Available online on www.ajper.com

Asian Journal of Pharmaceutical Education and Research

Vol -2, Issue-1, January-March 2013

ISSN: 2278 – 7496

REVIEW ARTICLE

A review on Histamine$_2$ receptor antagonist: pharmacological and analytical aspects.

Saswata Ku. Parida*, N. P. Jivani, Bimal N. Patel, Akruti S. Khodakiya,

Asit R . Sahu, Sibanarayan Acharya

C. U. Shah College of Pharmacy & Research, Wadhwancity, Surendranagar, Gujarat

ABSTRACT

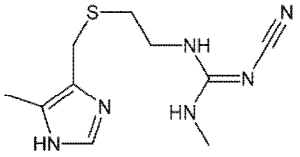
Histamine is an endogenous substance synthesized, stored and released in mast cells, (which are abundant in the skin, GI, and the respiratory tract), basophils in the blood, and some neurons in the CNS and peripheral NS. Histamine H2-receptor antagonists are a unique class of compounds. Pharmacologically they are characterized as a family by their ability to inhibit the secretion of gastric acid, and kinetically they are classified as a family by their similarity in absorption, distribution and elimination. They suppress the normal secretion of acid by parietal cells and the meal-stimulated secretion of acid. Histamine H2-receptor antagonists, also known as H2-blockers, are used to treat duodenal ulcers and prevent their return. They are also used to treat gastric ulcers and for some conditions, such as Zollinger-Ellison disease, in which the stomach produces too much acid. In over-the-counter (OTC) strengths, these medicines are used to relieve and/or prevent heartburn, acid indigestion, and sour stomach.

Keywords: Histamine H2-receptor, Analytical Methods.

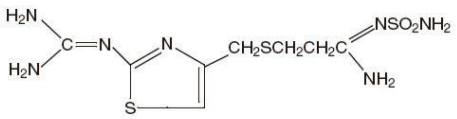
***Coresponding Author:**
Saswata Ku. Parida[1*]
C. U. Shah College of Pharmacy & Research,
Wadhwancity, Surendranagar, Gujarat.
Mobile No: +918000859396
Email: saswat3495@gmail.com

INTRODUCTION

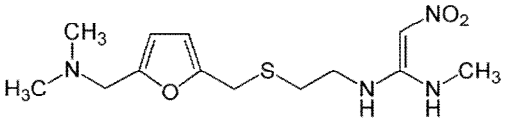
Histamine2 (H2) antagonists or blockers have been used for many years to treat peptic ulcer disease and symptoms of gastroesophageal reflux disease (GERD). Doses are often increased to two to four times normal when treating more severe cases of GERD. For patients who fail to achieve adequate acid suppression with the H2-antagonists, proton pump inhibitors (PPIs) with greater acid-suppressing capabilities are available. Here a review is done to compare the efficacy, safety, and administration of the currently available H2-receptor antagonists (H2RAs) in the treatment of peptic ulcer disease and other indications.



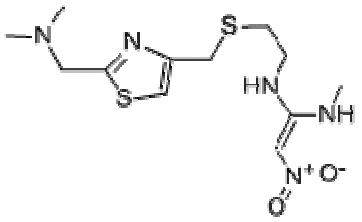
Cemitidine



famotidine



Ranitidine



nizatidine

Histamine receptor:

Histamine is a ubiquitous messenger molecule released from mast cells, enterochromaffin-like cells, and neurons. Its various actions are mediated by histamine receptors H1, H2, H3 and H4. The histamine receptor H2 belongs to the rhodopsin-like family of G protein-coupled receptors. It is an integral membrane protein and stimulates gastric acid secretion. It also regulates gastrointestinal motility and intestinal secretion and is thought to be involved in regulating cell growth and differentiation. [1]

Activation of the H2 receptor results in the following physiological responses:

- Stimulation of gastric acid secretion (Target of anti-histaminergics (H2 receptors) for peptic ulcer disease and GERD)
- Smooth muscle relaxation (Experimental histamine H2 receptor agonist used for asthma and COPD)
- Inhibit antibody synthesis, T-cell proliferation and cytokine production
- Vasodilation – PKA activity causes phosphorylation of MLCK, decreasing its activity, resulting in MLC of myosin being dephosphorylated by MLCP and thus inhibiting contraction. The smooth muscle relaxation leads to vasodilation.[2]

