Am J Transl Res 2021;13(4):2702-2709
www.ajtr.org /ISSN:1940-5901/AJTR0126931

Original Article

Protective effect of teprenone on gastric mucosal injury induced by dual antiplatelet therapy in rats

Xinyang Fu[1], Xiaowei Huang[1], Zhiqiang Lin[1], Shanshan Hong[1], Yifeng Cai[1], Apei Zhou[2], Namei Wu[1]

Departments of [1]Pharmacy, [2]Gastroenterology, Quanzhou First Hospital Affiliated to Fujian Medical University, Quanzhou, Fujian Province, China

Received November 24, 2020; Accepted December 21, 2020; Epub April 15, 2021; Published April 30, 2021

Abstract: Objective: To investigate the protective effect of teprenone on gastric mucosal injury induced by dual antiplatelet therapy in rats. Methods: Healthy, specifically pathogen free SD, rats were selected and divided into 4 groups: Normal group (normal rats, without any treatment), Model group (rats received dual antiplatelet therapy: aspirin and clopidogrel), Teprenone group (rats received dual antiplatelet therapy and teprenone) and Pantoprazole group (rats received dual antiplatelet therapy and pantoprazole). The gastric mucosal blood flow, ulcer index, gastric gel mucus thickness, the levels of gastrin (Gas), prostaglandin (PG), prostaglandin E_2 (PGE_2), endothelin-1 (ET-1) tumor necrosis factor (TNF)-α, interleukin (IL)-1β, IL-6 and IL-10 in serum, the levels of malondialdehyde (MDA), glutathione (GSH), superoxide dismutase (SOD) and myeloperoxidase (MPO) in the gastric mucosa, as well as the expression of vascular endothelial growth factor (VEGF) in the rat's stomach were measured. Results: Compared with the Normal group, the other groups showed more severe gastric injury, elevated levels of inflammatory factors (TNF-α, IL-1β, IL-6 and IL-10), elevated levels of MDA and MPO, as well as reduced levels of GSH, SOD and VEGF (all $P<0.05$). Compared with the Model group, the gastric mucosal lesions in the Teprenone group and the Pantoprazole group were improved significantly (both $P<0.05$). Compared with the Pantoprazole group, the Teprenone group had reduced levels of ET-1 and elevated levels of PG and PGE_2 (all $P<0.05$). Conclusion: Teprenone protects against gastric mucosal injury induced by dual antiplatelet therapy through inhibiting gastric mucosal inflammation inhibiting oxidative stress and improving gastric mucosa indices.

Keywords: Teprenone, aspirin, clopidogrel, rats, gastric mucosal injury

Introduction

Cardiovascular and cerebrovascular diseases are commonly seen in the middle-aged and elderly population, characterized by high morbidity and mortality [1, 2]. With the aging of the population, cardiovascular and cerebrovascular diseases have become a major threat by affecting an increasing number of patients worldwide and killing tens of millions people every year [3, 4].

The predominantly treatment for cardiovascular and cerebrovascular diseases is dual antiplatelet therapy: the use of aspirin and clopidogrel. Aspirin, as a non-steroidal anti-inflammatory drug, it inhibits the synthesis of prostaglandins, it is effective in anti-inflammation and analgesia, and it can prevent postoperative thrombosis [5, 6]. Clopidogrel is a new thienopyridine that acts in an antiplatelet role by inhibiting adenosine diphosphate receptors [7, 8]. Dual antiplatelet therapy has certain effects on cardiovascular and cerebrovascular diseases. However, most patients who received the combined therapy are accompanied by dyspepsia, gastric ulcers, and duodenal bulbar ulcers [9]. It is generally believed that the dual antiplatelet therapy can damage hydrophobic barriers and mucosa because of the drugs interaction with the phospholipid layer of the gastric mucosa causing the release of the inflammatory factors and free radicals, which lead to inflammation and oxidative stress injury [10]. The main drugs for gastric mucosal injury are proton pump inhibitors, including pantoprazole [11, 12]. Pantoprazole protects the gastric mucosa by inhibiting the secretion of gastric acid. Nevertheless, long-term use of pantoprazole may lead to an increased risk of cardiovas-

cular and cerebrovascular diseases, and whether more serious side effects will develop is still controversial [13-15]. Teprenone, a terpene agent, protects the gastric mucosa by inhibiting gastric ulcers. It was proved that teprenone has preventive effects on gastric mucosal damage caused by dual antiplatelet therapy [16]. The specific preventive mechanism is not fully understood yet.

In this study, animal experiments were conducted to investigate the protective mechanism of teprenone on gastric mucosal damage caused by dual antiplatelet therapy.

Materials and methods

Animals

A total of 48 healthy pathogen free SD rats (8 weeks old, weighing 216±10.27 g) were purchased from the Animal Center of the Chinese Academy of Sciences, and housed for a week with 12 h light per day as well as a normal diet and water for follow-up experiments. All the animal experiment procedures complied with the Principles of Laboratory Animal Care (NIH publication #85-23, revised in 1985), and this study was approved by the Experimental Animal Ethics Committee of Quanzhou First Hospital Affiliated to Fujian Medical University.

