THE NEW NASAL SPRAY WITH ANTI-INFLAMMATORY PROPERTIES: THE EFFICACY EVALUATION IN RABBITS WITH EXPERIMENTAL RHINOSINUSITIS

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Introduction Acute rhinosinusitis (ARS) treatment and prevention are connected to the rational choice of the drug dosage form to increase patients' quality of life by nasal congestion (stuffy nose) relief. A new nasal spray with Enisamium Iodide (EI) aqueous solution – original dosage form of a well-known pharmaceutical substance – has been developed by Farmak JSC (Ukraine). The anti-inflammatory action of EI potentially justifies high drug efficacy in the nasal spray dosage form for ARS treatment. It causes a direct positive effect on the inflammation and swelling into the nasal cavity, paranasal sinuses, and sinus ostium. However, the evaluation of this drug efficacy requires clear criteria, and nasal endoscopy is supposed to be one of the methods for presenting them. Therefore, nasal endoscopy could be used in experimental rhinology as a method of direct visualization for confirmation of induced pathology as well as a method for evaluation of the efficacy of test drugs. The study aimed to substantiate the efficacy of the new nasal spray with anti-inflammatory action, which contains EI at a concentration of 10 mg/mL administered intranasally (i.n.) via nasal endoscopy in rabbits with experimental rhinosinusitis (RS).

Materials and methods. The 10 mg/mL EI (nasal spray) was a study object at the dose of 0.1 mL i.n. per animal into the right rabbit nasal passage using Biohit Proline fixed volume pipettor 200 µl with Biohite pipettor tips. Sinupret®, «Bionorica SE» (Germany) (coated tablets, 78 mg) was a reference drug at the dose of 25 mg/kg orally as a water suspension via a special catheter with an elastic cannula. 0.9% saline in an equivalent dose and route of administration was used in the intact control and control pathology groups. Experimental RS in rabbits was induced on the 1st day by tamponade of the right halves of the nasal cavity under general anesthesia. After 15 days of pathology inducement, nasal swab (sponges) were removed. Starting from the 15th day and during the further 10 days, 0.9% saline, 10 mg/kg EI (nasal spray) and Sinupret® at the respective doses were administered to animals (4 groups, 6 rabbits in each group). Nasal endoscopic control was using Karl Storz rhinoscopes (Germany) on all stages (the 1st, 15th and 25th days) in all groups. The method of semi-quantitative score assessment was used to the result objectivity.

Statistical analysis of the results was performed using Kruskal-Wallis one-way analysis of variance and Mann-Whitney U test for a posteriori pairwise comparisons[23-24].

Utilized computer software included IBM SPSS Statistics v. 22 (IBM Corp., USA) and MS Excel 2016 (Microsoft Corp., USA). The level of statistical significance was considered as $p < 0.05$.

Study Results. *Intact control group.* The total score calculated for the intact group was 0 (0 ÷ 0) at the first and 0 (0 ÷ 1) at the second stages of the study which corresponds to the physiological state. *Control pathology group.* According to the results of the semi-quantitative assessment, the total score was 7.0 (6 ÷ 8) on the 15th day of the study and 6.0 (5 ÷ 7) on 25th day. Which is significantly greater than in the intact control group ($p<0.05$ vs. intact control group) and could be defined as severe RS, however with a slight regression of endoscopic sings on 25th day. *EI treated group*. The total score resulted from the semi-quantitative assessments on the 15th day of the study concluded 7.0 (6 ÷ 8) which is significantly greater than in the group of intact animals ($p<0.05$ vs. intact control group) and thus could be referred to severe RS. In contrast, on the 25th day of the study, the total score was 2.5 (2 ÷ 3) ($p<0.05$ vs. intact control group, control pathology group and Sinupret treated group), which corresponds to mild RS. *Sinupret treated group*. As a result, of the semi-quantitative assessment on the 15th day of the study, the total score was 7.0 (6 ÷ 8), which refers to the control pathology group ($p<0.05$ vs. intact control group) and confirms the manifestation of severe RS in rabbits. After Sinupret® administration, the total score has significantly lowered and was 4.0 (3 ÷ 4), which refers to moderate RS and proves the efficacy of the reference drug. It is worth to note that according to the criterion, which was used, Sinupret® had significantly lower activity compared to EI (nasal spray) ($p<0.05$ vs. Sinupret treated group). These data present the evidence in favour of the test object and demonstrate its advantage compared to the well-known drug for RS treatment, which is explained by the difference between their primary pharmacodynamic effects. Sinupret® has significant secretolytic activity in contrast to EI, which mostly shows the anti-inflammatory effect.

Conclusions. EI (nasal spray) at i.n. administration during 10 days showed a positive effect in rabbits with RS by endoscopic signs and outweighed the activity of the reference drug Sinupret® (tablets) by the parameter «The state of the maxillary sinus ostium» (more pronounced anti-exudative effect). The anti-exudative effect of EI (nasal spray) at i.n. administration has been developed faster than the secretolytic effect of the reference drug Sinupret® at oral administration according to endoscopic data. EI (nasal spray) is a perspective object for further pre-clinical and clinical studies aiming to substantiate the reasonability of its use for the treatment of RS, prevention of complication as well as its implementation to the clinical practice. The nasal endoscopy could be used in preclinical studies of new drugs as an informative visual method for confirmation of induced pathology as well as for the endoscopic evaluation of the treatment efficacy.