INVESTIGATING THE THERAPEUTIC POTENTIAL OF BENIDIPINE IN INDOMETHACIN-INDUCED PEPTIC ULCERS: AN EXPERIMENTAL STUDY IN RATS

Running Title: Benidipine's Potential for Treating Peptic Ulcers

Abdulmecit Albayrak[1*], Huseyin Bekmez[1*], Melis Kiliç[1], Kubra Aliyeva[2], Aytac Badalova[2], Farnaz Gharbali[1], Yasin Bayir[3]

[1] Department of Pharmacology, Faculty of Medicine, University of Ataturk, Erzurum, Turkey.

[2]Azerbaijan Medical University, Baku / Azerbaijan.

[3] Department of Biochemistry, Faculty of Pharmacy, University of Ataturk, Erzurum, Turkey.

** dramecit@gmail.com*

Key words: *Peptic ulcer, Benidipine, Indomethacin, oxidative stress, rats*

INTRODUCTION

Peptic ulcer is a gastrointestinal disease that is very common in the upper gastrointestinal tract, has become widespread with increasing mortality rates worldwide, and is characterized by an increase in gastric cancer. The prevalence of peptic ulcer is 2.4% in Western populated countries [1]. It is seen as 6.1% in China [2]. The prevalence of this disease varies between 2.4% and 6.07% [3]. Peptic ulcer significantly affects the gastric mucosa and submucosa layer [4]. Some of the causes of peptic ulcer include factors such as pepsin, stomach acid secretion, and decreased protective factors, which play a role in the formation of this disease [5]. Apart from these factors, drugs such as digestive enzymes, bile acids, helicobacter pylori, ethanol, and NSAIDs affect the gastric mucosa and predispose to the onset of peptic ulcer [6]. When alcohol is present in high concentrations in the body, it can directly affect the gastric mucosa and damage the mucosal blood circulation by inducing cell apoptosis. Due to impaired blood circulation, the release of free radicals in the body may increase and the damaging ability of invasive factors may increase [7,8]. In peptic ulcer disease, severe necrotic pathological changes with bleeding and perforations can be observed on the mucosal surface of the stomach and the mucosal muscularis [9]. It has been found that people with digestive problems have a high risk of neuropsychiatric diseases such as depression and anxiety behaviors [10,11]. Today, drugs that reduce gastric acid secretion, antacid drugs that neutralize acid, and cytoprotective drugs that prevent cellular apoptosis are used in the treatment of peptic ulcer [12]. Although the effectiveness of these drugs is high, side effects, relapse rates, and drug resistance may be observed after treatment [13]. Indomethacin (IND), which is used to create an ulcer model, is an indole-derived NSAID. The NSAIDs IND, are more effective in causing experimental ulcers than other NSAIDs due to their high ulcerogenic potential. Induction with IND is among the most common methods of inducing peptic ulcers in rats. [14]. The most important pathophysiological feature of IND is to suppress prostaglandin synthesis by inhibiting COX-1 and COX-2 enzymes [15]. Calcium channel blockers used in the treatment of peptic ulcers are known to inhibit gastric acid secretion [16,17]. Benidipine (BEN) is an L-type calcium channel blocker and a drug used in hypertension [18]. BEN reduces antioxidant levels in tissues and suppresses oxidative stress [19,20]. This study aims to investigate the effects of BEN on the IND-induced peptic ulcer model in rats.

MATERIALS AND METHODS

In this experimental study, 36 male albino Wistar rats, each weighing approximately 270-280 g, were used. The rats used in this experimental research were obtained from the Atatürk University Medical Experimental Application and Research Center. Before the experimental study, these animals were divided into groups and kept and fed at an average temperature of 22-23ºC. This experiment was approved by the Ataturk University Animal Experiments local ethics committee (28.09.2023- 2023/11-170).

Drugs

IND was purchased from Deva Holding AS (Istanbul, Turkey). We obtained thiopental sodium from IE Ulagay AS Istanbul, Turkey, Famotidine (FAM) (Famodin 40 mg Tb) Sandoz İlaç San. and Tic. AS Istanbul, Turkey. and BEN (Benipine 8 mg Tb) were obtained from the Saba İlaç San. and Tic. A.Ş., Istanbul, Turkey.

Animals

The study was approved by the Atatürk University Animal Experiments Local Ethics Committee. It was carried out with the permission of decision no. 36 adult male Wistar Albino rats weighing 270-280 g were used in the experiment. These animals, obtained from a legal vendor, were kept for 7 days to adapt before the experiment was carried out. Afterwards, experimental groups were formed with 6 rats in each group and they were starved for 24 hours.

