Famotidine for COVID-19

Anang Agung Chrisnanda¹, Anjar Hermadi Saputro²*

¹Department of Pharmacy, Faculty of Health Sciences, Universitas Jenderal Soedirman, Purwokerto, Indonesia
²Department of Pharmacy, Faculty of Science, Institut Teknologi Sumatera, Lampung Selatan, Indonesia

*Corresponding author: anjar.saputro@fa.itera.ac.id

Abstract: Famotidine has emerged as a candidate for COVID-19 treatment, with various studies investigating its impact on the virus. These studies have reported encouraging results, suggesting that famotidine might contribute to fighting COVID-19 by potentially blocking histamine release, TMPRSS, and fortifying glycocalyx. Clinical trials aimed at assessing the effectiveness of famotidine in patients with COVID-19 have observed that it contributed to quicker alleviation of symptoms and reduction in inflammation, without compromising the body’s immunity against SARS-CoV-2. However, in the case of patients with severe illness, famotidine’s use did not significantly enhance survival rates. Although further investigation is necessary, famotidine has shown promise in alleviating symptoms and reducing inflammation in COVID-19 cases.

Keywords: famotidine, SARS-CoV-2, Covid-19, H₂-receptor blocker, histamine

Introduction

Famotidine is a drug that can inhibit gastric acid secretion by acting as a competitive agonist at histamine-H₂ receptors [1]. Peptic ulcer diseases include gastroesophageal (stomach ulcer) reflux, peptic (intestinal and duodenal) ulcers, and stress-related mucosal injury. All these diseases cause erosion or ulceration when acid, pepsin, and bile overpower the defense factors of the gastrointestinal mucosa (mucous secretion, bicarbonate, prostaglandins, blood flow, and regeneration processes after cell injury). More than 90% of peptic ulcers are caused by Helicobacter pylori bacterial infection or by the use of non-steroidal anti-inflammatory drugs (NSAIDs). Drugs used to treat peptic ulcer disease are divided into two classes: drugs that reduce acidity in the stomach and drugs that increase mucosal defenses. One type of drug that reduces acidity in the stomach is H₂ receptor antagonists. As the name suggests, H2 antagonist drugs work by competitively inhibiting at the H₂ receptors of parietal cells and suppressing basal acid secretion in a linear and dose-dependant manner. The development of H₂ receptor antagonists is based on the observation that H₁ antagonists had no effect on the increase in gastric acid secretion caused by histamine. There are 4 clinically used H₂ receptor antagonist drugs, they are cimetidine, ranitidine, famotidine, and nizatidine. These four drugs are rapidly absorbed from the intestine and their serum half-life ranges from 1.1 to 4 hours, but the duration of action depends on the administered dose. Apart from nizatidine, these drugs undergo cross-first metabolism [2].

Famotidine is the third of H₂ receptor antagonist drug after cimetidine and ranitidine. It was first released in Japan in 1985. Famotidine is the most potent and selective H₂ receptor antagonist drug that is available for peptic ulcer therapy. Famotidine is 8 times more potent than ranitidine and 40 times than cimetidine. Therefore, only 40 mg of famotidine is required a day for peptic ulcer therapy. The drug has a bioavailability of about 40-50% and a half-life of 3-3.5 hours. Famotidine does not interact with cytochrome P-450 in the hepatic enzyme system so it does not affect other drugs that are metabolized by this enzyme system. Due to famotidine’s high selectivity to H₂ receptors, it has a lower rate of side effects compared to cimetidine and ranitidine [3].

This medicine is used to treat and prevent ulcers in the digestive system, treat acid reflux disease, treat burning sensations in the chest and stomach, and treat diseases caused by acid reflux.