Indications:

- The histamine H2-receptor antagonists are indicated in the healing of gastric and duodenal ulcers (peptic ulcer disease; PUD), treatment of gastroesophageal reflux disease (GERD), and prevention of stress ulcers. Recent guidelines recommend either proton pump inhibitors or H2-receptor antagonists as first-line treatment options for most gastrointestinal disorders. Recent clinical evidence suggests improved efficacy with the proton pump inhibitors (PPIs) and has led to PPIs replacing the H2-receptor antagonists in clinical practice. Overall, the optimal H2 antagonist agent, dose, and duration for patients with a gastrointestinal disease should be determined based on symptom control and routine disease assessment. There are currently four main indications for the use of H2RAs; they include: duodenal ulcer (treatment and maintenance), benign gastric ulcer (treatment and maintenance), gastroesophageal reflux disease (GERD) including erosive esophagitis and the treatment of pathologic hypersecretory conditions. [3]

Following are approved indications of H2 receptor antagonists.

Cimitidine	Short-term treatment of active duodenal ulcers and benign gastric ulcers; maintenance therapy of duodenal ulcer; treatment of gastric hypersecretory states; treatment of gastroesophageal reflux disease (GERD) OTC labeling: Prevention or relief of heartburn, acid indigestion, or sour stomach
Famotidine	Maintenance therapy and treatment of duodenal ulcer; treatment of gastroesophageal reflux disease (GERD), active benign gastric ulcer; pathological hypersecretory conditions OTC labeling: Relief of heartburn, acid indigestion, and sour stomach
Nizatidine	Treatment and maintenance of duodenal ulcer; treatment of benign gastric ulcer; treatment of gastroesophageal reflux disease (GERD)
Ranitidine	Short-term and maintenance therapy of duodenal ulcer, gastric ulcer, gastroesophageal reflux disease (GERD), active benign ulcer, erosive esophagitis, and Pathologica hypersecretory conditions; as part of a multidrug regimen for H. pylori eradication to reduce the risk of duodenal ulcer recurrence OTC labeling: Relief of heartburn, acid indigestion, and sour stomach

Disease Overview

Approximately one in five adults in the United States has symptoms of heartburn or gastroesophageal regurgitation at least once a week.[4, 5] Most cases of gastroesophageal reflux disease (GERD) are benign, but some can lead to severe erosive esophagitis, stricture formation or Barrett's esophagitis. In addition, nearly 500,000 new cases of ulcers are diagnosed and 4 million ulcer recurrences are reported each year in the US. Of the reported cases, the frequency of gastric ulcers appears to be increasing while the frequency of duodenal ulcers appears to be declining. Overall, costs of treating gastrointestinal disorders are considerable and can lead to decreased quality of life. The health economics implications of the management of gastrointestinal disorders include the costs associated with the diagnosis and treatment of the disease (endoscopy, surgery, and medications) as well as costs associated with lost productivity and reduced quality of life.[4,5]

Gastrointestinal disorders result when the normal protective barriers in the esophagus, stomach, and intestine become compromised. Gastric acid and pepsin in the stomach normally do not produce damage or symptoms but if the normal defense mechanisms fail, reflux, erosive esophagitis, dyspepsia, and/or ulceration, may result. The lower esophageal sphincter prevents acidic gastric contents to move up into the esophagus and is the primary esophageal defense mechanism. The stomach protects itself from acid damage by a number of mechanisms including the secretion and trapping of bicarbonate, the coating of the mucosal surface with an insoluble gel, and the prostaglandin-stimulated production of mucus. Drugs that inhibit prostaglandin formation (e.g., non-steroidal anti-inflammatory drugs, ethanol) decrease mucus secretion and increase the risk of acid-peptic diseases. The infectious agent, Helicobacter pylori, may also play a role in the pathogenesis of acid-peptic diseases.[5] Therapies for treatment of the gastrointestinal disorders are directed at decreasing gastric acidity, enhancing the lower esophageal sphincter, stimulating esophageal/gastrointestinal motility, and/or enhancing mucosal defense.4-8 Before the availability of the H2-receptor antagonists, the only therapeutic option was neutralization in the stomach lumen. The introduction of the H2-receptor antagonists provided a new, more effective treatment option, as they work to competitively inhibit acid production by gastric parietal cells. In time, the documented safety and efficacy of the H2-receptor antagonists led to their availability over-the counter.