Experimental Procedures

1st group (n=6) Healthy group, 2nd group (n=6) IND (20mg/kg), 3rd group (n=6) FAM 20 mg+10 minutes later IND (20mg/kg) 4th group (n=6) BEN 20 mg+10 minutes after IND (20mg/kg), 5th group (n=6) BEN 20mg+10 minutes after IND (20mg/kg), 6th group(n=6)) It was determined as FAM (20mg/kg) + BEN 40 mg + IND (20mg/kg) after 10 minutes. After the animals to be used in the experiment were fasted for 24 hours, BEN (40mg/kg) was administered orally to each group of rats divided into 6 groups. To the reference groups, FAM (20mg/kg) was prepared together with its preparations in pure water and given orally in the same way. Healthy groups were kept under the same conditions (temperature, humidity, etc.) as other animals without any experimental treatment. IND (20mg/kg) dose was given orally to all rats 15 minutes after these substances were administered orally. After 6 hours, high dose thiopental sodium (50 mg/kg) was administered intraperitoneally and all animals in the groups were sacrificed. Biochemical parameters were measured in the stomach tissues obtained as a result of sacrifice.

Preparation of Tissue Homogenates

The stomach tissues of the rats were ground into powder with liquid nitrogen in a mortar and pestle. Each rat group was weighed 0.025 and diluted 1/60 by adding 1.5 ml of buffer solution. These homogenates were homogenized in the homogenizer on ice for 10 minutes in the next step. The homogenates were then filtered through a filter paper, centrifuged and the supernatants were used for the desired biochemical investigations[21].

Total Glutathione (GSH) measurement

[5.5'-Dithiobis (2-nitrobenzoic acid)] disulfide present in the measurement medium has a chromogen structure and can be easily reduced. The yellow color resulting from reduction can be measured spectrophotometrically at 412 nm. Homogenates were centrifuged at 12,000 g 4°C for 10 min, and the supernatants were used to quantify GSH.

Measurement of Superoxide Dismutase (SOD) Activity

Superoxide radicals formed when xanthine is converted to uric acid via the xanthine oxidase (XO) enzyme, if NBT (nitro blue tetrazolium) is present in the environment, react with NBT and form formazan dye. This compound has maximum absorbance at a wavelength of 560 nm. If there is SOD enzyme in the environment, since superoxide radicals are converted into H_2O_2 by these enzymes, formazan formation will decrease and its effect will decrease and accordingly the absorbance measured at 560 nm will decrease. The amount of decrease in absorbance indicates SOD activity.

Measurement of Lipid Peroxidation Level (MDA)

Lactoperoxidase (LPO) occurs in the cell membrane of free radicals. Most of the methods used to determine the MDA level resulting from LPO activity deal with the reaction of MDA with thiobarbituric acid (TBA). One molecule of MDA and two molecules of TBA react to form a stable red color. LPO measurement is based on the principle of measuring the red color formed by the reaction of MDA with TBA in an acidic environment at 532 nm.

Statistical analysis

Statistical analyses in this study were performed using the IBM SPSS 20.0 software program [22]. Statistical differences and significance levels in all measurements were determined by the "One-way Analysis of Variance (ANOVA)" test and results at $p<0.05$ were considered significant.

RESULTS

Macroscopic examination results

In this study, the antiulcer effects on the experimental ulcer model created with FAM, BEN, and IND were investigated. In our study, the average values expressed with the same letters were considered statistically insignificant and/or insignificant ($p>0.05$), while the average values expressed with different letters were considered statistically different ($p<0.05$). The average amount of damage and the area covered in the experimental ulcer model created can be evaluated macroscopically. The density of the ulcer areas formed is an important

element in evaluating the effectiveness of the applied ulcer treatment.

