American Journal of Medicine and Medical Sciences 2021, 11(12): 887-890
DOI: 10.5923/j.ajmms.20211112.09

Study of the Influence of Calcium Channel Blockers on the State of Rat Stomach Mucosa in Indomethacin-Induced Gastropathy

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Abstract The experiments were carried out on sexually mature male rats with an initial weight of 180-200 g. The preventive effect on the state of the gastric mucosa in indomethacin-induced gastropathy was studied. Two hours before reproducing the model (indomethacin 60 mg/kg, introgastrically), amlodipine and dilteazem were administered intragastrically at a dose of 20 mg/kg to animals of the first and second groups, and the third group's animals received cinnarizine - 50 mg/kg, and the fourth group served as a control, and animal of this group received drinking water the CCB group have a distinct preventive effect on the gastric mucosa in indomethacin-induced gastropathy. Amlodipine, dilteazem, and cinnarizine clearly prevented damage of the gastric mucosa in white rats with indomethacin - induced gastropathy, in which there were a significant decrease in the total area of damage to the gastric mucosa, a decrease in the number of large and small puncture hemorrhages, as well as strip-shaped ulcers. In terms of its pharmacological activity, dilteazem was clearly superior to other drugs of the group of calcium channel blockers. It is considered possible to use calcium channel inhibitors in pathologies of the stomach and duodenum associated with arterial hypertension, coronary heart disease and arrhythmia.

Keywords Gastropathy, Indomethacin, Calcium channel blockers, Gastroprotective agents

1. Introduction

Nowadays, non-steroidal anti-inflammatory drugs (NSAIDs) are the most widely used pharmacotherapeutic group. They are of great importance for practical health care, since this group of drugs are intended for the treatment of inflammation - a common typical pathological process of various etiologies [1,2]. NSAIDs are agents of various chemical structures with a unique combination of anti-inflammatory, analgesic and antipyretic effects, each of which can be expressed to a certain degree. This group of drugs is always in the area of close attention of physicians, patients and pharmaceutical manufacturers [3].

NSAIDs have a wide range of indications for use - acute and chronic inflammatory diseases accompanied by fever and pain, from acute respiratory viral infection to arthrosis. This group of drugs is often prescribed to relieve moderate pain syndromes such as vertebrogenic radicular pain, postoperative and oncological pain, dysmenorrhea, migraine, etc. This group of drugs suppresses the synthesis of prostaglandins and thereby delays the development of inflammatory damage of tissues. However, prostaglandins are not only a mediator of inflammation, but also a substance that has many biological effects [4]. A decrease in the concentration of prostaglandins in the gastric mucosa generally leads to the development of gastropathy, which is one of the most frequent and formidable complications of NSAID therapy [5,6,7]. In this regard, it is actual to search for anti-inflammatory drugs that do not have a side effect on the gastrointestinal tract. We have previously established the presence of a distinct anti-inflammatory effect of calcium channel blockers (CCB) [8,9]. However, there are no data on the effect of CCB on the state of the gastric mucosa in the available literature, which served as the basis for this study.

The aim of this study was to study the gastroprotective activity of CCBs in indomethacin-induced gastropathy.

2. Material and Methods

2.1. Experiments

The experiments were carried out in accordance with the rules and International Recommendations of the "European Convention for the Defence of Vertebrates Used

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Received: Nov. 25, 2021; Accepted: Dec. 3, 2021; Published: Dec. 15, 2021
Published online at http://journal.sapub.org/ajmms

for Experiments or Other Scientific Purposes" (Strasbourg, 03/18/1986). The approval of Ethic Committee of Republic of Uzbekistan was taken before beginning of the experiment (protocol No 6/17-1579, 23/09/2021).

The experiments were carried out on sexually mature male rats with an initial weight of 180-200 g During the experimental studies, all laboratory animals were kept in standard vivarium conditions and were on a full laboratory diet with free access to water. In the first part of our experimental studies, the state of the gastric mucosa was studied in rats with rheumatoid arthritis treated with CCBs: amlodipine, dilteazem, and cinnarizine. The arthritis model was reproduced by subplantar injection of 0.1 ml of complete Freud's adjuvant (CFA) (Chondrex, Inc., USA), which contains killed mycobacterium H37RA at a concentration of 2 mg/ml suspended in oil, intended to reproduce the adjuvant of induced arthritis (AIA) in rats [10]. After the last injection of drugs, the animals were decapitated under general anesthesia. A macroscopic examination of the mucous layer of stomach was carried out after dissection of the stomach.

