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Evaluation of a novel Potentiator of Antibiotic (PA) effect on *Proteus mirabilis*-induced urinary tract infection (UTI) in mice

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Abstract. *Proteus mirabilis* is able to induce clinical symptoms of the urogenital tract infection (UTI) and form crystalline biofilm made of a variety of bacteria that are highly resistant to conventional antimicrobial drugs. The presented work was designed to study the antibiotic potentiation effect of PA in mice with UTI. They were divided into 5 groups: intact, positive control, Amoxicillin group, PA group, amoxicillin and PA group. UTI was induced by inoculation of *P. mirabilis* (1.5×10^9 CFU/mL), then animals received treatment for 14 days. Animals that received amoxicillin and PA displayed a normal rate of weight gain in comparison to the positive control ($p < 0.01$). The combined therapy also normalized in the levels of red blood cells, hematocrit, and hemoglobin, as well as white blood cells, lymphocytes, monocytes, and granulocytes ($p < 0.01$), indicating an alleviation of the inflammatory process. A significant rise of liver transaminases: ALT and AST, as well as in the levels of BUN and CREAT, was noted in the group of mice with UTI, no therapy ($p < 0.01$). However, the combined therapy of led to significant alleviation of all of these markers ($p < 0.01$), indicating normal function of the liver and kidneys. Finally, the histological examination revealed that the combined therapy had a nephroprotective effect, showing more intact structure, fewer degenerative processes and reduced congestion in contrast to the positive control. Thus, a novel drug PA, due to its ability to potentiate the efficacy of antimicrobial drugs, can offer a perspective approach for the treatment of infectious diseases.
Keywords: iodine complex, *Proteus mirabilis,* urogenital tract infection, kidneys, antibiotic potentiation

Introduction

The rising recurrence rate of urinary tract infections (UTI) makes its therapy challenging, substantially causing morbidity in females worldwide [1]. The acute UTI increases the chance for the development of chronic infectious diseases [2]; thus, the therapy with antimicrobial drugs became crucial at this point [3]. However, as widens the use of antibiotic the faster, bacteria adapt to the treatment, surviving, neutralizing the actions of antibiotics, and becoming

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antibiotic-resistant [4]. Even if the manufacture of novel antimicrobials was upgraded in order to fight the resistance issue, their inadequacy and irrationality as a band-aid led to the emergence of pathogens that are multiple drug-resistant and spreading at a dangerously higher rate [5-7]. Since the emergence of bacterial resistance to antibiotics cannot be stopped, the rate of its distribution can be slowed down with the proper use of antibiotics and by implementing novel ways to combat bacterial infections. The perspective approach is the use of antibiotic potentiators, which are already utilized in clinical practice [8].

Proteus mirabilis is a Gram-negative bacterium capable of inducing clinical symptoms of the UTI [9,10]. Its distribution mostly comes from person-to-person transmission, particularly in the healthcare system [11]. *P. mirabilis* is known for its ability to form biofilms due to the synthesis of urease that hydrolyzes urea into ammonia and carbon dioxide, resulting in an increase of pH [12]. Normally, pH in the urinary tract is acidic; thus, its alkalization leads to the interaction between calcium, magnesium ions, with phosphates, forming struvite and apatite urinary stones [13,14]. Moreover, the crystalline biofilm formed on the surface of catheters includes a variety of bacteria that have become highly resistant to conventional antimicrobial drugs [15,16]. In this regard, novel pharmaceutical formulations with antimicrobial effects will serve as an alternative approach for the treatment of infectious diseases.

Iodine is known for strong antimicrobial properties against a wide variety of bacteria, viruses, protozoa, and fungi, especially its complexes exhibit substantial long-lasting release of iodine, providing a long-term antimicrobial effect [17]. Due to the ability of iodine to form complexes, its application has expanded nowadays. Iodophors are formulations of iodine with other smaller molecular and water-soluble polymers, such as cyclodextrins [18]. FS-1 is one of such pharmaceutical formulations representing a complex of iodine with antibacterial and antiviral properties [19-21]. This drug is registered in Kazakhstan and widely used in clinical practice. On the basis of FS-1, a novel drug "PA" with an antibiotic potentiation effect was extensively studied and developed for the treatment of infectious diseases. The presented work was designed to study the effect of PA during the combined therapy with amoxicillin of urinary tract infection (UTI) induced by inoculation of *Proteus mirabilis* in mice.

