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RESEARCH ARTICLE

Pharmacological effect of Berotek and the leading mechanisms of Lung Pathology in miners Central Kazakhstan

Chergizova B.[1], Kharisova N.[1], Mkhitaryan X.[1], Ryspayeva G.[1], Akhmetova M.[1], Smirnova L.[2], Ishigov I.[3], Tatykayeva U.[3], Tastanova G.[3], Zhumabekova R.[3]
[1]Karaganda Medical University" NCJSC, Karaganda, Kazakhstan.
[2]Kazan State Medical University, Kazan, Tatarstan, Russia.
[3]Khoja Akhmet Yassawi International Kazakh-Turkish University, Turkistan, Kazakhstan.
*Corresponding Author E-mail: **harisova_nuriya@list.ru**, **Mhitaryan@qmu.kz**

ABSTRACT:
In modern production conditions, industrial aerosols are still among the most common harmful occupational factors that determine the increased risk of developing occupational respiratory diseases among workers at industrial enterprises. The dust respiratory diseases are significantly common among workers in the mining and coal industries of Kazakhstan. In recent years, there has been a clear increase in the incidence of chronic dust bronchitis. The particular attention should be paid to such types of metal dust as dust of beryllium, vanadium, molybdenum, tungsten, cobalt and their compounds, under the influence of which not only peculiar damage to the lungs are observed, but also pronounced changes in other organs and systems. Dust of these metals, according to numerous authors, has a general toxic and toxic-allergic effect. An urgent problem of modern occupational medicine is the study of the role of exogenous and endogenous factors in the development of occupational pathology of the bronchopulmonary system. To identify groups at increased risk of developing dust pathology of the bronchopulmonary system, it is necessary to comprehensively study clinical and genetic factors, as well as determine the most significant diagnostic markers for the development of this pathology. An important advantage of inhaled anticholinergic drugs is the minimal frequency and severity of adverse events.The broncholytic effect is expressed in the form of inhibition of phosphodiesterase isoforms with a further increase in intracellular cAMP content and relaxation of smooth muscles of the respiratory tract. Immunomodulatory and anti-inflammatory effects of bronchodilators have also been established.

KEYWORDS: Chronic bronchitis, silicosis, emphysema of the lungs, obstruction, polymetallic dust, bronchodilators, corrective effect, airway patency, inhalation effect.

INTRODUCTION:
According to recent researches[1,2,3,4], notes that loss of workability in workers due to occupational dust lung diseases occurs most often as a result of respiratory dysfunction, as well as associated negative factors.

In this regard, the purpose of the study was to determination of the leading mechanisms of lung patency disorders and the effect of bronchodilators on workers from exposure to polymetallic dust[5,6,7,8].

To achieve this goal, the following tasks were relevant: to study the state of external respiration function in workers with various forms of occupational pathology of the respiratory system and to establish the leading mechanisms in the dynamics of the formation of occupational pathology of the bronchopulmonary apparatus in workers of the Akchatau Mining and Processing Plant (AMPP)[9,10,11].

MATERIALS AND METHODS:
The research methods included sanitary and hygienic measurements at workplaces in the workshops of the Akchatau Mining and Processing Plant (AMPP); assessment of the dispersed composition of dust generated at various stages of enrichment of tungsten-molybdenum-containing ore and research of respiratory

function using an automated spirometric breath analyzer based on the National Center for Occupational Health and Occupational Diseases of the city of Karaganda.

The sanitary and hygienic assessment of dust at workplaces in workshops was based on data from the regional sanitary and epidemiological service (RSES) and the industrial hygiene department of (AMPP). The dispersed composition of the dust formed at various stages of enrichment of tungsten-molybdenum-containing ore consists of particles with a diameter of no more than 5-9microns, the speed of the air stream was 0.3-1.2m/s, which exceeds the maximum permissible standards.

To identify the leading mechanism of pathological disorders of the respiratory tract, pharmacological tests with a bronchodilator were used. The Bronchodilator tests included the adrenergic blocker Berotec B420 containing 0.2mg fenoterol hydrobromide (Berotec) to detect bronchospasm. The Berotec inhalation is the simplest and most reliable method, with high sensitivity (92%) and absolute specificity (100%), which makes it important for the diagnosis of obstructive bronchopulmonary diseases[12,13,14].

