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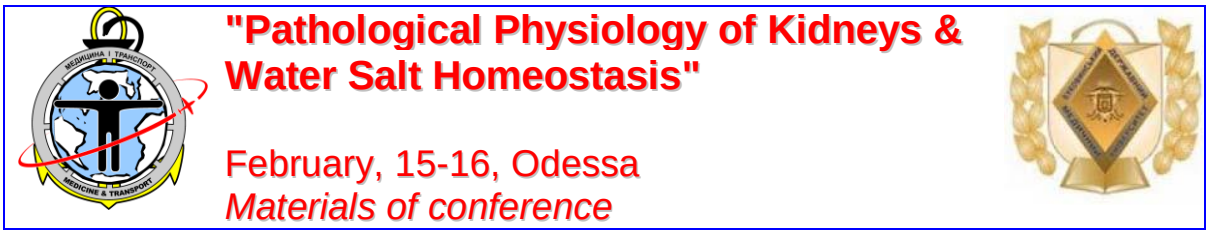

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DISORDERS OF WATER-ELECTROLYTE METABOLISM IN PULMONARY EDEMA UNDER INHIBITION OF THE RENIN-ANGIOTENSIN-ALDOSTERONE SYSTEM

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Abstract

The aim of the study was to study the disorders of water-electrolyte metabolism in pulmonary edema under conditions of inhibition of RAAS by ACE inhibitors. Studies were performed on 70 white rats weighing 160-180 g on two models of pulmonary edema: hemodynamic (adrenaline) and acute toxic. In rats with hemodynamic pulmonary edema the pulmonary coefficient increased 3.3 times as compared with the intact control, where it was 0.68 %. With acute toxic edema, this indicator also increased, but to a lesser extent – 2.4 times. We established that the minute diuresis in animals with hemodynamic pulmonary edema decreased by 1.9 times, and with acute toxic edema – by 1.5 times. There was also a

decrease in the concentration of sodium in the urine in groups of animals with hemodynamic edema and with acute toxic edema in 1.5 and 1.3 times, respectively. The use of ACE inhibitors for pulmonary edema leads to a decrease in the degree of their hyperhydration and normalization of water-electrolyte homeostasis. Compared with enalapril, zofenopril had a more pronounced anti-edematous effect in both hemodynamic and acute toxic edema of the lungs.

Key words: pulmonary edema, angiotensin-converting enzyme inhibitors, water-electrolyte metabolism.

ПОРУШЕННЯ ВОДНО-ЕЛЕКТРОЛІТНОГО ОБМІНУ ПРИ НАБРЯКУ ЛЕГЕНЬ В УМОВАХ ІНГІБІЦІЇ РЕНІН-АНГІОТЕНЗИН-АЛЬДОСТЕРОНОВОЇ СИСТЕМИ

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Реферат

Метою дослідження стало вивчення порушень водно-електролітного обміну при набряку легень в умовах інгібіції РААС інгібіторами АПФ. Дослідження проведені на 70 білих щурах массою 160-180 г на двох моделях набряку легень: гемодинамічного (адреналінового) і гострогіпоксичного. Встановлено, що у щурів з гемодинамічним набряком легень легеневий коефіцієнт збільшився в 3,3 раза у порівнянні з інтактним контролем, де він дорівнював 0,68%. При гострогіпоксичному набряку цей показник збільшився– в 2,4 раза. Встановлено, що хвилинний діурез у тварин з гемодинамічним набряком легень зменшувався в 1,9 раза, а з гострогіпоксичним набряком – в 1,5 раза. Також спостерігали зменшення концентрації натрію в сечі в групах тварин з гемодинамічним набряком і з гострогіпоксичним набряком в 1,5 і 1,3 раза відповідно. Застосування інгібіторів АПФ при набряку легень приводить до зменшення ступеня їх гіпергідратації і нормалізації водно-електролітного гомеостазу. У порівнянні з еналаприлом, зофеноприл чинив більш виражений протинабряковий ефект як при гемодинамічному, так і при гострогіпоксичному набряку легень.

Ключові слова: набряк легень, інгібітори ангіотензинперетворюючого ферменту, водно-електролітний обмін.

Hemodynamic disturbances and disturbances of water-electrolyte exchange between each other are closely related and largely depend on the state of the renin-angiotensin-aldosterone system (RAAS). Activation of this system promotes hypertension in a small circle of blood circulation, therefore it can be one of the pathogenetic links in the development of pulmonary edema [1, 2]. Inhibition of RAAS by inhibitors of angiotensin-converting enzyme (ACE) can, firstly, reduce pressure in the small circle of the circulation, and secondly, enhance diuretic and natriuretic effect, that can have positive effects in the treatment of pulmonary edema. In addition, among ACE inhibitors there are those that contain in their chemical composition the sulfhydryl group (captopril, zofenopril, etc.) [3]. If the role of ACE inhibitors in the treatment of systemic hypertension is well known [4], there is no information in the literature about the pharmacological blockade of vascular RAAS in pulmonary edema.

