ABSTRACT

Aims: Anionic oxygen is a very powerful antimicrobial and antiviral agent. In this study, it was aimed to investigate the harmful and side effects of anionic oxygen on rats.

Materials and Methods: We designed oral and inhalation tests to evaluate the any possible adverse effects of anionic oxygen. Male Sprague-Dawley rats were used in the study. The results were examined histopathologically under the light microscope.

Results: No significant histopathological changes were observed in the heart, liver, kidney, and stomach after the oral and inhalation administration of anionic oxygen. In both applications, squamous hyperplasia in the oropharynx, peribronchial lymphoid hyperplasia and emphysematous changes in the lung were observed. These effects were thought to be related to the dose and duration of administration.

Conclusions: This study demonstrated non-toxic effect of anionic oxygen on the lung parenchyma and oropharyngeal mucosa of rats as peribronchial lymphoid hyperplasia which might be due to the stimulation of the immune system.

INTRODUCTION

The Covid-19 pandemic, which the world deterringly struggling against in the last 2 years, has negatively affected the health systems of societies and deeply shook the perception of public health and hygiene of mankind. In this period, there has been an increase in fear and anxiety regarding infectious diseases, and economic and social problems have been observed to significantly clog the health system (1). Since the first ages of history, mankind has been exposed to infectious diseases and struggling with simple vaccination methods (2). The world has agonized with epidemics and pandemics, which has unfortunately lived through these struggles with excessive losses and painful lessons, many times before (1). This pandemic period has emerged in a time, that humanity allegedly had optimal increased access to medical attention along with promising developments in cancer treatment, led to people to evaluate their hygiene habits and personal health activities associated with demoralizing effects on all humanity.

Vaccination and medications for which have been used effectively primarilyin the fight against infections during these above-mentioned pandemic periods, have developed concerns and prejudice in people recently and led to the emergence of different searches due to disruptions

and losses in this last pandemic. These searches are particularly focused on empowering the immune system and preventing and neutralizing the infectious agents earlier developing the disease. During this pandemic, preventive medicine practices, which are the most important issue concerning public health, have reached instead of using medications. People have increasingly prefered to use mask, personal protective devices, and immune system related regulatory foods and pharmacological products (3).

Many active substances and ingredients have been tested for the purpose of preventing infection, and some of these substances, whose effectiveness have been proven by experimental studies. Active anionic octaoxidant liquid oxygen (H2O8), which is one of these active ingredients, is a biocidal and humoral antioxidant stimulator produced for therapeutic purposes regards to cease infectious agents and resolve disease(4).

In terms of the results of anionic oxygen's chemical analysis; there are 2 hydrogen and 8 oxygen molecules in its basic compound, and its chemical formula is 1S/H2O8/c1-3-5-7-8-6-4-2/h1-2H. Its molecular weight is 130.01108 g/mol and IUPAC name is 'Octaoxidant' (5). The compound has a pH of 7.55 as shown by the physiochemical analyzes of which this results is considered as tissue compatible with a structure close to alkaline and a density (pycnometer) of 0.9981 (5). It contains hypochlorous acid (220,676 ppm) in order to create biocidal and oxidizing activity along with chemical purposes (5).

With regards to the compound's microbiological analysis; it was shown that anionic octaoxidant liquid oxygen (H2O8) has strong bactericidal activity in a very short time of exposure against, P. aeruginosa (≥ 5.29 log, 1 min.), S. aureus (≥ 5.23 log, 1 min.) and E. coli (≥ 5.34 log, 1 min.) > 99.99 reductions (5). As per the fungicidal activity it was also effective against C. albicans (4.42 log, 5 min.) and A. brasiliensis (1.44 log, 15 min.) giving a 99.99% and 96.36% efficacy, respectively (3). More stronger microbicidal effect were observed against the viruses of, Poliovirus Type 1 (≥8.33 log, 2 min.), Adenovirus Type 5 (≥8.33 log, 2min.), Norovirus (≥7.83 log, 2min.) and SARS Cov-2 (Covid-19) (>7.5 log, 15 sec.) with greater than 99.999 % reduction in suspension tests (5).

Our main objective of this experimental animal study is to find and to evaluate the side effect profile of the compound and to contribute further studies in order to evaluate pharmacokinetic, pharmacodynamic and dosing of this compound in a preliminary manner, as conducted in line with the above information.

MATERIALS AND METHODS

Chemicals

The test product was, anionic oxygen containing the H2O8 compound was used. Its gas chromatographic and mass spectroscopic analysis demonstrated that it contains 32 mmol/L Na+, 16.9 mmol K+, 35 mmol Cl- and pO2 158 mmHg/L with an ORP value (unit of oxidizing and reducing power of the solution) of 960 mV (5). The ORP ~~is~~ value is a minimum of 725 mV (0.5 mL anionic oxygen) when the solution is diluted with 100 ml of distilled water (5). The anionic oxygen product content consists of a combination of 1-5% hypochlorous acid, 1-40% H2O8 octaoxidant liquid oxygen and 2-98% H20 pure water according to the formula weight ratio(5).

All animal experiments were performed at the Department of Animal Experiment and Research Centre, Gülhane Institute of Health Sciences, University of Health Sciences University of Health Sciences Gulhane Experimental Animal Research and Production Center. The study was conducted in accordance with the guidelines of the Institutional Animal Care and Use Committee and the protocol was approved by the Institutional Board (Ethics-2020/20, University of Health Sciences Gülhane Animal Experiments Local Ethics Committee).To conduct every study seperately, the animals were randomly selected among 100 Sprague-Dawley type, 4-6 months old male, rats weighing between 300 grams and 400 grams. The temperature of the animal rooms was set to 21-24˚C and 50%±20% relative humidity; a 12:12 hour light/dark cycle was used. A routine laboratory diet and water were supplied for rats ad libitum. The acclimatization period of 1 week was maintained to the rats which were randomly divided into 3, 2 and 6 groups regarding the first, second and third study desing respectively. The changes in body weight were recorded twice per week from the beginning of the study and clinical signs and symptoms were observed during the exposure period.

Study Design

Three different studies were designed and conducted using rats. The inhalation aerosols of anionic oxygen solutions were generated by using a compression atomizer with a clean air flow of 0,5 mL/min and a particle volume with 3.0 μm (Fig. 1). The syringe with 1 cc volume was used to give anionic oxygen solution orally. In terms of the studies' design, the rats were sacrificed by servical dislocation method and the pathologic specimens were transported by using container including %10 formaldehyde (6). Following the routine tissue processing, the tissues were embedded in paraffin and 3 μm slices were cut (6). The sections were stained with hematoxylin and eosin (H&E) for histological examination under a light microscope. The specmens were examined and graded, depending on severity.

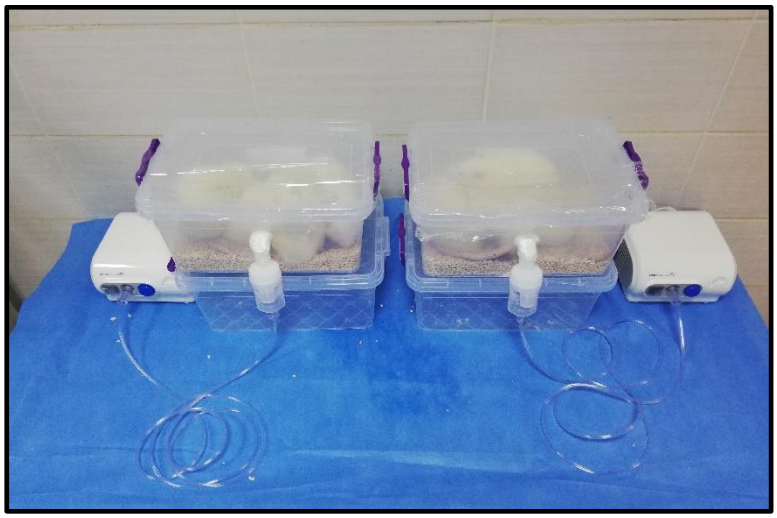

Fig. 1. Inhalation containers prepared for administration with a nebulizer

First study

A total of 24 rats were randomly divided into 3 groups. The study period was set for 21 days and at the end of the last application, the animals were sacrificed in the presence of veterinarians. Pathological samples were collected from the liver, heart, oropharynx, lung, stomach and kidney tissues of animals as whole organs. In the first group, 4 cc of 5% anionic oxygen liquid was administered by inhalation for 15 minutes through a nebulizer in a 7.5 lt gas-insulated transparent plastic box with an interval of 12 hours (Fig. 1) (7). In the second group, 0.5 cc 5% anionic oxygen liquid was administered orally with an injector every 12 hours. The third group was determined as the control group and no application was made.