This test was carried out in 25miners with uncomplicated silicosis (Si0) and 25 patients with silicosis complicated by chronic obstructive bronchitis (SiBr) before inhalation of fenoterol hydrobromide and 20 minutes after using the drug.

Currently, the clinical picture of dust diseases indicates damage to the lung tissue and respiratory tract with the development of pneumosclerosis or chronic bronchitis, bronchial asthma, as well as various combinations of these forms. At the same time, the physico-chemical characteristics of dust are not taken into account, although it is a complex chemical composition with multifactorial phenomena that act in complex with possible effects of summationor potentiation on the body[15,16].

According to the authors[17] after inhalation priming, a picture of the initial stages of desquamative bronchitis was recorded in the bronchi of rats and a pathological tumor in the middle lobes of the lungs with seals of the lung stroma of an oncological nature was revealed. Sometimes, an accumulation of polymetallic dust particles in the form of rounded formations surrounded by fibroblasts, fibrocytes and macrophages (cellular dust foci) was noted in the adventitial membrane of the bronchi. it can be assumed that polymetallic dust causes a polytropic effect on lung tissue, provokes the formation of tumors of a malignant nature and degeneration of fibrous tissue, cellular dust foci and pronounced subpleural emphysematous zones are formed.

The number of destroyed alveoli increased, and pronounced emphysematous zones formed subpleurally in the lungs of rats. The preserved alveoli acquired a different shape, the blood vessels were characterized by fullness and pronounced perivascular edema.

RESULT AND DISCUSSION:

A modern set of research methods has revealed that harmful production factors are caused by a high pathological concentration of dust and the composition of ore, the main elements of which have a toxic, allergenic and carcinogenic effect, leading to atrophy of the upper respiratory tract and tracheobronchial tree. In the laboratories of the Production Geological Association "Centrkazgeology" a spectral analysis of dust was carried out, 74.3% is SiO_2 and more than 26% heavy metals, the basis is microparticles with a diameter of 5-9 microns, which freely penetrates the alveoli and exerts its pathogenic effect. The speed of the air jet was 0.3-1.2 meters per second, which exceeds the maximum permissible standards. The ore contains heavy carcinogenic metals such as scandium - 0.012g/kg, phosphorus - 0.8g/kg, manganese - 0.8g/kg, titanium - 2.5g/kg, zirconium - 0.15g/kg , tungsten - 0.5g/kg, chromium - 0.04g/kg, nickel - $0.8x10^{-2}$g/kg, germanium - $4x10^{-3}$g/kg, bismuth - 0.05g/kg, beryllium - 0.12g/kg, molybdenum - 0.3g/kg, vanadium - 0.05g/kg, cobalt - 0.02g/kg, strontium - 0.3g/kg and other toxic metals.

The spinographic studies were carried out on 85 miners, of which 30 healthy workers with an average experience of 5-15 years and 55 miners with occupational lung diseases - 30 people (36.5%) with chronic dust bronchitis (CDB), 25 people (63.5%) with chronic obstructive dust bronchitis (CODB), complicated by pulmonary emphysema. Impaired respiratory function was detected in 90.1%, and first-degree pulmonary insufficiency in 70% of cases. In terms of professional affiliation, the group of those examined with CODB was dominated by workers of the main professions - drillers, tunnelers, blasters, scrapers (82%), in the group of CODB - shaft workers, electric mechanics, machinists, blasters (78%).

According to our data and other authors[12,13,14], by modeling the risk of work-related diseases by changing the levels of exposure to the production factor and work experience, it was established that for respiratory diseases, when the existing concentrations of a chemical substance in the air of the working area are reduced to the maximum permissible level, the risk of developing respiratory diseases decreases with 5 years of work experience for the population risk - from 14 cases per year to 6 cases[18]. It is noted that the pathogenesis of bronchial obstruction in dust lung diseases is complex and involves the participation of many factors.

