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Effect of phytoneering remedy BNO 2103 on the course of experimental exudative inflammation caused by different phlogogens

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A – research concept and design; B – collection and/or assembly of data; C – data analysis and interpretation; D – writing the article; E – critical revision of the article; F – final approval of the article

Key words: BNO 2103, herbal composition, anti-inflammatory properties, phytotherapy, preclinical study.

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Kidney and urinary tract diseases play an important role in the disease distribution in most countries of the world. The pharmaceutical industry offers many means for the treatment and prevention of these diseases, but there is a trending tendency to pay more attention to herbal medicines, their empirical application and scientific study.

The aim of this research is to study anti-inflammatory properties of standardized herbal composition BNO 2103 in a model of paw inflammation in rats caused by different phlogogens to justify the use of it in the treatment of chronic kidney disease (CKD).

Materials and methods. The experimental study was performed using 90 male white outbreed rats weighing 150–200 g, which were divided into 3 series of 30 animals each, each series included 3 groups. Inflammation of the paw was induced by subplantar administration of phlogogens – zymosan, histamine and serotonin. The study agent and the reference drug, diclofenac sodium, were administered intragastrically (i. g.) once. Edema was observed and recorded, and anti-inflammatory activity (AIA) was assessed in 0.5, 1.0, 2.0, 3.0 and 6.0 hours after phlogogen injection.

Results. BNO 2103 showed a remarkable anti-exudative effect in the model of zymosan and histamine edema, being significantly superior to diclofenac sodium. In the serotonin edema model, BNO 2103 was significantly superior to the comparator by the endpoints, showing the moderate but prolonged anti-exudative effect.

Conclusions. BNO 2103 has the significant anti-inflammatory effect, exerting an inhibitory effect on exudative inflammation caused by various phlogogens (zymosan, histamine, serotonin), mainly acting on the lipoxygenase pathway of arachidonic acid conversion, which is most likely due to the presence of flavonoids. This allows us to consider BNO 2103 as a promising drug for the treatment of CKD.

Ключові слова: BNO 2103, рослинна композиція, протизапальні властивості, фітотерапія, доклінічне вивчення.

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Вплив фітонірингового засобу BNO 2103 на перебіг експериментального ексудативного запалення, викликаного різними флогогенами

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Хвороби нирок і сечовивідних шляхів посідають важливе місце у структурі захворюваності населення більшості країн світу. Фармацевтична індустрія пропонує багато засобів для лікування та профілактики цих захворювань, але спостерігають тенденцію до посилення наукового інтересу до препаратів рослинного походження, їх емпіричного застосування та вивчення.

Мета роботи – доклінічне вивчення протизапальних властивостей стандартизованої рослинної композиції BNO 2103 на моделях запалення лапи в щурів, що викликане різними флогогенами, для обґрунтування застосування засобу в терапії хронічної хвороби нирок (ХХН).

Матеріали та методи. Експериментальне дослідження здійснили на 90 самцях білих безпородних щурів масою 150–200 г, яких поділили на 3 серії по 30 тварин, кожна серія включала 3 групи. Запалення лапи моделювали за допомогою субплантарного введення флогогенів – зимозану, гістаміну та серотоніну. Досліджуваний засіб і препарат порівняння (диклофенак натрію) вводили внутрішньошлунково одноразово. Спостереження, фіксацію об'єму набряку та оцінювання протизапальної активності (ПЗА) здійснили через 0,5, 1,0, 2,0, 3,0 та 6,0 години після введення флогогену.

Результати. BNO 2103 характеризувався вираженою антиексудативною дією на моделі зимозанового та гістамінового набряків, вірогідно перевершив диклофенак натрію. На моделі серотонінового набряку BNO 2103 вірогідно перевершив референс-препарат у кінцевих точках спостереження, показавши помірний, але пролонгований антиексудативний ефект.