One of the significant points in the pharmacological assessment of CCBs in terms of their ability to activate regenerative processes in the area of destructive formations of integumentary tissues, as well as their preventive effect on the state of the gastric mucosa in indomethacin-induced gastropathy (indometacin 60 mg/kg, orally) was also the studied. Two hours before reproducing the model, amlodipine and dilteazem were administered intragastrically at a dose of 20 mg/kg to animals of the first and second groups, and the third group's animals received cinnarizine - 50 mg/kg, and the fourth group served as a control and animal of this group received drinking water [7]. During the reproducing of indomethacin-induced stomach ulcer, the rats were deprived of food 24 hours before exposure to the ulcerogen. Destructive damage of the stomach was counted one day after the onset of ulcerogenic exposure (animals were sacrificed by decapitation under light ether anesthesia). After the decapitation of the animals, the stomach was removed and the number of formed destructions was counted on surface mucosa layer of stomach.

2.2. Statistical Analysis

The data obtained were processed by the method of variation statistics using the paired Student's test and one-way analysis of variance using the standard software package BIOSTAT 2009 with an assessment of the significance of indicators (Mean±Std error). Differences in the compared groups were considered significant at a significance level of 95% $p < 0.05$.

3. Results and Discussion

In the first series of experiments, amlodipine, diliazem and cinnarizine were administered to rats in an effective anti-inflammatory dose for 30 days. The macroscopic studies of the state of the gastric mucosawas carried outat the end of experiment. The administration of drugs of various generations of CCBs did not have a negative effect on the state of the gastric mucosa of experimental animals. Assuming that the intensifying of the inflammatory process or chronic inflammation may have a negative effect on the state of the gastric mucosa, and especially while using the substances that suppress inflammation, including CCB. We have studied the state of the gastric mucosa in animals with a model of adjuvant arthritis in early studies. The analysis of the results of the previous experiments showed that there was no noticeable damage of the gastric mucosa in animals with adjuvant arthritis. At the same time, both preventative and therapeutic use of the studied CCB drugs did not have any damaging effect on the gastric mucosa. These data confirm the differences in the mechanism of pro-inflammatory action of CCB drugs from NSAIDs.

Along with this, the investigation of the effect of drugs on the development of NSAID-induced gastropathy had an important practical interest.

The results of the experimental studies of this series showed that under the influence of indomethacin, there was significant damage of the gastric mucosa with an ulcerative surface area equal to 74.5 ± 4.3 mm^2, which consisted of erosion and ulcers in a total of 30.33 ± 1.49 pieces. At the same time, the number of small punctate erosions was 64.3%, large ones - 22.0%, and strip-shaped ones - 13.7%. These obtained results once again prove that severe gastropathy develops under the influence of the classic representative of NSAIDs. In contrast, in animals receiving amlodipine, the area of the ulcerative surface compared with the control was less by 33.1%, and the number of ulcers by 33.0%. At the same time, the number of strip-like, large and small-puncture ulcers decreased by 27.8%; 47.5% and 29.1%, respectively. A more pronounced positive effect was observed in animals treated with dilteazem. So, the area of the ulcerative surface and the number of ulcers decreased almost to the same degree - 52.0%, and the number of strip-like, large and small-punctured ulcers decreased by 60.0; 45.0 and 52.1%, respectively. As can be seen from the data in table 1, the positive effect of CCB in the face of cinnarizine was somewhat less. In animals preventatively treated with cinnarizine, the ulcerative surface area was less by 29.9%, and the total number of ulcers by 26.9%. The decrease in the number of stripe-shaped ulcers was by 21.0%, and the number of large and small-puncture lesions was by 42.6% and 23.0%, respectively.

Summarizing the obtained results of these experiments, we can conclude that drugs of the CCB group have a distinct preventive effect on the gastric mucosa in indomethacin-induced gastropathy. Wherein, the drugs are arranged in descending order according to their pharmacological activity,as follows: diltiazem> amlodipine> cinnarizine.