Materials and Methods

Animals and Design of the Experiment

Forty-five female Swiss albino mice (9-11 weeks old, 20-22g body weight) were used for the experiment. The experimental protocol was approved by the Ethical Committee of JSC "Scientific center for anti-infectious drugs" (No. 25/2) and carried out in accordance with the "Guide for the Care and Use of Laboratory Animals" and ARRIVE guidelines. Animals were provided with a standard rodent diet and tap water *ad libitum* and maintained at the Animal Facility under conventional laboratory conditions: environment temperature 25 ± 1 °C and the relative humidity 55 ± 5% with a light/dark cycle of 12/12 h. Mice were randomly divided into the following groups: 1st – intact group, 2nd – *P. mirabilis* group with no therapy (positive control), 3rd – *P. mirabilis* group treated with Amoxicillin alone, 4th – *P. mirabilis* group treated with PA alone, 5th – *P. mirabilis* group treated with Amoxicillin and PA. On the first day of the experiment,

all groups except the intact group were inoculated with *P. mirabilis* in a concentration of 1.5×10^9 CFU/mL by sterile catheter (No. 1.3×130 mm) in order to induce urinary tract infection (UTI), then received corresponding therapy for 14 days. During this period, animals were also observed daily for the presence of any clinical symptoms and weighed every couple of days.

Sample Collection for Hematological, Biochemical and Histological Analysis

At the end of the experiment, mice were euthanized under deep isoflurane narcosis, blood was collected via retroocular sinus puncture in clot-activator containers, and centrifuged at 3000 rpm for 10 minutes. Blood was then analyzed for hematological parameters on Z52 VET automatic hematology analyzer (Zytopia Ltd., China) and supernatant was analyzed for plasma biochemistry on fully automated benchtop chemistry analyzer A25 (BioSystems, Troisdorf, Koln, Germany) using special kits according to the manufacturer's instructions. Then, mice were sacrificed by cervical dislocation and subjected to gross necropsy. Macroscopic examination of internal organs was conducted, kidneys were excised and dehydrated in alcohol, then embedded in paraffin and sectioned into 3.0 μm fragments. Obtained histological slices were stained with hematoxylin-eosin and observed under a ZEISS Axio Scope A1 light microscope (Carl Zeiss, Germany).

Results

The efficiency of PA in combination with an antibiotic (Amoxicillin) was determined using hematological, biochemical and histological methods of research in mice with urogenital tract infection (UTI). Often, in clinical practice, *P. mirabilis* causes catheter-associated urinary tract infections, leading to irreversible damage to renal tissue, including sepsis. All animals survived up to the end of the experiment, except the positive control group, displaying no alteration in behavior, as well as in food and water consumption. Body weight measures are presented in Table 1.