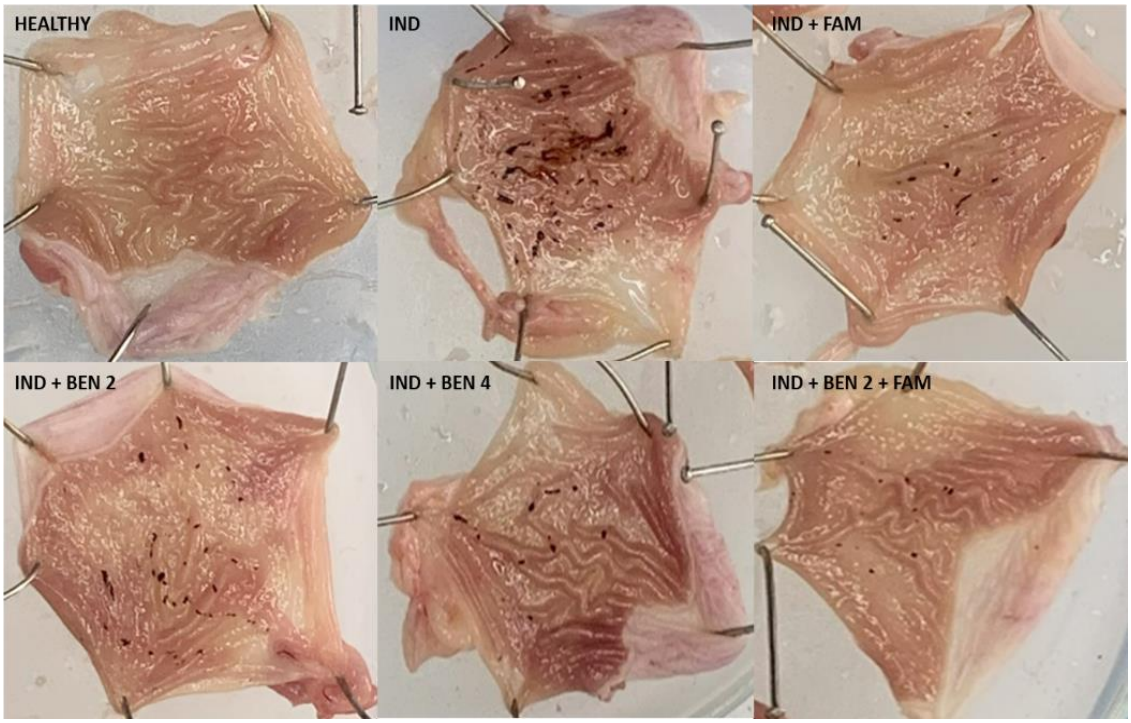


Figure 1. *Ulcer areas of stomach tissue*

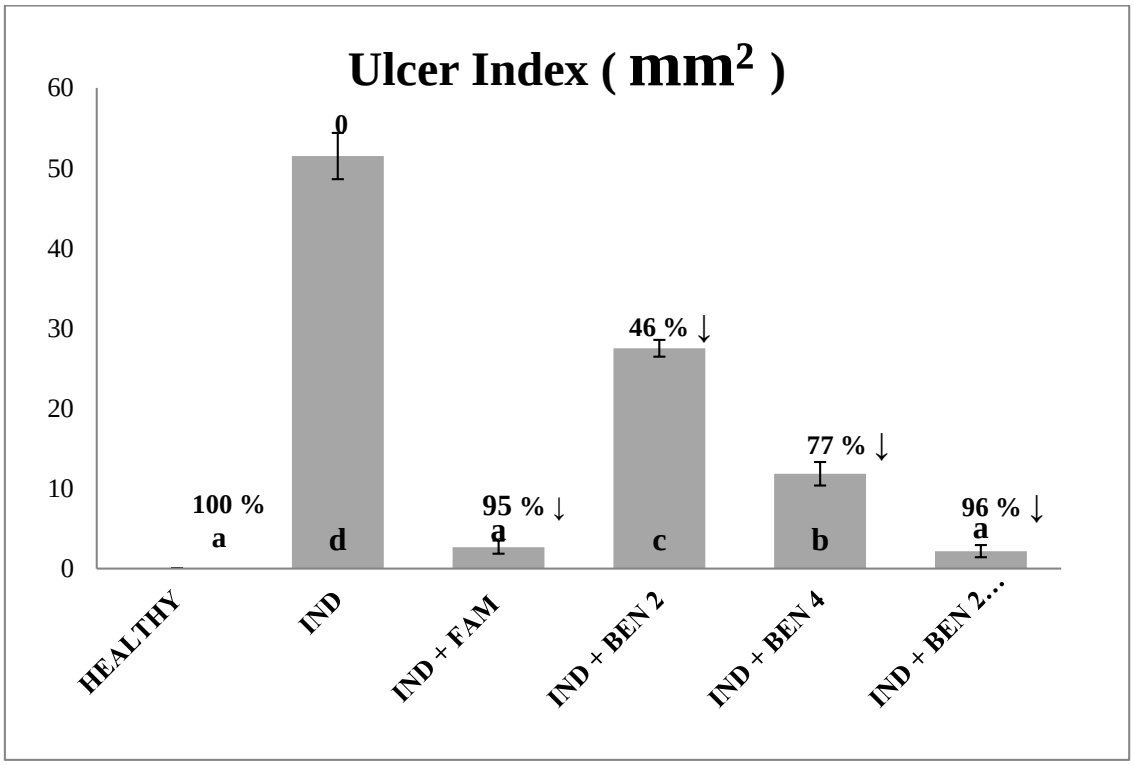
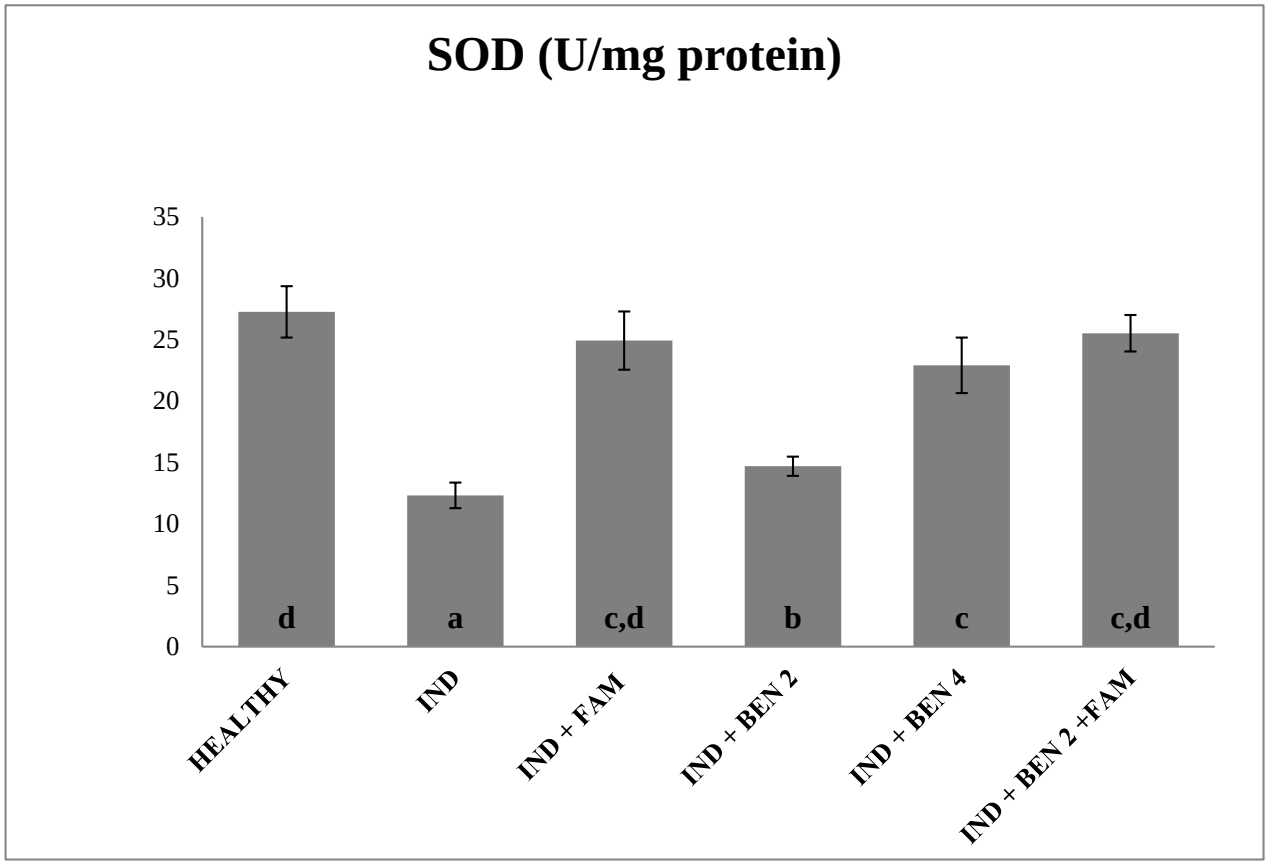