Висновки. BNO 2103 характеризується суттєвим протизапальним ефектом, здійснюючи інгібувальний вплив на ексудативне запалення, викликане різними флогогенами (зимозан, гістамін, серотонін), діє здебільшого на ліпооксигеназний шлях перетворення арахідонової кислоти; ймовірно, це зумовлено наявністю флавоноїдів у складі засобу. Отже, BNO 2103 можна вважати перспективним лікувальним засобом для терапії ХХН.

Влияние фитонирингового средства BNO 2103 на течение экспериментального экссудативного воспаления, вызванного разными флогогенами

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Болезни почек и мочевыводящих путей занимают важное место в структуре заболеваемости населения большинства стран мира. Фармацевтическая индустрия предлагает много средств для лечения и профилактики этих заболеваний, но

наблюдают тенденцию к усилению научного интереса к препаратам растительного происхождения, их эмпирическому применению и изучению.

Цель работы – доклиническое изучение противовоспалительных свойств стандартизированной растительной композиции BNO 2103 на модели воспаления лапы у крыс, вызванного различными флогогенами, для обоснования применения средства в терапии хронической болезни почек (ХБП).

Материалы и методы. Экспериментальное исследование проведено на 90 самцах белых беспородных крыс массой 150–200 г, которых поделили на 3 серии по 30 животных, каждая серия включала 3 группы. Воспаление лапы моделировали с помощью субплантарного введения флогогенов – зимозана, гистамина и серотонина. Исследуемое средство и препарат сравнения (диклофенак натрия) вводили внутрижелудочно однократно. Наблюдение и фиксацию объёма отека, оценку противовоспалительной активности (ПВА) проводили через 0,5, 1,0, 2,0, 3,0 и 6,0 часа после введения флогогена.

Результаты. BNO 2103 проявил выраженное антиэкссудативное действие на модели зимозанового и гистаминового отёков, достоверно превзошёл диклофенак натрия. На модели серотонинового отека BNO 2103 достоверно превзошёл референс-препарат в конечных точках наблюдения, проявив умеренный, но пролонгированный антиэкссудативный эффект.

Выводы. BNO 2103 характеризуется значительным противовоспалительным эффектом, осуществляя ингибирующее влияние на экссудативное воспаление, вызванное различными флогогенами (зимозан, гистамин, серотонин), преимущественно действует на липооксигеназный путь превращения арахидоновой кислоты; вероятно, это обусловлено наличием флавоноидов в составе средства. Таким образом, BNO 2103 можно рассматривать как перспективное лечебное средство для терапии ХБП.

Ключевые слова: BNO 2103, растительная композиция, противовоспалительные свойства, фитотерапия, доклиническое изучение.

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Kidney and urinary tract diseases play an important role in the disease distribution in most countries of the world and are a crucial problem in the global health sector. The pharmaceutical industry offers many means for the treatment and prevention of these diseases, but there is a trending tendency to pay more attention to herbal medicines, their empirical application and scientific study.

The object of our study is a standardized herbal composition BNO 2103, which is an active pharmaceutical ingredient of the combined phytoneering drug Canephron® N manufactured by Bionorica SE (Germany). The components of this herbal medicine have a complex pharmacodynamics, which is manifested in anti-inflammatory, antioxidant, antibacterial, diuretic, antispasmodic and analgesic effects [1]. These properties, along with a significant anti-inflammatory effect, allow Canephron® N to occupy a confident place among the drugs for correction of inflammatory processes in the urinary system. However, the registration of Canephron® N varies in different countries in terms of indications and dosage forms. For example, in the country of origin – Germany, as well as in Poland and Ukraine, the drug is officially declared for the use in the treatment of urinary tract inflammatory diseases, as well as for irrigation of the lower urinary tract, primary and secondary prevention of urolithiasis [1–3]. In Russia, the drug is registered with indications for the treatment of chronic infections of the bladder (cystitis) and kidneys (pyelonephritis), as well as non-infectious renal diseases (glomerulonephritis and interstitial nephritis) and urolithiasis [4]. It should be noted that in no country the drug is included in the treatment of chronic kidney disease (CKD), as there is a lack of evidence to consider such a prospect.