Table 1

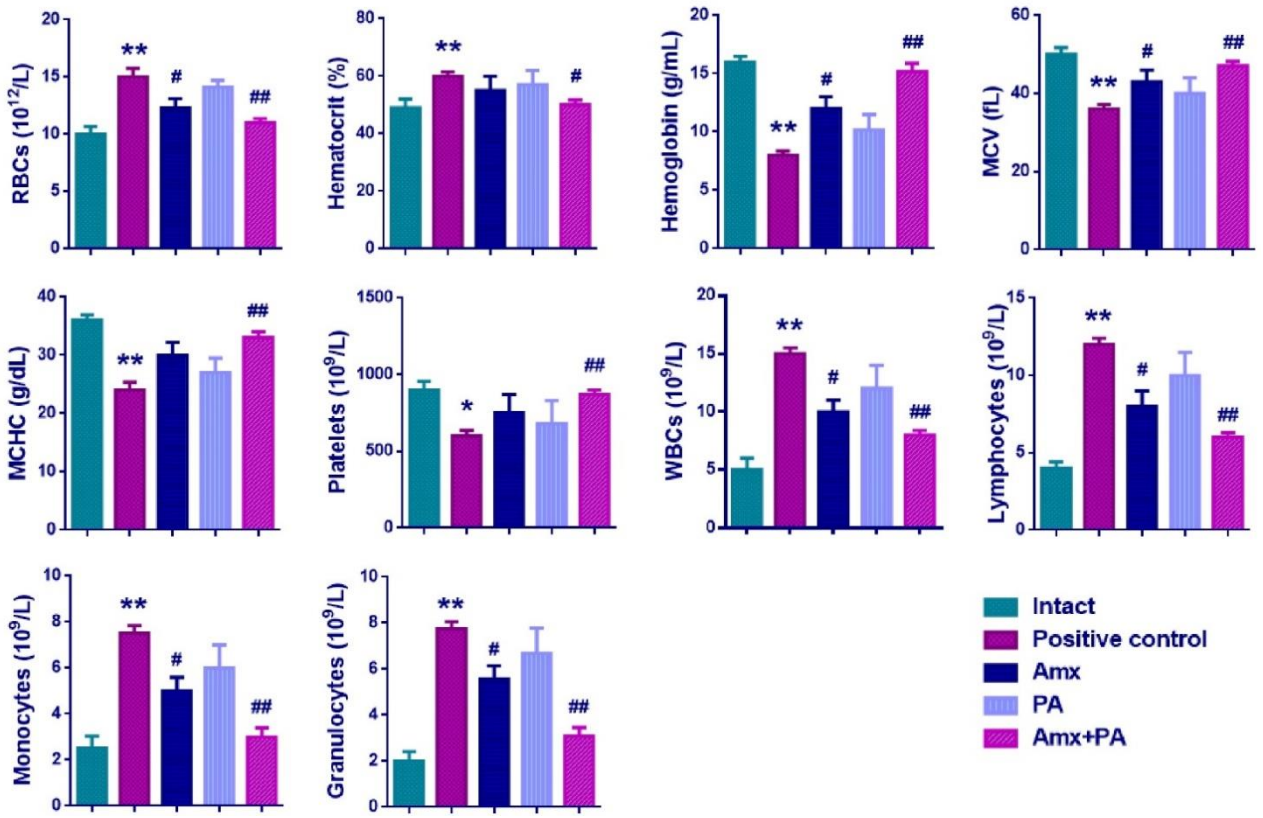
The tendency of body weight of mice (g)

Day	Intact	Positive control	Amx	PA	Amx + PA
1	20.92±0.30	21.08±0.50	21.24±0.67	20.66±0.53	20.96±0.50
4	21.14±0.30	19.66±0.47*	21.38±0.66	20.30±0.49	21.26±0.48
8	21.46±0.27	18.34±0.47*	21.48±0.61#	20.40±0.49#	22.04±0.39##
11	21.74±0.23	17.18±0.25**	21.82±0.30#	20.40±0.43#	22.46±0.36##
15	22.14±0.21	16.20±0.27**	22.04±0.25#	20.90±0.47#	22.80±0.39##

Note: Data are presented as Mean ± SD. *p < 0.05, **p < 0.01 compared to the intact group and #p < 0.05, ##p < 0.01 compared to the positive control group.

Mice of the intact group showed a normal rate of weight gain, unlike the positive control with UTI, no therapy showing significant body weight loss on Days 4 and 8 ($p < 0.05$), as well as on Days 11 and 15 ($p < 0.01$). Animals that received amoxicillin and PA separately displayed a normal rate of weight gain in comparison to the positive control ($p < 0.05$). However, a better rate of weight gain and a more significant difference compared to the positive control group were observed in mice that received the combined therapy of amoxicillin and PA ($p < 0.01$).