Depending on the severity and totality of pathological changes, various mechanisms of obstruction are observed: 1) the predominance of bronchospasm, 2) the predominance of tracheobronchial dyskinesia, 3) the predominance ofobstruction of the bronchial tree with viscous mucus and sputum, 4) the "valve mechanism".
Analysis of respiratory function showed that the vital capacity of the lungs (VC) in workers with CDB and CODB decreased significantly and amounted to 70,03±2,99% of the proper value (P≤0.001) and 67,10±2,51% (P≤0,001) respectively≤0.001) with a norm of 92,57±3,47% of the proper value. The smallest decrease in vital capacity compared to the control was observed in miners with CODB complicated by pulmonary emphysema (PE) – on the 25,47% of the proper value (P≤0.001) (Table 1).

Table 1. Spirogram indicators in workers with chronic dust bronchitis

Spirographyindicators	Control groupn=30	Group 1 with CDB n=30	Group 2 with CODB +PE n=25
Vital capacity of the lungs (VC, %)	92,57±3,47	70,03±2,99**	67,10±2,51*
Forcedvitalcapacity (FVC, %)	103,05±4,69	75,59±3,24**	70,89±3,13**
Forced inspiratory volume in 1 second (FEV1,%)	96,14±4,51	70,07±3,48**	66,32±3,41**
Tiffnoindex	93,57±1,98	78,11±2,23**	73,07±2,39**
Average volumetric velocity at the level of large and medium bronchi (AVV_{25-75}, %)	90,43±5,55	70,37±5,08**	61,94±4,19*
Average volumetric velocity at the level of small bronchi (AVV_{75-85}, %)	90,60±4,50	71,40±3,43*	64,40±3,73*

Note: *-difference is significant with control (P≤ 0.01)
**-difference is significant with control (P≤ 0.001)

The Forced lung volume significantly decreased in group 2(P≤ 0.001) compared to both group 1 and control values. When analyzing forced exhalation in 1 second, no significant differences were found between workers in groups 1 and 2, but in comparison with the control in the complicated form it was more pronounced. During forced exhalation, as the intrapulmonary volume decreases, dynamic compression of the airways (AW) increases, which causes their critical narrowing and limits the air flow.

Thus, the maximum expiratory flow is determined by the elasticity of the lung tissue (which allows air to pass through the airways and keeps them open), the diameter of the bronchi and the resistance to air flow. The Tiffno index progressively decreased in all workers examined. The Evaluation of indicators characterizing the condition of large and medium-sized bronchi indicated a mild degree of increase in bronchial resistance with the development of chronic bronchitis, regardless of its forms.

The most pronounced decrease in these indicators may indicate a complication of the mechanism of bronchial obstruction, possibly due to the presence of a "valve effect".

As a result of bronchospasm and edematous-inflammatory changes, narrowing of the bronchi occurs and resistance to air movement along the tracheobronchial tree increases both during exhalation and inhalation; reduced tone contributes to greater dynamic compression and tracheobronchial dyskinesia.

One of the components of bronchial obstruction in dust lung diseases is tracheobronchial dyskinesia, caused by the retraction of the attenuated membranous part into the lumen of the trachea and large bronchi and narrowing of the airways during exhalation and coughing.

Dust bronchitis is characterized by predominant diffuse damage to the bronchial tree with the spread of pathological changes in the mucous membrane from the trachea and large bronchi to the small bronchi.

The study of forced expiratory speed indicators along the flow-volume loop confirms a significant decrease in values compared to the control at the level of the proximal bronchi, especially pronounced when dust obstructive bronchitis is complicated by emphysematous disorders: 59.45±5.29 and 58.22±3.74, respectively (P≤0.001) (Table 2).

An analysis of the correlation of respiratory function indicators in miners with CODB has established an increase in the dependence of the FEV1 indicator on air flow speed at the level of the middle bronchi and small bronchi, and the relationship between FEV1 and forced inhalation indicators is increasing.

According to many authors[19,20], types of metal dust containing beryllium, vanadium, molybdenum, tungsten, cobalt or their compounds, when exposed to which not only peculiar lung damage is observed, but also pronounced changes in other organs and systems. The dust of these metals can most likely be classified as a group of substances that have general toxic, toxic-allergic and carcinogenic effects, and also lead to changes at the cellular and genetic level.