Grouping

The rats were randomly divided into 4 groups: Normal group (normal rats, without any treatment), Model group (rats received dual antiplatelet therapy: aspirin and clopidogrel), Teprenone group (rats received dual antiplatelet therapy, and, teprenone) and Pantoprazole group (rats received dual antiplatelet therapy, and, pantoprazole). Rats were gavaged once a day for 14 days, with a volume of 10 mL/kg each time [17]. The Normal group was given normal saline, and the other groups were given 10.41 mg/(kg·d) of aspirin (Chengdu Jiaye, China) combined with 7.81 mg/(kg·d) of clopidogrel (Shanghai Youkai, China). Besides, the Teprenone group and Pantoprazole group were given an additional 100 mg/kg of teprenone (Xiamen Biomart, China) or pantoprazole (Hubei Guangao, China), which was dissolved in drinking water (25 mg/mL), once a day for 14 days. During the modeling, the rats were given a normal diet and water. After the last gavage, they were fasted for 18 h and some animals in each group was measured for the gastric mucosal blood flow. Then, the rats were intraperitoneally injected with 30 mg/kg of pentobarbital acid (Shanghai Xinyu, China) for anesthesia; thereafter, their stomachs were harvested. One hour after that, the rats were sacrificed and blood was collected.

Gastric mucosal blood flow

First, a preparation of 99mTc frog red cells was prepared. Second, the rats were anesthetized with pentobarbital acid by intraperitoneal injection at an amount of 30 mg/kg. Third, a cannula was inserted through the right carotid artery into the left ventricle, and another cannula was placed proximal to the left femoral artery to collect a reference blood sample. Then 1 mL of 99mTc biological microspheres were uniformly injected into the left ventricle cannula at each period of the experiments (injection completed within 10 s); meanwhile, a reference blood sample was collected for 60 s with a rate of 1 mL/min. Fourth, the stomach of rats was excised, dissected, rinsed with physiological saline and dried. Then, the mucosa was scraped off, weighed, placed on a γ spectrometer (GC1200, University of Science and Technology of China) for radioactive measurement (cpm, per min). The blood flow = reference blood flow * radioactive count/(radioactive count of reference blood * mass of the organ).

Ulcer index and gastric gel mucus thickness

The ulcer index was evaluated by using Guth's method, which evaluated the length and width of the ulcer area, respectively. The length scoring was as follows: 1 point for ≤1 mm, 2 points for <2 mm, 3 points for <3 mm, 4 points for <4 mm, and 5 points for ≥4 mm. If the width was greater than 1 mm, the score * 2. The total ulcer index was the sum score of all the lesion areas.

The gastric gel mucus thickness was evaluated using thick smears. After the stomach was harvested, the gastric mucosa inside was turned out through an incision along the greater curvature. After observation, the stomach was rinsed gently with normal saline to prepare gastric mucosa specimens, which was then stained with ink, then placed under an inverted microscope (Thermo Fisher Scientific, China)

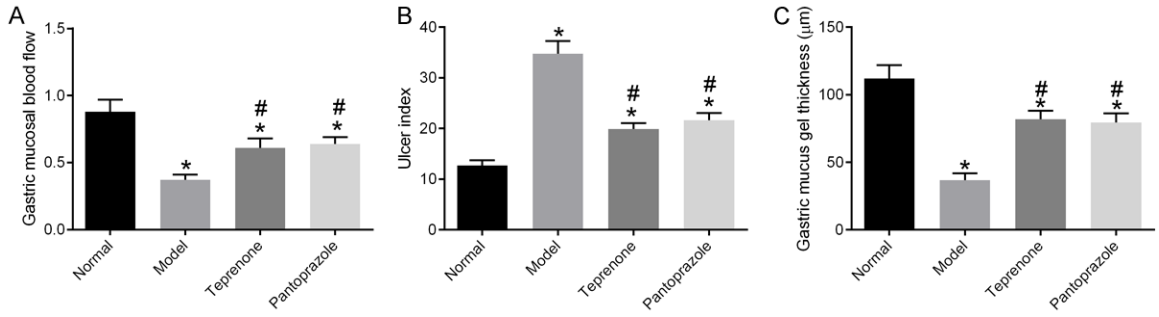

Figure 1. Comparison of gastric mucosal injury. A: Gastric mucosal blood flow; B: Ulcer index; C: Gastric mucus gel thickness. Compared with the Normal group, *P<0.05; compared with the Model group, #P<0.05.

and measured for the thickness of the bright band in the middle (that is, the gastric gel mucus thickness) through an eyepiece micrometer.

