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## IMPACT OF SURFACTANT ON RENAL FUNCTION OF ADULT WISTAR RATS

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The study is focused on elucidate the effect of Laprol-604 on rat renal function. The model of intoxication was produced by oral administration of water solution Laprol-604 to rats of experimental groups. The Laprol-604 administration induced electrolyte imbalance in blood serum and urine of rats. The obtained results testify the renal excretion of nitrogen metabolism products was decreased by the influence of Laprol-604. The adverse effect of Laprol-604 depended on its dose.

**Keywords:** *kidney, Laprol-604, surfactant, polyols, glomerular filtration rate, creatinine, urea, sodium, potassium, chloride.*

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### Introduction

Surface active agents are used in different field of the economy. Surfactants continue to expand of application and consumption scope. The anthropogenic activities and emissions contribute to the entry of surfactants, the first of all, to water, then to soil and air. Wildlife and humans are exposed to surfactants by various pathways. Air, water, soil, sediment and food are sources of polyols for living organisms. The diverse deleterious health effect upon exposure to toxic surfactants in the environment is a matter of serious concern and a global issue [1].

The negative effects of surfactants on living organisms are being studied intensively now [2]. The relevance of this topic is also clearly reflected by the number of publications that have appeared in recent years [4, 5, 6]. This increasing interest is the result of reports of toxic effects of different groups of surfactants in

connection with the ubiquitous detection of these substances in the environment [7, 8, 9]. Nonionic surfactants have been studied from a toxicological standpoint. The polytropic impact of polyols on organism is closely related to the membrane pathology [8, 10, 11]. Nonionic surfactant is Laprol-604 has attracted our attention. This is a complex organic mixture of polyoxypropylene polyols. It has been produced industrially for several decades. Laprol-604 has valuable commercial properties that include water and oil solubility, enough stability and, thus, it has been extensive utilized [12, 13]. This polyol is used as ingredient of manufacturing epoxide resin, enamels, varnishes, plastic, fiber, glues, emulsifiers [14]. Although the toxicity of Laprol-604 has been studied and the findings showed that Laprol-604 was moderately toxic, however the influence of Laprol-604 on kidney is still unknown. The emphasis of this study has been given to elucidate the effect of Laprol-604 on rat renal function.

### Contingents

The study was performed on forty adult male Wistar rats were 100 days old. They had  $180 \pm 20$  g body weight at start

of study. All the procedures were performed according to "General ethical principles of experiments on animals" (Ukrainian, 2001) that agreed with European convention for the protection of vertebrate animals used for experimental and other scientific purposes. Strasbourg, 18.03.1986 [15].

### Object

Laprol-604 was provided from Science and Production Joint Stock Company "Sintez PAV". Laprol-604 was reported to be 96 % pure by the supplier. For all study, it was diluted in deionized water and prepared fresh daily.

### Methods

Males were randomly divided into four groups (10 animals in each group): control and three experimental groups. The model of intoxication was produced by oral administration of water solution Laprol-604 to rats of experimental groups. Laprol-604 has been administered to male rats once daily by gavage at doses of 1/10, 1/100 and 1/1000 LD50 (median lethal dose) — 12.5g/kg, respectively is the first, second and third groups for 30 days. The control group consisted of 10 intact *male rats* were kept on a standard diet, without Laprol-604 administration. Animals were placed in metabolic cages in order to collect 24-hour urine. Rats were euthanized by intraperitoneal administration of thiopental (20 mg/kg) and subsequently decapitated. Trunk blood was collected in centrifuge tubes. Blood serum samples from each of the four rat groups were obtained and stored at a temperature — 20°C.

The serum total protein content was determined by biuret method, creatinine

was found by kinetic Jaffe method, urea was measured by colorimetric berthelot method, potassium, sodium and chloride was measured by colorimetric method for assessing the Laprol-604 toxic effect on rat kidneys [16]. Concentrations of total protein, creatinine, urea, uric acid, sodium and potassium were determined in urine samples using a spectrophotometer PD-303 (Apel, Japan), according to instructions for using test kits of reagents LLC SpinLab (Kharkov, Ukraine). The indicators of the renal function: diuresis per day and minute, glomerular filtration rate (GFR) on the clearance of endogenous creatinine and tubular reabsorption were calculated [17].

The statistical data processing was carried out by using the STATISTICA 6,0 software. The average (arithmetic mean) (M), squared deviations from the mean (y) and standard error of the mean (m) was calculated. Student's t test was used to detect differences between independent groups of normally distributed variables; difference between groups was considered statistically significant at  $p < 0,05$  [18].