That is why, in our study, we have drawn attention to the problem of phytopharmacological correction of this disease, which poses a dramatic population threat – the incidence and mortality from CKD is growing every year. According to the Global Kidney Health Atlas 2019, the prevalence of this pathology in Ukraine is 18.18 % (95 % CI, 16.81–19.64) [5]. In our research, we have studied BNO 2103 in terms of influence on biochemical, histomorphological, immunohistochemical and functional indicators of the kidneys, using a number of experimental models to comprehensively study its properties. CKD is a multifactorial disease with diverse etiopathogenesis, but inflammation is an integral part of many diseases from a CKD group. For this reason, we have given special attention to the study on the anti-inflammatory activity of the remedy, since without this the formation of the evidence base would be incomplete. Canephron® is already known as a remedy for the treatment of diseases from the CKD group with a significant inflammatory component, such as glomerulonephritis, pyelonephritis, interstitial nephritis [4], etc.

Therefore, it is advisable to continue this series of studies and investigate the anti-exudative properties of BNO 2103 in order to establish the embodying mechanisms of its anti-inflammatory effect, in particular, the influence on the pathways of arachidonic acid conversion. Given the following data, this contributes to the expansion of indications for the study drug use to empower patients and physicians to manage CKD. The long-term benefits of using BNO 2103 for the treatment of CKD is that the arsenal of drugs for the treatment of this nosological complex will be replenished with a herbal remedy with a sufficient evidence base, complex action, high efficiency and safety. The above characteristics will allow BNO 2103 to be included in the treatment profile of CKD at any stage of the disease with the expected effectiveness, enhancing patient compliance and doctor's trust in this remedy.

Aim

We consider the standardized herbal composition BNO 2103 produced by Bionorica SE (Germany) as a promising agent for the pathogenetic treatment of CKD, therefore, the aim of the research is to study anti-inflammatory properties of BNO 2103 in a model of paw inflammation in rats caused by various phlogogens.

Materials and methods

An experimental study was performed using 90 white male outbred rats weighing 150–200 g, which were obtained from the vivarium of the Educational and Scientific Institute of Applied Pharmacy of the National University of Pharmacy (ESIAPh NUPh, Kharkiv, Ukraine). Animals received a standard diet with unlimited access to water and were kept

in standard laboratory conditions in a well-ventilated room with an air temperature of 25 ± 1 °C, relative humidity of 55 ± 5 % and 12 h light-dark cycle [6,7].

All studies have been carried out in accordance with the EU Council Directive 2010/63/EC in compliance with the laws, regulations and administrative provisions of the EU Member States concerning the protection of animals used for scientific purposes [8]. The experimental protocols were approved by the NUPh Bioethics Commission (Approval No. 2 dated November 4, 2019).

Test object BNO 2103 contains a mixture of extracts of centaury herb, rosemary leaves and lovage root in the form of a fine amorphous hygroscopic brown powder with a characteristic odor of medicinal plants. BNO 2103 is slightly soluble in water; thus, it was administered to animals in the form of an aqueous suspension prepared with a vehicle (carboxymethylcellulose 0.5 % + Tween-80 0.1 %), without prior grinding in a mortar. The appropriate suspension was mixed with Vortex V-1 Plus (Biosan, Latvia) immediately before administration to laboratory animals.

Diclofenac sodium, 25 mg in tablets was chosen as a reference drug as a known anti-inflammatory agent of the NSAID class [9]. Test samples of diclofenac sodium were administered as an aqueous suspension prepared with a vehicle and pre-grounding in a mortar. All samples were administered once intragastrically (i. g.) using a gastric tube.

During the study, the animals were weighed, labeled and divided into equivalent groups. Throughout the experiment, laboratory monitoring of animals, control of their body weight, food intake and behavior were performed.