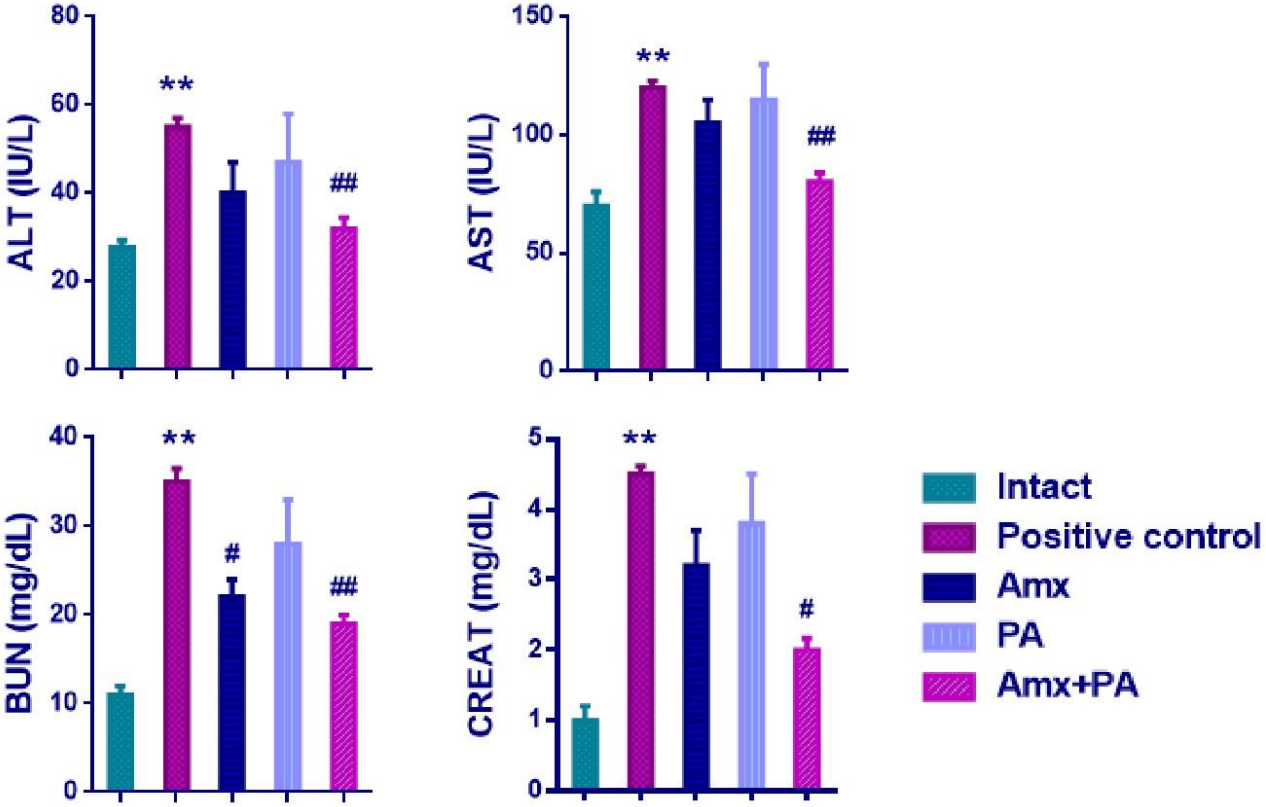
Analysis of hematological parameters of mice blood was conducted; results are presented in Figure 1. A significant increase in the levels of RBCs and hematocrit, but lower levels of hemoglobin, MCV, and MCHC were observed in animals with UTI, no treatment ($p < 0.01$). The monotherapy of either amoxicillin or PA normalized some of these parameters ($p < 0.05$). However, a significant improvement was observed in mice treated with amoxicillin and PA in combination ($p < 0.01$). The profile of immune cells displayed a significant surge of white blood cells, lymphocytes, monocytes, and granulocytes in the positive control group ($p < 0.01$). The combined therapy of amoxicillin and PA alleviated these cells, indicating a decrease in the degree of the inflammatory process ($p < 0.01$).



