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Research Article

Investigation of the Effect of Celecoxib on the Motor Activity of the Stomach and Duodenum in Normal and Gastroduodenal Ulcers

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Abstract

Purpose of the Study: The purpose of this study is to establish the possible gastro- and duodenoprotective effect of celecoxib in normal and experimental gastric and duodenal ulcers.

Research Methodology: The experiments were carried out on 12 Wistar rats. Previously, celecoxib was administered to rats for 10 days. Electromyography (EMG) of the antral and fundal parts of the stomach and ascending duodenum was recorded using a Nihon Kohen electromyograph (Japan).

A model of gastric and duodenal ulcers was created by applying 100% acetoacetic acid to the serous lining of the stomach and intestines.

Results and Conclusion: The effect of nonsteroidal anti-inflammatory drugs on the electromotor activity of the smooth muscles of the stomach and duodenum of a rat was studied in normal and when modeling gastric and duodenal ulcers. Cyclooxygenase blockers have been shown to increase the electromotor activity of the gastroduodenal complex and accelerate reparative processes in the area of gastric and duodenal ulcers.

Keywords: *Nonsteroidal Anti-Inflammatory Drugs; Stomach Ulcer*

Introduction

Nonsteroidal anti-inflammatory drugs (including celecoxib) are selective inhibitors of cyclooxygenase-2 (COX-2) [1,2]. COX-2 is induced in response to the inflammatory process, which leads to the synthesis and accumulation of inflammatory prostanoids (in particular, PGE2), which, in turn, causes inflammation, edema and pain syndrome. Prostaglandins increase the sensation of pain by initiating inflammation of the tissue at the site of its damage, therefore, along with the anti-inflammatory effect, these drugs have a pronounced analgesic effect [3,4]. Celecoxib does not inhibit COX-1, therefore, it does not affect prostanoids synthesized due to the activation of COX-1, and, due to this,

does not interfere with the development of processes associated with the action of COX-1 in tissues (ulcerative lesions of the stomach and duodenum, perforations, obstruction, lack of inhibition of COX-2-dependent aggregation platelet activity).

Purpose of the Study

The purpose of this study is to establish the possible gastro- and duodenoprotective effect of celecoxib in normal and experimental gastric and duodenal ulcers.

Research Methodology

The experiments were carried out on 12 Wistar rats weighing 200 - 250g. Previously, for 10 days, celecoxib was administered to rats at a dose of 1.5 mg/kg through a probe and 2.5 mg/kg intramuscularly. On the 10th day of the experiment, laparotomy was performed under gentle conditions and the electromotor activity of the stomach and duodenum was recorded. The control group consisted of 7 experimental animals of comparable body weight who were injected with saline solution. Electromyography (EMG) of the antral and fundal parts of the stomach and ascending duodenum was recorded using silver electrodes with a contact surface area of 1.5 - 2.0 mm^2 using a Nihon Kohen electromyograph (Japan).

A model of gastric ulcer was created by applying 100% acetoacetic acid in a volume of 0.1 ml to the serous lining of the stomach at the border of the antral and fundal sections; a model of duodenal ulcer was created by applying 100% acetoacetic acid in a volume of 0.05 ml to the bulbar section of the duodenum.

Statistical analysis was carried out by the Mann-Whitney small sample method at $p < 0.05$.

Results and Discussion

The fundal part of the stomach: The slow-wave activity of the fundal part of the stomach against the background of the administration of celecoxib at a dose of 1.5 mg/kg was: the frequency was 7.4 ± 1.1 per minute, and the amplitude was 0.62 ± 0.08 mV (199.9%, $p < 0.01$). Against the background of the administration of celecoxib at a dose of 2.5 mg/kg, the frequency of slow waves of the fundal gastric EMA increased to 16.0 ± 2.5 per minute (117.5%, $p < 0.01$), the amplitude decreased to 0.5 ± 0.05 mV (-19.3%, $p < 0.05$). Thus, the administration of celecoxib dose-dependently stimulates the frequency component of the slow-wave activity of the fundal part of the stomach.

Antral part of the stomach: The administration of celecoxib at a dose of 1.5 mg/kg slightly increases the frequency of slow waves of EMA of the antrum of the stomach to 6.3 ± 1.2 per minute (12.5%, $p < 0.05$), the amplitude to 0.43 ± 0.06 mV (138.8%, $p < 0.001$). Against the background of the administration of celecoxib at a dose of 2.5 mg/kg, the frequency of slow waves of EMA of the antrum of the stomach increased to 11.8 ± 1.5 per minute (87.3%, $p < 0.05$), the amplitude - to 0.82 ± 0.13 mV (90.7%, $p < 0.05$). Thus, the administration of celecoxib dose-dependently increases the amplitude-frequency characteristics of slow waves of EMA of the antrum of the stomach.