Figure 2. *Ulcer areas in the stomach tissue of study groups*

At the end of the experimental study, the stomachs of the rats were removed and analyzed. IND application to rats caused a large ulcer area ($p<0.05$) (Figure 1 and Figure 2). When comparing the reference group with the IND group, all doses of BEN and FAM were observed to significantly reduce the ulcer area ($p<0.05$). No significant difference was detected between the IND+FAM group and the IND+FAM+BEN 2 group ($p>0.05$).



When IND+BEN 2 and IND+BEN 4 were compared, it was determined that the IND+BEN 4 group reduced the ulcer area more than the other group ($p<0.05$) (Figure 1). If we look at the results of this study, the antiulcer effect of BEN has been demonstrated in macroscopic evaluation. Compared to other references, the effect of FAM was found to be dose-dependently better than the effect of BEN.

Figure 3. *SOD levels in the stomach tissue of study groups*

Biochemical Analysis

SOD activity

Superoxide oxidase (SOD) enzyme forms the main line of defense against free radicals in the cell.

It causes the formation of free radicals that cause damage to the cell. The SOD enzyme also provides information about the mechanism of the antioxidant defense system found in tissues and cells.

When the figure (Figure 3) showing the SOD measurement levels of the stomach tissue is examined, it is seen that IND application significantly reduces the SOD level ($p<0.05$). Although the SOD levels between the IND + FAM group and the IND + BEN2 + FAM group were similar to each other ($p>0.05$), the increases in enzyme activity in the IND + FAM4 group and the IND + BEN2 +FAM group were found to be significantly higher than the IND + BEN2 group ($p <0.05$).). The highest SOD level is seen in the healthy group.