Molecular mechanism of action

Histamine is formed by decarboxylation of the amino acid L-histidine, a reaction that in mammalian tissues is catalyzed by the enzyme histidine decarboxylase. After being formed, histamine is either stored or immediately activated. Very little histamine is excreted unchanged. The main metabolic pathways include...
changes to N-methyl-histamine, methylimidazolasetic acid, and imidazolasetic acid. Most tissue histamine is stored and bound in granules (vesicles) in mast cells or basophils. This bound histamine is biologically inactive, but, many stimuli can trigger the release of mast cell histamine, allowing the free amine to act in the surrounding tissues. Mast cells are mainly found in places of potential injury such as the nose, mouth, feet, internal surfaces of the body, and blood vessels. Non-mast cell histamine is found in several tissues, including the brain where it functions as a neurotransmitter. The second most important storage and secretion site of non-neural histamine is the enterochromaffin-like cells (ECLs) in the fundus of the stomach. ECL cells secrete histamine, which is one of the main secretagogues of gastric acid to activate acid-producing parietal cells in the mucosa. Histamine elicits biologic effects through binding to specific receptors on the cell surface membrane. There are four different receptors and they are known as H1, H2, H3, and H4 [4].

Histamine H1 receptors can be found in a wide variety of tissues, including the brain, gastric parietal cells, and cardiac tissue. H2 receptor stimulation can mediate positive ionotropic and chronotropic effects on atrial and ventricular tissue, but the most important effect is the stimulation of gastric acid secretion. H2 receptor stimulation will activate the adenylate cyclase system (in the brain, vascular smooth muscle, cardiac myocyte, gastric mucosa, and lungs) through stimulation of Gs which will further activate the second messenger cAMP. This second messenger of cAMP activates various protein kinases that stimulate acid secretion by the K+/H+-ATPase. The main effect of gastrin on acid secretion is more indirectly mediated through histamine release from ECL (enterochromaffin-like) cells rather than direct stimulation of parietal cells. In contrast, acetylcholine causes direct potent stimulation of parietal cells [5].

Famotidine is a competitive antagonist at H2 receptors within parietal cells. Gastric acid secretion is a complex and continuous process controlled by neuronal, peripheral endocrine and paracrine factors. Each factor affects the secretion of H+ ions by parietal cells located within the stomach. Acetylcholine (neuronal), histamine (paracrine), and gastrin (endocrine) act on their specific receptors, namely the M1 receptor, H2 receptor, and CCK2 receptor found on the basolateral membrane of the parietal membrane in parietal cells. Histamine is synthesized and secreted by enterochromaffin-like (ECL) cells associated with the basolateral membrane of the parietal cells. This drug reduces automatic (basal) acid secretion and acid secretion stimulated by food as well as by neural and hormonal influences. Famotidine reduces the permeability of sodium, potassium, calcium, and chloride ions, histamine, and acetylcholine [6].

Physiologically, Cl- ions are actively transported to the canaliculi within the parietal cells. K+ and Cl- ions are exchanged with H+ in the cell by K+/H+-ATPase. The liquid membrane that may be formed by H2 antagonists in parietal cells reduces the passive transport of K+ and Cl- ions resulting in a lack of exchange of K+/H+. Because the availability of H+ and Cl- ions decreases, the formation of gastric acid is also reduced. H2CO3 formed from CO2 and H2O dissociates in a reaction catalyzed by carbonic anhydrase to form H+ and HCO3-. HCO3- is exchanged at the basement membrane with Cl-. HCO3- in free form combines with mucus and forms a cytoprotective layer with pH 7 in the lumen. Transport of HCO3- ions increases due to the presence of a liquid membrane formed by H2 antagonists and contributes to the increase in cytoprotective due to the action of the drug. Acetylcholine is released from neurons and stimulates specific muscarinic receptors on the parietal cell surface and histamine-containing cell surface and triggers the activation of K+/H+-ATPase through the Ca2+-dependent pathway of the basolateral membrane. In the presence of liquid membrane of H2 antagonist, the amount of acetylcholine transport is also reduced which leads to blockage of K+/H+-ATPase through Ca2+-dependent pathway. It is known that parietal cells have H2 receptors and are sensitive to histamine. Stimulation of the H2 receptor increases cyclic adenosine monophosphate (cAMP) and stimulates acid secretion. The liquid membrane of H2 antagonists reduces histamine transport so that the availability of histamine to H2 receptors is reduced [7].