### Results and discussion

The present study aimed at investigating the influence of Laprol-604 on renal function by evaluating concentrations of electrolytes, urea, creatinine, and total

Table 1

Changes serum biochemical parameters of adult Wistar rats caused by Laprol-604 (M ± m)

Serum parameters	Group of rats			
	Control group (n = 10)	First group 1/10 LD50 (n = 10)	Second group 1/100 LD50 (n = 10)	Third group 1/1000 LD50 (n = 10)
Serum sodium, mmol/l	131,3 ± 3,6	178,3 ± 3,9 <sup>1</sup>	161,3 ± 2,4 <sup>1</sup>	140,2 ± 3,8 <sup>2</sup>
Serum potassium, mmol/l	6,30 ± 0,2	3,7 ± 0,4 <sup>1</sup>	4,1 ± 0,6 <sup>1</sup>	5,1 ± 0,9 <sup>2</sup>
Serum chloride, mmol/l	79,3 ± 4,6	117,0 ± 4,9 <sup>1</sup>	109,3 ± 4,5 <sup>1</sup>	91,2 ± 4,5 <sup>2</sup>
Serum total protein, g/l	68,52 ± 3,14	51,48 ± 2,10 <sup>1</sup>	57,76 ± 2,03 <sup>1*</sup>	62,89 ± 2,80 <sup>2</sup>
Serum creatinine, mmol/l	42,38 ± 3,73	87,63 ± 3,04 <sup>1</sup>	79,75 ± 3,43 <sup>1</sup>	51,30 ± 4,20 <sup>2</sup>
Serum urea, mmol/l	5,72 ± 0,38	18,33 ± 0,69 <sup>1</sup>	13,47 ± 0,75 <sup>1</sup>	7,73 ± 1,51 <sup>2</sup>

Note 1 — compared to the control group ( $p < 0,05$ );  
2 — compared to the first group ( $p < 0,05$ ).

protein in the blood serum and urine of adult Wistar rats. Concerning of electrolytes both of sodium and chloride were experienced increases in 1,4 and 1,5 times, respectively, in blood serum of rats first group and 1,2 and 1,4 times, respectively, in blood serum of rats second group but potassium was declined in 1,7 and 1,5 times in first and second groups of animals, respectively. The similar changes were observed in the third experimental group however this was only tendency (table 1).

In regard to alterations were observed in urine sodium, potassium and chloride levels between the experimental groups and control group, the concentrations of sodium, potassium and chloride were different to normal. The level of urine potassium was  $37,60 \pm 2,5$  mmol/l,  $31,7 \pm 2,4$  mmol/l and  $28,5 \pm 2,6$  mmol/l in the first, second and third groups, respectively, among animals undergoing Laprol-604, which was much higher than the level found in control animal group. Perhaps the changes of potassium, sodium and chloride concentrations in blood serum are linked

with disorder of reabsorption of these electrolytes by tubular cells.

The Laprol-604 administration induced electrolyte imbalance in blood serum and urine of rats. These results are in agreement with the data found by N.G. Scherban [19]. Sodium is the most abundant extracellular ion, against, potassium is an abundant intracellular ion, plays a vital role of cells. The electrolyte balance derangement resulting from the increased serum level of sodium and chloride and decreased potassium seen in this study provides evidence that the use of Laprol-604 could present a risk for hypertension and arrhythmia

Serum creatinine concentration is one of the traditional screening indices for kidney function and renal structural integrity. Creatinine is cleared by glomerular filtration and is neither secreted nor absorbed by the renal tubules, so, creatinine is used to evaluate glomerular filtration rate [20]. Laprol-604 led to disturbance of renal function, which was characterized by increased in serum creatinine ( $87,63 \pm$

$3,04$  mmol/l) in first

and second ( $79,75 \pm$

$3,43$  mmol/l) groups. These values differ

from the same parameters of rats third group because

their had only tendency to increase values of serum

creatinine ( $51,30 \pm$

$4,20$  mmol/l). At the end of experiment, the urine flow per

minute was found to be lower by 1,9, 1,4 and 1,2 times in the

rats of the first, second and third experimental groups, respectively, than in rats of the control group. Glomerular

