H2-Blockers, Application, and Impact on Gastroduodenal Ulcer

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Abstract

Introduction: The stomach is a muscular bag that performs important functions such as: receiving food coming from the esophagus, processing it, separating albumins and fats, and sending processed food to the intestines.

Diseases: one of the most problematic diseases is gastric ulcer, by which we mean the benign ulceration of the wall of the digestive tract, which includes the mucosa, submucosa, and muscular layer. Ulcer differs from erosion as it is localized only in the mucosa.

Treatment: It is medicinal and surgical, in the first group, among other drugs, H2-blockers are included. These include cimetidine, ranitidine, nizatidine, and roxatidine.

Action: All H2 antihistamines are orally active. With the competitive blocking of H2-receptors, the basal secretion of HCl decreases by 90%. They inhibit the secretion of HCl from the stomach, almost without affecting the formation of gastric mucus and pepsin.

Statistics: The results obtained on 2.11.2010 included 200 patients with gastroduodenal ulcers. 60% were women, aged over 40 years who dominated, the rest 40% were men, also here the age over 40 years dominated.

Aim of the paper: General theoretical aspects related to gastric ulcers in the human body and to analyze H2- blockers as drugs, and how they affect gastric ulcers.

Keywords: Gastric ulcer • Histamine • H2-blockers

Introduction

Stomach-Ventriculus-Gaster

The stomach is a real digestive organ, where food stays for a certain time. The stomach is a muscular bag that performs important functions such as: receiving food coming from the esophagus, processing it, separating albumins and fats, and sending the processed food to the intestines.

Function

The stomach is a secretory organ. It produces pepsin and hydrochloric acid, and has an excretory function, releasing into the stomach lumen the various substances that can inject. It has an incretory function, it releases Kesli's antianemic factor into the blood. It functions as an engine capable of peristaltic movement [1].

The stomach also has a compensation function, it expels some products, e.g. urea, and nucleoproteins in case of kidney failure. In the stomach, we distinguish the initial part (the part of the passage of the esophagus into the stomach) cardio or pars cardia, the middle part, the body or corpus, which constitutes the largest part, and the exit part, the part of the passage of the stomach into the duodenum, pars pyloric or pylorus. To the left of the cardia, the most protruding part of the body is called the fundus ventriculi. Between the cardia and the fundus is the incisura cardiaca. On the right, between the body and the pylorus, there is another notch incisura angularis. We distinguish two edges: curvature ventriculi minor and curvatura ventriculi major. There are also two faces, paries anterior and paries posterior [2].

Stomach Diseases

The most frequent diseases of the stomach are gastritis, ulcer diseases, neoplasms, and congenital anomalies.

Gastritis

By gastritis, we mean inflammatory and degenerative diseases of the stomach, most often in the limited layer of the mucous membrane of the stomach. Sometimes they appear as separate diseases, and quite often as accompanying diseases of the lungs or other organs.

Causes

The most common cause of gastritis is Helicobacter pylori, which also causes ulcers. Other causes of gastritis are alcohol abuse, smoking, and long-term use of analgesics such as aspirin and ibuprofen. It develops in circumstances of stress, burns, serious infections, etc. Crohn's disease, severe anemia, and radiation can be factored in the occurrence of gastritis.

Treatment

Lifestyle and diets can ease gastritis, while medications can help with healing. Stopping consuming alcohol and smoking are important steps in the control of gastritis because both of these irritate the stomach and development of inflammation. Also, avoiding fats and junk food is necessary. The drugs used to cure gastritis are antacids, H2-blockers, protein pump inhibitors, and in the case of Helicobacter pylori, combined therapy is used [3].

