ACTION OF HYDROGEN SULFIDE RELEASING 2-MERCAPTOACRYLIC ACID-BASED DERIVATIVE ON NITRIC OXIDE METABOLISM AND OXIDATIVE STRESS IN SMALL INTESTINE OF RATS WITH MEDICATION-INDUCED ENTEROPATHY

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Small intestinal injury is one of the most commonly appeared pathologies resulting in use of medications such as: nonsteroidal anti-inflammatory drugs (NSAIDs), anti-tumor drugs and inhibitors of angiotensin-converting enzyme (ACE). Taking into consideration the fact that these drugs are widely used for the treatment of various serious diseases, the search of new drugs without any side effects is an important medical and pharmaceutical problem. A new approach in this sphere may be demonstrated by novel sulfur-containing compounds based on mercaptoacrylic acids and thiazolidinones as their synthetic precursors which possessing a dual COX/lipoxygenase (LOX) inhibitory action. The purpose of this study is to evaluate the action of a novel 2-mercaptoacrylic acid-based, possessing dual COX/LOX inhibitory action and able to release H_2S on parameters of NO-synthase system and oxidative stress at the background of drug-induced enteropathy.

The structure of this study and the experimental procedures performed on the animals were approved by the Ethical Committee of Lviv National Medical University. Three types of medications were used to induce enteropathy: indomethacin, a NSAID (35 mg/kg); metothrexate, an anti-tumor drug (10 mg/kg); enalaprile, an ACE inhibitor (2 mg/kg/day). 2-[(4-chlor-phenyl-carbamoyl)-methyl]-3-(3,5-Di-tert-butyl-4-hydroxyphenyl)-acrylic acid (2C3DHTA) was introduced on the background of medication-induced entepopathy (10 mg/kg/day). In the mucosa of small intestine were determined: malonic dialdehyde (MDA) concentration, activity of mieloperoxydase (MPO), superoxide dismutase (SOD), catalase, NO-synthases (NOS).

Administration of indomethacin induced the development of ulcerative lesion of small intestine manifested by erosions and haemorrhages, localised mainly in its distal part. Neither metothrexate nor enalapril caused any visual changes of small intestine surface. It should be pointed out that metothrexate-treated animals were suffering from severe enterotoxicosis manifested by diarrhoea and vomiting. In spite of different mechanisms of their action upon metabolic processes in small intestine, all used medications (indomethacin, metothrexate and enelaprile) caused serious changes of NO-synthase system parameters. Administration of indomethacin and metothrexate caused a rise in iNOS activity. ACE-inhibitor decreased cNOS activity. 2C3DHTA demonstrated a cytoprotective effect: it returned iNOS activity to its control level and increased cNOS activity. Enterotoxic action of studied medication was accompanied by the development of oxidative stress manifested by rise of MDA concentration, activity of MPO was increased. 2C3DHTA reduced MPO activity and manifestations of oxidative stress.

Effects of 2C3DHTA on one hand can be explained by action of H_2S, released from this compound in gastrointestinal system, on the other hand by the dual inhibition of pro-inflammatory enzymes COX and LOX. Thus in our study we showed, that H_2S released from compound 2C3DHTA was involved in mechanisms cytoprotection in small intestine.