Radioimmunoassay

The serum of each group of rats was used to make an RIA standard curve. The levels of gastrin (Gas), prostaglandin (PG), prostaglandin E_2 (PGE_2), endothelin-1 (ET-1) were detected by radioimmunoassay. All the kits needed were purchased from Nanjing Camilo, China.

ELISA

The levels of tumor necrosis factor (TNF)-α, interleukin (IL)-1β, IL-6, and IL-10 in serum of each group were detected using *ELISA*. The *ELISA* kits were all from Abcam, USA: TNF-α (ab46070), IL-1β (ab100768), IL-6 (ab234570) and IL-10 (ab33471).

Colorimetry

The cleaned gastric mucosa tissues were used to prepare a tissue homogenate. The supernatant was taken after centrifugation and detected for levels of malondialdehyde (MDA), superoxide dismutase (SOD), myeloperoxidase (MPO), and glutathione (GSH). All kits were purchased from Abcam, USA.

Western blot

The washed gastric mucosa tissues were taken to prepare a gastric mucosa tissue homogenate and extracted for the total protein using RIPA in our laboratory. The protein was separated by SDS-PAGE gel electrophoresis, transferred to NC membrane, and blocked in 5% skim milk for 1.5 h. The protein was added with primary antibodies, rabbit anti-VEGF (ab2350, Abcam, USA), GAPDH (ab9285, Abcam, USA), blocked for 2 h at room temperature, and then washed 3 times with TBST, 5 min for each time. The protein was then incubated with HRP-labeled goat anti-rabbit IgG (ab97051, Abcam, USA) at room temperature for 1.5 h, and washed 3 times with TBST, 5 min for each time. Thereafter, color development was performed for NC membrane. Relative expression of protein = gray value of protein band/gray value of GAPDH * 100%.

Statistical analyses

Data were processed using SPSS 21.0 statistical software (SPSS, Inc, Chicago, IL, USA). The measurement data were expressed as mean ± standard deviation ($\bar{x}$ ± sd). One-way ANOVA and post-hoc Bonferroni pairwise comparison were performed for comparison among groups. A difference of P<0.05 was statistically significant.

Results

Gastric mucosal injury

The gastric mucosal injury was evaluated by measuring gastric mucosal blood flow (**Figure 1A**), ulcer index (**Figure 1B**) and gastric mucus gel thickness (**Figure 1C**). Compared with the Normal group, the other groups had reduced gastric mucosal blood flow and gastric mucus gel thickness to varying degrees, as well as an elevated ulcer index (all P<0.05). The Teprenone group and Pantoprazole group had the opposite results when compared with the Model group (all P<0.05). There was no signifi-