The aim of the study was to study the disorders of water-electrolyte metabolism in pulmonary edema under conditions of inhibition of RAAS by ACE inhibitors.

Materials and methods. Studies were performed on 70 white rats weighing 160-180 g on two models of pulmonary edema: hemodynamic (adrenaline) and acute toxic. Hemodynamic pulmonary edema was induced by intramuscular injection of adrenaline hydrochloride to rats at a dose of 5 mg / kg [5]. To reproduce acute toxic pulmonary edema was used a model developed in the department for the study of hypoxic conditions in Bogomolets Institute of Physiology NAS of Ukraine [6].

To establish some links in the pathogenesis of pulmonary edema and to study the effect of ACE inhibitors on its development, Enap (enalapril) (KRKA, Slovenia), administered to rats intravenously at a dose of 18 μmol / 100 g of body weight, and Zokardis (Zofenopril) (Berlin-Chemie, Germany) at a dose of 3.5 mg / kg intraperitoneally.

Statistical processing of the results was carried out using Student's t-test [5].

Results. Disorders of water-electrolyte metabolism in experimental pulmonary edema was accompanied by a significant increase in the lung mass ratio and a decrease in the relative mass of the dry residue of their tissue.

Thus, in rats with hemodynamic pulmonary edema the pulmonary coefficient increased 3.3 times as compared with the intact control, where it was 0.68 %. With acute toxic edema, this indicator also increased, but to a lesser extent – 2.4 times.

Since the pulmonary factor can grow not only due to excess water in the lungs, but also as a result of increased blood filling, we determined the dry residue of the lungs, which more reflects the degree of excess hydration. It was found that with hemodynamic pulmonary edema, the dry residue of the lungs was 1.5 times less than in intact animals, and in acute hypoxic edema animals – 1.3 times.

It is known that the regulation of the volume of extracellular fluid and blood plasma depends on the elimination or retention of sodium in the organism. Therefore, a change in the concentration of this element under certain conditions (acute hypoxia, adrenaline) can lead to disruption of metabolic processes and the appearance of pathological conditions. We established that the minute diuresis in animals with hemodynamic pulmonary edema decreased by 1.9 times, and with acute toxic edema – by 1.5 times (Table).

Table

Diuretic and natriuretic effects in hemodynamic and acute toxic pulmonary edema in rats, X ± Sx, n = 10

Group number	Object of study	Diuresis, ml / min	Concentration of sodium, mmol / l		
			in urine	in plasma	in lungs
1	Intact control	0,15±0,003	39,5±3,2	144,8±3,0	31,86±5,3
2	Hemodynamic edema	0,08±0,002*	26.4±4,4*	145,5±4,2	64,36±8,1*
3	Hemodynamic edema + enalapril	0,12±0,002**	35,6±3,6**	140,5±2,9	41,42±7,8*
4	Hemodynamic edema + zofenopril	0,13±0,005**	36,2±2,9**	139,5±6,0	39,65±8,9**
5	Acute toxic edema	0,10±0,006*	29,5±3,8*	142.7±6,1	57,35±9,3*
6	Acute toxic edema + enalapril	0,13±0,004**	36,1±4,6**	148,9±5,8	44,6±9,2*
7	Acute toxic edema + zofenopril	0,14±0,008**	37,8±5,2**	147,3±6,6	40,5±12,5**

Notes:

1. * – $p < 0.05$ – with respect to intact control;

2. ** – $p < 0.05$ – for animals with pulmonary edema without treatment.

There was also a decrease in the concentration of sodium in the urine in groups of animals with hemodynamic edema (the 2nd group) and with acute toxic edema (the 5th group) in 1.5 and 1.3 times, respectively.

No statistically significant changes in the concentration of sodium in the blood plasma were observed in any group. Reducing the concentration of sodium in the urine with a constant concentration in the blood plasma can be explained by the loss of sodium by blood and its transfer to another environment (most likely – in the lung tissue and edematous fluid that accumulated in them). To confirm this assumption, we determined the sodium concentration in the lung tissue homogenates. It was found that the concentration of sodium in the homogenate of the pulmonary tissue of animals with hemodynamic and acute toxic pulmonary edema increased by 2 and 1.8 times, respectively, in comparison with the intact control. Changes in the studied indicators of water-electrolyte metabolism for various experimental forms of pulmonary edema correspond to general ideas about their mechanism of development [1, 2]. It is known that the activation of RAAS plays an important role in the pathogenesis of pulmonary edema. This leads to an increase in the concentration of angiotensin II in the blood plasma, that has vasopressor, antidiuretic and antinatriuretic effects [3], that fully correlates with the results we obtained.