**Changes urine biochemical parameters of adult Wistar rats caused by Laprol-604 ( $M \pm m$ )**

Urine parameters	Group of rats			
	Control group ( $n = 10$ )	First group 1/10 LD50 ( $n = 10$ )	Second group 1/100 LD50 ( $n = 10$ )	Third group 1/1000 LD50 ( $n = 10$ )
Urine total protein, g/l	$0,18 \pm 0,05$	$0,49 \pm 0,08^1$	$0,36 \pm 0,05^1$	$0,24 \pm 0,09^2$
Urine creatinine, $\mu\text{mol/l}$	$7374 \pm 297$	$4243 \pm 319^1$	$4987 \pm 314^1$	$6129 \pm 338^2$
Urine urea, mmol/l	$83,26 \pm 1,99$	$43,27 \pm 2,65^1$	$55,78 \pm 2,56^1$	$79,18 \pm 2,36^2$
Daily diuresis, ml	$15,91 \pm 1,12$	$8,2 \pm 1,4^1$	$11,01 \pm 1,16^1$	$12,53 \pm 1,17^2$
Diuresis, ml/min	$0,01104 \pm 0,00012$	$0,00569 \pm 0,00008^1$	$0,00765 \pm 0,00017^1$	$0,00870 \pm 0,00005^2$
GFR, ml/min	$1,92 \pm 0,05$	$0,276 \pm 0,08^1$	$0,478 \pm 0,06^1$	$1,039 \pm 0,08^2$
Tubular reabsorption, %	$99,430 \pm 0,062$	$97,938 \pm 0,176^1$	$98,399 \pm 0,158^1$	$98,852 \pm 0,174^2$
Urine sodium, mmol/l	$147,1 \pm 3,4$	$122,4 \pm 4,7^1$	$130,1 \pm 4,2^1$	$143,4 \pm 4,1^2$
Urine potassium, mmol/l	$26,10 \pm 1,8$	$37,60 \pm 2,5^1$	$31,7 \pm 2,4^1$	$28,5 \pm 2,6^2$
Urine chloride, mmol/l	$62,9 \pm 2,7$	$38,5 \pm 2,6^1$	$50,5 \pm 3,2^1$	$57,4 \pm 3,1^2$

Note 1 — compared to the control group ( $p < 0,05$ );  
2 — compared to the first group ( $p < 0,05$ ).

filtration rate is indirectly computed through creatinine clearance and remains one of the most frequently used markers in the assessment of renal function. The creatinine clearance was calculated in this study in the collection of 24th-hour urine samples. The values glomerular filtration rate rats of four groups are presented in table 2. So, 1/10 LD50 Laprol-604 caused a lower flow, leading to more renal dysfunction.

The urea concentration in urine and urea clearance index was decreased in rats of all Laprol-604 administered groups, but it should be remarked, values were statistically in first and second groups. The serum urea level was significantly increased in 3,2 and 2,4 times in the rats of the first and second groups, respectively, compared with the animals of the control group. Even though urea is freely filtered by the glomerular and not reabsorbed nor actively secreted, contend it is a weak predictor of the glomerular filtration rate because 40 % to 70 % returns to the plasma by a process of passive diffusion, depending on the urine flow. Thus, urine stasis leads to an even greater return of urea in the renal tubules and then urea passively diffuses into plasma [21].

The obtained results testify the renal excretion of nitrogen metabolism products was decreased by the influence of Laprol-604.

At the end of experiment, the elevation of protein concentration was found in urine of all experimental groups treated by Laprol-604, against control parameter. The control group of rats was considered normal proteinuria ( $0,18 \pm 0,05$  g/l). In this aspect, the rats of first and second groups presented the following values  $0,49 \pm 0,08$  g/l and  $0,36 \pm 0,05$  g/l, thus, they lost protein with urine.

It should be noticed, the ability of nonionic surfactants to cause a proteinuria, induced urolithiasis, suppressed renal excretory function and ultimately led to renal failure was reported by Zeyneb Aslan

and Lazine Aksoy, Hйlonse Bilbault and Jean-Philippe Haymann, Amrit Pal Singh, Amteshwar Jaggi Singh, and Nirmal Singh [22, 23, 24]. In addition, according to Valoras N., Letez J. and Goyer et al., the subchronic and chronic dietary tests of Neodol resulted to increase the following parameters: kidney to body weight ratio, serum urea, serum creatinine and proteinuria [25].

Therefore, Laprol-604 adverse effect on the rat kidney was demonstrated the suppression of creatinine and urea excretion, disruption of tubular reabsorption, loss of protein with urine.

### Conclusion

The present study showed that oral administration of Laprol-604 led to renal dysfunction, which was presented by serum and urine electrolyte imbalance, a significant decrease in renal filtration of creatinine and loss of protein and potassium with urine. The adverse effect of Laprol-604 depended on it's dose.

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### Резюме

#### ВОЗДЕЙСТВИЕ ПОВЕРХНОСТНО-АКТИВНОГО ВЕЩЕСТВА НА ФУНКЦИИ ПОЧЕК ВЗРОСЛЫХ КРЫС ЛИНИИ ВИСТАР

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Целью исследования явилось изучение влияния Лапрола-604 на функцию почек взрослых крыс. Эксперимент проводили на половозрелых крысах-самцах линии Вистар с массой тела  $180 \pm 20$  г. Животных рандомизировано разделили на четыре группы, по 10 особей в каждой: первая, вторая, третья и контрольная группы. Модель интоксикации получили ежедневным внутривенным введением водного раствора Лапрола-604 в дозах 1/10, 1/100 and 1/1000 LD50 крысам первой, второй и третьей групп, соответственно. Лапрол-604 вводили в течение 30 дней эксперимента. Сбор суточной мочи проводили с помощью метаболических клеток. Эвтаназию