More recently, proton pump inhibitors (PPIs) are replacing the H2-receptor antagonists in clinical practice, as a result of improved efficacy in the treatment of a number of gastrointestinal diseases with PPIs. Lifestyle modifications (weight loss, elevation of the head, avoiding late meals, avoiding specific foods, etc.) may also be helpful in the treatment of the gastrointestinal disorders. Recent guidelines for the treatment of GERD and esophageal disease (2008) recommend initial treatment with a PPI once to twice daily.[6] According to the guidelines, long-term treatment with the PPIs should be avoided and use should be limited to the lowest dose and shortest course possible to relieve symptoms. Some clinicians advocate PPI use on an as needed or “on demand” basis only or with a "stepdown" approach by either decreasing the dose of the PPI or switching to an H2 receptor antagonist.[5,6] For the treatment of peptic ulcer disease (PUD, gastric and duodenal ulcers), both PPIs and H2-receptor antagonists are effective; although, PPIs may relieve symptoms and promote healing more rapidly than H2 antagonists.8 Non-steroidal anti-inflammatory drugs (NSAID) use is frequently reported with peptic ulcers/bleeding and should be avoided in patients who are at increased risk of PUD. Intravenous PPI therapy is recommended in patients with acute bleeding ulcers.[7]

Also implicated in the development of gastritis and peptic ulcers is the gram-negative bacteria, H. pylori. It is estimated up to 60% of peptic ulcers are associated with H. Pylori infection. [8] The American College of Gastroenterology Guideline on the Management of Helicobacter pylori Infection (2007) recommends first-line treatment with either a triple therapy regimen consisting of PPI, clarithromycin, and amoxicillin or a bismuth-containing quadruple regimen with an H2-receptor antagonist, metronidazole, and tetracycline. Evidence suggests eradication rates may be higher with 14 versus 7 or 10-day regimens. [8]Severe illness or trauma requiring intensive care is another risk factor for developing gastritis and ulceration of the stomach or duodenum. [9] Guidelines recommend H2- receptor antagonists, cytoprotective agents (sucralfate), or PPIs for the prophylaxis of stress ulcers in patients requiring intensive care.

According to the recommendations, antacids should not be used as stress ulcer prophylaxis.[9] Overall, the optimal drug therapy, dose, and duration for patients with a gastrointestinal disease should be determined based on symptom control and routine disease assessment.[5, 10, 11]

Clinical Efficacy

In total, seven comparative trials were identified for evaluation of the oral histamine H2-receptor antagonists. [12-19] Trials compared the agents in the treatment of symptoms and pain associated with heartburn/GERD (n = 1) [15], erosive esophagitis (n =3) [16, 18, 19] and/or peptic ulcer (n = 3). [12-14, 17]

Cimetidine vs. Ranitidine

Cimetidine was compared to ranitidine in three comparative clinical trials. Galmiche et al [15] compared cimetidine to ranitidine in the treatment of heartburn/GERD. The study investigators evaluated the efficacy of the agents in 1,336 adult patients with heartburn episodes. Patients were randomized to receive cimetidine 200 mg, ranitidine 75 mg, or placebo up to three times daily as needed for heartburn episodes over a two-week period. Overall, cimetidine and ranitidine were more effective in relieving GERD symptoms and reducing use of rescue medications compared to placebo. No differences in efficacy were reported between the cimetidine and ranitidine treatment groups.

McCarty-Dawson et al [18] evaluated cimetidine and ranitidine in the treatment of erosive esophagitis. The study investigators evaluated the efficacy of the agents in 696 adult patients with endoscopic-confirmed erosive esophagitis. Patients were randomized to receive cimetidine 800 mg twice daily, ranitidine 150 mg twice daily, or ranitidine 150 mg four times daily for 12 weeks. Healing rates in the ranitidine four times daily group (77%) were significantly higher than in the cimetidine treatment group (68%; $p < 0.02$). Antacid use was significantly lower in the ranitidine treatment groups compared to the cimetidine treatment group ($p < 0.005$). Although rare, drug-related adverse event discontinuation rates were significantly higher with cimetidine (4%) compared to ranitidine (1%; $p < 0.05$). No differences in overall all adverse events were reported between the treatment groups.