The study of anti-inflammatory properties of BNO 2103 was performed on a model of experimental exudative inflammation in rats caused by different phlogogens [10,11]. All animals were divided into 3 series of 30 animals each, each series included 3 groups (n = 10):

– Group 1 – control pathology (CP) (untreated animals receiving vehicle).

– Group 2 – rats with paw edema treated with BNO 2103 i. g. at a dose of 33.0 mg/kg (corresponding to the recommended human dose extrapolated according to FDA recommendations [12]).

– Group 3 – rats with paw edema treated with diclofenac sodium i. g. at a dose of 8.0 mg/kg (ED50 for anti-inflammatory activity [13]).

The experiment was performed using 3 groups of animals per day. Rats were involved in the study by turn without delay so that the evaluation of each animal was performed at equal time intervals after the formation of pathology – 0.5, 1.0, 2.0, 3.0 and 6.0 hours.

At the beginning of the experiment, the initial volume (cm^3) of the right hind paw was determined using a digital plethysmometer (IITC Life Science, USA).

After that, the test and reference drugs were administered once i. g. in the appropriate doses. Animals from the CP group received an equivalent amount of solvent i. g.

One hour later, all rats underwent inducing an aseptic exudative inflammation in the right hind paw by subplantar injection of 0.1 ml of various phlogogenic substances, such as: 2.0 % suspension of zymosan – for series I; 0.25 % histamine solution – for series II and 0.5 % serotonin solution – for series III.

The volume of edema was measured by digital plethysmometer (IITC Life Science, USA) at the site of pathology induction to see the trends for 0.5, 1, 2, 3 and 6 hours after phlogogen injection and presented in cm^3.

Anti-inflammatory activity (AIA) was assessed as a percentage of the edema reduction level in animals treated with the test drug compared to animals in the CP group. It was calculated by the following formula:

$$AIA = \frac{\Delta V_{control} - \Delta V_{test}}{\Delta V_{control}} \times 100\ \%,$$

where ΔVcontrol – average % of edema volume in the control group;

ΔVtest – average % of edema volume in the group of the test drug.

All results were processed by descriptive statistics and presented as mean ± standard error of the mean (ME ± SEM). Intergroup differences were analyzed using one-way ANOVA and the Tukey post-hoc test [14].

IBM SPSS Statistics v. 22 (IBM Corp., USA) and MS Excel 2016 (Microsoft Corp., USA) were used for this purpose. The level of statistical significance was considered as $P < 0.05$.

Results

Effect of BNO 2103 on the course of zymosan-induced edema in rats. In the pathogenetic mechanism of zymosan-induced inflammation, the main role belongs to the activation of the lipoxygenase pathway of arachidonic acid conversion and the formation of leukotrienes. They form the primary response to alteration by the development of exudation and launching an inflammatory cascade.

The study results have shown an inflammatory reaction under the influence of zymosan in the CP group throughout the study. The highest degree of exudation – 44.5 % of the initial level, was registered 1 hour after the onset of inflammation, then the edema gradually decreased to 15.2 % in 6 hours (*Fig. 1*).

The greatest anti-exudative activity was shown by BNO 2103, which had an inhibitory effect on the development of edema with significant differences from the CP group up to 3 hours of observation, with the highest rate of AIA – 77.8 % which was recorded in 0.5 hours. In the range from 0.5 to 1.0 hour, the BNO 2103 AIA rate clearly turned negative dynamics, but the AIA rate decreased gradually in the subsequent points (*Fig. 2*). Diclofenac sodium also reduced ($P < 0.05$) the development of edema compared to the CP, but showed less activity, inhibiting exudation for up to 3 hours. At the same time, up to 2 hours, it was inferior ($P < 0.05$) to BNO 2103 in terms of AIA. At the peak of exudation at the point of 1 hour, its AIA was 42.3 % and 1.7 times lower than in the group of BNO 2103 ($P < 0.05$) (*Fig. 2*).