Table 2. Speed indicators for the flow-volume loop in workers with chronic dust bronchitis

Spirography indicators	Control groupn=30	Group 1 with CDB n=30	Group 2 with CODB +PE n=25
Maximum volumetric velocity of large bronchi (MVV_{25}, %)	87,05±4,72	59,45±5,29**	58,22±3,74**
Maximum volumetric velocity of the middle bronchi (MVV_{50}, %)	82,19±4,45	66,22±3,90**	52,50±3,75**
Maximum volumetric velocity of small bronchi (MVV_{75}, %)	87,72±3,07	76,24±6,57*	52,60±2,60**
Peakvolumetricvelocity (PVV%)	82,62±5,34	67,85±4,60*	53,46±3,27**
Air flow transit time (AFT, s)	0,90±0,01	1,09±0,03*	1,72±0,09*
Air flow transit time (AFT8, s)	0,27±0,04	0,37±0,03	1,14±0,05**
Air flow transit time (AFT9, s)	0,60±0,05	0,73±0,02*	1,36±0,04**
Maximum inspiratory flow rate (MIR,%)	78,27±3,81	46,40±1,06**	44,00±1,13**

Note: *-difference is significant with control (P≤ 0.01)
**-difference is significant with control (P≤ 0.001)

Similar dynamics of changes in the maximum volumetric velocity at the level of the middle bronchi were revealed regardless of the form of bronchitis and the presence of emphysema; a significant decrease was noted compared to the control in all subjects. This allows doctors and patients to promptly identify possible triggers for asthma attacks, such as allergies or dust, and decide on appropriate treatment.

Peak volumetric velocity along the flow-volume loop is significantly reduced in chronic dust bronchitis by 14,77% (P≤0.01), and in combination with pulmonary emphysema it is aggravated by almost 30% (P≤0.001). The analysis of these indicators confirms the assumption of the predominance of tracheobronchial dyskinesia from the effects of polymetallic mine dust on bronchial patency to a greater extent.

An increase in partial transit time indicates changes in the distal bronchi, especially in complicated forms of bronchitis; this indicator can be used in the diagnosis of early disorders of bronchial obstruction. The most pronounced prolongation of expiratory time in miners with complications of dust pathology indicates a deterioration in the elastic properties of tissue and fibrosis at the level of the distal parts of the lungs, making it possible to understand whether the airway patency is under control or is significantly deteriorating for morphological reasons.

Thus, these speed indicators indicate that they are informative in cases of pronounced morphological changes in bronchopulmonary tissue.

Analyzing the results obtained, it can be assumed that bronchial resistance increases with the development and worsening of obstructive disorders. The nature of emphysema cannot be judged only by a spirogram and a flow-volume loop; one of the most informative methods for characterizing emphysematous disorders of the tracheobronchial tree is to determine the residual volume of the lungs.

The ability of dust to cause the development of fibrosis of lung tissue is largely determined by the physicochemical properties of inhaled dust. In particular, the dispersion of dust is of great importance. Particles with a diameter of more than 10 microns quickly fall out of the aerosol at an increasing speed and are therefore less dangerous for the body, since they are either not contained in the stream of inhaled air at all, or fall out of it before the air reaches the alveoli. Particles deposited on the mucous membrane of the upper respiratory tract are removed by sneezing, blowing your nose, or coughing. A significant part of the dust that enters the bronchi is released from the respiratory tract with the help of ciliated epithelium. Particles ranging in size from 10 to 0.1 microns settle in calm air slowly and at a constant speed. Ultramicroscopic particles, similar to the behavior of gas molecules, are in continuous Brownian motion and practically do not settle at all. It has been proven that fine dust with a diameter of dust particles from 2 to 5 microns is most dangerous to the body. Such dust particles remain suspended in the inhaled air longer and penetrate deeper into the respiratory tract. Consequently, the nature of changes in the lungs caused by dust largely depends on the degree of dispersion.