MDA Levels

There is a relationship between the amount of MDA and LPO. LPO is one of the most accepted parameters that shows oxidative damage in living tissues and cells. When determining the LPO level, is determined by the amount of MDA formed as a result of oxidative damage. In this study, MDA levels were taken into consideration to detect damage to the stomach tissue. When the figure (Figure 4) showing LPO levels in stomach tissues was examined, it was determined that MDA levels increased significantly in the IND group ($p<0.05$). It was observed that MDA levels decreased in the IND + FAM and IND + BEN4 groups. IND + FAM and IND + BEN2 + FAM groups showed a similar decrease ($p>0.05$). According to other findings, it was observed that BEN decreased MDA levels depending on the dose.

GSH Level

Peroxide radicals pose a danger to the health of tissues and cells. GSH is a very important agent for the activation of glutathione (GSH)-dependent enzymes such as glycerol phosphate oxidase (GPO) and Glutathione S-transferases (GST), which work

against dangerous radicals such as peroxide radicals. In addition to being effective in maintaining the activity of these enzymes, GSH plays a major role in the antioxidant defense system in the body because it has a direct antioxidant effect. For this reason, GSH amounts are very important in determining antioxidant levels.

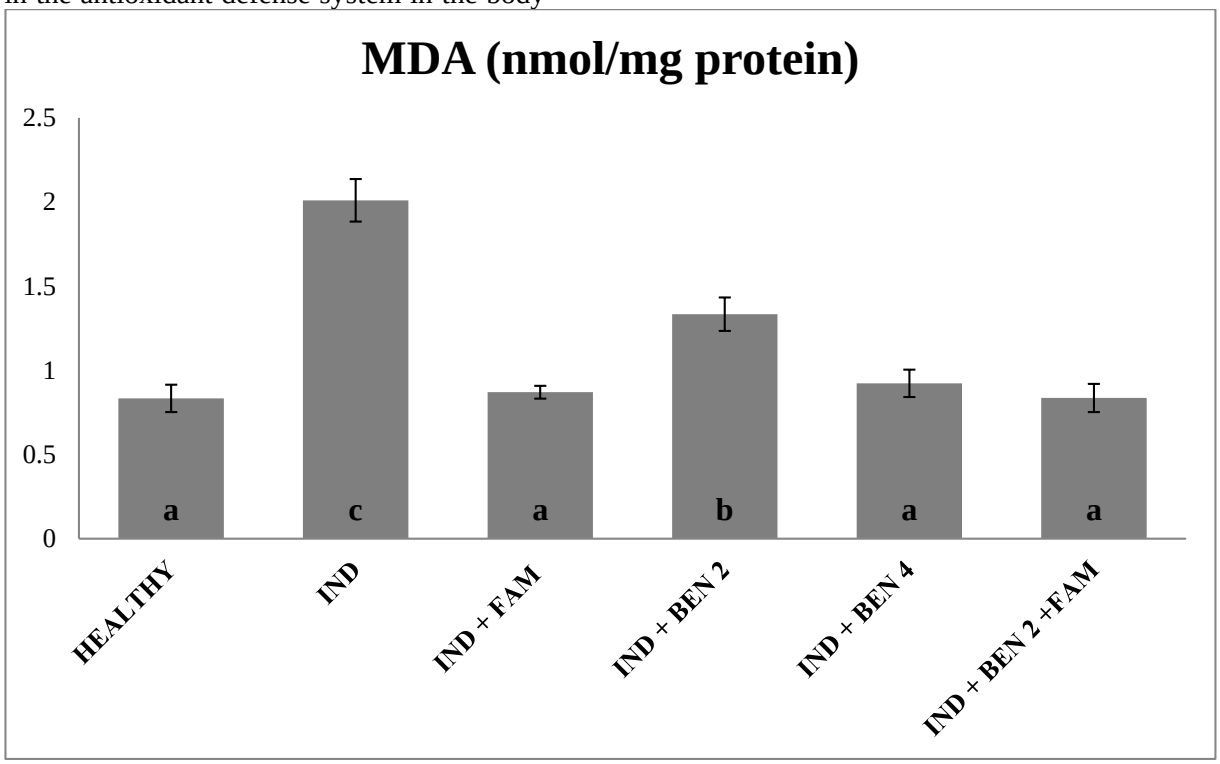


Figure 4. *MDA levels in stomach tissue of study groups*

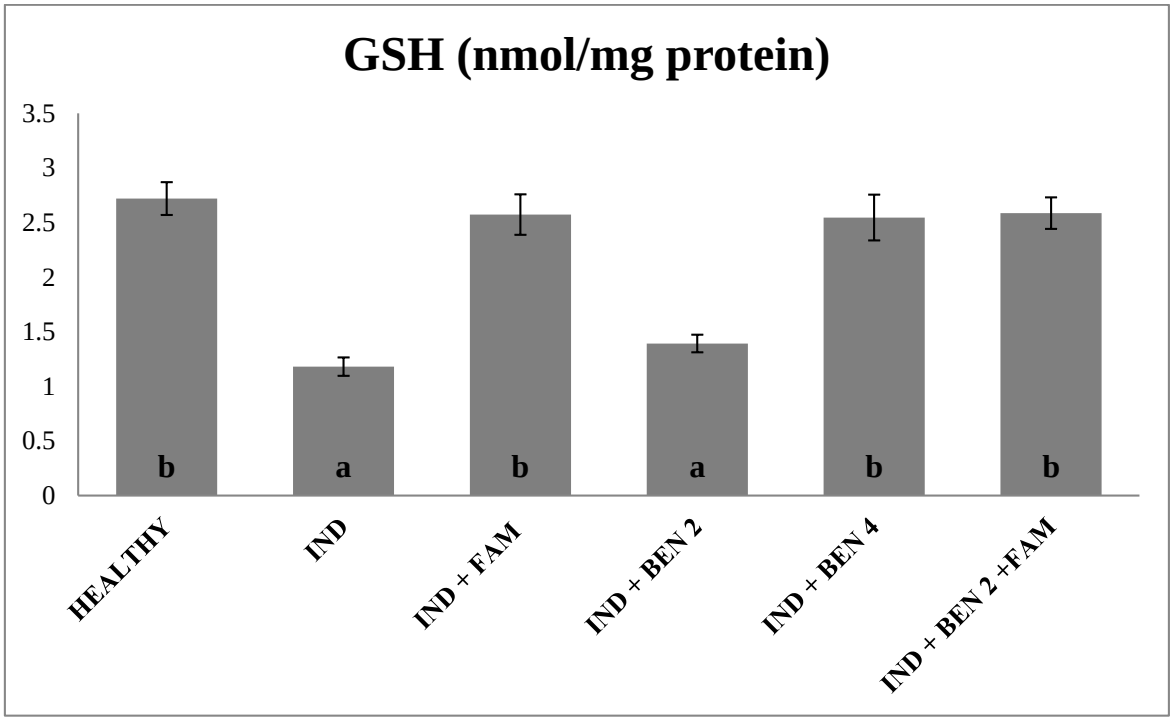


Figure 5. *GSH levels in stomach tissue of study groups*

When the figure (Figure 5) showing GSH levels in the stomach tissue was analyzed, it was determined that the levels of the IND group decreased significantly ($p<0.05$). While GSH and SOD levels were parallel, it was found to be in the opposite direction compared to ulcer areas and MDA levels. GSH level was measured significantly in IND+FAM, IND+BEN4, and IND+FAM+BEN2

groups compared to the IND group, and no significant difference was detected between them ($p>0.05$). It was determined that the GSH level of the IND+FAM, IND+BEN4, and IND+BEN2+FAM groups became close to the level of the healthy group.

DISCUSSION