Table 1. Investigation of the influence of the gastroprotective effect of CCBs in indomethacin-induced gastropathy (Mean ± std error, n = 6)

Groups	Dose, mg/kg	Strip-shaped ulcers (pcs)	Large round ulcers (pcs)	Small-point ulcers (pcs)	Total number of ulcers (pcs)	The total area of the ulcerative surface (mm^2)
Control	-	4.17 ± 0.29	6.67 ± 0.64	19.50 ± 1.16	30.33 ± 1.49	74.50 ± 4.03
Amlodipine P	20	3.01 ± 0.35 < 0.05	3.50 ± 0.41 < 0.01	13.83 ± 1.18 < 0.02	20.33 ± 1.29 < 0.01	49.83 ± 3.23 < 0.01
Diltiazem P	20	1,67 ± 0,54 < 0.01	3,67 ± 0,48 < 0.02	9,33 ± 0,69 < 0.001	14,67 ± 0,92 < 0.001	35,80 ± 2,87 < 0.001
Cinnarizine P	50	3,30 ± 0,41 > 0.05	3,83 ± 0,29 < 0.01	15,01 ± 0,86 < 0.05	22,16 ± 0,76 < 0.01	52,25 ± 2,72 < 0.01

Note: P-significant difference in relation to the control;

It should be noted that the presence of gastroprotective properties in CCB preparations is of great practical importance, because patients who systematically use antihypertensive, antiarrhythmic and antianginal drugs in the form of inhibitors of potential dependent calcium channels, at the same time mostly use antiplatelet agents containing acetylsalicylic acid (Thrombo ACC, Cardiomagnum). It is known that this NSAID causes damage of the gastric mucosa till the formation of ulcers complicated by bleeding, the development of peritonitis [11]. Since the exacerbation of peptic ulcer and duodenal ulcer is accompanied by an increase in blood calcium correlating with increased secretion of gastric juice [12], it can be assumed that blocking calcium ions in the epithelium of the stomach will reduce pepsin, acid formation, which is a factor of aggression. This idea was confirmed by experimental studies, which showed the inhibition of the secretion of hydrochloric acid by isolated parietal cells of the stomach of experimental animals [13]. It has been shown that verapamil inhibits acid secretion in response to histamine stimulation. Based on this, it is considered that possible, the site of action of calcium channel inhibitors is located near the "proton pump" of the parietal cell of the H+/K+ -ATPase enzyme [12,14]. Along with this, it is assumed that under the influence of phenoptin, the formation of one of the most important "protective factors" of the gastric mucosa, mucous formation, is enhanced [15]. The obtained results of this research confirm the results of other researchers, who have showed that the preventive application of CCBs has a protective effect on the gastric mucosa in rats from indomethacin-induced damage [16,17].

This is justified pathogenetically because under the influence of CCB, the content of PGE2 increases [18], and the intensity of lipid peroxidation decreases [19], which, in our opinion, is one of the links in the mechanism of the cytoprotective effect of CCB. Therefore, some researchers [20] considered that CCB is not inferior to cimetidine in terms of elimination of pain, dyspeptic syndromes, and the intensifying of the scarring of the ulcer was significantly higher than placebo. According to the foregoing, CCB can be used for gastric ulcers and other diseases of the gastrointestinal tract, especially when paired with arterial hypertension and ischemic heart disease in elderly patients.

4. Conclusions

1. Calcium channel blockers have a distinct gastroprotective effect in rats at indomethacin-induced gastropathy.
2. Dilteazem, in comparison with cinnarizine and amlodipine, decreases the area of damage of the gastric mucosa more than two times in indomethacin-induced gastropathy in rats.
3. In terms of their pharmacological activity, calcium channel blockers are arranged in a decreasing order by cytoprotective action, as following: dilteazem> amlodipine> cinnarizine.
4. The mechanism of the gastroprotective action of calcium channel blockers is associated not only with a decrease in the secretion of aggressive factors, but also with the suppression of the intensity of lipid peroxidation processes, increase formation of mucus and blood flow of the gastric mucosa.
5. Blockers of calcium channels can be recommended as a gastroprotector in patients with pathology of the gastrointestinal tract paired with arterial hypertension, ischemic heart disease and arrhythmia.

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