EFFECTIVENESS OF SOME INHIBITORS OF ANGIOTENSIN-CONVERTING ENZYME ON A STATE OF GASTRIC MUCOSAL BARRIER IN INDOMETACIN-INDUCED GASTROPATHY

Usmanova S.E., Khamraev A.A., Yakubov A.V.

Tashkent Medical Academy, Tashkent, e-mail: shakhnoza04@mail.ru

How it is known on set of adverse drug effects is consequence of uncontrolled taking of non-steroid anti-inflammatory drugs (NSAID). The majority of unwanted side effects of these means are developing within the limits of GIT.It is believed that gastric or duodenal injuries by taking of NSAID are approximately developing in each fifth patient [1].

Keywords: inhibitors, angiotensin-converting enzyme, gastric

The most serious complications are hemorrhage and perforation that substantially determine lethality related with using of these preparations [2].

Taking into consideration foregoing a problem of NSAID-gastropathy in the last decade takes an important place in treatment of rheumatoid patients. It is searched new mechanisms of formation of NSAID-gastropathy and elaboration of novel therapeutic preparations for treatment and prevention taking into account the data received [3].

It is known that inhibitors of angiotensin-converting enzyme (I-ACE) have a stimulating effect on synthesis of prostaglandins (PG-E2) in kidneys, vessels, brain. It is supposed that they also cause an analogous effect in gastrointestinal tract. Studies of O.M. Mikheyeva et al. [4] that established ulcer-healing effect of enalapril in patients with hypertension and concomitant ulcer diseasemay serveas corroboration.

Nafeeza Mohd Ismail et al. [5] established on a model of aspirin-induced gastropathy in rats comparatively studying effectiveness of captopril and ranitidine that captopril unlike ranitidine increased activity of glutathione reductase, composition of prostaglandin E2 and reliably decreased content of malon dialdehyde (MDA). Circumstances expounded servedgrounds to conduct this study.

The purpose of the research

Goal of research was to study effect of some I-ACE on a state of gastric mucosal barrier in indometacin gastropathy in animals with experimental rheumatoid arthritis.

Materials and methods of research

Experimental studies were carried out on 36 male rats of mixed population weighting 160–200 g that received usual ration of vivarium. Studies were performed in the following groups: 1st group – intact, 2nd group – animals with experimental rheumatoid arthritis and indometacin gastropathy (GERA), 3rd group – GERA + H_2O (without treatment), 4th group – GERA + enalapril, 5th group – GERA + lysinopril, 6th group – GERA + captopril. Every group consisted of 6 animals.

Experimental model of rheumatoid arthritis was challenged by a single administration of 0,2 ml of Freund' adjuvant into posterior right leg [6]. NSAID-gastropathy was challenged by administration of indometacin per os at a dose 2,5 mg/kg during 5 days [7]. After modeling the preparations studying were administered as water suspension per os during 10 days in the following doses: enalapril 10 mg/kg [8], lysinopril 8 mg/kg [9], captopril 7,5 mg/kg [10], omeprazole 50 mg/kg [11], cytotek 0,2 mg/kg [12].

To conduct biochemical investigation sall the animals were decapitated by a single-stage etherization, the stomach was extracted.The stomach was cleaned, washed by a cold physiological salt solution, proventriculus was removed. Mucosal layer was then scarified, weighed and slurried in distilled water in the porcelain mortarat a rate 30 mg/ml [13]. Stateo mucosal barrier was calculated by determination of compositions of carbohydrate and protein components of insoluble glycoproteins (IGP). Sialic acids were determined by a method of L.I. Linevik [14]. To determine fucose was used a method proposed by P.D. Rabinovich et al. [15]. Content of protein was estimated by a method of O.N. Lowry et al. [16].

Results of research and their discussion

Results of studying effect of some I-ACE on content of insoluble glycoproteins in gastric mucosa in indometacin gastropathy in animals are presented in a Table.

How it is shown from the data presented content of IGP in gastric mucosa was considerably decreased in GERA. Composition of sialic acids was decreased 3,4 times, fucose – almost 2,5 times, and protein – 2 times from control values. These changes in a group without treatment (H_20) remained the same.

An increase in content of sialic acids 60,8 %, fucose – 34,5 % and protein – 29,7 %from indicator in a group without treatment noted to be in a group treated with enalapril. Almost analogous results were also observed in a group treated with lysinopril.