Peptic ulcer disease occurs when the delicate balance between the protective mechanisms that safeguard the stomach's structure and the harmful factors that affect it is disrupted [23]. As a result of this imbalance, the gastric mucosa is seriously damaged, leading to the formation of ulcers. Peptic ulcers occur when aggressive factors such as gastric acid and pepsin overcome protective mechanisms like the mucus layer and mucosal blood flow [24].

This study investigates the potential effects of BEN as a potential agent in the treatment of gastric ulcers and compares this effect with FAM. BEN is a drug used as an L-type calcium channel blocker and is commonly used in the treatment of hypertension [25]. In this study, the potential use of calcium channel blockers like BEN in the treatment of gastric ulcers induced by NSAIDs is particularly explored.

Our results demonstrate, as in previous studies, that one of the NSAIDs, IND, causes damage to gastric tissue, resulting in ulcer formation [14]. In particular, we observed that IND significantly increased damage to the gastric mucosa. These findings confirm the potential of NSAIDs, commonly observed in the literature, to harm gastric tissue [26,27]. BEN treatment proved to be highly effective in reducing this damage. In our animal experiments, we observed that only the group receiving IND had lesions in the gastric tissue, which were macroscopically examined to be ulcers, as defined in previous studies [28]. The intensity of these lesions in the IND group in our study was higher than that in the FAM and BEN groups.

The mechanisms underlying the protective effect of BEN have been better understood by examining oxidative and antioxidant parameters [29]. According to our findings, MDA levels significantly increased in the IND group compared to the BEN, FAM, and healthy control groups. MDA is considered a marker of oxidative damage and indicates the damage caused by IND to the gastric tissue [28]. However, there have been no previous studies showing that BEN inhibits the increase in MDA levels caused by IND. Nevertheless, recent studies have shown that BEN can prevent the increase in MDA [30]. Similarly, in our study, MDA levels in the treatment groups decreased significantly.

