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THE EFFECTS OF BACLOFEN ON THE RESPIRATORY SYSTEM

***Olga Romanova*[1,2], *Pavel Dzhuvalyakov*[2], *Evgeniy Barinov*[1,3], *Maxim Kislov*[4], *Anton Ershov*[5]**

[1]*RUDN University, Moscow, Russia*
[2]*A.P.Avtsyn research institute of human morphology, Moscow, Russia*
[3]*A.I.Yevdokimov Moscow State University of Medicine and Dentistry, Moscow, Russia*
[4]*Sechenov First Moscow State Medical University, Moscow, Russia*
[5]*Federal Research and Clinical Center of Intensive Care Medicine and Rehabilitology, Moscow, Russia*

olgpharm@yandex.ru

ABSTRACT

Baclofen is a muscle relaxant. Due to its pronounced psychotropic effect the drug is often a subject of abuse especially among young people. The article deals with the dynamics of respiratory movement rate and lung histopathology in acute baclofen poisoning. The experimental studies were performed on 20 Wistar rats. The animals were divided into 4 groups (the controls and three experimental groups). The controls included 5 intact rats. The experimental groups included 5 animals each. All of them were treated with baclofen at a dosage of 85 mg/kg. The duration of the experiment was 3, 4,5 and 24 hours, respectively. The frequency of respiratory movements after baclofen intoxication decreased by the 3rd hour insignificantly. Then it increased significantly by the 4,5 hour if compared to the controls and the 3rd hour. Then, by the 24th hour, the frequency of respiratory movements decreased significantly if compared to all the other groups. Within histological study we revealed a complex of pathological changes in the lungs of the rats (circulatory disorders in all the elements of the microcirculatory bed (plethora of capillaries, venules), areas of emphysema, atelectasis and dystelectasis, WBC infiltration of intraalveolar septa and thickening of intraalveolar septa due to edema. Understanding the processes that occur in the lungs after baclofen poisoning will help to improve medical care in these cases. *The results of histological study along with the results of chemical analysis will be useful in establishing the fact of baclofen intoxication and the exact moment of the intoxication.*

Keywords: baclofen, lungs, histologic changes, poisoning

INTRODUCTION

Baclofen is widely used in clinical practice. This drug is a gamma-aminobutyric acid (GABA) agonist which is used as a skeletal muscle relaxant [1,2]. The mechanism of baclofen action still remains unclear. The drug has been shown to inhibit monosynaptic and polysynaptic reflexes, reduce excitability of gamma-motoneurons, which causes myorelaxant effect [1]. Baclofen is indicated in muscle pain, spasms, stiffness in case of multiple sclerosis or spinal cord injury or disease [3]. Baclofen was investigated for use in alcohol dependence [4-7] and withdrawal syndrome [8]. Still the evidence is limited and there is inconsistent data to suggest its clinical efficacy in managing alcohol dependence or withdrawal symptoms [4-8]. Further investigations are required. Having a pronounced psychotropic effect baclofen is often a

subject to abuse. The drug presumably produces physical dependence if used in chronic way. Once physical dependence to baclofen substance occurs, the user cannot stop using the drug abruptly without risking withdrawal symptoms (muscle tremors, anxiety, seizures) [9].

MATERIALS AND METHODS

The objective of the study was to evaluate the dynamics of the respiratory system indexes (frequency of respiratory movements) and the dynamics of lung histopathology in an animal experiment. The study was carried out 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 4 groups. The group of controls included 5 intact rats, three experimental groups included 5 rats treated with baclofen at a dose of 85 mg/kg. The frequency of respiratory movements was recorded after 3, 4,5 and 24 hours, respectively. Analysis of respiratory movements frequency was carried out using the RSM physiological indicators monitoring system with MouseMonitorS software (Indus Instruments, USA). Then the animals were euthanized by displacement of the cervical vertebrae. Their lungs were fixated in 10% neutral formalin and the samples were embedded in paraffin. Histological sections of 5 μm thickness were prepared, placed on slides and stained with hematoxylin and eosin. Then the sections were examined by light microscopy using a Nikon Eclipse E-400 microscope with a video system based on a Watec 221S camera (Japan) at ×400 magnification. The following signs were assessed: circulatory disorders (capillary and venular plethora, hemorrhages in interalveolar septa, hemorrhages in alveoli, sludge), atelectasis, emphysema, cellular response (increased WBCs in interalveolar septa), epithelial desquamation in the bronchial lumen. Fisher's criterion was used to assess the significance of a particular histological sign. The sign was considered to be significant if it was absent in one group and appeared in 4 or 5 cases in the other. The results of the study were processed using MS Excel and StatSoft STATISTICA 10.0.1011 Eneterpise (x86/x64)

RESULTS AND DISCUSSION

The results of respiratory movements frequency measurement are presented in table 1. The frequency of respiratory movements decreased by the 3rd hour if compared to the controls, however the difference was insignificant Then the frequency of respiratory movements increased significantly by the 4,5 hour if compared to the controls and the 3rd hour. Then, by the 24th hour, the frequency of respiratory movements decreased significantly if compared to all the other groups. The effects occurred due to a decrease in the tone of the respiratory muscles under the influence of baclofen which was followed by breathlessness.

