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BLOOD CREATININE CONTENT AND RAT KIDNEY STRUCTURE AFTER INTRAMUSCULAR INJECTION OF PEGYLATED ANTIBIOTIC ENROFLOXACIN

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Kozak, M., Zelenina, O., Ostapiv, D., Skrypka, M., Samaryk, V., & Vlizlo, V. (2023). Blood creatinine content and rat kidney structure after intramuscular injection of pegylated antibiotic enrofloxacin. *Studia Biologica*, 17(3), 47–56. doi:10.30970/sbi.1703.720

Background. Polyethylene glycol (PEG) is able to affect the permeability of membranes by increasing the entry of antibiotics into the cell of microorganism; therefore, PEGylation may improve the effectiveness of antibiotics due to chemical modification of their molecules. It is important to assess the safety and toxicity of new compounds for drug development activity. The aim of this research was to study the functional state and structure of the kidneys of laboratory rats after intramuscular administration of PEGylated antibiotic enrofloxacin, as well as commercial antibiotic enrofloxacin and polymer PEG-400, which were used for the synthesis of PEGylated antibiotic enrofloxacin.

Materials and Methods. PEGylated antibiotic enrofloxacin was obtained via the reaction between enrofloxacin chloride and PEG-400 polymer (polyethylene glycol with a molecular weight of 400 Da). The research was conducted on four groups of rats: control and three experimental ones, 12 animals in each group. Physiological saline solution was intramuscularly injected to the control rats; commercial antibiotic enrofloxacin – to rats of the first experimental group; polymer PEG-400 – to rats of the second experimental group; PEGylated antibiotic enrofloxacin – to rats of the third experimental group.

Results. The conducted studies did not show a significant difference between the serum creatinine in control rats and experimental ones on the 7th, 14th and 21st days after the last administration of the drugs**.** Creatinine levels in the blood of all groups of animals were within physiological ranges. Histological studies of the kidney structure in control rats indicated no changes during the experiment. Histological changes in the structure of the kidneys were observed within the first seven days after the end of the intramuscular administration of polymer PEG-400 and PEGylated antibiotic enrofloxacin. Injections of the commercial form of antibiotic enrofloxacin to experimental rats caused histological changes in the kidney structure for 21 days of the experiment.

Conclusions. Quadruple intramuscular administration of PEGylated and commercial antibiotics enrofloxacin to rats showed that PEGylation reduces nephrotoxicity and shortens the duration of adverse effects in the kidneys.

Keywords: rats, polymer PEG-400, PEGylated antibiotic enrofloxacin, creatinine, kidney structure

INTRODUCTION

Kidney damage occupies one of the leading places in human morbidity and mortality after the use of antibiotics (Klein *et al.*, 2021). Therefore, the main task for creating new antimicrobial drugs or modification of available ones is to minimize side their effects on the organism, and ensure their high therapeutic effectiveness (Gray & Wenzel, 2020). In particular, low nephrotoxicity is an important criterion (Morales-Alvarez, 2020).

Antibacterials of the fluoroquinolone group belong to low-toxic synthetic drugs (Alhassani *et al.*, 2021). An effective representative of this group is antibiotic enrofloxacin (Trouchon & Lefebvre, 2016). It has a wide spectrum of antibacterial activity against a number of gram-negative and gram-positive bacteria (Fuchs *et al.*, 2023). However, some studies indicate that for the antimicrobial effectiveness of enrofloxacin, its dose should be increased, which can cause a toxic effect on the body (Kang *et al.*, 2019). It has been established that fluoroquinolone antibiotic therapy causes renal failure within two months after the end of their administration (Alhassani *et al.*, 2021).

Currently, new drug delivery systems have been developed using polymer carriers of natural and synthetic origin, which reduce the toxic effect on the organism (Soultan *et al.*, 2019; Stasiuk *et al.*, 2022). In particular, antibacterial drugs combined with polyethylene glycol (PEG) via PEGylation are promising (Lam *et al.*, 2020). Drug delivery systems based on PEGylation method play an important role in safe drugs development, preventing their accumulation in the organism (Panlilio *et al.*, 2021). Most importantly, PEGylation can improve the effectiveness of antibiotics against common microorganisms (Gu *et al.*, 2020). Therefore, the creation of new antibiotics with carriers should provide a targeted effect on bacterial cells, have low organotoxicity and ensure highly effective treatment for patients.

The aim of the research was to determine the serum creatinine content and the structure of the kidneys of laboratory animals after intramuscular injection of PEGylated antibiotic enrofloxacin and compare the data obtained for the commercial form of antibiotic enrofloxacin and polymer PEG-400, which were used to create PEGylated enrofloxacin.

MATERIALS AND METHODS

Polyethylene glycol with a molecular weight of 400 Da was used for synthesis of PEGylated enrofloxacin. PEGylated antibiotic enrofloxacin was obtained by attaching the carboxyl group of antibiotic enrofloxacin to the ends of the PEG-400 polyoxyethylene hydrophilic chain (Dron *et al.*, 2018). The purity of the created PEGylated antibiotic enrofloxacin was 98–99% (Zelenina *et al.*, 2021).