BEN has also been shown to be effective in preventing the decrease in GSH levels and increasing SOD levels [30]. Previous studies have found that both BEN and FAM significantly reduce GSH and SOD levels [30, 31]. In another study, BEN was shown to have the ability to reduce SOD and GSH levels in brain tissue [30]. When looking at GSH and SOD levels, we observed a significant decrease in these levels in the IND group compared to the healthy control, FAM, and BEN groups. These findings indicate that IND disrupts the balance between antioxidants and oxidants within the stomach [24, 32]. Particularly, the simultaneous decrease in GSH and SOD levels in gastric tissue, along with an increase in MDA levels, which is an indicator of oxidative stress, is noteworthy. These findings are consistent with previous studies [26, 33].

CONCLUSION

In conclusion, this experimental study suggests that BEN is as effective as FAM in mitigating IND-induced peptic ulcers. These findings open avenues for further research on BEN as a potential treatment for peptic ulcer disease.

Ethics Committee Approval: The study was approved by the Ethics Committee Board of Atatürk University (28.09.2023- 2023/11-170).

Conflict of Interest: The authors do not declare any conflict of interest.

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INVESTIGATING THE THERAPEUTIC POTENTIAL OF BENIDIPINE IN INDOMETHACIN-INDUCED PEPTIC ULCERS: AN EXPERIMENTAL STUDY IN RATS

Abdulmecit Albayrak[1], Huseyin Bekmez[1*], Melis Kiliç[1], Kubra Aliyeva[2], Aytac Badalova[2], Farnaz Gharbali[1], Yasin Bayir[3]

[1] Department of Pharmacology, Faculty of Medicine, University of Ataturk, Erzurum, Turkey.
[2]Azerbaijan Medical University, Baku / Azerbaijan.
[3] Department of Biochemistry, Faculty of Pharmacy, University of Ataturk, Erzurum, Turkey.

Key words: *Peptic ulcer, Benidipine, Indomethacin, oxidative stress, rats*

Objective: Peptic ulcer disease is a prevalent gastrointestinal disorder associated with escalating global mortality rates and a heightened risk of gastric cancer. This study investigates the therapeutic potential of Benidipine, an L-type calcium channel blocker known for its antioxidant properties, in an indomethacin-induced peptic ulcer model in rats.

Methods: Thirty-six male albino Wistar rats were divided into six groups and subjected to various drug treatments, including Indomethacin, Famotidine, and Benidipine. Stomach tissue samples were collected for analysis.

Results: Macroscopic examination revealed that indomethacin significantly increased ulcer areas in the stomach tissue, while Benidipine and Famotidine treatments effectively reduced these ulcer areas. Biochemical analysis indicated that Indomethacin-induced oxidative stress, as evidenced by elevated levels of malondialdehyde, a marker of lipid peroxidation, and decreased levels of total glutathione and superoxide dismutase, are crucial antioxidants. However, Benidipine treatment mitigated these changes, restoring antioxidant levels and reducing malondialdehyde levels.

Conclusion: This study demonstrates that indomethacin induces gastric damage and oxidative stress, leading to ulcer formation, while Benidipine, with its antioxidant properties, effectively counteracts these effects and exhibits comparable efficacy to Famotidine in ulcer reduction. These findings suggest that Benidipine may hold promise as a therapeutic agent for mitigating peptic ulcers induced by nonsteroidal anti-inflammatory drugs like Indomethacin, warranting further exploration in clinical settings.

İNDOMETASİNİN SƏBƏB OLDUĞU MƏDƏ XORALARINDA BENİDİPİNİN TERAPEVTİK POTENSİALININ ARAŞDIRILMASI: SİÇOVULLARDA EKSPERİMENTAL TƏDQİQAT

Abdulmecit Albayrak[1], Huseyin Bekmez[1*], Melis Kılıç[1], Kubra Alıyeva[2], Aytac Badalova[2], Farnaz Gharbalı[1], Yasin Bayır[3]

[1] Atatürk Universitesi, Tibb Fakültəsi, Farmakologiya kafedrası, Ərzurum, Türkiyə.
[2]Azərbaycan Tibb Universiteti, Bakı, Azərbaycan.
[3] Atatürk Universitesi, Əczaçılıq Fakültəsi, Biyokimya kafedrası, Ərzurum, Türkiyə.

Açar sözlər: *mədə xorası, Benidipin, İndometasin, oksidləşdirici stress, siçanlar.*

Məqsəd: Peptik xora xəstəliyi qlobal ölüm hallarının artması və mədə xərçəngi riskinin yüksəlməsi ilə əlaqəli yayılmış mədə-bağırsaq xəstəliyidir. Bu tədqiqat indometasinin səbəb olduğu mədə xorasının siçovul modelində antioksidant xüsusiyyətləri ilə tanınan L tipli kalsium kanal blokatoru olan benidipinin terapevtik potensialını araşdırır.