Second Study

A total of 16 Sprague-Dawley type male 4–6-month-old rats, whose weights range from 300 grams to 400 grams, were randomly selected. 16 rats were randomly divided into 2 groups. Animals were sacrificed on the 21st day in the presence of veterinarians. The animals' oropharynx and lung, as whole organs, were collected in pathological samples. In the first group, 4 cc 15% anionic oxygen liquid was administered by inhalation for 15 minutes through a nebulizer, in a 7.5 lt volume of gas-insulated transparent plastic box at 12 hour intervals for 7 days (Fig. 1) (7). In the second group, 4 cc of 15% anionic oxygen liquid was administered by inhalation for 15 minutes through a nebulizer, in a 7.5 lt gas-insulated transparent plastic box at 12-hour intervals for 14 days.

Third Study

A third study was conducted to provide regarding toxicity profile and side effect profile in lower doses along with minimal administration times. For this purpose, the authors had used Organization for Economic Co-operation and Development (OECD), Acute Inhalation Toxicity – Acute Toxic Class Method (2009). OECD Guideline for Testing of Chemicals No. 436. The inhalation toxicity method was determined in terms of the above-mentioned guideline. In third study either toxicity or low dose administration of anionic oxygen protocol were conducted.

A total of 24 Sprague-Dawley type male 4–6-month-old rats, whose weights vary between 300 grams and 400 grams, were randomly selected. 24 rats were randomly divided into 6 groups.

In the 1st group, 20,000 ppm equivalent 40 cc 5% anionic oxygen liquid was administered for 4 hours in a 30 lt volume of gas-insulated transparent plastic box by inhalation through a nebulizer to assess toxicity (8). These rats were sacrificed on the same day after the last intervention. Lung and oropharyngeal tissues, as a whole organ, pathological samples were collected. In the 2nd group; 4cc anionic oxygen liquid for 7 days with 12-hour intervals were administered by inhalation via a nebulizer in a transparent plastic box with a volume of 30 liters. These rats were sacrificed on the same day after the last application. Pathological specimens of lung and oropharynx, as whole organ, were collected. In the 3rd group were determined as the control group, no intervention was made, and the lung and oropharynx tissues were collected as whole organ by sacrificing on the day of the selection.

In the 4th group, the rats were administered 20,000 ppm equivalent 40 cc 5% anionic oxygen liquid for 4 hours in a transparent plastic box with a volume of 30 lt in a gas-insulated transparent plastic box through a nebulizer to assess toxicity, and these rats were sacrificed 14

days after the last intervention (8). The lung and oropharyngeal tissues, as whole organs, were collected. In the 5th group; 4cc anionic oxygen liquid for 7 days with 12-hour intervals were administered by inhalation via a nebulizer in a transparent plastic box with a volume of 30 lt of, and these rats were sacrificed 7 days after the last intervention and pathological samples were collected as written above. In the 6th group were determined as the control group, no intervention was made and 7 days later they were sacrificed and the lung and oropharynx tissues, as whole organs, pathological samples were collected.

RESULTS

First Study;

The pathological examination which was made after 21 days of administration. Rats in group 1 (nebulizator); No macroscopic or microscopic pathological findings were revealed in the liver, heart, kidney and stomach. In the lung examination of these rats; focal changes were observed in 2 subjects and diffuse emphysematous changes were observed in 6 subjects. Besides, peribronchial lymphoid tissue hyperplasia was observed in 5 subjects and signs of purulant bronchitis in 1 subject. In terms of the pathologic oropharynx examination; mild hyperkeratosis in 3 subjects, epithelial thickening in 4 subjects and focal mucosal necrosis in 1 subject were observed (Table 1).

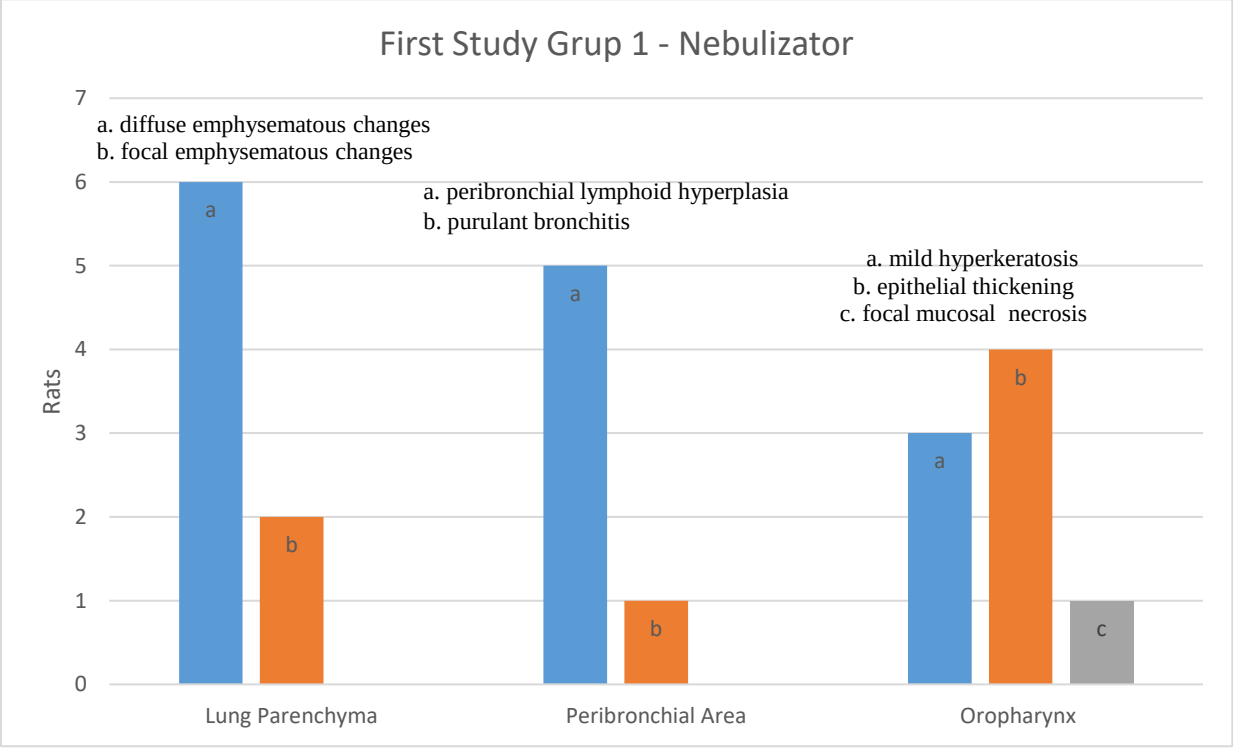

Table 1. First Study Grup 1 - Nebulizator

Rats in group 2 (oral); neither macroscopic nor microscopic findings were found in the liver, heart, kidney, and stomach. In the pathologic lung examination of these rats; focal emphysematous changes were observed in 4 subjects and diffuse emphysematous changes in 4 subjects (Fig. 5). Peribronchial lymphoid tissue hyperplasia was observed in 5 subjects and signs of purulant bronchitis in 1 subject. Pathologic oropharynx examination revealed that the mild hyperkeratosis was observed in 6 subjects and epithelial thickening in 5 subjects (Table 2).