Dixon et al [13, 14] evaluated cimetidine compared to ranitidine in the treatment of duodenal ulcer disease. The study investigators evaluated the efficacy of the agents in healing duodenal ulcers in patients aged less than 60 years compared to patients aged 60 years or greater. Patients were randomized to receive cimetidine 800 mg or ranitidine 300 mg every night at bedtime for four weeks. No differences in ulcer healing rates or adverse event rates were reported between

cimetidine compared to ranitidine or between patients aged < 60 compared to patients aged > 60. A small, but statistically significant difference in epigastric pain was reported between the treatment groups in favor of ranitidine (60% vs. 54%; $p < 0.05$). Overall, the evidence evaluating cimetidine compared to ranitidine suggests comparable efficacy. Some evidence suggests ranitidine may be more effective in healing erosive esophagitis and relieving epigastric pain than cimetidine.

Famotidine vs. Ranitidine

Famotidine was compared to ranitidine in two comparative clinical trials. Simon et al [19] compared famotidine to ranitidine in the treatment of erosive esophagitis. The study investigators evaluated the efficacy of the agents in 440 adult patients with endoscopic-confirmed erosive esophagitis. Patients were randomized to receive famotidine 20 mg twice daily, famotidine 40 mg twice daily, or ranitidine 150 mg twice daily for up to 12 weeks. Ulcer healing rates were higher in the famotidine 40 mg group compared to the ranitidine treatment group; however, no differences in symptomatic improvement were reported between the agents. Higuchi et al64 evaluated 69 patients with gastric ulcers randomized to receive either famotidine or ranitidine daily for 12 weeks. According to this small trial, no differences in ulcer healing rates were observed between famotidine and ranitidine in the treatment of erosive esophagitis. Overall, the evidence comparing famotidine to ranitidine suggests comparable efficacy.

Nizatidine vs. Ranitidine

One trial compared nizatidine to ranitidine in the treatment of peptic ulcers. Battaglia et al [12] evaluated the efficacy of the agents in 245 patients aged > 65 years diagnosed with either duodenal ulcer or gastric ulcer over a 3-month period. Patients were randomized to receive nizatidine 300 mg or ranitidine 300 mg every night at bedtime for 12 weeks. At the end of the study period, no differences in ulcer healing rates were reported between the agents. Overall, this evidence suggests comparable efficacy for nizatidine and ranitidine in the treatment of peptic ulcers in patients aged over 60 years old.

Famotidine vs. Nizatidine

One trial compared famotidine to nizatidine in the prevention of erosive esophagitis in patients with a recent history of esophageal disease. Hamamoto et al [16] evaluated the efficacy of the agents in the prevention of disease recurrence in 72 patients with endoscopically-healed erosive esophagitis. Patients were randomized to receive famotidine 20 mg twice daily or nizatidine 150 mg twice daily for 6 months. Disease non-recurrence rates were significantly higher in the nizatidine treatment group (~50%) compared to the famotidine treatment group (~25%; p = 0.049). Of importance, no differences in remission rates were found in patients with disease grade A, C, D. The statistically significant differences in recurrence rates were only demonstrated in patients with endoscopic grade B disease. Overall, the evidence suggests nizatidine may be more effective in preventing erosive esophagitis recurrence in patients diagnosed with moderate (grade B) esophageal disease.

The available comparative clinical evidence evaluating the oral H2-receptor antagonists suggests comparable efficacy in the treatment of heartburn/GERD, erosive esophagitis, and peptic ulcer disease. Some evidence suggests ranitidine may be more effective in healing erosive esophagitis and relieving epigastric pain than cimetidine. One trial found higher rates of discontinuation due to adverse events with cimetidine compared to ranitidine. In addition, limited evidence suggests nizatidine may be more effective in preventing erosive esophagitis recurrence in patients diagnosed with moderate esophageal disease. Overall, the H2-receptor antagonists are effective in treating gastrointestinal diseases.