Table 1The frequency of respiratory movements under effect of baclofen

Group	Controls	Experimental group 1 (baclofen, 3 hrs.)	Experimental group 2 (baclofen, 4,5 hrs.)	Experimental group 3 (baclofen, 24 hrs)
The frequency of respiratory movements per minute	66	64	85	52
	60	65	90	54
	62	70	88	60
	64	62	89	61
	65	60	90	55

**The difference between the controls and experimental group 1 is not significant (p>0,05); the difference between the controls, experimental group 2 and experimental group 3 is significant (p>0,05); the difference between experimental group 1, group 2, group 3 are significant (p>0,05).*

Then histological signs in the lungs of the rats were investigated. No histopathological changes in the

lungs were observed in animals of the control group. Three hours after administration of baclofen (85 mg/kg), circulatory disorders such as venular and capillary plethora, sludge, emphysema, atelectasis and cellular response (WBC infiltration of interalveolar septa), as well as thickening of interalveolar septa due to edema were considered to be significant. Four and half hours after baclofen administration circulatory disorders, such as venular and capillary plethora, sludge, intraalveolar hemorrhages (which were not found 3 hours after baclofen administration) were also detected. We also observed emphysema, atelectasis and cellular response (WBC infiltration of interalveolar septa), thickening of interalveolar septa due to edema were considered significant. 24 hours after baclofen administration we also observed emphysema in the lungs of experimental animals. The presence of distelectases, areas of thickening of the interalveolar septa (due to edema) was also significant, as well as circulatory disorders (capillary, venular plethora, a significant number of hemorrhages in the interalveolar septa). We also revealed hemorrhages in the alveoli and desquamation of the epithelium into the bronchi which was not observed 3 or 4,5 hours after baclofen administration (Figure 1).

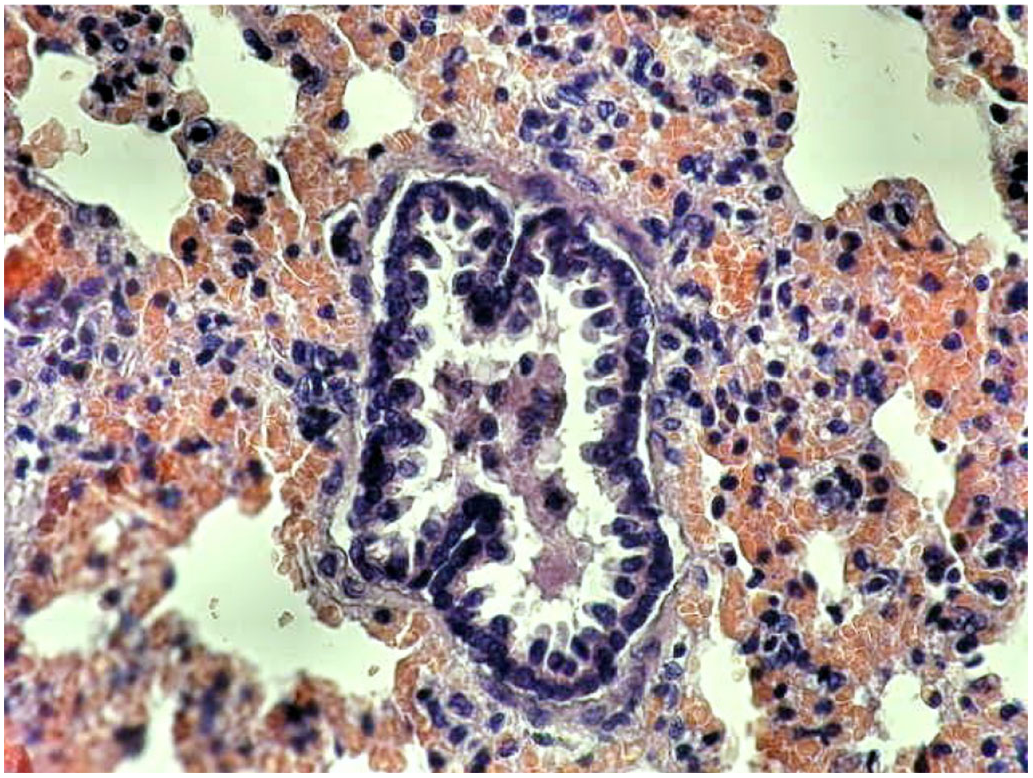

Figure 1. Rat lung. 24 hours after baclofen administration. Intraalveolar hemorrhages, WBC infiltration of intraalveolar septa, desquamation of epithelium in the lumen of the bronchioli

DISCUSSION

Baclofen has no direct toxic effect on the bronchi and lungs. However, the drug increases presynaptic blockade of nerve impulses originating in the spinal cord, which inhibits their transmission. As a result, the tone of muscles, including the intercostal ones, decreases. Their excessive relaxation can lead to breathing difficulties followed by hypoxia, which we observed in our study (the increase of respiratory movement frequency followed by breathlessness). Besides, the effects of GABA receptor stimulation on bronchial smooth muscles and lungs are worth special attention. According to the literature, GABA A receptor agonists cause bronchial contraction accompanied by spasm and breathing difficulties [10-11]. Although baclofen is a selective agonist of GABA B receptors, it can also cause stimulation of GABA A receptors at high doses. This effect was observed in all experimental groups. Emphysema was observed in the lungs of the experimental animals in all groups.

CONCLUSION

Understanding the processes that occur in the lungs after baclofen poisoning will help to improve medical care in these cases. The results of histological study along with the results of chemical analysis will be useful in establishing the fact of baclofen intoxication and the exact moment of the intoxication.

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