Note: *$p < 0.05$, **$p < 0.01$ compared to the intact group and #$p < 0.05$, ##$p < 0.01$ compared to the positive control group. RBCs – red blood cells, MCV – mean corpuscular volume, MCHC – mean cellular corpuscular hemoglobin concentration, WBCs – white blood cells.

Figure 1. Hematological parameters of mice blood

Analysis of mice plasma biochemistry was also carried out; results are presented in Figure 2. Results of plasma biochemistry were presented as a significant rise of liver transaminases: ALT and AST in the group of mice with UTI, no therapy ($p < 0.01$). The same tendency was observed in the levels of BUN and CREAT, showing a significant increase of both markers in animals of the positive control group ($p < 0.01$). Amoxicillin monotherapy normalized the level of BUN ($p < 0.05$). The combined therapy of amoxicillin and PA led to significant alleviation of all plasma biochemistry markers in comparison to the group with UTI, no therapy ($p < 0.01$). Values of ALT, AST, BUN and CREAT were within the normal range in mice of the group that received amoxicillin and PA, indicating normal function of the liver and kidneys.

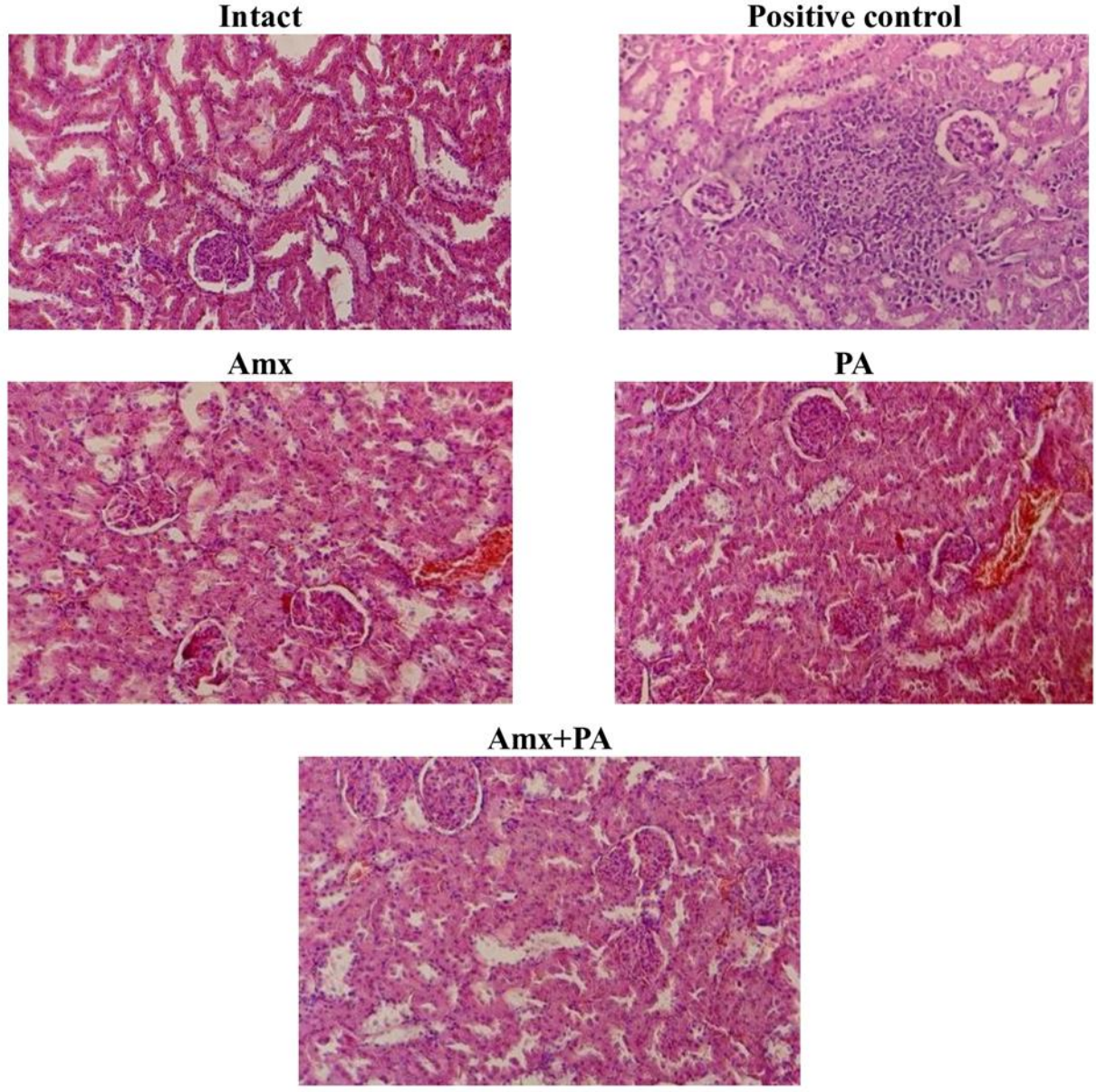


Note: *p < 0.05, **p < 0.01 compared to the intact group and #p < 0.05, ##p < 0.01 compared to the positive control group. ALT – alaninaminotransferase, AST – aspartataminotransferase, BUN – blood urea nitrogen, CREAT – creatinine.

Figure 2. Biochemical analysis of mice's blood plasma

Histological examination of the structure of the kidneys was carried out in order to observe any histopathological process inside the tissue. Microphotographs of kidneys are presented in Figure 3. Well-defined glomeruli, intact proximal and distal tubules, no inflammation, and necrosis were observed in the histological structure of the kidneys of the intact group of mice. In contrast, in the positive control group, inflammatory cell infiltration, glomerular distortion or possible atrophy, tubular dilation, and degeneration were noted. Treatment with amoxicillin