Thus, BNO 2103 showed the statistically significant anti-exudative effect in the model of zymosan edema, being reliably superior to diclofenac sodium.

Effect of BNO 2103 on the course of histamine-induced edema in rats. The anti-exudative activity of BNO 2103 was studied in a model of histamine – induced paw edema in rats. The results are shown in *Figs. 3, 4.*

In the CP group, the most prominent exudation was observed 1 hour after administration – 32.0 % of a baseline. Then, the edema gradually decreased towards the end of the 6-hour observation (*Fig. 3*).

BNO 2103 showed the anti-exudative effect ($P < 0.05$) comparing to the CP group within 0.5, 1.0 and 3.0 hours after the injection of phlogogen. At the same time, the highest rate of AIA in this model – 44.1 %, was recorded in an hour of observations. Despite a very similar dynamics of edema development in the group of test and reference agents between 2 and 6 hours, the AIA rate differed significantly at the corresponding time points with clear benefits of BNO 2103 (*Figs. 3, 4*).

The reference drug diclofenac sodium showed a weak anti-exudative effect throughout the study and had differences from the CP group only at 1-hour point ($P < 0.05$). Also, at all points, it was inferior ($P < 0.05$) to BNO 2103 in terms of activity. At the time of the peak exudation (1 hour), its AIA was 8.9 %, which was 5.0 times lower than in the group of BNO 2103 ($P < 0.05$) (*Fig. 4*). The obtained data indicate that BNO 2103 has an expressed inhibitory influence on the pro-inflammatory effects of histamine, being significantly superior to diclofenac sodium due to the presence of biologically active substances in its composition and their effects.

Effect of BNO 2103 on the course of serotonin-induced edema in rats. The effect of BNO 2103 on the course of the paw edema caused by serotonin as one of the additional inflammatory mediators was also studied. The injection of serotonin in the CP group caused the development of edema, most prominent at 1- and 2-hour points, when the degree of exudation was 28.9 % and 28.0 % of the baseline, respectively (*Fig. 5*). Over time, its intensity gradually decreased. BNO 2103 showed a moderate anti-exudative effect, which was significant ($P < 0.05$) compared to the CP group in 1 hour after induction, with the highest level of AIA – 27.7 %. Then its activity was in the range of 20.1–17.2 % (*Fig. 6*).

Diclofenac sodium showed 1.6 times higher levels of AIA than BNO 2103 ($P < 0.05$), 1 hour after administration of serotonin (44.4 %). But, subsequently, it was inferior ($P < 0.05$) to BNO 2103 in 3 and 6 hours of observation. Moreover, BNO 2103 1.7 times exceeded the reference drug as to the AIA level in 3 hours, and 2.5 times – in 6 hours, indicating a remarkably prolonged anti-exudative effect in serotonin inflammation (*Fig. 6*). Thus, BNO 2103 performed well, compared to the reference drug due to the moderate but prolonged anti-exudative effect in contrast with significant but short-lived impact of diclophenac sodium, and was superior ($P < 0.05$) to it in terms of AIA levels at later observation points of 3 and 6 hours after phlogogen administration.

Discussion

There is no doubt that inflammation is an important link in the pathogenesis of CKD, especially in the case of its autoimmune or rheumatic origin, which leads to the destruction of membrane structures of nephrocytes, activation of proliferative processes and, consequently, the formation of renal failure (RF). The anti-inflammatory effect of drugs is one of the basic pharmacological effects underlying the organoprotective effect and, in particular, nephroprotective. This determines the feasibility of studying the anti-inflammatory

