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ON ANTI-INFLAMMATORY AND ANTIPYRETIC MECHANISM OF COMBINATION DRUG EMPLOYED FOR THE TREATMENT OF BRONCHOPULMONARY ABNORMALITIES

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Abstract. *The study on 30 rats experimentally established the mechanism of anti-inflammatory and antipyretic action of amkesol. These effects depend on polytropic pharmacodynamics of the drug and are associated with restoration of oxidative balance and pro-inflammatory serum cytokine profile, impaired in bronchoalveolitis model.*

Key words: *combination drug, mechanism of action, antipyretic and anti-inflammatory effects, broncho-pulmonary pathology*

The employment of combination drugs, widely practiced in all clinical branches of modern medicine [1], is known to have a range of significant advantages in comparison to monotherapy. Along with reinforcement of therapeutic effect, combination drugs exert influence on basic pathogenesis elements of the abnormality and may even manifest new types of pharmacological action, not typical for their components [2].

Amkesol (AKS) is a combination drug administered for the treatment of respiratory system diseases with antitussive (ambroxol), anti-allergic (ketotifen), broncholytic, expectorant (theobromine, ambroxol, licorice root extract), anti-inflammatory and antipyretic action [3]. Two latter effects are achieved owing to pharmacodynamic interaction of AKS components, though their mechanism requires further study.

Purpose: to carry out a trial study of anti-inflammatory and antipyretic AKS mechanism.

Materials and methods. The experiment was performed according to the requirements of current international and national bioethics (Strasbourg, 1968; Kiev, 2001) on 30 adult outbread white rats of both sexes weighing 120-150 g who were

divided into 3 groups: 1 - intact control, 2 - pathology without treatment; 3 – pathology with treatment.

Proceeding from the premise that both types of the studied AKS action are not typical for its contents and they obviously develop due to its multicomponent pharmacodynamics, the study of their action mechanism was performed on bronchoalveolitis model mimicking inflammatory process directly in the lung tissue [4] and accompanied by an increase in body temperature. The model was induced by inhalation irritant (Sephadex A-25, Sweden) in the upper respiratory tract with further development of aseptic immune inflammation. Administration was carried out under thiopental anesthesia (60 mg/kg) at a dose of 5 mg/kg by Cyclohaler inhaler after which the development of inflammation was observed over 7 and 14 days. The mechanism of anti-inflammatory AKS action was investigated by oxidative equilibrium indices (diene conjugates (DC), malondialdehyde (MDA) and superoxide dismutase (SOD) and catalase activity (CAT)), which are considered to be the universal basis of inflammation, regardless of its origin, and pro-inflammatory cytokines (IL-1β, IL-8, TNF-α) were regarded as antipyretic AKS mechanism indices, reflecting the state of the immune response to thermal protection.

AKS (powder) was administered in isotherapeutic dose of 8 mg/kg, recalculated according to sensitivity of animals to drugs [5], in the form of 10% suspension in 1% starch mucus intragastrically once 1 hour prior to modeling. Diclofenac sodium was used as reference preparation (8 mg/kg).

Results. In bronchoalveolitis model oxidative equilibrium is impaired by an increase in lipid peroxidation (LPO) and a reduction in the activity of antioxidant (AO) enzymes, which is generally reflected in AO ratio value (Table 1).

Besides, cytokine inflammation profile was found to be activated (Table 2), which is accompanied by an increase in body temperature in rats, with a peak in 4 hours following the modeling onset, exceeding the norm during the day.

It is to be noted that the balance between LPO and AO system in the model was impaired to a greater extent at earlier stages of the trial and mainly involved peroxidation processes in comparison to AO-protection, reflecting the severity of the

disease, conditioned by a combination of lung tissue inflammation and processes in their cell membranes [6].

Table 1.