alone caused nephrotoxicity, while monotherapy of PA induced a little protective effect, but mild congestion was still present in the histological structure of the kidneys. However, animals that received combined therapy of amoxicillin and PA demonstrated more intact structure with moderate preservation of cells and tissue, fewer degenerative changes, and reduced congestion. As a result of the histological examination of the antibiotic potentiation effect of PA, attenuation of the renal pathology was noted in the histological structure of the kidneys (Figure 3).



Note: Hematoxylin & Eosin stain. Bar, 100 μm (200x magnification).

Figure 3. Histological structure of mice kidneys

Discussion

The present study aimed to evaluate the antibiotic potentiation effect of PA in mice with UTI induced by inoculation of *P. mirabilis.* All animals participating in this experiment were observed daily for any changes in behavior, food and water consumption, and/or mortality, and also weighed weekly for 14 days after the inoculation.

The weekly measurement showed a strong tendency toward weight loss in mice that were inoculated with P. mirabilis but did not receive any therapy, indicating an acute clinical response to infection. However, the combined therapy of PA and amoxicillin provided a normal rate of weight gain in mice ($p < 0.01$), displaying attenuation of the inflammatory reaction to infection (Table 1). Our results for body weight measurement are in alignment with the previously conducted studies, where the tendency of body weight loss and gain served as an indicator of the health condition of animals during the infectious process [22,23].

During the analysis of hematological parameters, a significant increase in the levels of RBCs and hematocrit, but decreased levels of hemoglobin, MCV, MCHC and platelets were observed, indicating a compensatory response to anemia in mice (Figure 1). Similar findings were obtained in the study conducted by Silva et al., where infected animals displayed alterations in blood cellular profile, as well as in the platelet content [24]. A surge in the profile of immune cells including WBCs, lymphocytes, monocytes and granulocytes was observed in infected mice, that received no therapy. Our results indicate the acute inflammatory response, as it was obtained in the results of the previously conducted studies [25]. The combined therapy of PA and amoxicillin led to a significant alleviation of the inflammatory response, as well as normalized the blood cellular and viscosity profile ($p < 0.01$), exhibition the antibiotic potentiation effect [26].