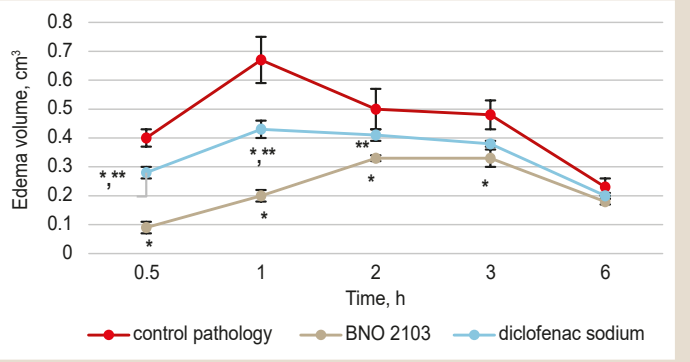

Fig. 1. Effect of BNO 2103 on the course of zymosan – induced edema in rats.Data are presented as M ± SEM; *****: $P < 0.05$ relating to the CP group; ******: $P < 0.05$ relating to the BNO 2103 group.

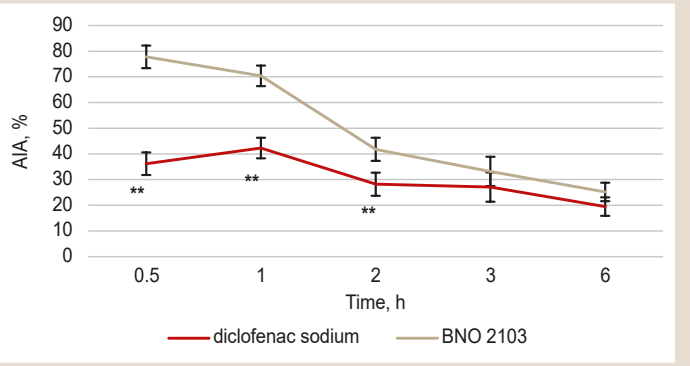

Fig. 2. The effect of BNO 2103 on the course of zymosan – induced edema in rats. Data are presented as M ± SEM; *****: $P < 0.05$ relating to the CP group; ******: $P < 0.05$ relating to the BNO 2103 group.

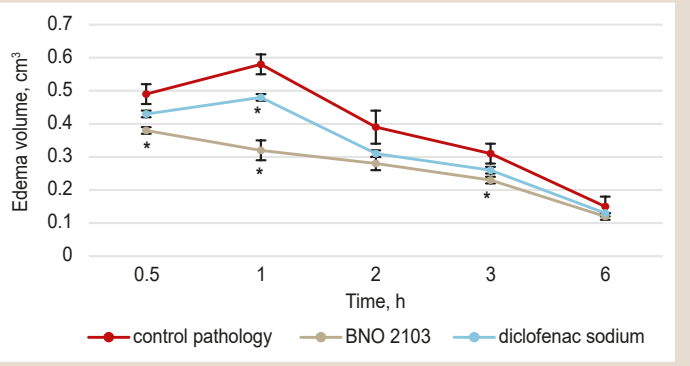

Fig. 3. Effect of BNO 2103 on the course of histamine-induced edema in rats. Data are presented as M ± SEM; *****: $P < 0.05$ relating to the CP group; ******: $P < 0.05$ relating to the BNO 2103 group.

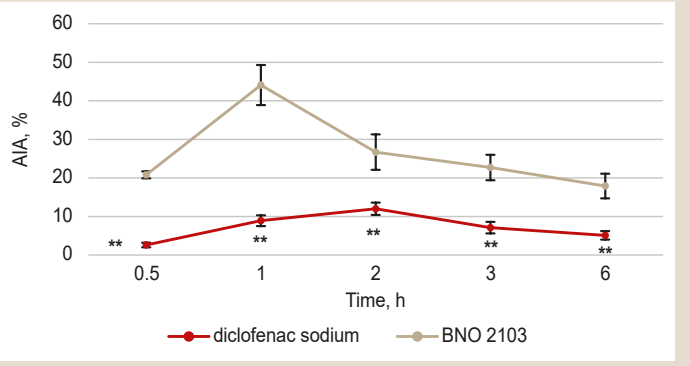

Fig. 4. Effect of BNO 2103 on the course of histamine-induced edema in rats. Data are presented as M ± SEM; *****: $P < 0.05$ relating to the CP group; ******: $P < 0.05$ relating to the BNO 2103 group.

