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THE DYNAMICS OF HISTOMORPHOLOGICAL CHANGES IN ACUTE BACLOFEN POISONING

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ABSTRACT

Aim: to assess the dynamics of histolological changes in the lung under acute baclofen poisoning.

Materials and methods: The study was performed on 20 male Wistar rats weighing 200-215 g and aged 20 weeks. The animals were divided into four groups (5 animals in each) – controls, group 1 (baclofen, 3h.), group 2 (baclofen, 4,5 h.) and group 3 (baclofen, 24 h.).

Results: The thickness of intraalveolar septi in group 1 (baclofen, 3 h.) was considerably lower than in the group of controls. 4,5 hours after baclofen administration the thickness of intraalveolar septa was significantly higher than in group 1 (baclofen, 3 h.) and in the group of controls. 24 hours after baclofen administration the thickness of intraalveolar septa was significantly higher than in group 1 (baclofen, 3 h.) and in the group of controls. The diameter of the alveoli was considerably higher in all study groups than in the group of controls. The diameter of the alveoli 3 hours after baclofen administration was higher than 4,5 and 24 hours after baclofen administration, but the difference was not significant.

Conclusion: In baclofen poisoning, a certain complex of general pathological processes in lungs develops. It includes circulatory disorders, increased vascular permeability, infiltration of intraaveolar septa. The quantitive assessment of the changes can be used to assess the severity of general pathological process in acute baclofen poisonings and to determine the exact time of the poisoning.

Keywords: *baclofen, acute poisoning, lungs, histological alterations, morphometry*.

INTRODUCTION

Baclofen (also known as Baclosan, Lioresal - beta-[4-chlorophenyl]-GABA) is a chlorophenyl derivative of gamma-aminobutyric acid (GABA), which is a naturally occurring inhibitory neurotransmitter in the brain and spinal cord [1,2].

The drug is an agonist at the beta subunit of gamma-aminobutyric acid on mono and polysynaptic neurons at the spinal cord level and brain [3,4]. The drug is thought to reduce the release of excitatory neurotransmitters in the pre-synaptic neurons; it stimulates inhibitory neuronal signals in the post-synaptic neurons with resultant relief of spasticity. Baclofen is also found to have an affinity for voltage-gated

calcium channels. However, its clinical efficacy in this regard remains unclear [1,2].

Baclofen has a proven therapeutic value in managing reversible spasticity, particularly for the relief of flexor spasms, clonus, and concomitant pain, common sequelae of spinal cord lesions, and multiple sclerosis [5]. The recommended oral dose of baclofen is 5 mg, which can be carefully increased. The total daily dose of this drug should not exceed 80 mg. Baclofen also has several off-label uses. For example, it is used for the treatment of intractable hiccups.

The aim of the study is to assess the dynamics of histolological alterations in the lungs in case of baclofen poisoning.

MATERIALS AND METHODS

The study was performed on 20 male Wistar rats weighing 200-215 g. and aged 20 weeks.

Keeping animals and working with them were performed in accordance with the Directive 2010/63/EU of the European Parliament and of the Council of the European Union on the protection of animals used for scientific purposes.

The animals were divided into four groups (5 animals in each):

- Controls (n=5) – animals that did not receive either baclofen or ethanol.
- Group 1 (n=5) – animals treated with baclofen at a dose of 85 mg/kg, the duration of the experiment was 3 hours.
- Group 2 (n=5) – animals treated with baclofen at a dose of 85 mg/kg, the duration of the experiment was 4,5 hours.
- Group 3 (n=5) – animals treated with baclofen at a dose of 85 mg/kg, the duration of the experiment was 24 hours.

The animals of the study groups were euthanized by displacement of cervical vertebrae 3, 4,5 and 24 hours, respectively.

The lungs of the rats were fixated in 10% neutral formalin, the samples were embedded in paraffin. We prepared histological sections of 5 μm thickness, placed them on slides and stained with hematoxylin and eosin. We examined the sections by light microscopy using a Nikon Eclipse E-400 microscope with a video system based on a Watec 221S camera (Japan) at ×400 magnification.

We measured the diameter of alveoli, the thickness of intraalveolar septa, the diameter of venules and arterioles.