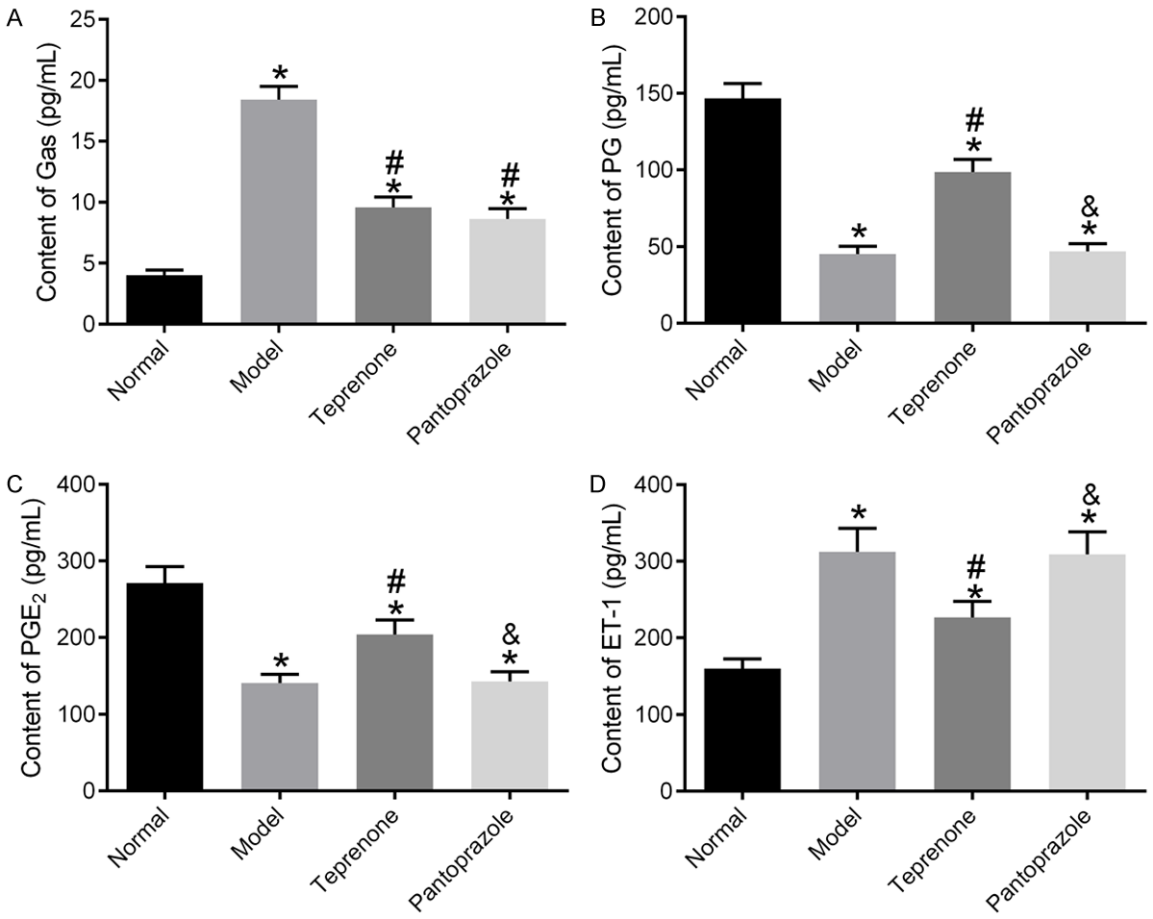

Figure 2. Changes in gastric injury indices. A: Changes in level of Gas; B: Changes in level of PG; C: Changes in level of PGE_2; D: Changes in level of ET-1. Compared with the Normal group, *P<0.05; compared with the Model group, #P<0.05; compared with the Teprenone group, &P<0.05. Gas: gastrin; PG: prostaglandin; PGE_2: prostaglandin E_2; ET-1: endothelin-1.

cant difference in between the Teprenone group and the Pantoprazole group (all P>0.05).

Changes in gastric injury indices

In order to further clarify the gastric injury, we measured the levels of Gas, PG, PGE_2 and ET-1 in the serum of each group (**Figure 2**). Compared with the Normal group, the other groups had elevated levels of Gas and ET-1, as well as reduced PG and PGE_2 in the serum (all P<0.05). The Teprenone group had the opposite results when comparing with the Model group (all P<0.05); and the Pantoprazole group also had reduced Gas (P<0.05), but the other 3 indicators were not significantly different when comparing with the Model group (all P>0.05). Compared with the Teprenone group, the Pantoprazole group had elevated levels of ET-1, and reduced levels of PG and PGE_2 (all P<0.05).

Inflammation of rats in each group

The levels of TNF-α, IL-1β and IL-6 in the serum of each group of rats were detected by *ELISA* (**Figure 3**). Compared with the Normal group, the other groups had elevated levels of TNF-α, IL-1β and IL-6 in serum in varying degrees (all P<0.05). The Teprenone group and the Pantoprazole group had the opposite results when compared with the Model group (all P<0.05). There were no significant differences between the Teprenone group and the Pantoprazole group (P>0.05).

Oxidative stress injury of rats

The levels of MDA, GSH, SOD and MPO in the gastric mucosa were measured in each group of rats to see the effect on gastric mucosal oxidative stress injury (**Figure 4**). Compared with the Normal group, the other groups had elevat-

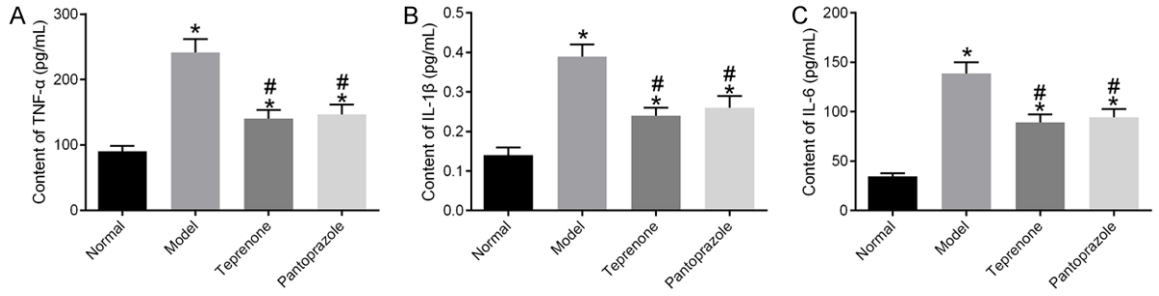

Figure 3. Inflammation of rats in each group. A: Level of TNF-α in serum; B: Level of IL-1β in serum; C: Level of of IL-6 in serum. Compared with the Normal group, *P<0.05; compared with the Model group, #P<0.05. TNF-α: tumor necrosis factor-α; IL: interleukin.