Peptic Ulcer

By peptic ulcers, we mean the benign ulceration of the wall of the digestive tract, which includes the mucosa, submucosa, and muscular layer. Ulcer differs from erosion as it is localized only in the mucosa. It most often appears after the use of salicylates and alcoholic beverages and is distinguished by exulceratio simplex involving the mucosa and submucosa. For the peptidic ulcer to occur, the presence of HCl and Pepsin is necessary (an inactive precursor substance called pepsinogen is formed in the stomach mucosa, which under the action of stomach acid and the decomposition catalyzed by its component sequence of this substance (autocatalysis) is transformed into pepsin. It must have proteolytic activity, according to the European pharmacopeia, at least 0.5 Units (UI) per mg, while peptic ulcer occurs if the content exceeds the protective mechanisms of the mucous membrane of the stomach (the protective layer of mucus, the ability to re-epithelize the mucosa and vascularization of the esophagus and duodenum) [4]. Peptic ulcer most often appears in the initial part of the duodenum (duodenal bulbus) - duodenal ulcer, gastric ulcer is also quite common in the small loop of the duodenum. Less often, it appears in the pyloric canal - the pyloric ulcer, in the duodenum between the bullar - postbullar ulcer, in Meckel's diverticulum (in the ectopic area of the mucous membrane of the esophagus), in the stoma, the so-called marginal ulcer. A peptic ulcer can occur in the lower part of the esophagus (due to the reflux of acidic contents into the esophagus) [2,3].

Etiology and Pathogenesis

It is assumed that many factors participate in the etiology of peptic ulcers: the duodenogastric reflux of bile is quite important in the pathogenesis of peptic ulcers since the alkalization of the gastric contents prevents the secretion of somatostatin, which increases the secretion of gastrin and increases the sensitivity of the parietal cells to the action of gastrin.

If there is chronic gastritis, then the acid more easily damages the injured mucosa. Bile salts are important in maintaining the protective mucosal layer of the mucous membrane of the stomach. The most powerful stimulators of acidity in the stomach are Acetylcholine, histamine, and gastrin. The mucous membrane of the stomach itself is protected from the acidic content of the stomach so that the surface epithelium of the mucous membrane of the stomach secretes alkalis that neutralize the excess acid that has reached the protective layer mucosal. The protective layer of mucus slows down the diffusion of acid, while the secreted alkalis neutralize the excess acid in the lungs. Emotional disturbances are also counted as etiological causes [5].

The action of psychic and emotional factors is explained in this way: irritating factors from the cortex of the brain are carried to the vegetative centers in the hypothalamus, then from the front part of the hypothalamus to the vagus nerve and end up in its postganglionic fibers in the mucous membrane of the brain itself and through them, it is secreted acetylcholine and histamine. Impulses from the back of the hypothalamus are carried to the front of the pituitary gland where it triggers the release of ACh which stimulates the adrenal cortex to release powerful Cortisone. Corticosteroids reduce mucus secretion and stimulate the secretion of acidic contents [3].

Numerous chemical, neural, and humoral factors participate in the regulation of acid secretion. Gastrin is the most powerful stimulator of gastric secretion. They are secreted by G cells in the antrum of the brain. Histamine is found in large quantities in the mast cells of the lamina propria, in the parts of the gastric mucosa that contain large numbers of HCl-secreting parietal cells. Genetic factors also play a role in the pathogenesis of peptic ulcers.

Consuming large amounts of coffee is harmful in causing peptic ulcers as caffeine stimulates the acid secretion of the stomach. Alcoholic beverages and tobacco have the same effect. Nicotine does not stimulate gastric secretion but reduces the exocrine secretion of bicarbonate from the pancreas so that the duodenum remains acidic, which is also the reason for the activation of the ulcer. Likewise, various types of drugs, especially aspirin, nonsteroidal antirheumatic drugs, and corticosteroids, are harmful [1].

Not infrequently, a duodenal ulcer appears in chronic kidney failure, alcoholic cirrhosis of the liver, kidney transplantation, hyperparathyroidism, and chronic pulmonary heart disease. Recently, the cause of peptic ulcers is thought to be Helicobacter pylori, which is probably responsible for chronic gastritis and duodenitis, atrophy of the gastric mucosa, and intestinal metaplasia. Helicobacter pylori are present in the mucous layer of the astral mucosa, in chronic gastritis in more than 95%, then in duodenal ulcer in 84% of cases, gastric ulcer in 54% of cases, while in healthy people it is detected in 25% of cases.

