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Original Research Article

Dependency of Acute Toxicity and Diuretic Activity upon the Chemical Structure in A 7-Substituted 8-Amino-3-Methylxanthines Row

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Abstract: Derivatives of 7-substituted-8-amino-3-methylxanthines is a promising group of substances for synthesis and pharmacological screening in order to create diuretics, for pharmacological correction of the kidneys, on their basis. The acute toxicity and diuretic activity dependence on the chemical structure for the first synthesized 7-substituted-8-amino-3-methylxanthines in experiments on rats was investigated. 3-Methyl-7-(2-hydroxy-3-p-methoxyphenoxy)propyl-8-(2-furyl)methylaminoxanthine, increases urine excretion at 201.3% and is higher in the diuretic effect comparing to hydrochlorothiazide up to 111.3%.
Keywords: 7-substituted 8-amino-3-methylxanthines, diuretic activity, acute toxicity, renal function

INTRODUCTION

An important issue of modern pharmacology is the creation and introduction into medical practice of more safe and effective medicines that eliminate the violation of cellular metabolism, ion homeostasis and can affect the regulating mechanisms of hemodynamics, water and sodium balance in physiological and pathological conditions. Regulation the sodium and water balance - one of the most important homeostatic functions is very important to develop methods for the rational treatment of diuretic renal function [2, 3].

Renal transport of electrolytes and water is realized through different levels from the molecular to organismic and is controlled by multiple regulatory factors. Violation of balance of intracellular and extracellular fluids has an important role in various human diseases [15].

Pathological processes in the kidneys appear under hypertension, chronic heart failure, nephrotic syndrome, chronic renal insufficiency, diabetes insipidus and other diseases [5, 13]. In the treatment of hypertension, disorders of fluid and electrolyte balance, pharmacological correction of renal excretory function using diuretic drugs is carried out. Despite the progress, achieved in the prevention and treatment by diuretic drugs, much of these problems are relevant, and they need to be in an active research. Along with a strong diuretic effect, diuretics exhibit undesirable side effects: hypochloremic alkalosis, metabolic acidosis, hyperlipidemia, hyperglycemia, azotemia, breach of protein metabolism and others. [9], which limit their use in clinical practice [7, 13].

In this regard, an important task of the experimental pharmacology is to create new drugs effective for improvement of the kidneys and increase urine under pathological conditions.

Our attention was directed on first synthesized organic compounds in a row of 7-substituted-8-amino-3-methylxanthines [14]. Prediction of biological activity of the 7-substituted-8-amino-3-methylxanthines conducted using a unified description of chemical structures and universal mathematical algorithm for dependencies achieving using PASS program (Prediction of Activity Spectra for Substances) using Java applet in site *http://www.pharmaexpert.ru/PASSonline/predict.php.* Chemical structures of compounds were drawn by a computer program Chem Office 2006 (ChemDraw Ultra 10.0) and spectrum of biological activity was measured. Biological activity is presented in the program and expressed qualitatively as "active" / - "inactive» (Pa/Pi) (Pa ≥ 0,300) [8].

PASS prediction of pharmacological activity for 7-substituted-8-amino-3-methylxanthines, shows a wide range of biological effects, and the availability of

diuretic activity was the basis for the further data research.

The aim of the study was the acute toxicity and diuretic activity dependence on the chemical structure for the first synthesized 7-substituted-8-amino-3-methylxanthines in experiments on rats.

Object and methods

The object of the study was a number of 7-substituted-8-amino-3-methylxanthines (comp.1-11), which were synthesized at the Department of Biological Chemistry of Zaporozhye State Medical University under the direction of Doctor of Pharmacy, Professor Romanenko M.I.

The structures of synthesized compounds were confirmed by modern physicochemical methods: elemental analysis, UV-, IR-, HNMR- and mass-spectrometry, by counter synthesis; the purity of synthesized substances controlled by TLC. These substances are white crystalline powder, odorless, with bitter taste. They are not soluble in water, soluble in dimethyl formamide, dimethyl sulfoxide, practically insoluble in ether, ethanol, chloroform [14].

Studies of acute toxicity of 7-(2-hydroxy-3-*p*-methoxyphenoxy)propyl-8-substituted theophylline performed on intact white nonlinear mice of 20-24 g weight, LD_{50} calculated by the Körber method [11]. The study of diuretic activity of these compounds was performed on Wistar white rats weighing 180-195 g by Berkhin method [1, 4]. The substances at a dose of 0.05 LD_{50} and the reference drug hydrochlorothiazide were intragastric administered using a metal probe. In experimental studies conducted animal were held in standard conditions in accordance with the norms and principles of the EU Council Directive on the protection of vertebrate animals used for experimental and other scientific research [4].

The results calculated by methods of variation statistics. The data presented in the form of arithmetic mean and standard error. Differences probability between average values was determined by Student's test with normal distribution. The comparison of groups for qualitative characteristics was performed using the x^2criterion. Research results processed using statistical software packages «Microsoft Office Excel 2003», «IBM SPSS Statistics v. 20 »,« STATISTICA 6.0 ». A statistically significant difference was considered at significance level of at least 0.05 [6, 9].