Pharmacokinetic:

Although the absorption for cimetidine, ranitidine and famotidine is rapid, the bioavailability for these agents is diminished due to extensive first-pass hepatic metabolism. Nizatidine undergoes little first-pass and as a result bioavailability reaches close to 100% in normal patients. Only minimum protein binding occurs with these agents (range 15 - 35%). All are eliminated by a combination of hepatic metabolism, renal tubular secretion and glomerular filtration. Cimetidine, ranitidine and famotidine are primarily eliminated through hepatic metabolism. Because cimetidine has a high affinity for the cytochrome P450 it may reduce the hepatic metabolism of drugs metabolized through the cytochrome P450 system. Ranitidine weakly binds to the

cytochrome P450 system whereas famotidine and nizatidine have little to no interaction with this pathway. Only nizatidine is primarily eliminated by renal excretion, however dosage adjustments are required for all agents in renal dysfunction. When severe hepatic disease is present with renal dysfunction a further dosage reduction may be necessary. [20, 21]

Analytical methods for H2 receptor antagonists:

Several methods for analysis of H2 receptor antagonist are available. K. Rama rao et al [22] Developed bioanalytical method for ranitidine from plasma using high performance liquid chromatography using Nizatidine as an internal standard. Sample preparation was accomplished through solid phase extraction and chromatographic separation on a reverse phase column. The mobile phase consists of mixture of phosphate buffer and methanol at a flow rate of 1 ml/min. The wavelength used for the detection of ranitidine was 315nm with a total run time of 8 minutes. The retention times of ranitidine and nizatidine were found to be 6 and 4.5 minutes respectively. The method was developed and tested for the linearity range of 10 ng/ml to 1000 ng/ml.

Chih Ho et al [23] developed HPLC method for simultaneous estimation of Famotidine, Ranitidine HCl, Cimetidine, and Nizatidine in Commercial Products. The method) was developed using a two-level, full-factorial design with three variables (volume of methanol, percentage of triethylamine, and concentration of phosphate buffer) to select an acceptable mobile phase. A column (15cm × 4.6 mm ID) of Inertsil ODS-2 (5 µm) was used, and 0.04M aqueous sodium dihydrogen phosphate/acetonitrile/methanol/TEA at a proportion of 345/20/35/0.7 (v/v/v/v) was the selected mobile phase (1 ml/min). The detection wavelength was set at 230 nm, and procaine HCl was used as the internal standard. Precision and linearity of the method were assessed.

Safila naveed et al [24] developed two different HPLC methods for Simultaneous determination of lisinopril and H2 antagonists in API, formulations and human serum. An isocratic reversed phase high-performance liquid chromatographic method has been developed for the simultaneous determination of lisinopril and H2 antagonists (cimetidine, ranitidine, and famotidine) in bulk, dosage formulations, and human serum at 225 nm. Chromatographic separation was achieved using mobile phase, acetonitrile:water (70:25 v/v) adjusted to pH 3.0 via phosphoric acid 85%

with flow rate of 1 ml/min at room temperature. Calibration curves were linear over range of 0.7–12.50 µg/ml for H2 antagonists and 2.5–100 µg/ml for lisinopril with a correlation coefficient ± 0.999. Limit of detection and limit of quantitation were in the ranges of 0.07–10.4 ng/ml. Intra- and inter-day precision and accuracy results were 98.0–102%.

Parekh Ravishankar et al [25] developed UV spectrometric method for estimation of lufatidine in bulk and pharmaceutical dosage form. The wavelength maxima of Lafutidine in 0.1N HCL was found to be 286 nm. The drug follows linearity in the concentration range 5-50µg/ml with correlation coefficient value 0.9995. The proposed method was applied to pharmaceutical formulation and % amount of drug estimated 99.19 % was found in good agreement with the label claim.

M. Saeed Arayne et al [26] developed HPLC method for simultaneous determination of Metformin, Cimetidine, Famotidine, and Ranitidine in Human Serum and Dosage Formulations. These drugs were separated on a Purospher Star RP18 endcapped (250 mm × 4.6 mm i.d.) column packed with 5-µm particles. The mobile phase, optimized through an experimental design, consisted of methanol-water-triethylamine (20:80:0.05), whose pH was adjusted to 3.0 with phosphoric acid (85%) pumped at a flow rate of 1.0 mL/min. UV detection was performed at 229 nm.