Clinical Overview

From the clinical symptoms domino epigastric pain, which appears on an empty stomach, more easily after taking food, milk, and alkalis. The pains have the character of beginning in the stomach, in the form of burning (pyrosis), cramps, narrowing, and in the form of piercing. Epigastric pain with expansion on the right side corresponds to a duodenal ulcer, while on the left side it corresponds to a gastric ulcer. Pain that extends to the back and back to the shoulders indicates the existence of a peptic ulcer in the back wall of the stomach or duodenum. If the pain appears from half to 2 hours after a typical meal, it is for a gastric ulcer, while from 2 to 5 hours after a typical meal, it is for a duodenal ulcer [5].

Pains at night and during the early hours of the morning are characteristic of duodenal peptic ulcers. Diffuse pains in the upper part of the abdomen that extends back to the back and are continuous (do not decrease but only intensify after taking food) are characteristic of penetrating peptic ulcers.

In esophageal ulcers or esophagitis, pain occurs during the passage of food through the esophagus or when the patient is lying down. The most important symptom is vomiting of liquid contents, yawning, burning, regurgitation, and finally hematemesis and melena. Physical examination - tenderness to palpation in the upper abdomen. In the case of a duodenal ulcer, the sensitivity point is located to the right of the umbilicus (at a distance of 5 cm - the so-called Obrascev's sign).

Diagnosis

Laboratory analyzes are important for ulcer diseases. Accelerated sedimentation of erythrocytes may indicate some complications in peptic ulcers, but it is for malignant alternation of peptic ulcers. Secondary posthemorrhagic and sideropenic anemia appear after bleeding, mainly after hematemesis and melena (the appearance of bleeding in peptic ulcers is a more frequent complication). Likewise, erythrocytosis is not a rare symptom in duodenal peptic ulcers when there is hypersecretion and hyperchlorhydria. Hyperleukocytosis indicates the existence of any of the complications in peptic ulcer (penetration, perforation). The investigation of gastric secretion is of great importance since in duodenal ulcers hypersecretion and hyperchlorhydria are present in 83% of cases [4].

The X-ray examination in the diagnosis of peptic ulcer is very important and in most cases only with this method can the presence of ulcers be detected. The X-ray examination reveals the duodenal ulcer in 70-80% of cases, while with the use of contrast (barium+air) the ulcer can be detected in 90% of cases. The endoscopic examination (fibro esophago gastro duodenoscopy) is of great importance because with this method material can be obtained for cytological and pathohistological analysis and represents the most important method as it can distinguish benign from malignant material. The most common complication of peptic ulcer is bleeding, which can sometimes be the first and only sign of the disease.

Bleeding often appears in the form of vomiting and 15-20% of cases of patients with duodenal ulcers. In 1/3 of the patients, bleeding relapses occur later. In young people, bleeding is not as serious as it comes to hemostasis, while in elderly people, bleeding is dangerous because homeostasis is weak and the blood vessels are sclerotic. In most patients, medical therapy (blood transfusion, Fe injection, H2 receptor blockers, antacids) succeeds in stopping the bleeding with nasogastric suction.

Penetration and perforation are serious complications of peptic ulcers. In the case of penetration, the crack in the wall of the esophagus and duodenum goes almost to the serosa. Penetration penetrates the pancreas and liver. Perforation occurs when it passes through all the layers of the stomach and duodenum and then the stomach contents pass into the free abdominal space and unbearable pain occurs in the upper part of the abdomen. The picture of acute diffuse perforating peritonitis with muscle defense, severe vomiting, shock state, rapid filiform pulse, and high temperature soon appears [6].