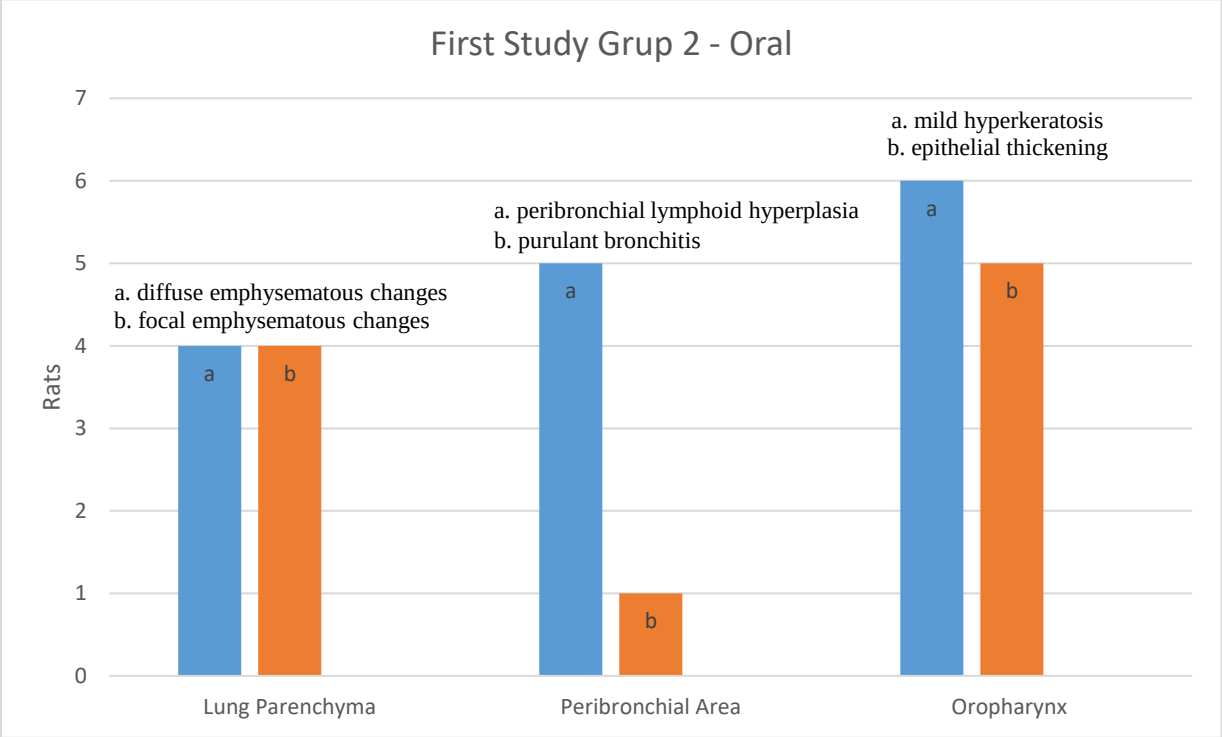

Table 2. First Study Grup 2 - Oral

Neither macroscopic nor microscopic pathological findings were found in the liver, heart, kidney and stomach in the 3rd group (control) of the first study. Focal emphysematous changes were observed in 6 subjects of this group and oropharyngeal epithelial thickening was observed in 1 subject. Apart from this, the oropharyngeal mucosa, lung parenchyma and peribronchial area were unremarkable (Fig. 2,3,4).

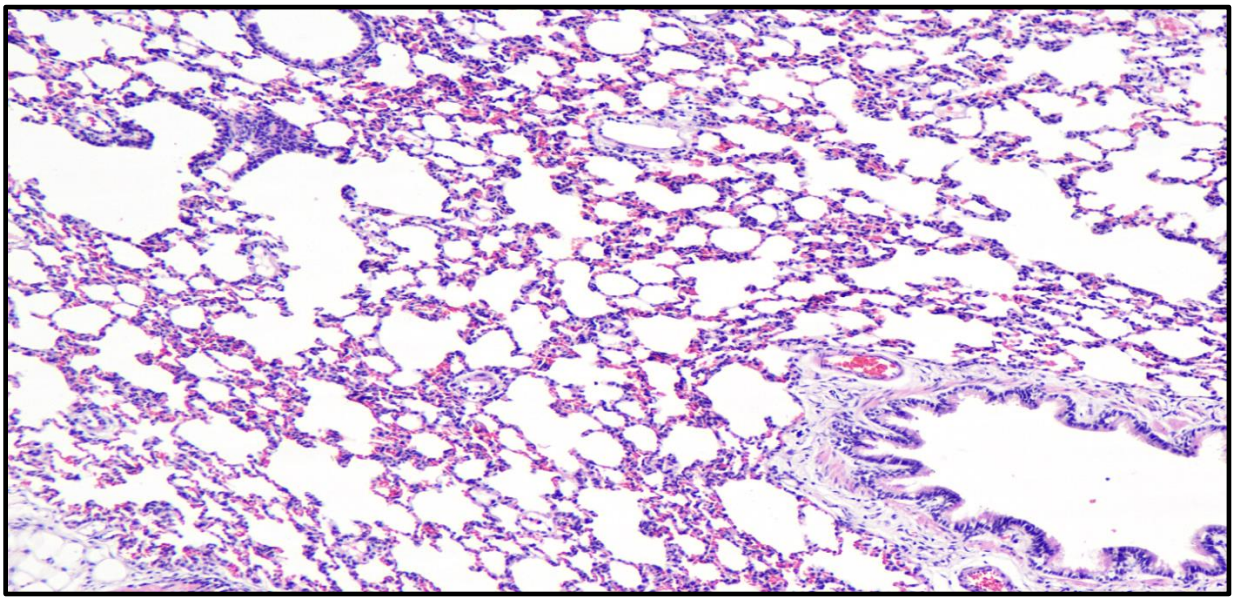

Fig. 2. Rat lung parenchyma with normal histological appearance (First Study Grup 3 – Control). Light microscopy, HE X100.

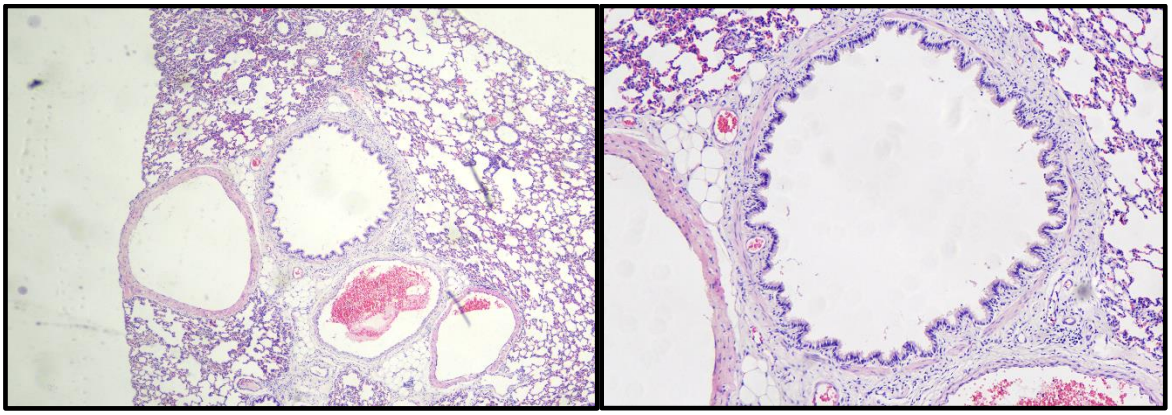

Fig. 3. Rat peribronchial area with normal histological appearance (First Study Grup 3 – Control). Light microscopy, HE X40 and X100.

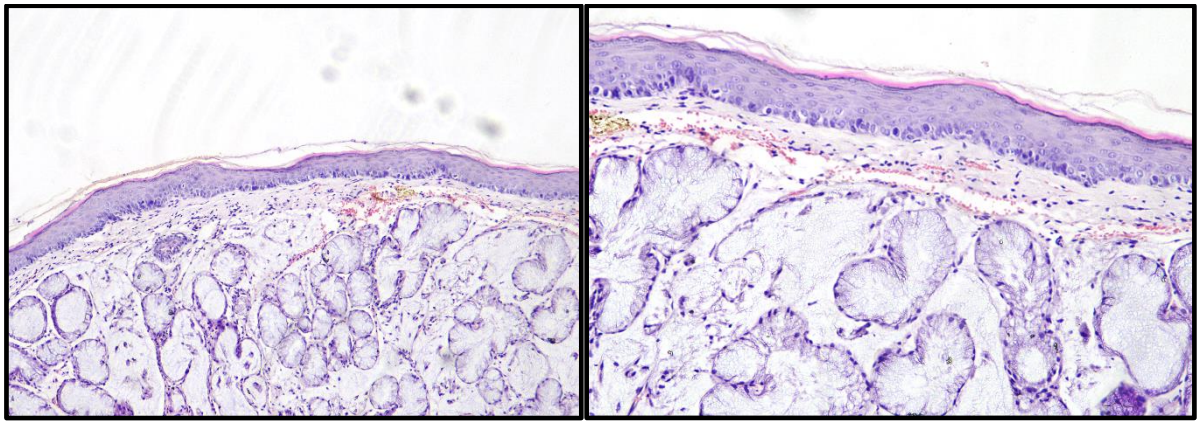

Fig. 4. Rat oropharyngeal mucosa with normal histological appearance (First Study Grup 3 – Control).Light microscopy, HE X40 and X100.

Second study

With regards to the first group's (7 days nebulizator) lung pathological results; minimal emphysematous changes were observed in 2 subjects and mild emphysematous changes in 4 subjects. Mild peribronchial lymphoid hyperplasia was observed in 5 subjects and moderate in 3 subjects. In the oropharynx; mild hyperkeratosis was observed in 6 subjects and moderate hyperkeratosis was observed in 2 subjects. Mild squamous hyperplasia was observed in 4 subjects, moderate in 2 subjects, and severe hyperplasia in 2 subjects (Table 3).