The plasma biochemistry analysis showed an increase in the levels of liver transaminases ALT and AST, indicating the hepatic injury in animals of the positive control group. The same tendency was detected in the levels of BUN and CREAT, showing the damage to the kidneys (Figure 2). However, mice that received the combined therapy displayed significantly lower levels of these parameters in comparison to the positive control ($p < 0.01$). Similar results were obtained in previous studies [27,28].

Lastly, during the histopathological examination more intact structure of the kidney was observed in mice that received the combined therapy of PA and amoxicillin, unlike the positive control group, receiving no therapy (Figure 3). Similar findings were obtained in the work conducted by Johnson, where a mixed pattern of both acute and chronic inflammatory responses was detected in the structure of the kidneys in infected mice [29].

Thus, results obtained in our study suggest that PA can represent a novel perspective for the therapy of infectious diseases, particularly for the treatment of UTI with bacterial origin, and the introduction of this approach into clinical practice.

Conclusion

Our work was conducted in order to study the antibiotic potentiation effect of a novel drug “PA” during the combined therapy with amoxicillin of UTI induced by inoculation of *P.*

mirabilis. in mice. A normal body weight gain was observed in the group of mice that received the combined therapy, unlike the positive control group with UTI, no therapy displayed gradual weight loss. Analysis of hematological parameters showed a significant decrease in the levels of red blood cells, hematocrit and hemoglobin, along with a surge in the levels of white blood cells, lymphocytes, monocytes, and granulocytes. The combined therapy of amoxicillin and PA alleviated these symptoms, increasing the levels of red blood cells, hematocrit, and hemoglobin, as well as a decrease in the levels of white blood cells, lymphocytes, monocytes, and granulocytes, indicating attenuation of the inflammatory process. Moreover, the combined therapy of amoxicillin and PA led to a significant alleviation of all plasma biochemistry markers in comparison to the group with UTI, no therapy. Levels of ALT, AST, BUN, and CREAT were within the normal range in mice of the group that received combined therapy, indicating normal function of the liver and kidneys. Finally, the histological examination of kidneys revealed inflammatory cell infiltration, glomerular distortion or possible atrophy, tubular dilation and degeneration in the positive control group, while animals that received combined therapy of amoxicillin and PA demonstrated more intact structure with moderate preservation of cells and tissue, fewer degenerative changes, and reduced congestion. Thus, the therapeutic effect of PA is based on its ability to potentiate the efficacy of antimicrobial drugs. Based on these results, a novel drug "PA" can offer a novel perspective for the treatment of infectious diseases.

Author Contributions

N.I. – conceptualization; **M.L –** supervision; **T.G., A.K., K.S.,** and **D.I.** – conduction of the experiment; **N.I.** and **G.P. –** discussion of results; **A.A. –** writing and editing of the article.

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Conflicts of Interest

Authors declare no conflicts of interest.

Compliance with ethical standards

All animal procedures complied with the ethical standards of the institution where the studies were conducted and the approved legal acts of the Republic of Kazakhstan and international organizations. (No. 25/2).

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Тышқандардағы Proteus mirabilis-индукцияланған несеп-жыныс жолдарының инфекциясына (ЖЖИ) жаңа антибиотик күшейткішінің (ПА) әсерін бағалау

Н. Ибрагимова[1], М. Лю[1], А. Айтынова*[1], Т. Гапурхаева[1], А. Красноштанов[1], Г. Пономарева[1], К. Шойбек[1], Д. Иса[1]

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Аңдатпа. *Proteus mirabilis* несеп-жыныс жолдарының инфекциясының (ЖЖИ) клиникалық симптомдарын тудыруға қабілетті және әдеттегі микробқа қарсы препараттарға төзімділігі