RESULTS

No pathological changes were observed in the lungs of the rats of the control group. Moderate plethora of venules was found. There were no signs of emphysema. The bronchial lumen was free. Signs of edema (periarterial, perivenular) were absent. No circulatory disorders were observed.

Three hours after baclofen administration at a dose of 85 mg/kg (group 1), the development of venous and capillary plethora was observed; emphysema was found, atelectases and distelectases appeared, cellular reaction (infiltration of intraalveolar septa by WBCs) were discovered. The interalveolar septa were thickened due to edema.

4,5 hours after baclofen administration (group 2), circulatory disorders (arterial, venous, capillary plethora, sludge, hemorrhages in the interalveolar septa) were present, which was observed neither in the group of controls, nor in group 1. Atelectases, distelectases located mainly subpleurally, thickening of the interalveolar septa due to edema were found. In areas of emphysema, the interalveolar septa were thinned.

24 hours after baclofen administration, the development of venous, arterial plethora, sludge, hemorrhages in the interalveolar septa was observed. The presence of atelectasis and distelectasis, thickening of the interalveolar septa due to edema, the appearance of emphysema were also noted.

We performed a morphometric study. We measured the thickness of intraalveolar septa and the diameter of the alveoli. The results of the morphometric study are presented in table 1 and table 2.

Table 1. The thickness of intraaveolar septa after baclofen administration

	Controls	Group 1 (baclofen, 3	Group 2 (baclofen, 4,5	Group 3 (baclofen,24

		h.)	h.)	h.)
Thickness of intraalveolar septa, μm	7,74 (6,23; 9,27)	4,32* (3,82; 5,08)	15,4*^ (13,6; 17,9)	15,9*^ (13,9; 18,4)

*Note: * - p<0,01 – in relation to controls; ^ - p<0,01 in relation to group 1.*

The thickness of intraalveolar septa in group 1 (baclofen, 3 h.) was considerably lower than in the group of controls. 4,5 hours after baclofen administration the thickness of intraalveolar septa was significantly higher than in group 1 (baclofen, 3 h.) and in the group of controls. 24 hours after baclofen administration the thickness of intraalveolar septa was significantly higher than in group 1 (baclofen, 3 h.) and in the group of controls.

Table 2. Diameter of alveoli after baclofen administration

	Controls	Group 1 (baclofen, 3 h.)	Group 2 (baclofen, 4,5 h.)	Group 3 (baclofen,24 h.)
Diameter of alveoli, μm	41,45 (35,18; 51,6)	70,2* (54,03; 86,25)	64,25* (55,58; 74,95)	60,10* (52,05; 70,55)

*Note: * - p<0,01 – in relation to controls; ^ - p<0,01 in relation to group 1.*

The diameter of the alveoli was considerably higher in all study groups than in the group of controls. The diameter of the alveoli 3 hours after baclofen administration was higher than 4,5 and 24 hours after baclofen administration, but the difference was not significant.

Baclofen is known not to have any direct toxic effect on the bronchi and lungs. However, the drug is known to increase the presynaptic blockade of nerve impulses, which originate in the spinal cord, and to inhibit their transmission. The tone of muscles, including the intercostal ones, decreases. The excessive relaxation of these muscles can cause breathing difficulties followed by hypoxia. GABA A receptor agonists are known to cause contraction of bronchial and bronchiolar smooth muscles accompanied by spasm and breathing difficulties [6]. Baclofen is known to be a selective agonist of GABA B receptors, but at high enough doses is also capable of stimulating GABA A receptors [7].

An increase in the diameter of the aveoli can be explained by the compensatory reaction to developing hypoxia. Developing hypoxia causes an increase in vascular-tissue permability followed by edema. Within our study we observed thickening of intraalveolar septa, which may occur due to increased permeability of microcirculatory vessels caused by hypoxia.

CONCLUSION

In baclofen poisoning, a certain complex of general pathological processes in lungs develops. It includes circulatory disorders, increased vascular permeability, infiltration of intraaveolar septa. The quantitive assessment of the changes can be used to assess the severity of general pathological process in acute baclofen poisonings and to determine the exact time of the poisonings.

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