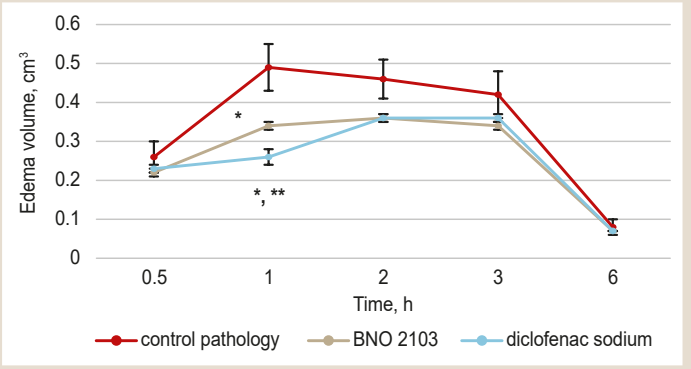

Fig. 5. Effect of BNO 2103 on the course of serotonin-induced edema in rats. Data are presented as M ± SEM; ***:** P < 0.05 relating to the CP group; ****:** P < 0.05 relating to the BNO 2103 group.

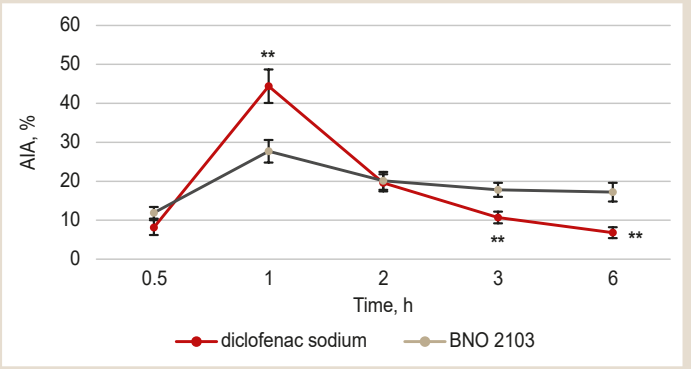

Fig. 6. Effect of BNO 2103 on the course of serotonin-induced edema in rats. Data are presented as M ± SEM; ***:** P < 0.05 relating to the CP group; ****:** P < 0.05 relating to the BNO 2103 group.

properties of the agent proposed for the treatment of CKD in models of experimental inflammatory process.

For this purpose, models of zymosan, histamine and serotonin paw edema in rats were used, which were combined according to the principle of inflammation development mainly through the lipoxygenase pathway of arachidonic acid conversion. This has allowed us to assess the effect of the test object for the lipoxygenase pathway of arachidonic acid metabolism, as well as for the action of additional inflammatory mediators such as serotonin and histamine.

The results of the study on the anti-exudative effect of the combined herbal remedy BNO 2103 in models of paw edema in rats caused by different phlogogens (zymosan, histamine and serotonin) showed that the test drug had a variably expressed inhibitory effect on the development of exudation in all models. Due to the fact that BNO 2103 showed the highest level of activity in the model of zymosan-induced edema, it can be claimed that the most important in the mechanism of its anti-inflammatory effect is the ability to inhibit lipoxygenase pathway of arachidonic acid conversion and leukotriene formation. This is probably associated with the presence of flavonoids in its composition. There has also been demonstrated the ability of BNO 2103 to inhibit the pro-inflammatory action of histamine and serotonin, especially at the beginning of inflammation, which is also possibly related to its antileukotriene activity.

These pharmacological properties of BNO 2103 are determined by a complex of biologically active substances (flavonoids, phenolic acids, essential oils), which are contained in the plant material of the test drug – a mixture of centaury herb, rosemary leaves and lovage root [15]. It is important to note that BNO 2103 is a fixed composition of plant components and a special attention is paid to standardization and reproducibility of technology in the manufacturing process, which is an undeniable advantage of this remedy, taking account of a great variability of plant ingredients.