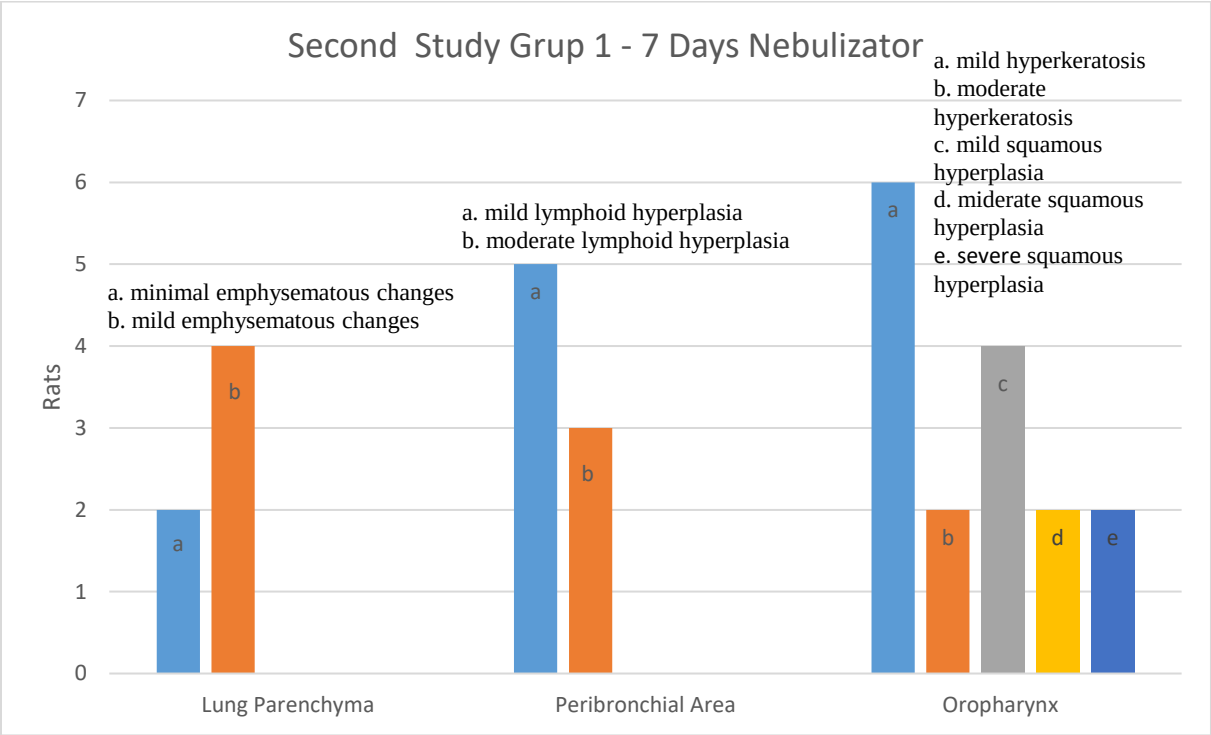

Table 3. Second Study Grup 1 -7 Days Nebulizator

Rats in group 2 (14 days nebulizator); minimal emphysematous changes were observed in 1 subject, mild in 3 subjects, moderate in 2 subjects, and severe in 2 subjects (Fig. 5). In addition, minimal peribronchial lymphoid hyperplasia was observed in 1 subject, mild in 4 subjects, moderate in 2 subjects, and severe in 1 subject (Fig. 6, 7). Mild hyperkeratosis of oropharyngeal mucosa was observed in 3 subjects and moderate hyperkeratosis of oropharynx was observed in 5 subjects. In addition to these oropharynx results, mild squamous hyperplasia (Fig. 8) was observed in 3 subjects, moderate in 3 subjects, and severe in 2 subjects (Fig. 9) (Table 4).

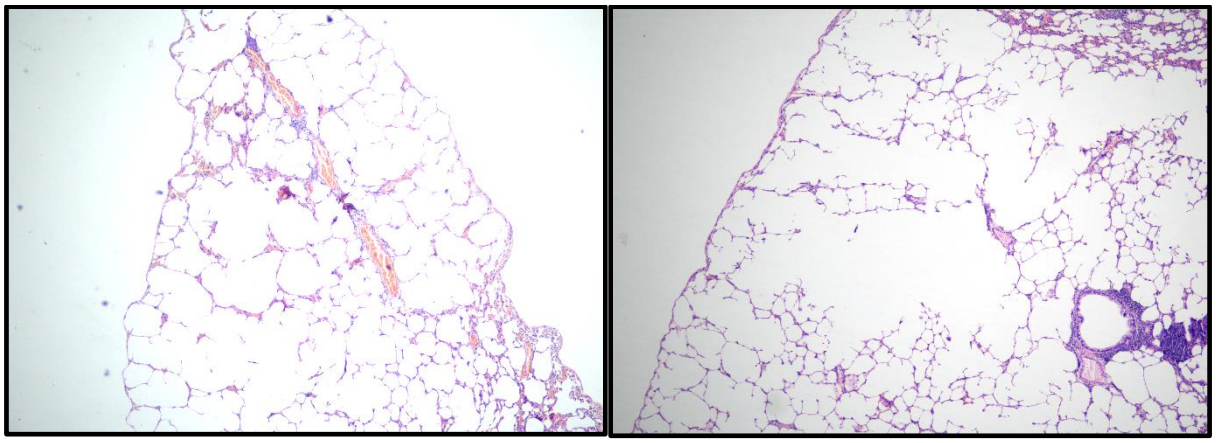

Fig. 5. Severe emphysematous changes in the lungs of rats in the application group (Second Study Grup 2 -14 Days Nebulizator). Light microscopy, HE X40.

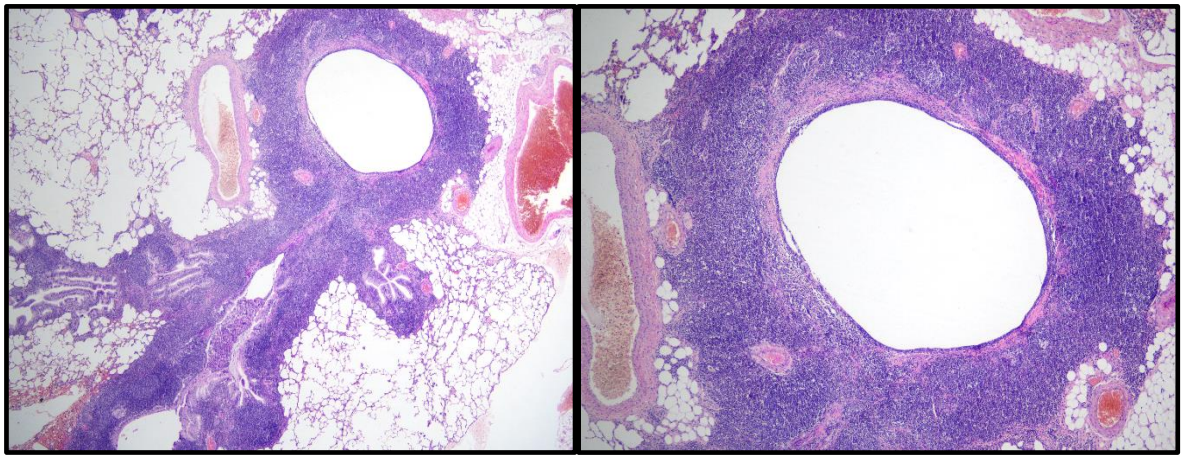

Fig. 6. Severe peribronchial lymphoid hyperplasia and moderate amphithematous changes in the lung of rats in the application group(Second Study Grup 2 -14 Days Nebulizator).Light microscopy, HE X20 and X40.

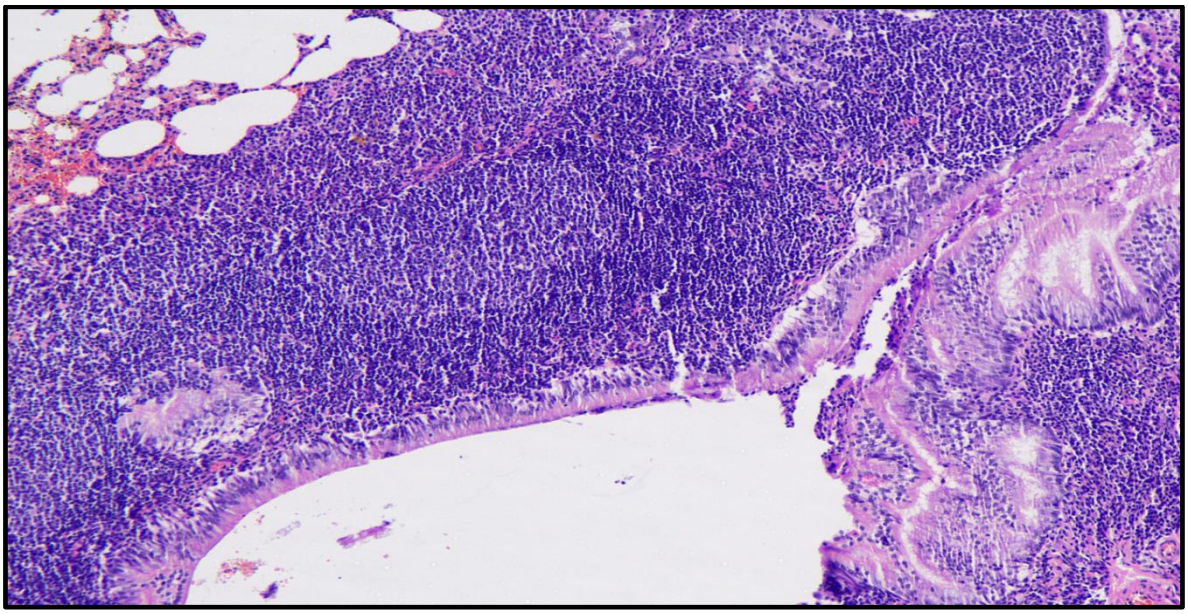

Fig. 7. Severe peribronchial lymphoid hyperplasia in the lung of rats in the application group (Second Study Grup 2 -14 Days Nebulizator). Light microscopy, HE X100.

