Recommended by Doctor of Medicine, professor T.I.Tiupka

UDC 615.015.13:615.038:616.1

THE STUDY OF THE EFFECT OF THE CHEMOPYRONE SUBSTANCE ON THE ARTERIAL BLOOD PRESSURE UNDER CONDITIONS OF PROPHYLACTIC APPLICATION IN INDUCED HYPERTENSION

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Key words: chemopyrone; diuretic activity; hypertension; systolic and diastolic arterial blood pressure

The most important stage of development of effective and safe new medicines is the methods of preclinical evaluation of their pharmacological activity. Since the existing range of antihypertensive medicines is large enough and the current demands for them are different from those presented several years ago, the aim of this research is to study the effect of the chemopyrone substance on the arterial pressure under conditions of prophylactic application on the experimental model of hypertension induced by Mesatonum. While studying the effect of the chemopyrone substance in the dose of 10 mg/kg on the level of systolic and diastolic arterial pressure it has been determined that the antihypertensive effect is achieved due to the impact on the function of the kidneys. The maximum effect is observed on the 10-th min and equals 64-62% compared to the group of intact animals. The results obtained testify the expressed and prolonged hypotensive effect, and the substance can be recommended for hypertensive states correction in the conditions of prophylactic application.

Increase of effectiveness of the arterial hypertension treatment is still a topical problem of medicine and pharmacy because the causes of this disease, in spite of intensive research in this area, are still unknown [5].

Based on medical statistics data the role of some factors ("risk factors"), such as heredity, age, sex, nutritional peculiarities, weight and others, which can influence on the arterial hypertension development was determined [2].

The results of the study not only demonstrate dependence of cardiovascular pathology development on the arterial pressure level (AT), but also allow to evaluate quantitatively the contribution of the systolic (ATS) and diastolic (ATD) arterial pressure to the risks degree [10]. Usually, ATS increases continually with age and is a strong, independent, but variable index of cardiovascular complications of hypertension. Underestimation of its value leads to underestimation of the prevalence of hypertension and untimely prescription of antihypertensive medicines.

Most studies indicate the promising use of rational combinations of diuretics and *β*-adrenoreceptor antagonists (in low doses) that provide the additive effect, as well as the use of drugs with multiple mechanisms of activity to reach the target level of AT.

As the alternative in regards to the mentioned above the medicines based on pyrol[3,2,1-*ij*]quinoline may be applied for the treatment of hypertension [11]. They do not lead to water and electrolyte imbalance and do not cause the secondary hypertension, as well as exhibit the diuretic activity.

At the Pharmaceutical Chemistry Department of the NUPh 4-methoxyanilide of 1-hydroxy-3-oxy-5,6-dihydro-3*H*-pyrol[3,2,1-*ij*]quinoline-2-carbolic acids under the conditional name of chemopyrone was synthesized. This compound is practically nontoxic and exhibits the expressed diuretic activity [12].

The aim of the present study was to study the effect of the chemopyrone substance on the arterial pressure under conditions of prophylactic application on the experimental model of induced hypertension.

Materials and Methods

The research was conducted on nonlinear white male rats weighting 180-230 g. The effect of the chemopyrone substance on the arterial pressure was studied both on intact animals and on the background of Mesatonum-induced hypertension.

Mesatonum stimulates postsynaptic α_1-adrenoreceptor antagonists and increases percussive emission, thereby, rises systolic and diastolic AT by decreasing the pulse reflectively [3]. Mesatonum was injected intraperitoneally in the dose of 1 mkg/kg [8, 9]. The observation time of animals after Mesatonum injection lasted for 10 minutes.

In total, three experimental groups were formed (each group consisted of 6 animals).

Group 1 – the intact animals injected with Mesatonum only.

Group 2 – the positive control (a single intragastrical dose of peryndopril + Mesatonum in 1 hour).

"Prestarium" tablets (the active substance – 4 mg of perindopril) produced by "Servier's Laboratory" company, France was used as a reference drug. The total mass of a tablet is 90 mg. Dosing was carried out based on the active component. Since the maximum therapeutic dose for human equals 0.15 mg/kg, the extrapolated dose of 1.5 mg/kg was calculated for rats.

Group 3 – the chemopyrone substance in the dose of 10 mg/kg + Mesatonum in 1 hour.

Table 1

Characteristics of Mesatonum-induced hypertension in the control group

No.	AP MmHg before Mesatonum injection Systolic / Diastolic		AP MmHg + Mesatonum on the 10-th min Systolic / Diastolic	
1	134	83	150	91
2	122	76	145	80
3	127	70	132	75
4	136	83	140	90
5	119	78	125	80
6	130	71	136	75
M	128.00	76.83	138	81.83
m	2.72	2.30	6.30	1.24

Table 2

Characteristics of Mesatonum-induced hypertension in the group with the chemopyrone substance

No.	AP MmHg before Mesatonum injection Systolic / Diastolic		AP MmHg + Mesatonum on the 10-th min Systolic / Diastolic	
1	137	86	142	90
2	135	75	145	82
3	123	65	130	63
4	142	94	140	96
5	124	82	134	79
6	124	59	129	63
M	130.83	76.83	136.67	78.83
m	3.34	5.38	4.59	3.98

During the research with the help of a RM-6000 polygraph (Japan) the ATS and ATD indices of non-anesthetized animals were registered. The rats were placed into special cages-cases of a transparent plastic. The cuff and transducer were put on the tail. Automatically, the pressure was given into the cuff, and the value of the external pressure was determined when the transducer stopped registering the pulse vibrations [1].

