal power may do. In support of which Declaration, we have signed our names, and have caused the Seal of the United States to be hereunto affixed.

The Declaration of Independence in Congress, July 4th, 1776

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