Pyloric stenosis is a very serious complication of peptic ulcers. The patient vomits food that was taken two or three days earlier. There is a large loss of body weight, dehydration, loss of electrolytes, metabolic alkalosis, and shallow and slowed breathing (low concentration of H+ ions induces depression in the respiratory center). Due to the decrease in the concentration of Ca+ ions, tetama may appear. Gastrojejunocolic fistula is a serious complication of peptic ulcer. In addition to the typical ulcer pain, patients have vomiting with fecal content, diarrhea, and the presence of undigested food with constant loss of body weight. All complications of peptic ulcers are treated surgically. Only in the penetrating peptic ulcer and the most bleeding ulcer that responds well to drug therapy and blood transfusion, surgical treatment can be avoided, as well as by taking H2-blockers.

Mechanism Of Gastric Acid Secretion

The secretion of Gastric Acid (HCl) is carried out by the parietal cells of the gastric mucosa, in the composition of gastric juice in the amount of 2-3 liters per day with values of pH~1. Several messengers (mediators, neurotransmitters, and hormones) participate in the regulation of its secretion, through their system of receptors located in the basolateral membrane.

Thus histamine, employing H2 receptors located in the parietal region, increases the level of the secondary messenger cyclic AMP, while ACh through the influence on muscarinic receptors and the hormone gastrin by interaction with receptors, affects calcium ion channels, increasing the intracellular content of Ca^{+} ions. The final effect of these messengers is realized by the enzyme $^{H+/K+}$-ATPase (proton pump), which exchanges hydronium ion HsO+ with K+ ions.

In the parietal cells, the series of prostaglandins E intervenes, inhibiting the

system of adenylate cyclase stimulated by histamine (thus reducing the concentration of cyclic AMP). Other parietal cells, under the influence of prostaglandins, secrete bicarbonates and gastric mucus, contributing to the protection of the stomach lining from the effect of increased acidity. Prostaglandins accelerate the re-epithelialization of the mucosa and make it resistant to the harmful action of lactic acid [7].

In many cases, it seems that the increased secretion of gastric acid is related to the presence and infection caused by Helicobacter pylori, which can damage the mucosal defense system. This is the reason that after verifying the presence of the bacterium, combined therapy is recommended, where an antibiotic is also given in addition to antiulcerosis. The most adequate therapy is omeprazole+metronidazole+amoxicillin.

Treatment

It is medicinal and surgical. In the treatment, antacids, anticholinergics, and sedatives should be given simultaneously. Intensive treatment takes 4-8 weeks. The treatment sometimes takes even longer. Apaurin, Librium, lexilium, etc. are used as sedatives. In case of failure of this therapy, many agents are used which, with different mechanisms, manage to reduce the production or secretion of HCl in the gastric space:

- Antagonists of H2-histamine receptors
- Inhibitors of the protein pump (H+/K+-ATPase enzyme)
- Parasympatholytics
- Gastrin antagonists
- The gastric ulcer should be regularly checked with an endoscope based on the need, also histologically. ferent mechanisms, manage to reduce the production or secretion of HCl in the gastric space:

H2-Antihistaminics

The creation of H2 Receptor Antagonists (H2-antihistamines) is an example of the rational design and benefit of new drugs. The rational procedure that led to the design of H2 receptor antagonists followed this path: starting from the observation that the antihistaminic compounds known until then (H1 receptor antagonists) were unable to antagonize histamine-induced gastric secretions. Black and his collaborators hypothesized that there must exist a hitherto unknown subset of these receptors (later called H2 receptors). In 1964 a systematic research program for specific antagonists of these receptors was initiated. The starting point was guanylhistamine, which possessed weak antagonistic properties concerning histamine-induced gastric secretion [8].

The lateral string seemed to determine mainly the power of the action. Its prolongation led to an overall increase in H2-antagonist action, but some agonist effect was still retained. Replacement of the very basic guanidinic function with a univalent thioureic led to the source amide. Although quite active, this compound was unsuitable, as it had poor oral bioavailability. The addition of a metal group in position 4 of the imidazole ring, as well as the introduction of an electron-withdrawing sulfur atom into the side chain, led to slightly ionizable and at the same time very active compound, properties that enable oral use. The obtained derivative was methiamide, it was 10 times more active than the source amide [7].