Amkesol effect on oxidative equilibrium state in rats with bronchoalveolitis

Trial conditions	LPO		AO-enzymes		AO-ratio (%)
	DC (%)	MDA (%)	SOD (%)	CAT (%)	
Intact	100	100	100	100	8,32
Bronchoalveolitis, 7th day	186*	129	74	63	2,06
Bronchoalveolitis, 14th day	161*	132	84	90	3,25
AKS, 7th day	134*,**	117	83	109**	3,33
AKS, 14th day	127*,**	104	88	91	5,88

Note: *– P<0,05 in comparison to intact control
** – P<0,05 in comparison to pathology

Table 2.

Amkesol effect on cytokine profile in rats with bronchoalveolitis

Trial conditions	Blood serum cytokines (%)		
	IL-1β	IL-8	TNF-α
Intact	0	0	0
Bronchoalveolitis,7th day	60	20	120
Bronchoalveolitis, 14th day	110*	80*	158*
AKS, 7th day	50**	18	100
AKS, 14th day	10**	5	50**

Note: *– P<0,05 in comparison to intact control
** – P<0,05 in comparison to pathology

At the same time, cytokines increase at later stages reflected the development of chronic inflammation. Against this background, AKS significantly reduces the amount of lipid peroxidation products, especially diene conjugates (from 186% to 134%) and increases catalase activity (109%), even more than in the control group. In view of the above, we can assume that anti-inflammatory AKS mechanism is associated with oxidative balance restoration owing to inhibition of lipid peroxidation processes and stimulation of enzymatic antioxidant protection activity. The dynamics of antioxidant factor alteration in this period confirms the targeting of antioxidant anti-inflammatory AKS action mechanism.

Antipyretic AKS effect as a 2.2% reduction in temperature in milk fever, exceeding the effect of diclofenac sodium both by the extent and duration, was associated with lower levels of blood serum cytokines in animals with bronchoalveolitis. In terms of their productive role in inflammation development in the lung tissue, one can assume that one of antipyretic AKS mechanisms involves a decrease in inflammation inducers IL-1β and TNF-α, which reduces fever manifestation as a pathogenic element of inflammatory response. Given that pro-inflammatory interleukins are considered to be major pathogenic factors of inflammation and its manifestation, namely hyperthermia, we can conclude that a reduction in the number of different forms of cytokines, including IL-1β, determined in our trials, reflects general mechanism of the studied AKS activity.

Conclusions:

1. The mechanism of anti-inflammatory amkesol action (8 mg/kg) is associated with restoration of oxidative equilibrium, impaired in bronchoalveolitis.

2. In the same dose amkesol reduces cytokine production, including IL-1β, elevated in bronchoalveolitis model, reflecting anti-cytokine mechanism of its antipyretic action.

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Звягинцева Т.В., Киричек Л.Т., Мироненко С.И., Кривошапка А.В., Стороженко Е.В.

К механизму противовоспалительного и жаропонижающего действия комбинированного препарата для лечения бронхо-легочной патологии

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Резюме. Экспериментально на 30 крысах установлен механизм противовоспалительного и жаропонижающего действия амкесола. Указанные эффекты зависят от политропной фармакодинамики препарата и связаны с восстановлением окислительного равновесия и провоспалительного профиля

сывороточных цитокинов, нарушенных в условиях модельного бронхоальвеолита.

Ключевые слова: комбинированный препарат, механизм действия, жаропонижающее и противовоспалительное эффекты, бронхо-легочная патология

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До механізму протизапальної і жарознижувальної дії комбінованого препарату для лікування бронхо-легеневої патології

Харківський національний медичний університет, Україна

Резюме. Експериментально на 30 щурах встановлений механізм протизапальної і жарознижувальної дії амкесола. Вказані ефекти залежать від політропної фармакодинаміки препарату й пов'язані з відновленням окислювальної рівноваги та прозапального профілю сироваткових цитокінів, порушених в умовах модельного бронхоальвеоліту.

Ключові слова: комбінований препарат, механізм дії, жарознижувальний і протизапальний ефекти, бронхо-легенева патологія

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