The comparative effectiveness in the groups was estimated according to several indices [4, 6, 7, 8]:

- Systolic arterial pressure.
- Diastolic arterial pressure.

The hypotensive activity was examined when reducing the arterial pressure by 25 MmHg and more.

Experiments on animals were conducted according to the Council Directive 2010/63/EU of 22 September 2010 on the protection of animals used for scientific purposes.

The results of the studies were processed in accordance with the Van der Waerden's criterion (SW package Statistica 6).

Results and Discussion

Introduction of Mesatonum to the group of intact animals accompanied with a rapid development of hypertension – in all cases the increase of systolic (by an average of 80 MmHg) and diastolic (by an average of 40 MmHg) arterial pressure was observed. At the same time it was determined that the level of ATS was 212±±8.5 MmHg, and ATD 125±7.6 MmHg. The effect reached the maximum on the 10-th min of observation and equaled 60-47% of the baseline values.

Prophylactic introduction of perindopril in the group of animals with Mesatonum-induced hypertension within the time of observation prevented the arterial pressure rising and equaled: ATS 138±6.3 MmHg, ATD 81.83±±1.24 MmHg (Table 1).

Injection of chemopyrone in the dose of 10 mg/kg on the model of Mesatonum-induced hypertension presumably prevents increasing arterial pressure. The maximum effect is observed on the 10-th min and equals 64-62% compared to the group of intact animals.

As the data presented in Table 2 testify with the prophylactic use of the chemopyrone substance no significant increase of systolic and diastolic pressure was observed. It indirectly reflects a pronounced and prolonged hypotensive effect in this dose. Significant distinctions compared to perindopril were not observed as well.

CONCLUSIONS

1. On the model of Mesatonum-induced hypertension the chemopyrone substance has revealed the expressed hypotensive activity, considerably reducing the level of systolic and diastolic arterial pressure.

2. The data obtained allow to consider the chemopyrone substance as a promising chemical compound for creating a medicine on its basis for hypertensive states correction under conditions of prophylactic application.

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ДОСЛІДЖЕННЯ ВПЛИВУ СУБСТАНЦІЇ ХІМОПІРОН НА АРТЕРІАЛЬНИЙ ТИСК В УМОВАХ ПРОФІЛАКТИЧНОГО ЗАСТОСУВАННЯ ПРИ ІНДУКОВАНІЙ ГІПЕРТЕНЗІЇ

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Ключові слова: *хімопірон; діуретична активність; гіпертензія; систолічний і діастолічний артеріальний тиск*

Найважливішим етапом розробки ефективних та безпечних нових лікарських засобів є методи доклінічної оцінки їх фармакологічної активності. Оскільки існуючий арсенал антигіпертензивних засобів великий і сучасні вимоги, які висуваються до них, відрізняються від тих, що мали місце кілька років тому, метою даної роботи стало вивчення впливу субстанції хімопірон на артеріальний тиск в умовах профілактичного застосування на експериментальній моделі індукованої мезатоном гіпертензії. При дослідженні впливу субстанції хімопірон у дозі 10 мг/кг на рівень систолічного та діастолічного артеріального тиску встановлено, що антигіпертензивний ефект досягається за рахунок впливу на діяльність нирок. Максимальний ефект спостерігається на 10-ій хв та становить 64-62% у порівнянні з групою інтактних тварин. Одержані результати свідчать про виражений та тривалий гіпотензивний ефект, а субстанція може бути рекомендована для корекції гіпертензивних станів в умовах профілактичного застосування.

ИССЛЕДОВАНИЕ ВЛИЯНИЯ СУБСТАНЦИИ ХИМОПИРОН НА АРТЕРИАЛЬНОЕ ДАВЛЕНИЕ В УСЛОВИЯХ ПРОФИЛАКТИЧЕСКОГО ПРИМЕНЕНИЯ ПРИ ИНДУЦИРОВАННОЙ ГИПЕРТЕНЗИИ

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Ключевые слова: *химопирон; диуретическая активность; гипертензия; систолическое и диастолическое артериальное давление*

Важнейшим этапом разработки эффективных и безопасных новых лекарственных средств являются методы доклинической оценки их фармакологической активности. Поскольку существующий арсенал антигипертензивных средств большой и современные требования, предъявляемые к ним, отличаются от тех, что имели место несколько лет назад, целью данной работы стало изучение влияния субстанции химопирон на артериальное давление в условиях профилактического применения на экспериментальной модели индуцированной мезатоном гипертензии. При исследовании влияния субстанции химопирон в дозе 10 мг/кг на уровень систолического и диастолического артериального давления установлено, что антигипертензивный эффект достигается за счет воздействия на деятельность почек. Максимальный эффект наблюдается к 10-й мин и составляет 64-62% по сравнению с группой интактных животных. Полученные результаты свидетельствуют о выраженном и длительном гипотензивном эффекте, а субстанция химопирон может быть рекомендована для коррекции гипертензивных состояний в условиях профилактического применения.