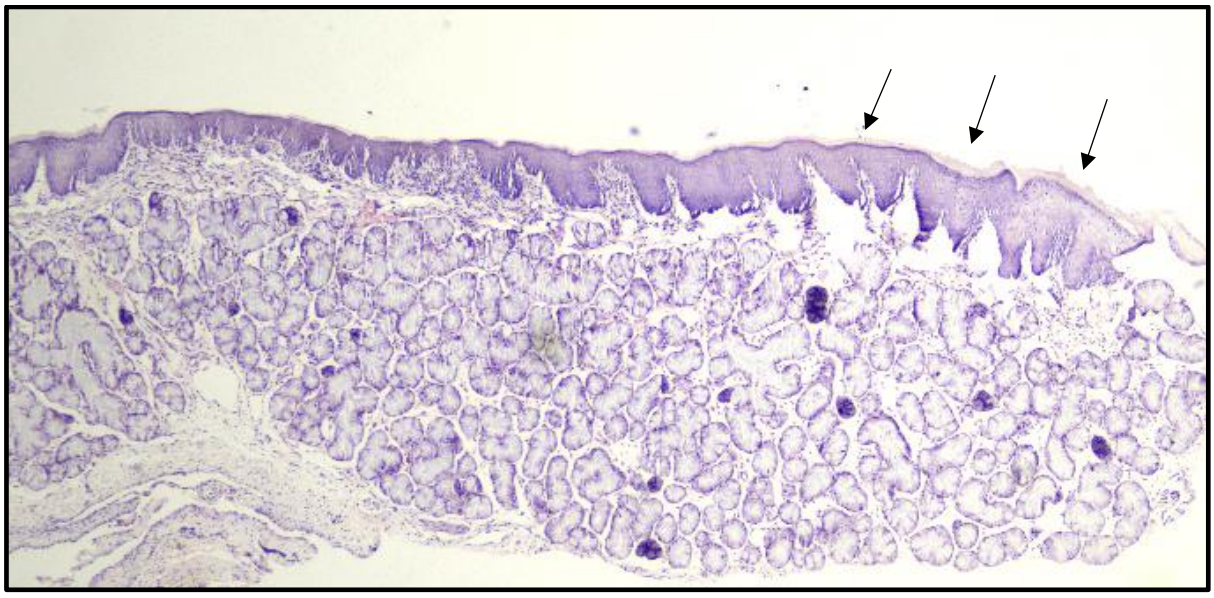

Fig. 8. Mild squamous hyperplasia of the oral mucosa of rats in the application group (Arrows). (Second Study Grup 2 -14 Days Nebulizator). Light microscopy, HE X40.

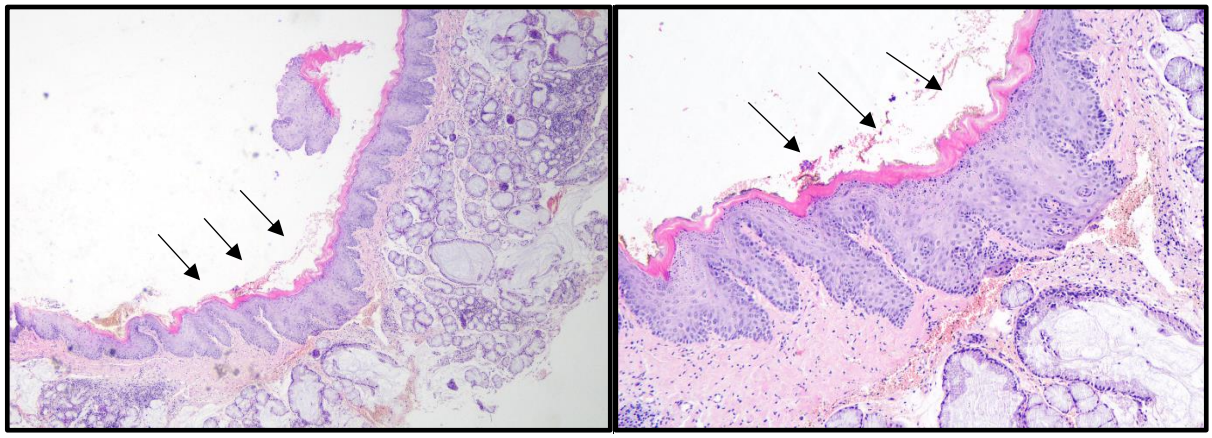

Fig. 9. Severe squamous hyperplasia of the oral mucosa of rats in the application group(Arrows). (Second Study Grup 2 -14 Days Nebulizator). Light microscopy, HE X40 and X100.

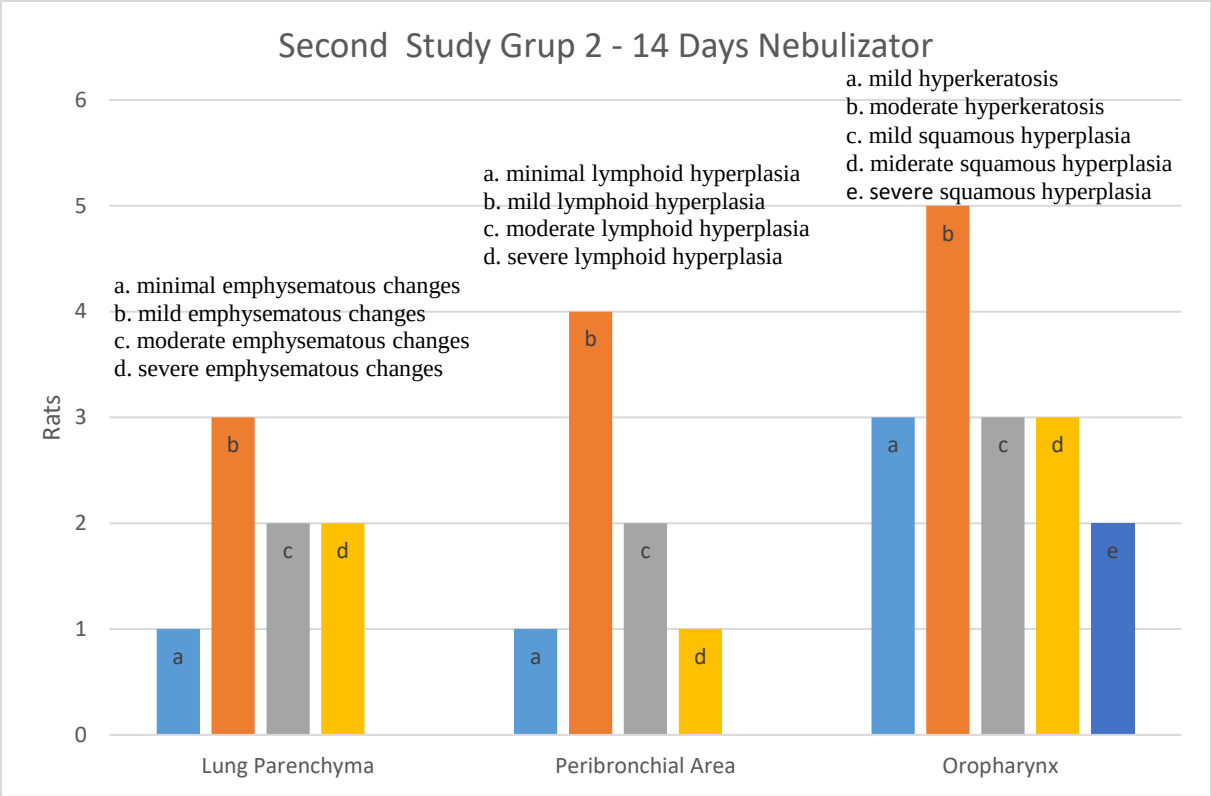

Table 4. Second Study Grup 2 -14 Days Nebulizator

Third Study

In the group 1 (toxicity/nebulizator - sacrificed on the same day); focal emphysematous changes of the lung were observed in all 4 subjects. Besides, mild peribronchial lymphoid hyperplasia was observed in 3 subjects and moderate peribronchial lymphoid hyperplasia in 1 subject. Mild squamous hyperplasia of the oropharynx was observed in 3 subjects and diffuse squamous hyperplasia was observed in 1 subject (Table 5).