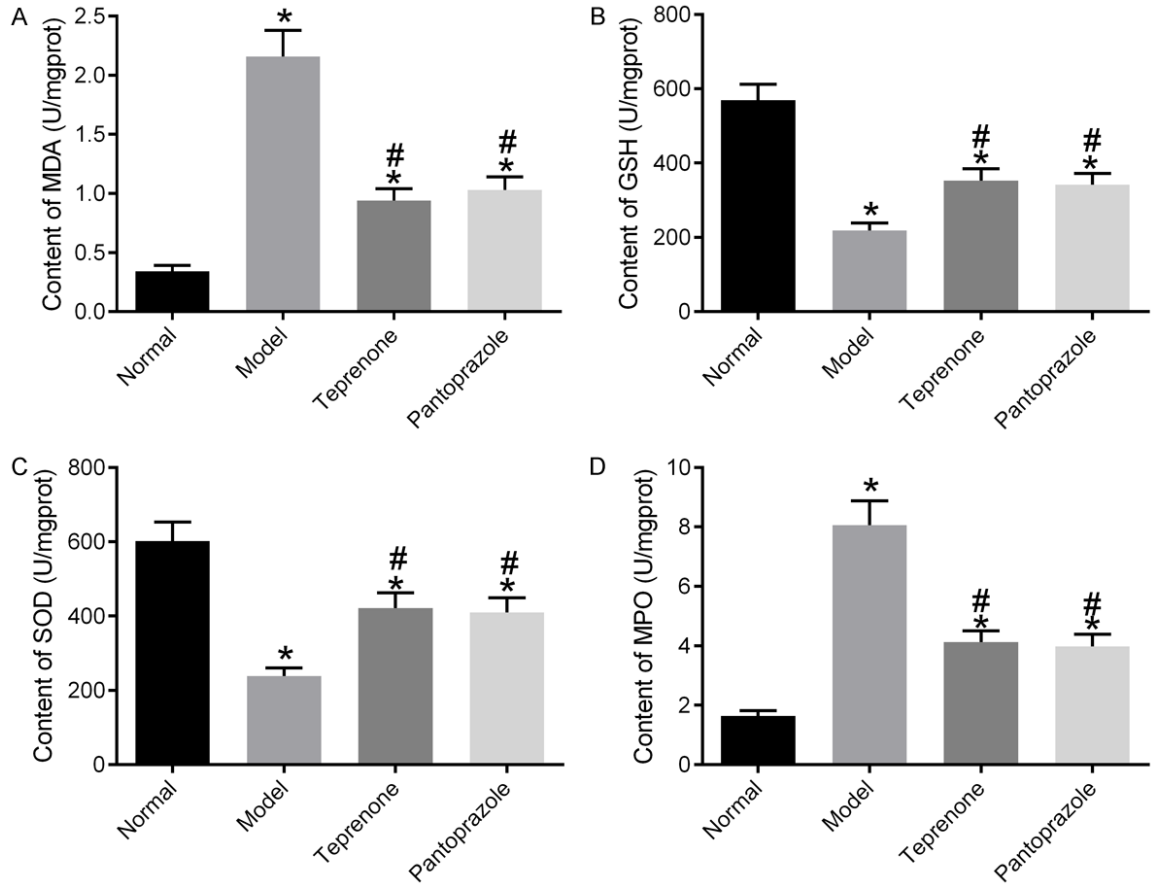

Figure 4. Indices of oxidative stress injury. A: Level of MDA in serum; B: Level of GSH in serum; C: Level of SOD in serum; D: Level of MPO in serum. Compared with the Normal group, *P<0.05; compared with the Model group, #P<0.05. MDA: malondialdehyde; GSH: glutathione; SOD: superoxide dismutase; MPO: myeloperoxidase.

ed levels of MDA and MPO, as well as reduced levels of GSH and SOD in the gastric mucosa (all P<0.05). The Teprenone group and the Pantoprazole group had the opposite results when comparing with the Model group (all P<0.05). There was no significant difference between the Teprenone group and the Pantoprazole group (all P>0.05).

VEGF protein expression in gastric mucosa

The VEGF expression in gastric mucosa was detected by Western Blot to evaluate the gastric mucosal damage at a molecular level (**Figure 5**). Compared with the normal group, the expression of VEGF protein in the gastric mucosa in the other groups were reduced (all