RESULTS AND DISCUSSION

The results of acute toxicity for 7-substituted-8-amino-3-methylxanthines (comp.1-11) are presented in Table. 1. The data analysis shows that the LD_{50} for synthesized compounds is ranged 290-835 mg/kg. The most toxic (LD_{50} = 290 mg/kg) was compound 6 - 3-methyl-7- (2-hydroxy-3-*p*-methoxyphenoxy) propyl-8-*n*-butylaminoxanthine. Substitution of the *n*-butyl amine (comp. 6) radical in the position 8 of a 7-substituted-8-amino-3-methylxanthines molecule with the 4-benzylpiperazyn-1-yl (comp. 11), *p*-ethoxyphenyl amine (comp. 10), N,N-diethylaminoethylamino radical (comp.14), 4 methylpiperazyn-1-yl (comp. 1), N,N-dimethylaminoethylamino (comp. 3), N-methyl-N-benzylamino (comp. 2), pyrrolidine-1-yl (comp. 7), *m*-tolilamino (comp. 9), β-hydroxyethylpiperazyn-1-yl (comp. 8), (furyl-2)methylamino (comp. 5) leads to reduce the acute toxicity of these substances.

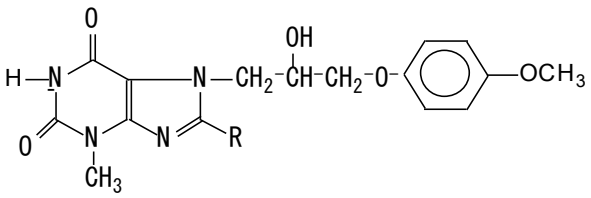

Table 1: Acute toxicity of 7-substituted-8-amino-3-methylxanthines

№	R	$LD_{50, mg/kg}$
1	4-methylpiperazin-1-yl	405.0 ±
2	N-methyl-N-benzylamino	515.0 ±
3	N,N-dimethylaminoethylamino	428.0 ±
4	N,N-diethylaminoethylamino	365.0 ±
5	(furyl-2)methylamino	835.0 ±
6	*n*-butylamino	290.0 ±
7	(pyrrolidin-1-yl)	545.0 ±
8	(β-hydroxyethylpiperazin-1-yl)	695.0 ±
9	*m*-tolylamino	620.0 ±
10	*p*-ethoxyphenylamino	344.0 ±
11	4-benzylpiperazin-1-yl)	302.0 ±

According to the Sydorov's classification of the toxicity for synthetic substances [10], intraperitoneal administration of all tested 7-substituted-8-amino-3-methylxanthines (comp. 1-11) shows that they are practically non-toxic substances.

Analysis of the diuretic activity research results (Tab. 2) shows that the original 7-substituted-8-amino-3-methylxanthines (comp. 1-11) increase the excretion of urine in the range of 25.1% to 201.4% ($p<0.05$).

Table 2: Diuretic activity of 7-substituted-8-amino-3-methylxanthines

Compound №	Dose, mg/kg	**Diuresis after**			
		2 hours		4 hours	
		M±m, ml	% to control	**M±m, ml**	% to control
1	20,3	**2,23±0,17***	155,9	**4,46±0,11***	157,6
2	25,8	**3,27±0,12***	228,7	**5,27±0,12 ***	186,2
3	21,4	**2,90±0,13***	202,8	**4,51±0,14***	159,4
4	18,3	**2,74 ±0,11***	181,6	**5,64±0,26****	199,3
5	41,8	**3,94±0,17****	275,5	**8,53±0,22****	301,4
6	14,8	**3,14±0,16***	219,6	**6,56±0,27***	231,8
7	27,3	**2,53±0,14***	176,9	**3,54±0,23**	125,1
8	34,8	**2,37±0,11***	165,7	**4,17 ±0,20**	147,3
9	31,0	**2,97±0,21***	207,7	**6,89±0,23****	243,5
10	17,2	**3,39±0,17***	237,1	**5,97±0,15***	211,0
11	15,1	**2,70±0,21***	188,8	**5,24±0,23***	185,2
Hydrochlorothiazide	25,0	**2,72±0,09***	190,2	**5,38±0,13***	190,1
Control	–	**1,43±0,13**	100	**2,83±0,28**	100

Notes: * $p<0.05$ and ** $p<0.01$ relative to control

The most pronounced diuretic activity was detected for compound 5 - 3-methyl-7-(2-hydroxy-3-*p*-methoxyphenoxy)propyl-8-(2-furyl)methylaminoxanthine that in the dose of 41.8 mg/kg increased the water diuresis at 201.4% ($p<0.01$).