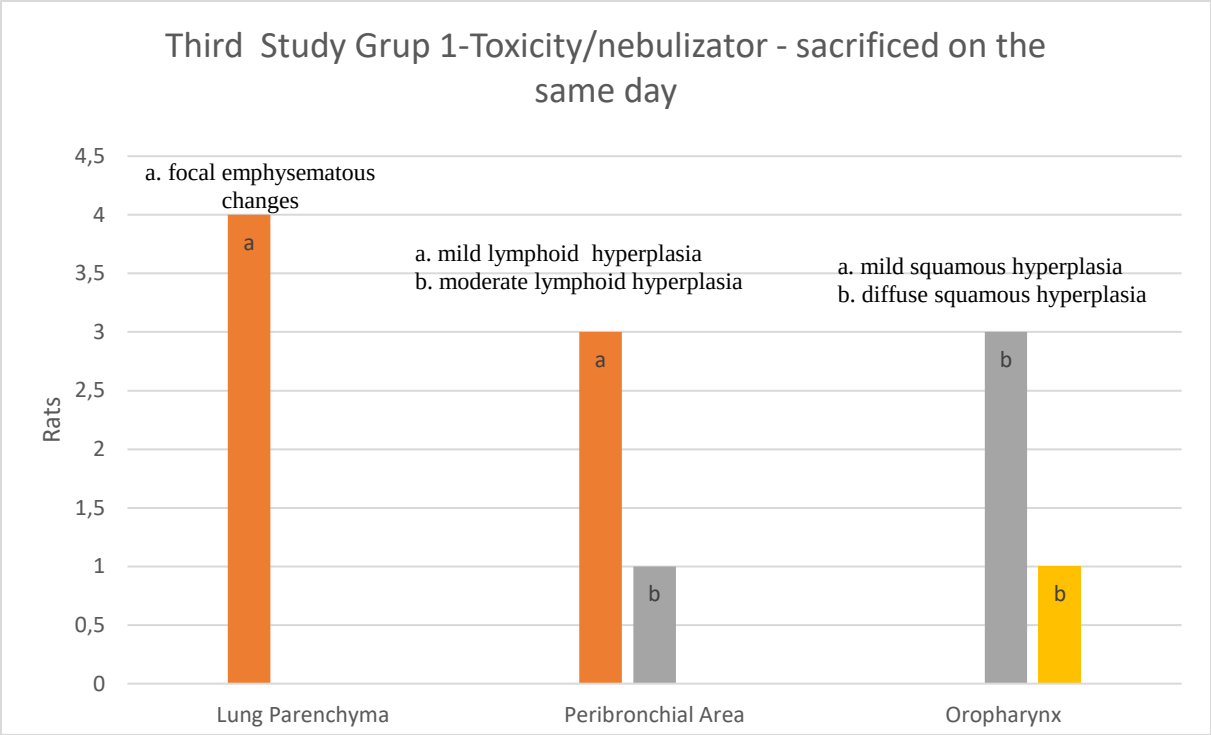

Table 5. Third Study Grup 1-Toxicity/nebulizator - sacrificed on the same day

In the 2nd group (7 days with nebulizator - sacrificed on the same day); focal emphysematous changes of the lung and mild peribronchial lymphoid hyperplasia were observed in all 4 subjects. In terms of oropharynx results; minimal squamous hyperplasia was observed in 3 subjects (Table 6).

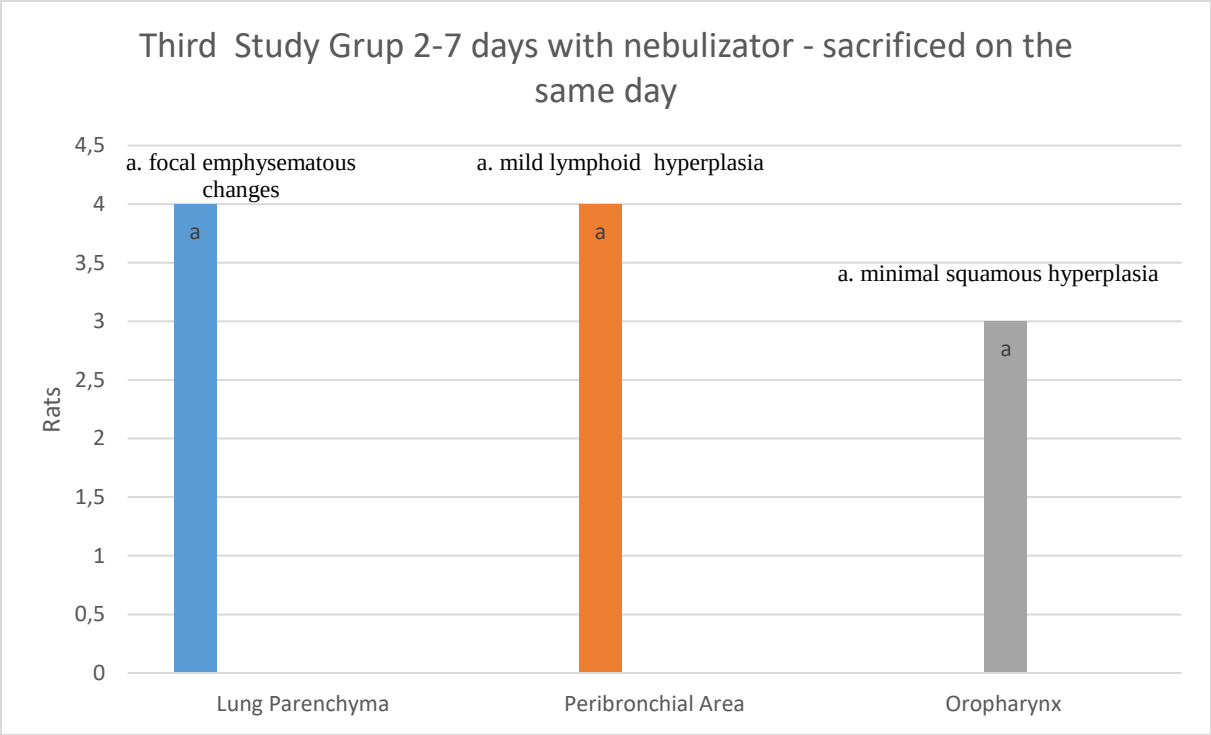

Table 6. Third Study Grup 2-7 days with nebulizator - sacrificed on the same day

In the group 3 (control-sacrificed on the same day); minimal peribronchial lymphoid hyperplasia of the lung was observed in 3 subjects. No pathological findings were observed in oropharymx examination (Table 7).

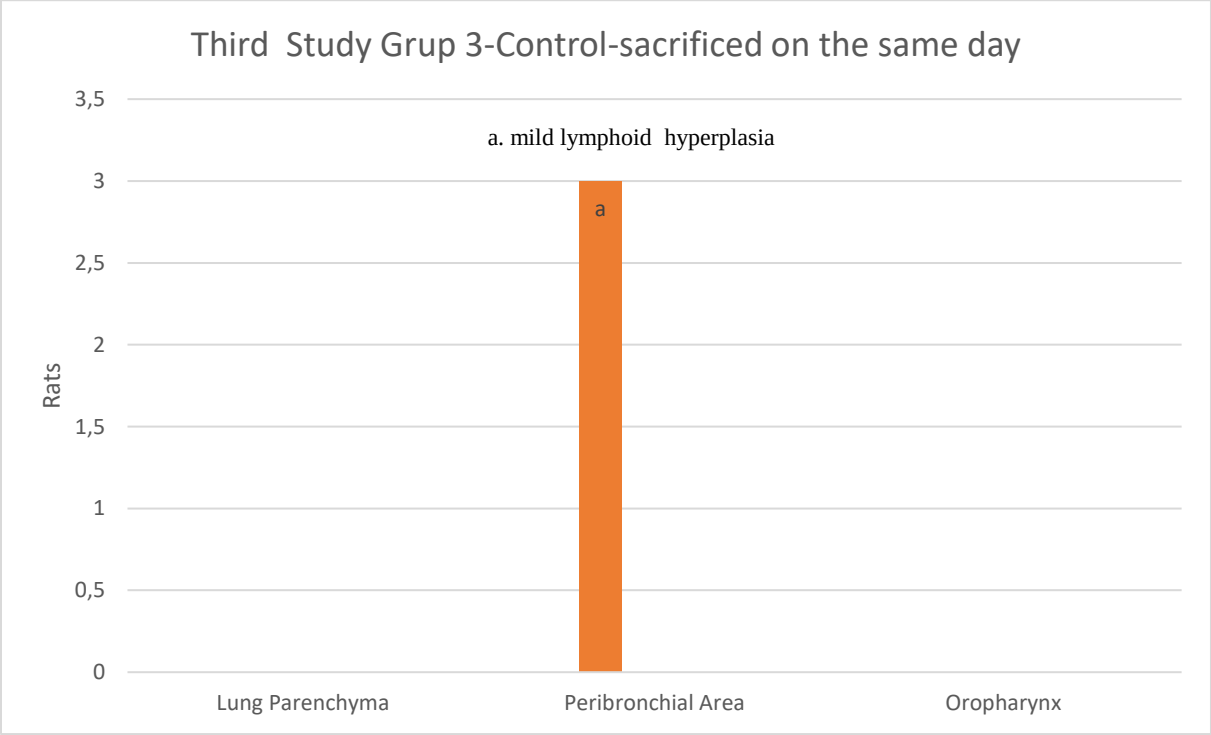

Table 7. Third Study Grup 3-Control-sacrificed on the same day

In the group 4 (toxicity/nebulizator - sacrificed after 14 days); minimal emphysematous changes of the lung were observed in 2 subjects and moderate in 1 subject. In addition, moderate peribronchial lymphoid hyperplasia was observed in 1 subject. In the examination of the oropharynx, minimal focal hyperplasia was observed in 2 subjects and moderate squamous hyperplasia was observed in 2 subjects (Table 8).