Application of captopril was found the most effective in treatment of GERA. In this group composition of sialic acids was increasing 136,2 %, fucose – 69,7 % and protein – 37,4 %. But despite of substantial increase in fractions' composition in this group the results obtained remained lower compared with values in control (intact) group.

Effect of some I-ACE omeprazole and cytotek on content of fractions of insoluble glycoproteins in gastric mucosa in indometacin gastropathy in animals with experimental rheumatoid arthritis.

Number	Groups of animals	Sialic acids mkg in ml of suspension	Fucose mg in ml of suspension	Whole protein mg in ml of suspension
1	Control	4,12 ± 0,158	6,73 ± 0,125	15,22 ± 0,655
2	GERA	1,22 ± 0,067	2,78 ± 0,100	7,65 ± 0,257
3	GERA + H_2O	1,38 ± 0,072	2,85 ± 0,121	8,55 ± 0,352
4	GERA + enalapril	2,22 ± 0,047*	3,82 ± 0,089*	9,92 ± 0,400
5	GERA + lysinopril	2,47 ± 0,085*	4,12 ± 0,051*	10,12 + 0,397*
6	GERA + captopril	3,27 ± 0,041*	4,82 ± 0,106*	11,75 ± 0,546*

N o t e . * – $p < 0,05$ from indicator of GERA group without treatment (GERA + H_2O).

It was established that sialic acids and fucose play special role in IPG functioning of full value. These carbohydrate components provide elasticity and viscosity of mucosal barrier [17, 18]. Results received in a group with GERA allow assert that injury of mucosal barrier of stomach was caused by decrease of IPG synthesis and its functional insufficiency characterized by changes of its rheological features. Negative effect of indometacin on mucosal barrier in the literature availableis accounted for inhibition of COX enzymes, suppression of prostaglandins' production with the future damage of microcirculation. It is assumed that this mechanism is not the only one.

Convincing data are available in the literature confirming ulcer-healing effect of enalapril [19, 20]. The authors relate it with stimulation of prostaglandins' synthesis. We suppose that it is one of the mechanisms of positive effect of drug that is also a cause of correcting action of preparation on other mechanisms of pathogenesis. Nikonov E.L. [21] investigated an effect of captopril and lysinopril on a state of gastric mucosal membrane in patients with arterial hypertension and osteoarthritis over a long period of time taken NSAID. It was established by author that I-ACE have positive effect not only on cardiovascular system but also improve morpho-functional indices of gastric mucosal membrane. S.A.Alexeyenko et al. [19] affirm that mechanisms of positive effect of preparations of I-ACE group on gastric mucosal membrane need the further investigation.

Conclusions

1. Synthesis of insoluble glycoproteins in gastric mucosal barrier is considerably suppressed in indometacin gastropathy in animalswith experimental rheumatoid arthritis.

2. I-ACE enalapril, lysinopril and captopril stimulating glycoproteins' synthesis in gastric mucosa have cytoprotective effect. Captopril is the most effective in treatment of NSAID-induced gastropathy.

References

1. Hawkey C., Hudson N. Mucozal injury caused by drugs, chemicals and stress // Bockus Gastroenterology. – 5ed. NY. – Saunders, 1994. – P. 656–699.

2. Nikoda V.V., Khartukova N.E. Application of inhibitors of proton pump inintensive therapy and resuscitation // Pharmateka. – 2008. – № 13. – P. 9–15.

3. Sanchez-Fidalgo S., Martin-Lacave I., Illanes M. et al. Administration of L-arginine reduces the delay of the process caused by ibuprofen. Implication of COX and growth factors expression // Histol. Histopathol. – 2005. – № 8 (1). – P. 59–62.

4. Mikheyeva O.M., Lazebnik L.B., Belostotsky N.I., Khomeriki S.G. Clinical experimental substantiation of positive effect of hypotensive preparations on defect of gastric mucosal membrane in ulcer disease // Experimental& Clinic Gastroenterology. – 2007. – № 5. – P. 11–20.

5. Nafeeza Mohd Ismail, Ibrahim Abdel Aziz Ibrahim, Najihah M.B., Kamsiah Jaarin. Effects of captopril on factors affecting gastric mucosal integrity in aspirin-induced gastric lesions in Sprague-Dawley rats // Arch Med Sci. – 2012. – № 1. – P. 1–6.