In animals of the 3rd and 6th groups, that took prophylactic enalapril, the expressiveness of the pulmonary edema was less in comparison with the 2nd and 5th groups of rats that did not take enalapril. This was indicated by the index of pulmonary coefficient, which was 1.4 times lower with hemodynamic edema and 1.2 times with acute toxic edema. In addition, when enalapril was used, there was a tendency to normalize the amount of dry residue of the lungs: in hemodynamic edema it increased 1.2 times, and in acute toxic edema it increased 1.1 times. Thus, the prophylactic administration of enalapril to animals with various experimental forms of pulmonary edema leads to a reduction in the phenomena of hyperhydration in the lungs.

After using enalapril in animals with hemodynamic edema, diuresis increased 1.5 times, and with acute toxic edema – 1.3 times. It was also established that in these groups the concentration of sodium in the urine increased and had a clear tendency towards normalization. Thus, in rats of the 3rd group it increased by 1.3 times and in rats of the 6th group – by 1.2 times.

The sodium concentration in the pulmonary homogenate of the rat tissues of the 4th and 5th groups was increased by 1.3 and 1.4 times, respectively, in comparison with the intact animals. The use of enalapril in hemodynamic and acute toxic edema of the lungs led to a

decrease in the concentration of sodium in the lung tissue compared with untreated animals of the 2nd and 5th groups in 1.6 and 1.3 times, respectively.

Compared with enalapril, zofenopril had a more pronounced anti-edematous effect in hemodynamic and acute toxic edema. When it was used in conditions of hemodynamic edema, the pulmonary coefficient decreased by 11 %, and the dry residue increased by almost 8 %. With acute toxic edema, the pulmonary coefficient under the influence of zofenopril decreased by 7 %, and the dry residue increased by 9 % compared with the use of enalapril. Most likely, the differences in the mechanisms of action of enalapril and zofenopril are related to the chemical structure of these drugs, namely, the presence in the zofenopril of the sulfhydryl group, which role in the development of pulmonary edema was proved by us earlier [7].

Conclusions

1. The use of ACE inhibitors for pulmonary edema leads to a decrease in the degree of their hyperhydration and normalization of water-electrolyte homeostasis.

2. Compared with enalapril, zofenopril had a more pronounced anti-edematous effect in both hemodynamic and acute toxic edema of the lungs.

Reference

1. Gandhi SK, Powers JC, Nomeir AM. The pathogenesis of acute pulmonary edema associated with hypertension. *Engl. J. Med.*, 2001; 344:1–17-22. (in English)

2. Lorraine B. Ware M., Matthay A. Acute Pulmonary Edema. *The New Engl. J. of Med.*, 2005; 353–2788-2796. (in English)

3. Mikhailov AA Ingibitory APF v klinicheskoy praktike [ACE inhibitors in clinical practice]. *Russkiy medicinskiy zhurnal*, 2006;14:6.–480–483. (in Russian)

4. Preobrazhenskiy DV, Sidorenko BA, Skavronskaya TV. Zofenopril – kardioprotektivnyiy ingibitor angiotenzin-prevraschayuschego fermenta: klinicheskaya farmakologiya i opyit primeneniya pri lechenii arterialnoy gipertenzii [Zofenopril – cardioprotective inhibitor of angiotensin-converting enzyme: clinical pharmacology and experience in the treatment of hypertension] // *Rossiyskiy kardiologicheskiy zhurnal*, 2006:1–87–94. (in Russian)

5. Sernov LN, Gatsura VV. *Elementy eksperimentalnoy farmakologii* [Elements of experimental pharmacology], Moscow: Medicine; 2000–192.

6. Rozova KV, Nazarenko AI, Tavolzhanova TI. *Vzaemozv'yazok tkanynnogo dyhannya ta deyakyh stereometrichnyh harakterystik mitohondriy i tkanini legen pri riznyh modyfykatsiyah gipoksichnoyi gipoksii* [Interconnection of tissue respiration and some

stereometric characteristics of mitochondria in lung tissue under various modifications of hypoxic hypoxia]. *Fiziologichnyiy zhurnal,* 2005.51:6–26–29. (in Ukrainian)

7. Tiupka TI, Bereznyakova AI. *Vmist vilnyih sulfgidryilnyih grup v legeneviy tkanyny ta yih patogenetyichna rol' u rozvyitku eksperymentalnogo nabryaku legen* [The content of free sulfhydryl groups in the pulmonary tissue and their pathogenetic role in the development of experimental pulmonary edema]. *Medyichna himiya,* 2008.4–42–45. (in Ukrainian)