Summary :

Four oral histamine H2-receptor antagonists are currently available as either prescription or over-the-counter use in the United States. The histamine H2-receptor antagonists are indicated in the healing of gastric and duodenal ulcers, treatment of GERD, and prevention of stress ulcers. The management of the gastrointestinal disorders includes costs associated with the diagnosis and treatment of the disease as well as costs associated with lost productivity and reduced quality of life. Therapies for treatment of the gastrointestinal disorders include antacids, sucralfate, H2-receptor antagonists, and proton pump inhibitors. Guidelines recommend proton pump inhibitors as first-line treatment for most gastrointestinal disorders. H2-antagonists may be used as step-down therapy in the treatment of GERD, as a first-line treatment option in mild to moderate peptic ulcer disease, or in combination with bismuth, metronidazole, and tetracycline in the treatment of H. pylori. Guidelines do not recommend a specific H2-receptor antagonist over

another. Overall, the optimal H2 antagonist agent, dose, and duration for patients with a gastrointestinal disease should be determined based on symptom control and routine disease assessment.

Seven comparative clinical trials were identified for evaluation of the oral histamine H2-receptor antagonists in the treatment heartburn/GERD, erosive esophagitis, and/or peptic ulcer disease. The available comparative clinical evidence suggests comparable efficacy for all four agents. Some evidence suggests ranitidine may be more effective in healing erosive esophagitis and relieving epigastric pain than cimetidine and nizatidine may be more effective in preventing erosive esophagitis recurrence in patients diagnosed with moderate esophageal disease. Clinical evidence evaluating the H2-receptor antagonists in the treatment of weight gain associated with psychotropic agent therapy failed to demonstrate efficacy. With regard to safety, the oral histamine H2- receptor antagonists are well tolerated and the most common drug-related adverse effects include diarrhea, constipation, headache, drowsiness, and muscular pain. Less common adverse effects may include central nervous system toxicity, hormone imbalances, and blood dyscrasias. Risk of CNS toxicity may be higher in patients with severe liver disease and in the geriatric population. Drug interactions with H2-receptor antagonists are rare and occur mainly with cimetidine. All four H2 antagonists require dose-reduction in patients with decreased creatinine clearance. Overall, the oral histamine H2-receptor antagonists are safe and effective in treatment options for gastrointestinal diseases.

References:

1. Entrez Gene: HRH2 histamine receptor H2.
2. Walter F., PhD. Boron (2005). Medical Physiology: A Cellular and Molecular Approaoch. Elsevier/Saunders. ISBN 1-4160-2328-3. Page 479
3. Histamine antagonists in Facts and Comparisons, Olin BR, ed. St. Louis, MO: Facts and Comparisons, Inc., 1996.
4. Jones RH. Clinical economics review: gastrointestinal disease in primary care. Aliment Pharmacol Ther. Jun 1996;10(3):233-239.
5. Wallace JL, Sharkey KA. Chapter 45. Pharmacotherapy of Gastric Acidity, Peptic Ulcers, and Gastroesophageal Reflux Disease. In: Brunton LL, Chabner BA, Knollmann BC, eds.

Goodman & Gilman's The Pharmacological Basis of Therapeutics. 12th ed. New York: McGraw-Hill; 2011.