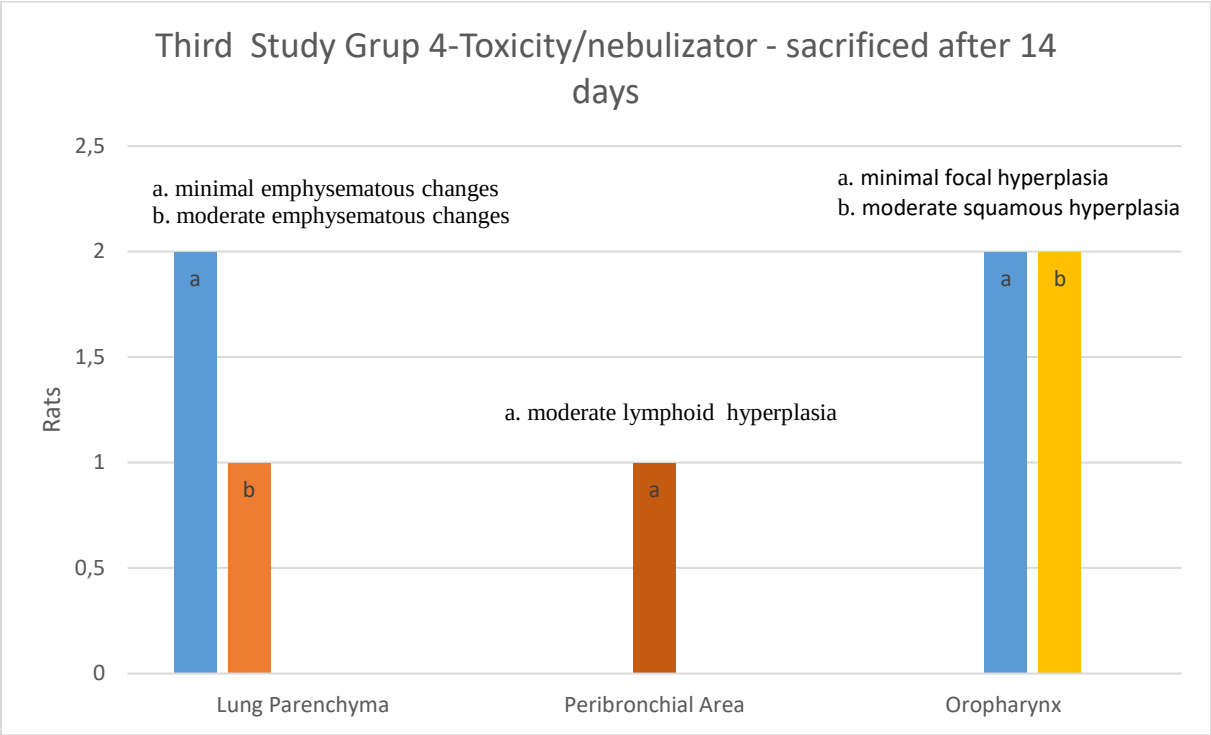

Table 8. Third Study Grup 4-Toxicity/nebulizator - sacrificed after 14 days

In the 5th group (7 days of nebulizator – sacrificing followed by 7th day of last intervention); focal minimal changes of the lung were observed in 2 subjects, focal moderate in 1 subject, and focal severe emphysematous changes in 1 subject. In addition, mild peribronchial lymphoid hyperplasia of the lung was observed in 3 subjects and moderate in 1 subject. Focal minimal hyperplasia of oropharynx was observed in 2 subjects and moderate squamous hyperplasia was observed in 2 subjects (Table 9).

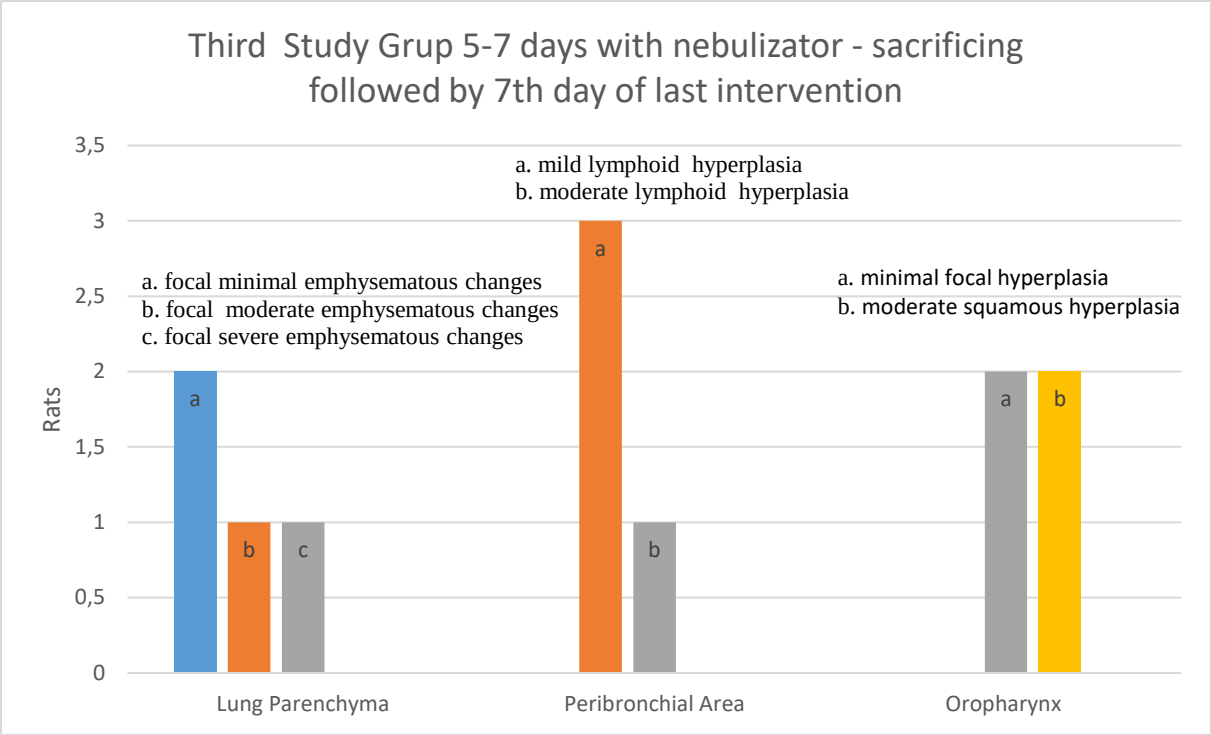

Table 9. Third Study Grup 5-7 days with nebulizator - sacrificing followed by 7th day of last intervention

In the group 6 (control- sacrificed in the 7th day of selection); focal minimal emphysematous changes of the lung were observed in all 4 subjects. In addition, minimal peribronchial lymphoid hyperplasia was observed in 3 subjects. In terms of the oropharyngeal examination, focal minimal squamous hyperplasia was observed in all 4 subjects (Table 10).