6. Experimental rheumatoid arthritis / O.V. Sinyachenko, E.F. Barinov, S.V. Zyablitsev et al. // Rheumatology. – 1991. – № 3. – P. 36–40.

7. Cyclooxigenase 1 contributes to inflammatory responses in rats and mice: implications for gastrointestinal toxicity / Jonn L.Wallace, Agrian Bak, Webb, Mckhight et al. // Gastroenterol. – 1998. – Vol. 115. – P. 101–109.

8. Timoshin S.S. Implication of neuropeptids in maintenance of tissue homeostasisof mucosal membrane of gastrointestinal tract // Appendix № 14 to: materials of the 16th session of the Academic School-Seminar and modern problems of Physiology & Pathology of Digestion. – 2001. – № 4. – P. 38–43.

9. Kovaleva M.V., Afonin V.Yu., Shilov V.V., Nadina N.G., Ogurtsova S.E. Evaluation of hypotensive effect and sode effect

of generic preparation lysinopril // Materials of the Russian Science Conference with international participation: Actual problems of toxicology & radiobiology Saint Petersburg 19–20 Mai 2011. – P. 17.

10. Anna Gvozdjáková, Fedor Šimko, Jarmila Kucharská, Zuzana Braunová, Peter Pšenek and JÁN Kyselovič. Captopril increased mitochondrial coenzyme Q10 level, improved respiratory chain function and energy production in the left ventricle in rabbits with smoke mitochondrial cardiomyopathy // Journal Biofactors. – 1999. – Vol. 10. – № 1. – P. 61–65.

11. Daminov Sh.N., Inoyatova F.Kh. Comparative estimation of action of quamatel and omez on glutathione system on different sections of digestive system in experimental duodenal ulcer // Experimental& Clinic Pharmacology. – 1998. – № 4. – P. 26–28.

12. Halil Asci, MK Ozer, M Calapoglu, M Savran, M Oncu, S Yesilot, IA Candan, E Kulac, E Cicek. Effects of Misoprostol on Methotrexate-Induced Hepatic and Renal Damages // Journal of Biology and Life Sciences. – 2011. – Vol 2. – № 1. – P. 32–37.

13. Properties of gastric and duodenal mucus: Effect of protivolizis disulfide reduction, bibe, acid, ethanol, and hypertonicity on mucus gel structure / A.E. Bell, L.A. Sellers, A. Allen, W.J. Cunliffe // Gastroenterol. – 1995. – Vol. 88. – № 1. – P. 269–280.

14. Linevik L.I. Achievements of Biological Chemistry. – M., 1962. – Vol. 4. – 193 p.

15. Rabinovich P.D., Milyshkin P.V. Biological oxidation and main functions of stomach in patients with ulcer disease // Therap. archives. – 1979. – № 11. – P. 103–105.

16. Protein measurement with the folin phenol reagent / O.H. Lowry, N.J. Rosebrough, A.L. Farr, R.J. Randall // J. Biol. Chem. – 1951. – Vol. 193. – № 1. – P. 265–275.

17. Khamraev A.A. Peculiarities of injury of gastric mucosal barrier in Helicobacter pylori infection in patients with duodenal ulcer. – 2005. – № 7. – P. 34–36.

18. Vatier J., Poitevin C., Mignoum K. L'acide sialique, marqueur de la proteolyses peptique des-dlycoproteines du mucus gastrique: interet physiopathologique chez l'homme // Gastroenterol. Clin. Biol. – 1985. – Vol. 9. – № 12. – P. 108–110.

19. Effect of enalapril, lysinopril and amlodipin on a course of chronic gastritis in patients with arterial hypertension / Alexeyenko S.A., Timoshin S.S., Avilova A.R. et al. // Clinical Medicine. – 2004. – № 9. – P. 42–45.

20. Smirnova L.E. About a problem of co-morbidity of ulcerous erosive destructions of gastro-duodenal zone and arterial hypertension // Clin Medicine. – 2003. – № 5. – P. 9–15.

21. Nikonov E.L. Effect of anti-hypertensive therapy on a state of gastric mucosal membrane in patients with arterial hypertension and osteoarthritis prolonged taken non-steroid anti-inflammatory drugs (NSAID) // Russian Journal of Gastroenterology & Hepatology & Coloproctology. – 2001. – № 5. – P. 49.