The main pharmacological effect based on the nephroprotective properties of BNO 2103, is most likely anti-inflammatory. It is known that rosemary acid, which is the main ingredient of BNO 2103, inhibits nonspecific activation of complement and lipoxygenase, and, as a consequence, the synthesis of leukotrienes, as well as breaks the chain of free radical reactions [16].

Diterpenes and polyphenols in rosemary leaves have antioxidant, antibacterial, antiviral, anti-inflammatory activity [17]. Furanocoumarins of lovage root were shown to have antispasmodic and diuretic effects, so they are used for irrigation therapy in inflammatory processes of the lower urinary tract [18,19].

These data are confirmed by studies of Wagenlehner, Nausch et al., which showed a positive therapeutic effect of the test drug on infectious and inflammatory processes of the urinary tract [20,21].

Significant anti-adhesive and anti-inflammatory activity of Canephron® N was also demonstrated in an in vitro and in vivo study by G. Künstle et al. [22].

In a non-interventional prospective clinical study evaluating the use of Canephron® N in pediatric practice, the drug was administered to more than a half of patients as monotherapy for cystitis, pyelonephritis, nephritis, and other urinary tract diseases, and 65 % showed improvements in condition, and 20 % – complete recovery, which also proves the significant anti-inflammatory properties of the drug [23].

Data from a clinical study including 30 patients with chronic calculous prostatitis receiving Canephron® N in addition to extracorporeal shock wave therapy, indicate remarkable symptomatic and anti-inflammatory effects of the drug with excellent compliance with therapy for 90 days [24].

Since the main goal of our research was to substantiate the use of BNO 2103 in the treatment of CKD, the objectives of the study were designed to investigate the nephroprotective, anti-inflammatory, diuretic, hypoazotemic, antiproteinuric effects of BNO 2103. Thus, the first goal was to study the BNO 2103 effect on the course of RF in rats in the model of chromate – induced RF. The second task was to examine the AIA of the active ingredients of the test drug in the model of phlogogen – induced paw inflammation in rats. According to the study results in the model of RF using laboratory and histomorphological methods, it was proved that the composition BNO 2103 has nephroprotective, diuretic, hypoazotemic and antiproteinuric effects and is superior to comparator drugs in most respects [25]. This article presents the results of the second stage of the study – to examine the anti-inflammatory activity of the test drug. Thus, the evidence base is gradually taking shape to build a strong argument for the expansion of indications for the use of BNO 2103 in the treatment of CKD.

A study on the BNO 2103 potential effect on cyclooxygenase – mediated inflammatory pathways using other types of phlogogens (carrageenan, prostaglandin

E2) is one of the subtasks within the framework of the main study purpose. In this research, we have not considered the possibility of combination therapy using BNO 2103 and other drugs for the treatment of CKD, as well as its use in underlying comorbidity. Also, no dose-escalation regimen or other dosing regimens have been used.

Conclusions

Therefore, experimental studies have shown that:

1. The combined herbal composition BNO 2103 has a significant anti-inflammatory effect, exerting an inhibitory effect on exudative inflammation caused by various phlogogens (zymosan, histamine, serotonin).

2. The presence of flavonoids in the composition most likely causes the predominant effect on the lipoxygenase pathway of arachidonic acid conversion, resulting in anti-inflammatory activity.

3. BNO 2103 can be considered as a promising antiphlogistic agent for the correction of inflammatory renal pathology due to its antileukotriene activity and inhibitory effect on the lipoxygenase pathway of arachidonic acid conversion, and therefore on the development of inflammatory reaction, that is very useful in the treatment of CKD, as inflammation is an integral part of its pathogenesis.

Prospects for further research. Further clinical studies are needed to confirm the obtained results and provide a basis for their implementation in real clinical practice.

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