An increase in the correlation between the patency coefficient of large and medium bronchi and indicators characterizing bronchial patency at all levels of the bronchi was noted. Patency at the level of small bronchi decreased significantly (P≤0.001) and depended on the structure of the residual lung capacity. The dynamics of indicators SOS25-75 and SOS75-85 indicate the increasing influence of the obstructive process at the level of the distal bronchi.

The dynamics of spirogram indicators before and after the use of Berotek (Table 3) led to an improvement in lung volumes in workers with silicosis, air flow patency significantly increased by 12.6% (P≤0.05) at the level of large and medium bronchi, improvement in bronchial patency at the level of small bronchi there was a reversible component.

Table 3. Respiratory function (RF) in workers before and after inhalation of a bronchodilator.

Indicators FIR	Workers with silicosisSi0 before and after inhalation	Workers with complicated silicosisSiBr before and after inhalation
vitalcapacity VC	80,13±3,00/ 87,90±4,14	63,59±4,94/ 77,90±4,14**
FVC	85,10±3,13/ 96,69±3,77*	74,50±3,84/ 95,85±3,77**
FEV1	84,29±3,11/ 94,48±3,56**	52,00±4,24/ 73,16±4,95***
Tiffnoindex	80,82±2,76/ 86,88±3,83	58,60±2,83/ 75,50±3,13**
MOS25	71,27±3,22/ 86,38±3,02**	26,50±2,77/ 43,00±2,78**
MOS50	73,18±4,01/ 83,50±3,89**	41,50±3,18/ 58,00±3,54*
MOS75	64,09±4,37/ 70,30±3,30**	59,42±3,44/ 71,75±3,66**
SOS25-75	75,18±5,05/ 87,57±4,35**	66,90±2,66/ 81,25±2,50*
SOS75-85	72,09±3,40/ 84,69±4,24**	73,33±4,63/ 88,50±4,24

Note: * - the difference is significant (P≤ 0.01), ** - the difference is significant (P≤0.05),
***- the difference is significant (P≤0.001)

One of the components of bronchial obstruction in dust lung diseases is tracheobronchial dyskinesia, caused by the retraction of the attenuated membranous part into the lumen of the trachea and large bronchi and narrowing of the airways during exhalation and coughing.

According to researchers[21,22], depending on the reversibility, the pathogenetic mechanisms of obstruction can be functional and organic. The former undergo reverse development spontaneously or during treatment, the latter are pronounced changes in tissue structure and do not disappear on their own or under the influence of drugs[23].

The dynamics of respiratory function in workers of group 2 with SiBr showed a significant increase in lung volumes after inhalation with a pronounced decrease in residual volume and total lung capacity by 15% or more (P≤0.001) compared with group 1. In workers with silicosis complicated by COPD after inhalation of a bronchodilator, an increase in FVC by 16%, FEV1 by 10%, and a more pronounced increase in speed indicators at the level of medium and small bronchi was found. FEV1 increased significantly after the test and, accordingly, led to an increase in the Tiffno index by 16.9% (P≤0.05). In this group, Berotek caused a significant increase in speed indicators at the level of small bronchi 2 times more often (12.33%) than in uncomplicated silicosis (6.21%) (P≤0.05) (Table 4).

Table 4. The values of bronchial resistance, capnographic index and residual volume in a comparative aspect.

Indicators FIR	1 group Si before andafter inhalation	2 group SiBr before and after inhalation
CI	13,44±0,04/ 13,0±0,05*	16,18±0,95/ 13,00±0,75*
Ri	4,28±0,02/ 3,89±0,06**	4,53±0,33/ 3,70±0,37*
Re	4,58±0,04/ 4,00±0,07**	4,00±0,18/ 4,89±0,16
RVL	159,51±3,03/ 138,50±4,29***	175,72±5,22/ 131,99±5,52***
RCL	98,10±3,60/ 84,19±3,61***	108,68±3,67/ 93,09±3,55***
RVL/RCL	52,74±2,11/ 48,49±2,90**	54,50±3,54/ 47,76±3,72***

Note: * - the difference is significant (P≤ 0.01), ** - the difference is significant (P≤0.05),
***- the difference is significant (P≤0.001)

In this group, Berotec caused a significant increase in speed indicators at the level of small bronchi 2 times more often (12.33%) than in uncomplicated silicosis (6.21%) (P≤0.05) (Table 4).