Introduction into the position 8 of the 7-substituted-8-amino-3-methyxanthine molecule instead of furyl-2-methylamino (comp. 5) radical the *m*-tolylamino (comp. 9), *n*-butylamino (comp. 6) and *p*-ethoxyphenylamino (comp. 10) fragments leads to a reduction of renal excretory function at 143.5%; 131.8% and 111% respectively. By reducing effects on urine other 7-substituted-8-amino-3-methylxanthines depending on various substituents in the position 8 of the molecule this series can be arranged in the following sequence: N,N-diethylaminoetylamino (comp. 4), N-methyl-N-benzylamino (comp. 2), 4-benzylpiperazyn-1-yl (comp. 11), N,N-dimethylaminoethylamino (comp. 3), 4-methylpiperazyn-1-yl (comp. 1), causing rats increase of water diuresis in the range from 57.6% to 99.3% respectively. The reference drug - hydrochlorothiazide increases water diuresis at 90.1% in dose of 25 mg/kg.

We can assume that the diuretic effect for first synthesized derivatives of 7-substituted-8-amino-3-methylxanthines realized by increasing the excretion of sodium in urine and stimulation of renal function [2].

Thus, the most diuretic activity has the compound 5, which exceeds the effect of hydrochlorothiazide up to 111.3% ($p<0.05$) and was selected for further study of specific activity.

CONCLUSIONS

1. All the tested substances in a series of 7-substituted-8-amino-3-methylxanthines related to almost non-toxic compounds.
2. 3-Methyl-7-(2-hydroxy-3-*p*-methoxyphenoxy)propyl-8-(2-furyl)methylaminoxanthine (comp. 5), increases urine excretion at 201.3% and is higher in the diuretic effect comparing to hydrochlorothiazide up to 111.3%.

PROSPECTS FOR FURTHER RESEARCH

Derivatives of 7-substituted-8-amino-3-methylxanthines is a promising group of substances for synthesis and pharmacological screening in order to create diuretics, for pharmacological correction of the kidneys, on their basis.

REFERENCES

1. Берхин, Е. Б. (1977). Методы изучения действия новых химических соединений на функцию почек. *Хим. фарм. журн*, *11*(5), 3-11.
2. Глезер, Г. А. (1993). Диуретики. Руководство для врачей. *М.: Интербук-бизнес*, *352*, 3.
3. Джеймс, А. (1999). Шейман. Патофизиология почки/Пер. с англ. 2-е изд., испр. *М., С. Пб.:«Изд-во БИНОМ»–«Невский Диалект», 1999.–206 с*.

4. Стефанов, О. В. (2001). Доклінічні дослідження лікарських засобів/За ред. ОВ Стефанова. *К.: Авіцена*, 528.
5. Експериментальна артеріальна гіпертензія: вплив лікарських засобів / М.І.Завгородний, Р.С.Довгань, О.О.Нагорна та інші // Київ: ПВП «Задруга», 2014. – 272 с.
6. Лапач, С.Н. (2000). Статистические методы в медико-биологических исследованиях с использо-ванием EXCEL / С.Н. Лапач, А.В. Чубенко, П.Н. Бабич // Київ : Морион, 320 с.
7. Машковский М.Д. Лекарственные средства / М.Д. Машковский. (2009). /изд. 15-е, перераб., испр. и доп.]. - М.: Новая Волна, 1206 с.
8. Методологічне обгрунтування оптимізації комп'ютерного прогнозу біологічної активності вперше синтезованих сполук для проведення скринінгу фізіологічно активних речовин / Б.А. Самура, В.І. Корнієнко, М.І. Романенко // Методичні рекомендації.–К. – 2015. – 16 с.
9. Побочное действие лекарств /С.М. Дроговоз, А.П. Гудзенко, Я.А. Бутко [та ін.] //Х.: «СИМ», 2010. – 480 с.
10. 10 Сернов, Л. Н. (2000). лемент⌋⌇ ксперимен тальной фармакологии/ ЛН Сернов. *ВВ Гацура.□М*, 192.
11. Сидоров, К. К. (1973). О классификации токсичности ядов при парентеральных способах введения. *Токсикология новых промышленных химических веществ*, *13*, 47-57.
12. Ng, G. Y. (2006). Aminophylline as an adjunct diuretic for neonatesa case series / G.Y. Ng, E.H. Baker // *Int. J. Cardiol,110*(1), 122-124.
13. Nadai, M., Kato, M., Yoshizumi, H., Kimura, M., Kurono, S., Abe, F., ... & Hasegawa, T. (2007). Possible involvement of organic anion and cation transporters in renal excretion of xanthine derivatives, 3-methylxanthine and enprofylline. *Life sciences*, *81*(15), 1175-1182.
14. Romanenko, N. I., Kornienko, V. I., & Pakhomova, O. A. (2013). Synthesis, physicalchemical and biological properties of 8-aminosubstituted 7-β-hydroxy (oxo) alkyl (aryl)-xanthenes. In *Xth International Symposium on the Chemistry of Natural Compounds Nov* (p. 269).
15. Djaladat, H., Tajik, P., & Fard, S. A. (2008). The effect of aminophylline on renal colic: A randomised double blind controlled trial. *European Urology Supplements*, *7*(3), 152.