Duodenum: The administration of celecoxib at a dose of 2.5 mg/kg increases the frequency of slow waves of EMA to 27.0 ± 3.3 per minute (50.3%, $p < 0.05$) and the amplitude to 0.7± 0.08 mV (204.3%, $p < 0.001$). In 66% of observations, spike activity appears with a frequency of 0.75 ± 0.05 and an amplitude of 1.7 ± 0.3 mV. Thus, celecoxib enhances and increases slow-wave electromotor activity and promotes the appearance of spike activity, enhancing the motility of the duodenum as a whole.

Thus, the electromotor activity of the fundal part of the stomach changes slightly: under the influence of celecoxib, the amplitude characteristics of slow waves reflecting depolarization processes are mainly subject to changes.

The antral part of the stomach reacts to the administration of NSAIDs unidirectionally: the frequency and amplitude of slow EMG waves increases.

The response of the duodenum to the introduction of celecoxib is an increase in slow-wave and spike activity. That is, the most pronounced reaction of the duodenum is noted on the introduction of celecoxib.

Thus, the introduction of nonsteroidal anti-inflammatory drugs that inhibit the synthesis of prostaglandins leads to an increase in the electrical activity of the smooth muscle tissue of the stomach and duodenum, while the increase in the amplitude-frequency characteristics of the EMA of the stomach and duodenum against the background of the action of celecoxib is dose-dependent.

Stomach and duodenal ulcer

Modeling of gastric and duodenal ulcers against the background of the action of celecoxib at a dose of 2.5 mg/kg leads to an increase in the electromotor activity of the fundal and antral parts of the stomach. The EMA of the fundal stomach on the 10^{th} day of ulcer modeling increased: frequency - up to 26.0 ± 3.0 per minute (62.5%, $p < 0.05$), amplitude - up to 0.9 ± 0.1 mV (80.0%, $p < 0.05$); spike activity appeared with a frequency of 1.3 ± 0.1 and an amplitude of 1.2 ± 0.2 mV.

The EMA of the antral part of the stomach during ulcer modeling also increased: the frequency of slow waves - up to 29.3 ± 3.0 per minute (148.2%, $p < 0.05$), the amplitude - up to 1.83 ± 0.3 mV (123.1%, $p < 0.05$).

Consequently, the introduction of celebrecoxib in high doses leads to activation of the EMA of the stomach in ulcers stomach, especially pronounced in the fundal region, where there was an increase in the motor component proper; in the antral region, a change in the electrophysiological characteristics of smooth muscle cells was observed: the rate of depolarization and repolarization of smooth myocytes increased.

Modeling of gastric and duodenal ulcers against the background of the action of celecoxib at a dose of 2.5 mg/kg leads to activation of the electromotor activity of the bulbar duodenum: in all experiments, high-amplitude spike activity appears with a frequency of 1.15 ± 0.3 and an amplitude of 1.3 ± 0.4 mV; the frequency of slow waves is 25.6 ± 3.0 per minute (decrease by 5.3%, $p < 0.05$), the amplitude doubled.

The study of gastric and duodenal EMA on the 10^{th} day of ulcer modeling showed the disappearance of spike activity and a decrease in the amplitude-frequency characteristics of slow waves to their values after 10-day administration of celecoxib at a dose of 2.5 mg/kg (the frequency of slow waves of fundal EMA is 19.0 ± 2.3 per minute, the amplitude is 0.37 ± 0.05 mV; the frequency of slow waves of duodenal EMG is 26.6 ± 2.2 v min, the amplitude is 0.17 ± 0.03 mV).

Thus, the modeling of gastric and duodenal ulcers against the background of celecoxib action is accompanied by an increase in motor activity of the fundal stomach and bulbar duodenum, which is leveled to the background level on the 10^{th} day of ulcer modeling.

Morphological examination

Morphological examination of stomach ulcers under the conditions of administration of celecoxib at a dose of 1.5 mg/kg showed that on the 10^{th} day the bottom of the ulcer was formed by the forming connective tissue with hemorrhage sites. The density of connective tissue varies, there are areas of denser connective tissue with non-dilated vessels. Gastric ulcer on the 10^{th} day in the control is characterized by cystic enlargement of the gastric glands, sharp vasodilation with blood stasis and initial thrombosis; the ducts of the glands are clogged with a viscous secret.