More pronounced and reliable dynamics were noted in terms of indicators of maximum and average volumetric velocities in the flow-volume loop with fluctuations from 15.17% to 22.33% (P≤0.05). Bronchial resistance after inhalation decreased by 0.89 cmH2O/l/s on inhalation and by 0.83 cmH2O/l/s on exhalation, CapnograficIndeks decreased significantly by 3.18% (P≤0.01).

Thus, the dynamics of indicators in workers with complicated silicosis indicates a greater impairment of bronchial obstruction at the level of the proximal bronchi and a significant increase in parameters in the distal parts of the lungs. An increase in lung volume indicators indicates an equal degree of participation of the restrictive component in both groups of miners; a decrease in RVL and RCL compared with speed indicators and confirms the greater severity of transient bronchial obstruction in silicosis complicated by chronic bronchitis.

CONCLUSION:

A study of respiratory function using a spirogram in miners with chronic dust bronchitis from exposure to tungsten-molybdenum polymetallic dust revealed a decrease in lung volumes, while the dynamics of indicators indicate a greater influence on them from complications of destructive changes in lung tissue (emphysema). Inspiratory bronchial resistance increased significantly more in workers with CODB than in workers with CDB (P≤0.01) 6.33±0.24 cmH2O/l/s and more pronounced in the CODB group with PE 6.93±0.28 cmH2O /l/s. The most pronounced changes were detected at the level of the proximal parts of the lungs, regardless of length of service, and in the distal bronchi they significantly decreased with experience of 11-15 years.

The dynamics of residual lung volume and capnography confirm the reason for the decrease in speed indicators, decrease in elasticity, morphological and fibrous changes in the lung tissue after 5 years of experience and progression after 11-15 years of experience. These results indicate a complication of the mechanism of bronchial obstruction due to the presence of a “valve effect.” TBL in workers with CODB increases by 36.45% ($P \leq 0.01$), with the complication of pulmonary emphysema it increases to 198.54±4.16% of the proper value with control 128.77±4.31% of the proper value. The capnographic index (CI) revealed a significant increase in all groups, especially with CODB and emphisem1.13±0.14 kPa ($P \leq 0.001$), with CODB 0.87±0.18 kPa ($P \leq 0.05$) in workers with non-obstructive dust bronchitis tended to a significant increase in indicators.

The study of the effect of Berotek on the respiratory function of workers with complicated silicosis based on the dynamics of indicators and the bronchodilation coefficient indicates a greater significant decrease in speed indicators characterizing the level of medium and small bronchi compared with indicators for uncomplicated silicosis.

When working to mine tungsten-molybdenum-containing ore, workers experience deviations not only at the level of the respiratory tract, but also biochemical, immunological, morphological changes from the norm; the body's response to the influence of certain external unfavorable factors may be due to genetic predisposition or resistance to development of this disease and progresses with increasing underground work experience[23,24,25,26,27].

Thus, as a result of the studies obtained in chronic obstructive bronchitis, a violation of the ventilation function of the lungs is characterized by a pronounced irreversible component at the level of large and medium bronchi, a completely reversible component of bronchial obstruction is present at the level of the distal bronchi. Numerous literature data confirm the changes obtained[28-35].

The use of a bronchodilator test with Berotec makes it possible to establish the mechanisms of disturbance in these types of pathology; in workers with uncomplicated silicosis - especially at the level of the proximal lung; with complicated silicosis, changes are observed throughout the entire bronchial tree. These changes are determined by both irreversible and reversible components of impaired bronchial resistance (bronchospasm) - the restoration of pulmonary volume indicators to normal physiological values and an increase in velocity values at all levels of the bronchial tree after the use of a bronchodilator.

The dynamics of indicators are influenced by obstructive processes and, to a greater extent, by the presence of emphysematous phenomena, which emphasizes the dependence of these changes on the state of the elastic properties of the lung tissue. Early manifestations are already detected in healthy miners and progress with increasing underground work experience and the development of an occupational disease.

CONFLICT OF INTEREST:

The authors declare that there is no conflict of interest.

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