жоғары әртүрлі бактериялардан тұратын кристалды биопленка түзеді. Ұсынылған жұмыс ЖЖИ бар тышқандардағы ПА-ның антибиотикті күшейту әсерін зерттеуге арналған. Олар 5 топқа интакт, оң бақылау, амоксициллин тобы, ПА тобы, амоксициллин және ПА тобы болып бөлінді. ЖЖИ *P. mirabilis* (1.5×10^9 ККБ/мл) егу арқылы индукцияланды, содан кейін жануарлар 14 күн бойы емделді. Амоксициллин мен ПА қабылдаған жануарлар оң бақылаумен салыстырғанда салмақ қосудың қалыпты жылдамдығын көрсетті ($p < 0.01$). Біріктірілген терапия сонымен қатар эритроциттердің, гематокрит пен гемоглобиннің, сондай-ақ лейкоциттер, лимфоциттер, моноциттер және гранулоциттер ($p < 0.01$) деңгейінде қалыпқа келтірілді, бұл қабыну процесінің жеңілдеуін көрсетеді. Бауыр трансаминазаларының айтарлықтай жоғарылауы: ALT және AST, сондай-ақ BUN және CREAT деңгейлерінің ИЖИ бар тышқандар тобында байқалды, ем жүргізілмеген ($p < 0.01$). Дегенмен, біріктірілген терапия бауыр мен бүйректің қалыпты жұмысын көрсететін осы маркерлердің барлығын айтарлықтай жеңілдетуге әкелді ($p < 0.01$). Соңында, гистологиялық зерттеу біріктірілген емнің нефропротекторлық әсері бар екенін, құрылымның тұтастығын, дегенеративті процестердің аздығын және оң бақылаудан айырмашылығы тоқырауды азайтатынын көрсетті. Осылайша, жаңа ПА препараты микробқа қарсы препараттардың тиімділігін арттыру қабілетіне байланысты жұқпалы ауруларды емдеудің перспективалық әдісін ұсына алады.

Түйін сөздер: йод кешені, *Proteus mirabilis,* несеп-жыныс жолдарының инфекциясы, бүйрек, антибиотиктерді күшейту

Оценка эффекта нового потенциатора антибиотиков (ПА) на инфекцию мочевыводящих путей (ИМП), индуцированной Proteus mirabilis у мышей

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Аннотация. *Proteus mirabilis* способен вызывать клинические симптомы инфекции мочевыводящих путей (ИМП) и формировать кристаллическую биопленку из различных бактерий, обладающих высокой устойчивостью к традиционным антимикробным препаратам. Представленная работа была разработана для изучения эффекта потенцирования антибиотиков ПА у мышей с ИМП. Они были разделены на 5 групп: интактные, положительный контроль, группа амоксициллина, группа ПА, амоксициллин и группа ПА. ИМП вызывали инокуляцией *P. mirabilis* (1.5×10^9 КОЕ/мл), затем животные получали лечение в течение 14 дней. Животные, получавшие амоксициллин и ПА, показали нормальную скорость набора веса по сравнению с положительным контролем ($p < 0.01$). Комбинированная терапия также нормализовалась в уровнях эритроцитов, гематокрита и гемоглобина, а также лейкоцитов, лимфоцитов, моноцитов и гранулоцитов ($p < 0.01$), что указывает на облегчение воспалительного процесса. Значительный рост печеночных трансаминаз: АЛТ и АСТ, а также уровней мочевины и креатинина были отмечены в группе мышей с ИМП, не получавших терапию ($p < 0.01$). Однако комбинированная терапия привела к значительному снижению всех этих маркеров ($p < 0.01$), что свидетельствует

о нормальной функции печени и почек. Наконец, гистологическое исследование показало, что комбинированная терапия оказала нефропротекторное действие, показав более сохранную структуру, меньше дегенеративных процессов и снижение застоя в отличие от положительного контроля. Таким образом, новый препарат ПА благодаря своей способности потенцировать эффективность антимикробных препаратов может предложить перспективный подход для лечения инфекционных заболеваний.

Ключевые слова: йодный комплекс, *Proteus mirabilis,* инфекция мочевыводящих путей, почки, потенцирование антибиотиков

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