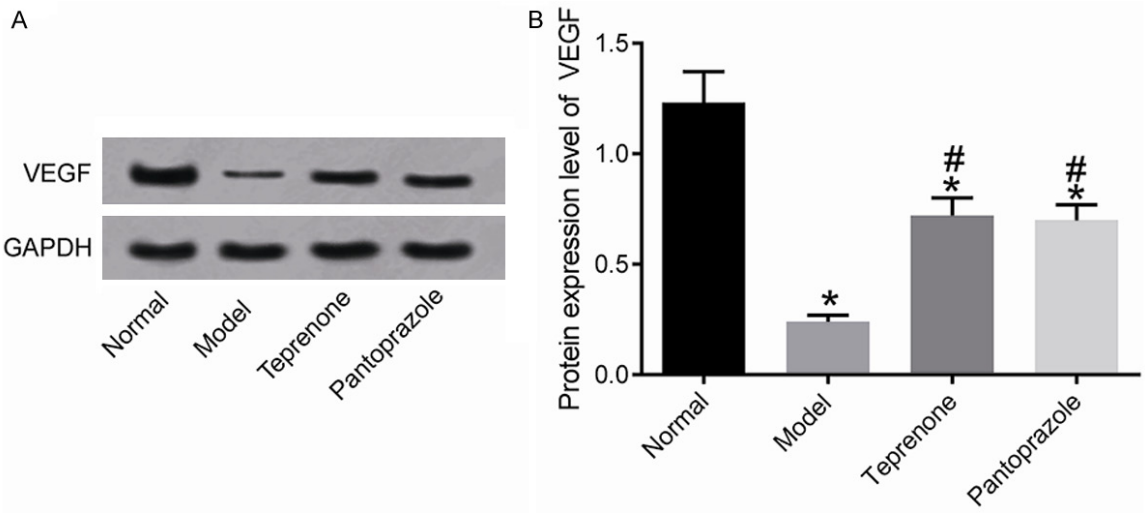

Figure 5. VEGF protein expression in gastric mucosa. A: Protein bands; B: VEGF protein in gastric mucosa in each group. Compared with the Normal group, *P<0.05; compared with the Model group, #P<0.05. VEGF: vascular endothelial growth factor.

P<0.05). Compared with the Model group, the expression in the Teprenone group and the Pantoprazole group were elevated (both P<0.05). There was no significant difference between the Teprenone group and the Pantoprazole group (P>0.05).

Discussion

Aspirin combined with clopidogrel also known as duel antiplatelet drugs, are currently widely used for cardiovascular and cerebrovascular diseases such as myocardial infarction, cerebral infarction, stable angina pectoris and unstable angina pectoris [18, 19]. The wide and long-term use of dual antiplatelet therapy brings attention to the side effects, and gastric mucosal damage. The side effects caused by long-term use of dual antiplatelet therapy include indigestion, nausea, acid regurgitation, vomiting or even hematemesis [20, 21]. The gastric mucosa consists of a mucosal muscle layer, a propria layer and an epithelial cell layer. Normally, each factor in the gastric mucosa is in a state of dynamic equilibrium. Long-term use of dual antiplatelet drugs can lead to a disruption of the dynamic balance such as damage on the mucosal barrier, resulting in gastric mucosal damage [22-24]. In this study, we performed gavage with duel antiplatelet drugs in SD rats, and found elevated ulcer indices, reduced gastric mucosal blood flow and gastric mucus gel thickness, obvious gastric mucosal lesions, worsened gastric indicators at varying degrees, severe oxidative stress injury, injured gastric epithelial cells and inflammatory reactions. The above results indicate that dual antiplatelet therapy can cause severe gastric mucosal damage, which is consistent with previous studies.

To improve this situation, proton pump inhibitors have been found to be effective for gastric mucosal damage through inhibiting the proton pump of gastric mucosal parietal cells, which greatly reduces the secretion of gastric acid, thereby improving gastric mucosal damage [25, 26]. Pantoprazole is currently the main drug for gastric mucosal injury. The data in this study also indicate that pantoprazole has a significant effect on gastric mucosal damage and level of Gas, but not on the levels of ET-1, PG and PGE_2.

However, the use of proton pump inhibitors can increase the incidence of cardiovascular and cerebrovascular diseases, and the long-term use can change the regular physiological environment of the stomach because long-term low-acid environments may cause gastric mucosal atrophy or even gastric cancer [27, 28]. Teprenone is a new agent that protects against gastric mucosal damage. It has been shown that teprenone has a certain protective effect against gastric mucosal damage caused by dual antiplatelet therapy. Teprenone improves gastric mucosal damage by inhibiting ulcers and is expected to replace proton pump

inhibitors [29, 30]. We performed dual antiplatelet therapy with teprenone in rats and confirmed that teprenone can reduce the gastric mucosal damage. Studies have also confirmed that teprenone can improve gastric mucosal damage and inhibit inflammation by improving pepsinogen levels [31]. Better than pantoprazole, teprenone could also improve the gastric indices of ET-1, PG and PGE_2. Moreover, we believe that teprenone can increase the gastric mucosal blood flow by promoting the level of PGE_2, thereby repairing the damaged gastric mucosa and inhibiting ET-1, then inhibiting the release of cellular free radicals and inhibiting further damage to the gastric mucosa. Additionally, teprenone can indirectly promote the level of PGE_2 by promoting the expression of COX-1, which is an important rate-limiting enzyme required for PGE_2 synthesis [32]. Teprenone also acts on the expression of VEGF and promotes the regeneration of mucosal blood vessels. When dual antiplatelet drugs inhibit the expression of adenosine diphosphate receptors and reduce the expression of VEGF and neovascularization, teprenone may promote the expression of adenosine diphosphate receptors, restore the expression of VEGF, and promote neovascularization by competitively inhibiting dual antiplatelet drugs [33].