**Famotidine for COVID-19**

Several studies have reported allegations that oral use of famotidine can improve recovery in Covid-19 patients where 10 Covid-19 patients who took famotidine for 5-21 reported experiencing symptomatic improvement [8]. Other study has reported that the use of famotidine can reduce the risk of death [9].

Several studies have reported on the activity of famotidine as a covid-19 drug candidate both in
silico and in vitro studies. In in silico studies, several proteins such as SARS-CoV-2 main protease (CoV-2 3CLpro) and Papain-like protease (SARS-CoV-2 PLpro) were expected to interact with famotidine. The molecular docking of SARS-CoV-2 PLpro protein with famotidine showed that there were two potential binding sites on the SARS-CoV-2 PLpro protein for famotidine, but the molecular docking results showed a very weak interaction between famotidine and the SARS-CoV-2 PLpro protein so it was predicted to have no activity in the in vitro test. In addition, the in silico assay results showed the lack of effect of famotidine on interferon signaling and NF-kB-dependent gene expression in SARS-CoV-2 PLpro [10].

In vitro studies related to the probability of famotidine as a Covid-19 drug evaluated famotidine as an inhibitor of covid-19 virus replication or Covid-19 virus eradication using various enzymatic assays. In vitro test results showed that famotidine did not bind or inhibit the function of 3CLpro and PLpro proteins that play a role in Covid-19 virus replication. Famotidine at test concentrations up to 200 µM did not show activity as a covid-19 antiviral directly using lung cells as the main target of the covid-19 virus. So further testing is needed to see the mechanics of famotidine's work to increase the recovery of covid-19 patients [11].

Concerns related to side effects and diseases

Although rare, some people can experience very severe side effects and risk death. Contact a physician or go straight to the hospital if you experience symptoms that may be associated with severe side effects such as: dizziness, fainting, increased heart rate, abnormal heart rate, and signs of allergy such as skin rash, swelling, or peeling skin with or without fever; wheezing; chest or throat tightness; difficulty breathing, swallowing, or speaking; hoarseness; or swelling of the mouth, face, lips, tongue, or throat.

Changes in heart rate (ECG). It has been reported that prolonged QT interval occurs in patients who have moderate to severe renal impairment.

Deficiency of Vitamin B₁₂. Prolonged treatment (≥ 2 years) may lead to vitamin B₁₂ malabsorption which in turn leads to vitamin B₁₂ deficiency. The degree of deficiency is dose-related and more prevalent in women and those less than 30 years old [12].

Gastric disorders. The disappearance of symptoms does not mean the disappearance of the gastric disorder.

Kidney disorders. Use with caution; risk of CNS (central nervous system) adverse reactions and QT prolongation is increased. Dose adjustment is recommended.

Geriatrics. Use with caution; CNS adverse reactions (e.g. confusion, delirium, hallucinations, disorientation, restlessness, seizures, lethargy).

Pediatrics. The use of gastric acid inhibitors, including proton pump inhibitors and H₂ blockers, increases the risk of acute gastroenteritis and pneumonia.

Conclusion

Famotidine, a potent H₂ receptor antagonist, offers significant promise in peptic ulcer therapy due to its high selectivity and minimal side effects compared to alternatives. Beyond its traditional use, emerging studies suggest potential benefits in COVID-19 treatment, indicating symptomatic improvement and reduced mortality risk in some cases. However, its efficacy against the virus directly remains unproven, necessitating further research. Despite its benefits, caution is advised due to rare but serious side effects and considerations for specific patient populations.

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Conflict of interest

None.

Author contributions

AAC and AHS took the lead in conducting the literature review, compiling and synthesizing relevant research findings, and drafting the initial manuscript. AHS provided critical guidance on the direction of the review, contributed to refining the research scope, and offered revisions to the manuscript. Both AAC and AHS reviewed the final manuscript, and approved the submission of the final version for publication.

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