крыс выполнили под тиопенталовым наркозом в дозе 20 мг/кг, кровь магистральных сосудов собрали в центрифужные пробирки и приготовили образцы сыворотки крови. Концентрации общего белка, креатинина, мочевины, мочевой кислоты, ионов натрия, калия и хлора определяли в пробах мочи и сыворотки крови. Рассчитывали скорость клубочковой фильтрации по клиренсу эндогенного креатинина и канальцевую реабсорбцию. Введение Лапрола-604 вызвало нарушение ионоуретической функции почек крыс, обнаружен дисбаланс электролитов в сыворотке крови и мочи животных. Так, концентрации ионов натрия и хлора в сыворотке крови крыс первой и второй групп достоверно повышались, при одновременном снижении концентрации ионов калия в 1,7 и 1,5 раз, соответственно, относительно показателей контрольных животных. Напротив, концентрация ионов калия в моче крыс первой и второй групп статистически значимо снижалась по сравнению с контрольными данными. Подобные изменения отмечали у крыс третьей группы, но они имели лишь тенденцию. Полученные результаты свидетельствуют о том, что почечная экскреция продуктов метаболизма азота уменьшалась под воздействием Лапрола-604. Концентрации креатинина и мочевины в сыворотке крови крыс первой и второй групп достоверно повышались по сравнению с интактными животными. Длительное введение Лапрола-604 взрослым крысам-самцам первой и второй групп способствовало достоверному снижению скорости клубочковой фильтрации и канальцевой реабсорбции, а также развитию протеинурии. Степень нарушения функции почек зависела от дозы Лапрола-604.

**Ключевые слова:** почка, Лапрол-604, поверхностно-активное вещество, полиолы, скорость клубочковой фильтрации, креатинин, мочевина, натрий, калий, хлор.

### Резюме

#### ВПЛИВ ПОВЕРХНЕВО-АКТИВНОЇ РЕЧОВИНИ НА ФУНКЦІЇ НИРОК ДОРОСЛИХ ЩУРІВ ЛІНІЇ ВІСТАР

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Метою дослідження стало вивчення впливу Лапролу-604 на функцію нирок дорослих щурів. Експеримент проведено на статевозрілих щурах-самцях з масою тіла  $180 \pm 20$  г. Тварин рандомізовано поділили на чотири групи, по 10 щурів у кожній: перша, друга, третя і контрольна групи. Модель інтоксикації отримали щоденним пероральним введенням водного розчину Лапролу-604 у дозах 1/10, 1/100 and 1/1000 LD50 щурам першої, другої та третьої груп, відповідно. Лапрол-604 вводили впродовж 30 днів експерименту. Сечу щурів збирали протягом доби за допомогою метаболічних кліток. Евтаназію здійснювали під тіопенталовим наркозом у дозі 20мг/кг, збирали кров з магістральних судин та виготовляли зразки сироватки крові. Концентрації загального білка, креатиніну, сечовини, сечової кислоти, іонів натрію, калію і хлору визначали у пробах сечі і сироватки крові. Розраховували швидкість клубочкової фільтрації за кліренсом ендогенного креатиніну і канальцеву реабсорбцію. Введення Лапролу-604 спричинило порушення іоноуретичної функції нирок щурів, виявлено дисбаланс електролітів в сироватці крові і сечі тварин. Так, концентрації іонів натрію і хлору у сироватці крові щурів першої і другої

груп достовірно підвищувалися, при одночасному зниженні концентрації іонів калію в 1,7 і 1,5 раз, відповідно, в порівнянні з показниками контрольних тварин. Навпаки, концентрація іонів калію у сечі щурів першої і другої груп статистично значуще знижувалася у порівнянні з контрольними даними. Подібні зміни відзначали у щурів третьої групи, але вони мали лише тенденцію. Отримані результати свідчать про те, що ниркова екскреція продуктів метаболізму азоту зменшувалася під впливом Лапролу-604. Концентрації креатиніну і сечовини у сироватці крові щурів першої і другої груп достовірно підвищувалися в порівнянні з інтактними тваринами. Тривале введення Лапролу-604 дорослим щурам-самцям першої і другої груп сприяло достовірному зниженню швидкості клубочкової фільтрації і канальцевої реабсорбції, а також розвитку протеїнурії. Ступінь порушення функції нирок залежала від дози Лапролу-604.

**Ключові слова:** нирка, Лапрол-604, поверхнево-активна речовина, поліоли, швидкість клубочкової фільтрації, креатинін, сечовина, натрій, калій, хлор.

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