6. Kahrilas PJ, Shaheen NJ, Vaezi MF, et al. American Gastroenterological Association Medical Position Statement on the management of gastroesophageal reflux disease. Gastroenterology. Oct 2008;135(4):1383-1391, 1391 e1381-1385.
7. Soll AH. Consensus conference. Medical treatment of peptic ulcer disease. Practice guidelines. Practice Parameters Committee of the American College of Gastroenterology. JAMA. Feb 28 1996;275(8):622-629.
8. Anderson J, Gonzalez J. H pylori infection. Review of the guideline for diagnosis and treatment. Geriatrics. Jun 2000;55(6):44-49.
9. Dellinger RP, Levy MM, Carlet JM, et al. Surviving Sepsis Campaign: international guidelines for management of severe sepsis and septic shock: 2008. Crit Care Med. Jan 2008;36(1):296-327.
10. Lacy CF, Armstrong LL, Goldman MP, Lance LL, eds. Drug Information Handbook. 12th ed. Hudson, OH: Lexi-Comp; 2011.
11. McEvoy GK, Snow EK, Kester L, Litvak K, Miller J, Welsh OH, eds. AHFS 2011 Drug Information. Bethesda, MD: American Society of Health-System Pharmacists; 2011.
12. Battaglia G, Di Mario F, Vigneri S, Dal Santo P, Pilotto A, Mazzacca G. Peptic ulcer in the elderly--a double-blind, short-term study comparing nizatidine 300 mg with ranitidine 300 mg. GISU (Interdisciplinary Ulcer Study Group). Aliment Pharmacol Ther. Dec 1993;7(6):643-648.
13. Dixon JS, Ehsanullah RS, Mills JG, Wood JR. Early evening dosing of ranitidine. Comparison with nighttime dosing of ranitidine or cimetidine in duodenal ulceration. Dig Dis Sci. Aug 1993;38(8):1459-1467.
14. Dixon JS, Mills JG, Ehsanullah RS, Wood JR. Association of age with the efficacy and safety of ranitidine and cimetidine in acute duodenal ulcer disease. Age Ageing. Nov 1993;22(6):411-418.
15. Galmiche JP, Shi G, Simon B, Casset-Semanza F, Slama A. On-demand treatment of gastrooesophageal reflux symptoms: a comparison of ranitidine 75 mg with cimetidine 200 mg or placebo. Aliment Pharmacol Ther. Sep 1998;12(9):909-917.

16. Hamamoto N, Hashimoto T, Adachi K, et al. Comparative study of nizatidine and famotidine for maintenance therapy of erosive esophagitis. J Gastroenterol Hepatol. Feb 2005;20(2):281-286.
17. Higuchi K, Watanabe T, Tominaga K, et al. Effects of ranitidine on quality of gastric ulcer healing compared with famotidine: a randomized, controlled, multicenter trial. Int J Clin Pharmacol Res. 2005;25(4):187-194.
18. McCarty-Dawson D, Sue SO, Morrill B, Murdock RH, Jr. Ranitidine versus cimetidine in the healing of erosive esophagitis. Clin Ther. Nov-Dec 1996;18(6):1150-1160.
19. Simon TJ, Berlin RG, Tipping R, Gilde L. Efficacy of twice daily doses of 40 or 20 milligram famotidine or 150 milligrams ranitidine for treatment of patients with moderate to severe erosive esophagitis. Famotidine Erosive Esophagitis Study Group. Scand J Gastroenterol. May 1993;28(5):375-380.
20. Histamine antagonists in Facts and Comparisons, Olin BR, ed. St. Louis, MO: Facts and Comparisons, Inc., 1996.
21. Feldman M, Burton ME. Histamine-2 receptor antagonists. Standard therapy for acid-peptic diseases (first of two parts). NEJM 1990;323 (24):1672-1680.
22. K.Rama rao, k.prakash and CVN Prasad. Bioanalytical method development and validation of ranitidine from plasma using high performance liquid chromatography. Journal of analytical chemistry, 2010, 2 (3), 58-62.
23. Chih Ho, Hsi-Min Huang, Shu-Ying Hsu, Ching-Yih Shaw and Ber-Lin Chang. Simultaneous High-Performance Liquid Chromatographic Analysis for Famotidine, Ranitidine HCl, Cimetidine, and Nizatidine in Commercial Products 1999, Vol. 25, No. 3 , Pages 379-385
24. Safila Naveed, Najma Sultana and M. Saeed Arayne. Simultaneous determination of lisinopril and H2 antagonists in API, formulations and human serum by using two different HPLC systems. Medicinal Chemistry Research , 2011,3(2), 69- 81.
25. Parekh Ravishkumar R, Patel Pinkal H, Patel Chinmay D, Patel Krupali S, Patel Hardik N. Development and Validation of UV Spectrophotometric method for estimation of Lafutidine in bulk and Pharmaceutical dosage form. International Journal of Drug Development & Research. 2012. 4(1).

26. M. Saeed Arayne, Najma Sultana, M. Hashim Zuberi1 and Farhan Ahmed Siddiqui. Simultaneous Determination of Metformin, Cimetidine, Famotidine, and Ranitidine in Human Serum and Dosage Formulations Using HPLC with UV Detection. IJPSR (2009), Vol. 1, Issue 5. 151-155.