Morphological examination of the duodenal ulcer on the 10th day under the conditions of celecoxib administration showed that detritus is detected at the wall of the ulcerative defect, the intestinal villi are deformed and infiltrated by lymphoid cells, granulation tissue is formed, the vessels of the usual structure are somewhat dilated.

Morphological examination of the rat liver with the introduction of celecoxib and subsequent modeling of gastric and duodenal ulcers showed that the central veins and sinusoids of the usual structure, some sinusoids are dilated, contain red blood cells. Lymphocytic infiltration is found around some triads. Dilation of some bile ducts is noted.

Morphological examination of the pancreas of rats with the introduction of celecoxib and subsequent modeling of gastric and duodenal ulcers showed that there is a lot of connective tissue and collagen fibers in the perivasal areas. Connective tissue separates individual exocrinocytes of the pancreas. The septa separating the lobules contain dilated venous vessels. Small accumulations of neutrophils are found in adipose tissue.

Morphological examination of gastric and duodenal ulcers under conditions of preliminary administration of celecoxib at an increased dose (2.5 mg/kg) showed that celecoxib has a gastroprotective effect by improving the functioning of the gastric glands, restoring blood supply to the affected area, which contributes to faster epithelialization of the ulcer. The duodenoprotective effect of the introduction of celecoxib is less pronounced, which may be associated with a more pronounced increase in the electromotor activity of the duodenum against the background of the introduction of celecoxib before the formation of ulcers.

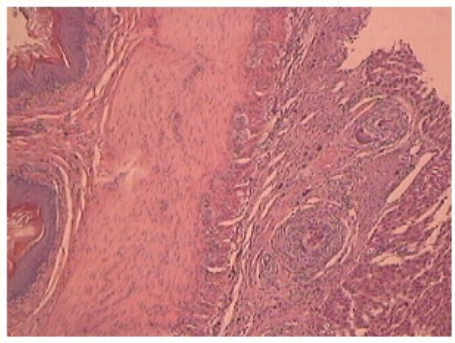

Figure 1: *Ulcer of the stomach and duodenum of a rat under conditions of preliminary administration of celecoxib. Adhesions between the fundal part of the stomach and the left lobe of the liver. Uv. x 120.*

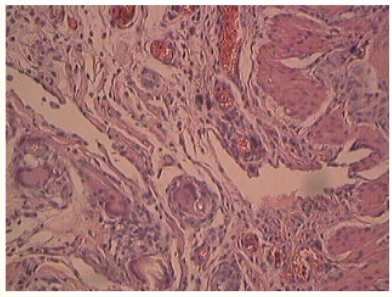

Figure 2: *Ulcer of the stomach and duodenum of a rat under conditions of preliminary administration of celecoxib. Auerbach plexus and giant multinucleated cells in the formation of adhesions of the fundal stomach and liver. Uv. x 300.*

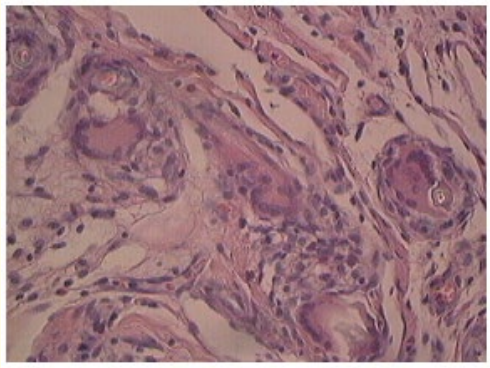

Figure 3: *Ulcer of the stomach and duodenum of a rat under conditions of preliminary administration of celecoxib. Granuloma with giant cells. Uv. x 300.*

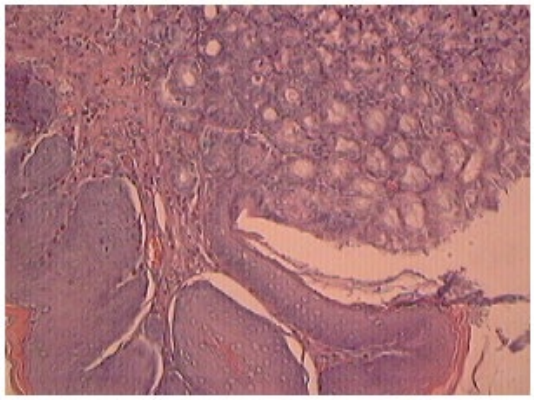

Figure 4: *A model of gastric and duodenal ulcer of a rat under conditions of preliminary administration of celecoxtb on the 10th day. Stomach. The boundary of the acid-producing zone and the multilayer flat epithelium. (There is no ulcer). Uv. x 250.*