In this study, we performed gavage with dual antiplatelet drugs as well as with pantoprazole and teprenone, respectively, and confirmed the effects of pantoprazole and teprenone on gastric mucosal injury. Besides, a series of indicators we tested and further clarified the mechanism of teprenone on gastric mucosal injury. Teprenone may be more suitable for long-term use in patients with cardiovascular and cerebrovascular diseases. However, the side effects of teprenone still needs to be explored by further clinical or basic research.

Acknowledgements

This work was supported by the Science and Technology Program of Quanzhou (2018Z045).

Disclosure of conflict of interest

None.

Address correspondence to: Xinyang Fu, Department of Pharmacy, Quanzhou First Hospital Affiliated to Fujian Medical University, No.250 East Street, Licheng District, Quanzhou 362000, Fujian Province, China. Tel: +86-13615918337; Fax: +86-0595-22277221; E-mail: fuxinyang3kd6@163.com

References

[1] Sun Z and Lee SY. A systematic review of 3-D printing in cardiovascular and cerebrovascular diseases. Anatol J Cardiol 2017; 17: 423-435.

[2] Li N, Zhou H and Tang Q. Red blood cell distribution width: a novel predictive indicator for cardiovascular and cerebrovascular diseases. Dis Markers 2017; 2017: 7089493.

[3] Lin RT, Chien LC and Kawachi I. Nonlinear associations between working hours and overwork-related cerebrovascular and cardiovascular diseases (CCVD). Sci Rep 2018; 8: 9694.

[4] Fiorito G, Vlaanderen J, Polidoro S, Gulliver J, Galassi C, Ranzi A, Krogh V, Grioni S, Agnoli C, Sacerdote C, Panico S, Tsai MY, Probst-Hensch N, Hoek G, Herceg Z, Vermeulen R, Ghantous A, Vineis P and Naccarati A. Oxidative stress and inflammation mediate the effect of air pollution on cardio and cerebrovascular disease: a prospective study in nonsmokers. Environ Mol Mutagen 2018; 59: 234-246.

[5] Schol-Gelok S, van der Hulle T, Biedermann JS, van Gelder T, Klok FA, van der Pol LM, Versmissen J, Huisman MV and Kruip M. Clinical effects of antiplatelet drugs and statins on D-dimer levels. Eur J Clin Invest 2018; 48: e12944.

[6] Morelli F, Schol-Gelok S, Arends LR, Boersma E, Kruip M, Versmissen J and van Gelder T. Effect of antiplatelet drugs on D-Dimer levels: a systematic review and meta-analysis. J Cardiovasc Pharmacol 2019; 73: 343-351.

[7] Runyon MS. Topical tranexamic acid for epistaxis in patients on antiplatelet drugs: a new use for an old drug. Acad Emerg Med 2018; 25: 360-361.

[8] Xie HG, Jia YM, Tai T and Ji JZ. Overcoming clopidogrel resistance: three promising novel antiplatelet drugs developed in China. J Cardiovasc Pharmacol 2017; 70: 356-361.

[9] Pannach S, Goetze J, Marten S, Schreier T, Tittl L and Beyer-Westendorf J. Management and outcome of gastrointestinal bleeding in patients taking oral anticoagulants or antiplatelet drugs. J Gastroenterol 2017; 52: 1211-1220.

[10] Spoendlin J, Gagne JJ, Lewey JJ, Patorno E, Schneeweiss S and Desai RJ. Comparative effectiveness and safety of antiplatelet drugs in patients with diabetes mellitus and acute coronary syndrome. Pharmacoepidemiol Drug Saf 2018; 27: 1361-1370.

[11] Long L and Jianxin D. Clinical analysis of antiplatelet dug-induced upper gastrointestinal bleeding and preventive effect of pantoprazole against antiplatelet dug-induced upper gastro-