However, methiamide, due to the thioureic group, also had side effects (caused agranulocytosis and was nephrotoxic), which limits its clinical use. Replacement of the thioureic group with an isosteric group having the same pKa eventually led to cimetidine, which remains a drug of choice in the treatment of gastric ulcers today. Further research showed that the imidazole ring, present in histamine and all H2-antagonists known up to that time, was not necessary for the activity of H2-receptors [5,8].

Therapeutic Application

They are useful in acute pain (quick acting), given as a single dose in the evening cimetidine 800mg, and famotidine 400mg. Side effects Headache, fatigue, nausea, muscle pain, and dizziness may occur. Rarely, do antiandrogen actions (galactorrhea, gynecomastia, loss of libido, and impotence) occur? Dyskinesia and hallucinations may also occur.

The protein pump or H+/K+-ATPase enzyme, located in the parietal cell membrane is the last cell stage that enables the extraction of HCl into the gastric space. This enzyme catalyzes the exchange of hydrogen ions with potassium ions (KT ions enter the cell, while those of H^+ leave the cell and enter the lumen of the eye) and its action is independent of the effect initiated by histamine, ACh, and gastrin. Thus, the final effect of the secondary messengers C^{a+2} and cyclic AMP cannot be realized if the functioning of the protein pump is blocked. The main protein pump blocker is Omeprazole, which transports protons and Cl ions into the stomach, versus K^+ ions. Lansoprazole, pantoprazole, and other -prazoles also act in this way [6].

Aim

The purpose of this paper is: general theoretical aspects regarding gastric ulcers in the human organism -to analyze H^-blockers such as Bama, and how they affect gastric ulcers.

Material and Methods

Patients with gastroduodenal ulcers were analyzed in this paper. Of them, 120 patients were women, and 80 were men, who were treated at the Tetova Hospital in the Intemos ward. Their ages ranged from 25-70 years old. The diagnosis is determined by an X-ray examination.

It is very important and in most cases, only with this method, the presence of ulcer nodules has been detected. The rest was subjected to endoscopic examination (fibro esophago gastro duodenoscopy) is of great importance as this method can distinguish between benign and malignant material.

Statistics

There were 200 patients with gastrointestinal ulcers in the internal medicine department in Tetovo. Most of the patients were women, over 60% or 124 patients, the rest about 40% or 76 patients were men. The ages were different from 25 to 70 years old, where the age of 40-50 years dominated in both sexes with a percentage of 70% of cases (Table 1).

Table 1. Patients with gastrointestinal ulcers in the internal medicine department.

Wome	120	60%
Men	80	40%
Total	200	100%

Classic cases with only gastric ulcers were rarer, more dominated by patients with other complications such as:

- In addition to gastric ulcer, patient 1 also had bronchitis. His therapy included:
- Patient II also had diabetes. His therapy included: Physiological Digestion, Insulin, Cap. Omeprazole 20mg.
- Patient III had a gastric ulcer accompanied by bleeding. His therapy included Amp Almatex 3 times a day from 2 ampoules, but the dose after 2-3 days is decreasing, Amp. Famotidine 2 times a day by one, Vit K.

Conclusion

Based on our results we can conclude that:

- Gastric ulcer most often occurs after the use of salicylates and alcoholic beverages involving the mucosa and submucosa
- It can appear in the lower part of the esophagus, quite often it is in the small loop of the stomach - gastric ulcer, but most often it appears in the initial part of the duodenum (duodenal bulb) - duodenal ulcer.
- Helicobacter pylori are present in the mucous layer of the astral mucosa, in chronic gastritis in more than 95%, then in duodenal ulcer in 84% of cases, gastric ulcer in 54% of cases, while in healthy people it is detected in 25% of cases.
- H^-blockers, the main drugs in the treatment of ulcers as cimetidine, famotidine, nizatidine, and roxatidine.
- In our analyzed group, there were 200 patients, 60% female, and 40% male.
- The most attacked age was that of 40-50 years.

Disclosure

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