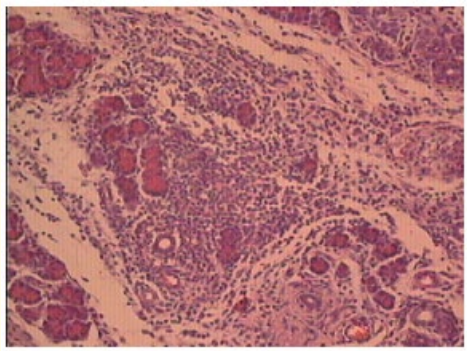

Figure 5: *Pancreas on the 10th day of gastric and duodenal ulcers under conditions of preliminary administration of celecoxib. (Chronic pancreatitis). Uv. x 500.*

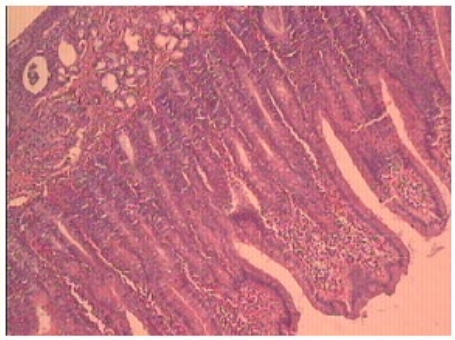

Figure 6: *Unchanged duodenum on the 10th day of gastric and duodenal ulcers under conditions of preliminary administration of celecoxib. Uv. x 250.*

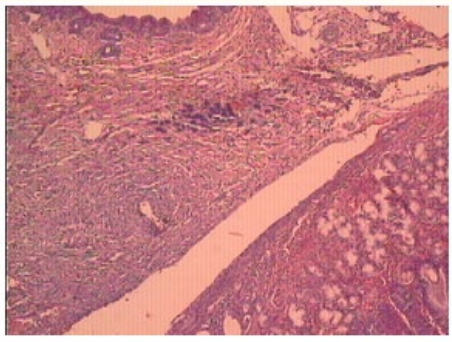

Figure 7: *Adhesions between the pancreatic duct, liver and duodenum on the 10th day of gastric and duodenal ulcers under conditions of preliminary administration of celecoxib. Uv. x 120.*

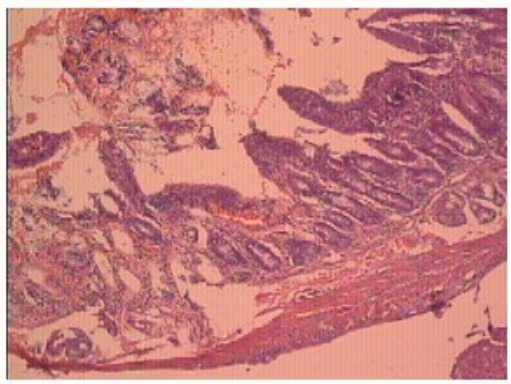

Figure 8: *10th day of gastric and duodenal ulcers under conditions of preliminary administration of celecoxib. Duodenal ulcer. Uv. x 120.*

Conclusion

When analyzing the effect of celecoxib on the motor function of the stomach and duodenum, it was shown that the administration of the drug dose-dependently stimulates the frequency component of the slow-wave activity of the fundal stomach; the introduction of celecoxib dose-dependently increases the amplitude-frequency characteristics of slow waves of the EMA of the antral stomach and enhances and increases slow-wave electromotor activity and promotes the appearance of spike activity of the smooth muscles of the duodenum.

Thus, the introduction of nonsteroidal anti-inflammatory drugs that inhibit the synthesis of prostaglandins leads to an increase in the electrical activity of the smooth muscle tissue of the stomach and duodenum, moreover, an increase in the amplitude-frequency characteristics of the EMA of the stomach and duodenum against the background of the action of celecoxib is dose-dependent. The gastroprotective effect of celecoxib in gastric and duodenal ulcers is carried out by improving the functioning of the gastric glands, restoring blood supply to the affected area, which contributes to faster epithelialization of the ulcer.

The protective effect of celecoxib in gastric and duodenal ulcers may be associated not only with the blockade of COX-2 and a decrease in the production of pro-inflammatory prostaglandins, but also with other mechanisms of action of the drug, for example, with its activity against the histaminergic and serotonergic systems.

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