intestinal bleeding. Eval and Anal Drug-Use in Hosp China 2015; 6: 815-817.
[12] Choi YJ, Kim N, Jang IJ, Cho JY, Nam RH, Park JH, Jo HJ, Yoon H, Shin CM, Park YS, Lee DH and Jung HC. Pantoprazole does not reduce the antiplatelet effect of clopidogrel: a randomized controlled trial in Korea. Gut Liver 2017; 11: 504-511.
[13] Shamliyan TA, Middleton M and Borst C. Patient-centered outcomes with concomitant use of proton pump inhibitors and other drugs. Clin Ther 2017; 39: 404-427, e436.
[14] Alhazzani W, Guyatt G, Alshahrani M, Deane AM, Marshall JC, Hall R, Muscedere J, English SW, Lauzier F, Thabane L, Arabi YM, Karachi T, Rochwerg B, Finfer S, Daneman N, Alshamsi F, Zytaruk N, Heel-Ansdell D and Cook D. Withholding pantoprazole for stress ulcer prophylaxis in critically Ill patients: a pilot randomized clinical trial and meta-analysis. Crit Care Med 2017; 45: 1121-1129.
[15] Tan Q, Joshua AM, Wang M, Bristow RG, Wouters BG, Allen CJ and Tannock IF. Up-regulation of autophagy is a mechanism of resistance to chemotherapy and can be inhibited by pantoprazole to increase drug sensitivity. Cancer Chemother Pharmacol 2017; 79: 959-969.
[16] Gong Y, Huang X, Chen M and Xiong L. Teprenone improves gastric mucosal injury and dyspeptic symptoms in long-term nonsteroidal anti-inflammatory drug users. J Gastroenterol Hepatol 2019; 34: 1344-1350.
[17] Tuuminen R, Jouppila A, Salvail D, Laurent CE, Benoit MC, Syrjälä S, Helin H, Lemström K and Lassila R. Dual antiplatelet and anticoagulant APAC prevents experimental ischemia-reperfusion-induced acute kidney injury. Clin Exp Nephrol 2017; 21: 436-445.
[18] Liu J, Xu D, Xia N, Hou K, Chen S, Wang Y and Li Y. Anticoagulant activities of indobufen, an antiplatelet drug. Molecules 2018; 23: 1452.
[19] Zhang JZ, Gao J, Han L, Wang XW and Sun TS. Safety of early minimally invasive surgical treatment of elderly patients with hip fractures without ceasing anti-platelet drugs. Acad J Second Mil Med Univ 2017; 38: 447-451.
[20] Sepúlveda C, Palomo I and Fuentes E. Antiplatelet activity of drugs used in hypertension, dyslipidemia and diabetes: additional benefit in cardiovascular diseases prevention. Vascul Pharmacol 2017; 91: 10-17.
[21] Olier I, Sirker A, Hildick-Smith DJR, Kinnaird T, Ludman P, de Belder MA, Baumbach A, Byrne J, Rashid M, Curzen N and Mamas MA; British Cardiovascular Intervention Society and the National Institute for Cardiovascular Outcomes Research. Association of different antiplatelet therapies with mortality after primary percutaneous coronary intervention. Heart 2018; 104: 1683-1690.
[22] Amie B. Antiplatelet use in practice. Br J Card Nurs 2018; 13: 272-278.
[23] Wang Y, Wang L, Li B, Cheng Y, Zhou D, Chen X, Jing X and Huang Y. Compact vesicles self-assembled from binary graft copolymers with high hydrophilic fraction for potential drug/protein delivery. Acs Macro Letters 2017; 1186-1190.
[24] El-Megharbel SM, Hussien MA and Refat MS. In-Situ Copper (II) complexes of some quinolone drug ligands were discussed for their molecular structures: synthesis in binary solvent. J Comput Theor Nanoence 2017; 14: 561-576.
[25] Meunier L, Ursic-Bedoya J, Pageaux GP and Larrey D. Pantoprazole-induced autoimmune chronic hepatitis. Liver Int 2018; 38: 995-999.
[26] Mansour-Ghanaei F, Pedarpour Z, Shafaghi A and Joukar F. Clarithromycin versus gemifloxacin in quadruple therapeutic regimens for helicobacter pylori infection eradication. Middle East J Dig Dis 2017; 9: 100-106.
[27] Vandenberghe F, Challet C, Maitrejean M, Christin L and Schaad N. Impact of drugs on hypoglycaemia in hospitalised patients. Eur J Hosp Pharm 2019; 26: 199-204.
[28] Osman AS, Labib DA and Kamel MM. Carvedilol can attenuate histamine-induced paw edema and formaldehyde-induced arthritis in rats without risk of gastric irritation. Int Immunopharmacol 2017; 50: 243-250.
[29] Wang Y, Ouyang Y, Liu B, Ma X and Ding R. Platelet activation and antiplatelet therapy in sepsis: a narrative review. Thromb Res 2018; 166: 28-36.
[30] Kapil N, Datta YH, Alakbarova N, Bershad E, Selim M, Liebeskind DS, Bachour O, Rao GHR and Divani AA. Antiplatelet and anticoagulant therapies for prevention of ischemic stroke. Clin Appl Thromb Hemost 2017; 23: 301-318.
[31] Xie M, Chen H, Nie S, Tong W, Yin J and Xie M. Gastroprotective effect of gamma-aminobutyric acid against ethanol-induced gastric mucosal injury. Chem Biol Interact 2017; 272: 125-134.
[32] Tan S, Chen X, Xu M, Huang X, Liu H, Jiang J, Lu Y, Peng X and Wu B. PGE_2/EP_4 receptor attenuated mucosal injury via β-arrestin1/Src/EGFR-mediated proliferation in portal hypertensive gastropathy. Br J Pharmacol 2017; 174: 848-866.
[33] Yang Y, Wang Z, Zhang L, Yin B, Lv L, He J, Chen Z, Wen X, Qiao B, Sun W, Fang M and Zhang Y. Protective effect of gentiopicroside from gentiana macrophylla pall. in ethanol-induced gastric mucosal injury in mice. Phytother Res 2018; 32: 259-266.