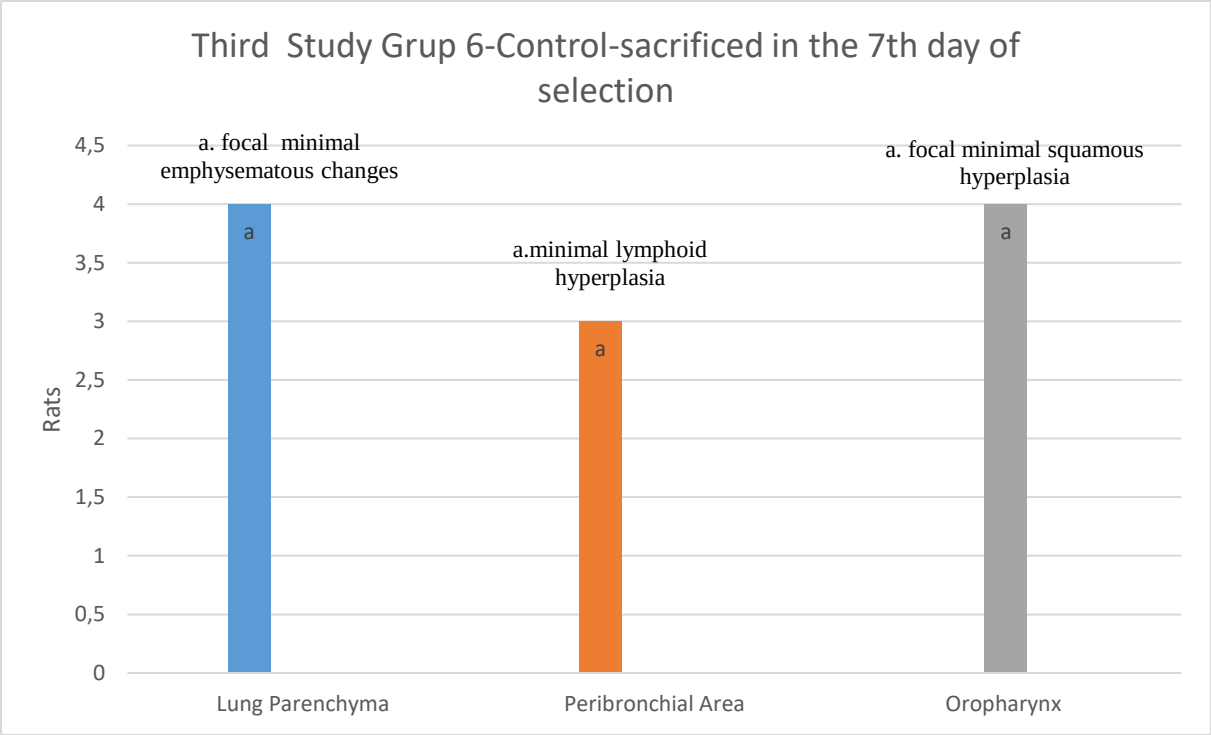

Table 10. Third Study Grup 6-Control-sacrificed in the 7th day of selection

DISCUSSION

Alveoli are small, thin-walled air sacs found in clusters at the end of the bronchi in the lungs. When you breathe in air, the alveoli stretch, pulling in oxygen and carrying it into the blood. When you exhale, the alveoli shrink, forcing carbon dioxide out of the body. Emphysema is damage to the walls of the air sacs (alveoli) of the lung. When emphysema develops, alveoli and lung tissue are destroyed. With this damage, the alveoli cannot support the bronchial tubes. The bronchi collapse, causing an obstruction that keeps air inside the lungs. Also, because there are fewer alveoli, less oxygen will be able to enter the bloodstream (10).

The results of our studies showed that some pathological changes such as emphysematous changes, peribronchial lymphoid hyperplasia and squamous hyperplasia develop on the lung tissue and oropharyngeal mucosa ~~by~~ as a result of oral and respiratory administration of the anionic oxygen active substance ~~on~~ to the animals (7). However, in subsequent studies, it ~~is~~ was demonstrated that the severity and frequency of the pathological changes and the affected subjects decrease with the reduction of the intervention time and the amount of anionic oxygen given. The mild pathological changes that developed in the control groups of the 1st and 3rd

studies indicate that independent factors of which have effects on these pathological alterations, may exist and vary.

In terms of side effect profile assessment, that the doses administered to rats were are too high in weight compared to humans. The fact that none of the rats did not die as a result of toxicity and the mentioned pathologies and did not show toxicity symptoms during the administraion of anionic oxygen. These studies could provide some information that a safe use and dosing profile of the active substance can be developed in humans. In addition, according to the life cycle of the subjects, the duration of the application of the active substance, excluding the toxicity application, corresponds to 210 to 630 days, considering the weight / mass ratios, 4cc / day / 300 g = one in 75, which corresponds to 1000cc per day in a person with an average weight of 75 kg It is equivalent to 210,000 to 630,000 cc for humans, which is considered to support studies that it can be used at much lower doses and in an appropriate time (9). In laboratory analysis, the fact that the product in 1cc volume kills 10,000,000 virus units in less than 1 minute reinforces this opinion. (5)

With regard to pathological findings detected in animals by the use of inhaled anionic oxygen, it might be considered that they may occurred as a result of local immune reaction of the lung and oropharynx. Owing to the previous microbological and physiochemical studies, anionic oxygen has biocidal and immune-related effect on the living tissues. In particular, the development of peribronchial lymphoid hyperplasia was thought to be the result of T-lymphocyte activity and increased cellular defence mechanism of the lungs induced by the anionic oxygen. This effect might result in the emergence of free oxygen radicals in the tissue of the rats when using higher doses of the anionic oxygen leading to the emphysema and peribronchial lymphoid hyperplasia. It is therefore considered that such effects in a living tissue subjected to the anionic oxygen might be related to lymphocyte activity and cellular immune response.

During the first study, wounds developed on the bilateral cheeks of 2 subjects due to local irritation, and the solution was applied unilaterally on the wound of these 2 subjects, and it was observed that the wound on the applied side healed earlier than the non-applied side. Based on this subjective observation, we believe that the active substance may also support animal or human studies on open wounds of the skin and mucous membranes.

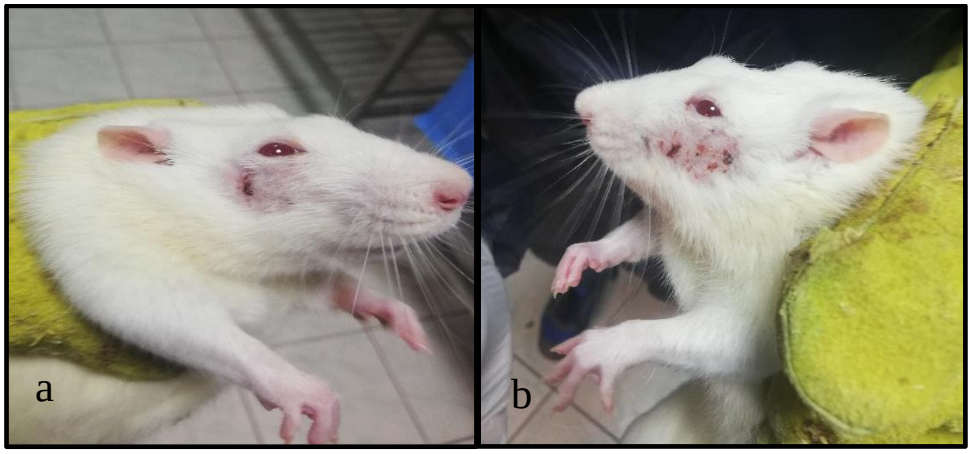

Fig. 10. The condition of the wound on the 5th day of the rats with a wound on the cheek. Better healing is observed on the side that is applied topically anionic oxygen (a).

Consequently, this study which was designed for rats with very high doses and administration times showed that further studies are warranted to determine the dose and side effect profiles for human.

CONCLUSION

Given above described results and observations, related formulation seems to exert a TH2 immuno response capable of initiating a T cell mediated counter response to the acutely elevated oxidation signaling triggered by the formula, thus exhibiting a potent immunostimulant and indirect antiviral effect while minimizing the risk of a potential immunostimulation related cytokine storm hence the efficient antiviral effect. New studies should be developed by consideringthe results of this study, and these data could be used forpreliminary purposes of further studies and medical purposes.

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Effects of Oral and Inhaled Anionic Oxygen on Parenchymal Organs and Oropharyngeal Mucosa of Male Sprague-Dawley Rats

Mustafa Gerek[1], Salih Bağlıcakoğlu[1], Okan Ali Aksoy[2], Erdal Can Alkoçlar[3], Mehmet Burak Aşık[1], Fuat Atabay[4], Murat Demiriz[4], Onur Erdem[5], Cevdet Erdöl[6]

[1]**MG,** Professor, Gülhane Medical School, Department of Otolaryngology, Head and Neck Surgery, University of Health Sciences Turkey, Ankara, Turkey

[1]**SB,** Resident, Gülhane Medical School, Department of Otolaryngology, Head and Neck Surgery, University of Health Sciences Turkey, Ankara, Turkey

[1]**BAA,** Associate Professor Gülhane Medical School, Department of Otolaryngology, Head and Neck Surgery, University of Health Sciences Turkey, Ankara, Turkey

[2]**ECA,** Innovation Director, MAS Pharmaceutical Company, Istanbul, Turkey

[3]**AOA,** Assistant Professor, Gülhane Medical School, Department of Animal Experiments and Research Centre, University of Health Sciences Turkey, Ankara, Turkey

[4]**FA,** Assistant Professor Gülhane Medical School, Department of Pathology, Ankara, Turkey

[4]**MD,** Professor Gülhane Medical School, Department of Pathology, Ankara, Turkey

[5]**OE**, Professor, Gülhane Pharymacy School, University of Health Sciences Turkey, Ankara, Turkey

[6]**CE,** Professor and Rector, University of Health Sciences Turkey, Ankara, Turkey

Corresponding Author: Mustafa Gerek, M.D., Professor and Chairman, Gülhane Medical School, Department of Otolaryngology, Head and Neck Surgery, University of Health Sciences Turkey, Ankara, Turkey

Telephone number: +9 0 312 304 57 01

e-mail: mgerek@gmail.com

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