Metodlar: Otuz altı erkək Wistar albino siçovulları altı qrupa bölündü və indometasin, famotidin və benidipin də daxil olmaqla müxtəlif dərman müalicələrinə məruz edildi. Təhlil üçün mədə toxuması nümunələri toplandı.

Nəticələr: Makroskopik tədqiqatlar indometasinin xora sahələrini əhəmiyyətli dərəcədə artırdığını, Benidipin və Famotidin müalicələrinin isə bu xora sahələrini effektiv şəkildə azaltdığını müəyyən etdi. Biokimyəvi analizlər göstərdi ki, indometasinin yaratdığı oksidləşdirici stress, lipid peroksidləşməsinin göstəricisi olan malondialdehid səviyyəsinin artması və ümumi qlutatyon, superoksid dismutaz səviyyəsinin azalması ilə sübut olunduğu kimi, əsas antioksidantlardır. Bununla belə, benidipinlə müalicə antioksidant səviyyələrini bərpa etməklə və malondialdehid səviyyələrini azaltmaqla bu dəyişiklikləri zəiflətdi.

Qərar: Bu tədqiqat, indometasinin mədə xorasının yaranmasına gətirib çıxaran mədə zədələnməsinə və oksidativ stresə səbəb olduğunu göstərir, lakin Benidipine öz antioksidant xüsusiyyətləri ilə bu effektlərə qarşı xoranın azaldılmasında Famotidin ilə müqayisə olunan təsir nümayiş etdirir. Bu nəticələr, Benidipine'nin indometasin kimi qeyri-steroid antiinflamatuar dərmanlar tərəfindən yaradılan mədə xoralarını yatışdırmaq üçün terapevtik bir vasitə kimi potensiala sahib olduğunu göstərir və klinik

şəraitdə daha ətraflı araşdırmaların aparılmasını tələb edir.

ИССЛЕДОВАНИЕ ТЕРАПЕВТИЧЕСКОГО ПОТЕНЦИАЛА БЕНИДИПИНА ПРИ ПЕПТИЧЕСКИХ ЯЗВАХ, ИНДУЦИРОВАННЫХ ИНДОМЕТАЦИНОМ: ЭКСПЕРИМЕНТАЛЬНОЕ ИССЛЕДОВАНИЕ НА КРЫСАХ:

Абдулмечит Албайрак [1], Хусейн Бекмез[1*], Мелис Килидж[1], Кубра Алиева[2], Айтач Бадалова[2], Фарназ Гарбали [1], Ясин Байир[3]

[1] Кафедра фармакологии, медицинский факультет, Университет Ататюрка, Эрзурум, Турция.
[2] Азербайджанский медицинский университет, Баку, Азербайджан.
[3] Кафедра биохимии, фармацевтический факультет, Университет Ататюрка, Эрзурум, Турция.

Ключевые слова: язвенная болезнь, бенидипин, индометацин, окислительный стресс, крысы.

Цель: Язвенная болезнь является распространенным желудочно-кишечным заболеванием, связанным с ростом глобальной смертности и повышенным риском рака желудка. В данном исследовании изучается терапевтический потенциал бенидипина, блокатора кальциевых каналов L-типа, известного своими антиоксидантными свойствами, на модели пептической язвы, вызванной индометацином, у крыс.

Методы: Тридцать шесть самцов крыс-альбино Wistar были разделены на шесть групп и подвергнуты различным медикаментозным обработкам, включая индометацин, фамотидин и бенидипин. Образцы тканей желудка были взяты для анализа.

Результаты: Макроскопическое обследование показало, что индометацин значительно увеличил площадь язв в ткани желудка, в то время как лечение бенидипином и фамотидином эффективно сокращало эти площади язвы. Биохимический анализ показал, что индометацин вызывает окислительный стресс, о чем свидетельствуют повышенные уровни малонового диальдегида, маркера перекисного окисления липидов, и снижение уровней общего глутатиона и супероксиддисмутазы, важных антиоксидантов. Однако лечение бенидипином смягчило эти изменения, восстановив уровень антиоксидантов и снизив уровень малонового диальдегида.

Заключение: Это исследование показывает, что индометацин вызывает повреждение желудка и окислительный стресс, приводящий к образованию язвы, в то время как бенидипин с его антиоксидантными свойствами эффективно противодействует этим эффектам и демонстрирует эффективность, сравнимую с фамотидином в уменьшении язв. Эти результаты позволяют предположить, что бенидипин может оказаться перспективным в качестве терапевтического средства для смягчения пептических язв, вызванных нестероидными противовоспалительными препаратами, такими как индометацин, что требует дальнейшего изучения в клинических условиях.

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