The studies were conducted on clinically healthy male rats (Wistar line), three months old, body weight 180–200 g, which were kept in usual vivarium conditions on a standard diet. Four groups of animals – control and three experimental ones were formed to study the effect on the functional state and structure of the kidneys of PEGylated antibiotic enrofloxacin and the substances that were used for its creation: antibiotic enrofloxacin and polymer PEG-400. Each group included 12 laboratory rats. The animals were injected intramuscularly with 0.03 mL of physiological solution (control group), 0.03 mL of commercial antibiotic enrofloxacin solution (the first experimental group), 0.03 mL of PEG-400 solution (the second experimental group), 0.03 mL of PEGylated enrofloxacin solution (the third experimental group). The doses of antibiotic enrofloxacin in the PEGylated and commercial forms were 2.7 mg per 1 kg of body weight. The dose of PEG-400 in the second and third experimental groups was 1.5 mg per 1 kg of body weight. The drugs were administered daily for four days.

Blood and kidney tissue samples for the research were collected after the decapitation of rats. Animals were euthanized under thiopental anesthesia. Blood was collected in a tube with a blood coagulation activator (SiO_2) on the 7th, 14th and 21st days after the last administration of the studied drugs. Serum creatinine content was determined by the Jaffe method on a biochemical analyzer (Evolution 3000, Italy) using sets of reagents from the company “SpineLab” (Ukraine).

Kidney tissue samples for histological studies were fixed in a 10% formalin solution, dehydrated in alcohols of increasing concentration and embedded in paraffin, and then the sections with a thickness of 5–7 μm were cut on a sledge microtome. The obtained kidney sections were placed onto glass slides and stained with hematoxylin and eosin. The structure was examined with a light microscope at a 400-fold magnification.

Statistical analysis of the results was carried out using a personal computer and Excel software. In each group of indicators, the arithmetic mean (M) and its error (m) were calculated, as well as the probable difference (p) between the indicators of different groups was established, a p-<0.05–0.001 was considered probable. Data normal distribution, which includes experimental samples, was verified using the Shapiro–Wilk test. The values of blood creatinine content, depending on the type of substances and the duration of experiment, were compared using atwo-way ANOVA.

The housing, feeding, care of the animals and all manipulations were carried out in accordance with the European Convention for the Protection of Vertebrate Animals Used for Experimental and Other Scientific Purposes (Strasbourg, 1986) and the General Ethical Principles of Animal Experimentation adopted by the First National Congress on Bioethics (Kyiv, 2001). Experiments were conducted in compliance with the principles of humanity outlined in the directive of the European Union (Directive 2010/63/EU). The Committee on Bioethics of the Institute of Animal Biology NAAS of Lviv provided a permission to conduct this research (Protocol No. 86; of 26 June, 2020).

RESULTS AND DISCUSSION

A daily examination of laboratory rats indicated that there was no effect of the administered drugs on the physiological state of the control and experimental animals. It is known that antibacterials can cause structural and functional disorders of the kidneys without visible clinical signs (Morales-Alvarez, 2020). Serum creatinine contents of rats did not differ much between the control and experimental groups on the 7th, 14th and 21st days after the end of administration of the drugs, and the indicators were within the physiological range (**Fig. 1**). Normal serum creatinine levels for rats are 0.4–0.8 mg/dL or 35.37–70.74 μmol/L (Thammitiyagodage, 2020). We found decreased creatinine content on days 7 and 14 of the experiment in all groups, including the control. Considering that creatinine levels were within normal physiological range, this effect can be explained by age changes. Serum creatinine is one of the main biomarkers of the functional state of kidneys, but its content in the blood increases with significant damage to the organ (Levchenko & Vlizlo, 2019).

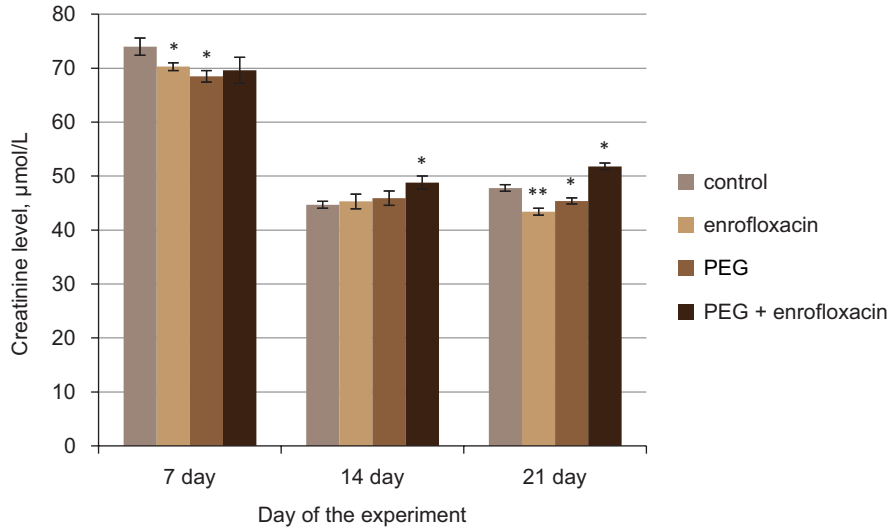

Fig. 1. The content of creatinine in the serum of rats, μmol/L
Note: the difference is statistically significant compared to the control * – $p < 0.05$; ** – $p < 0.01$

The kidney structure of the control group is demonstrated on **Figure 2**.

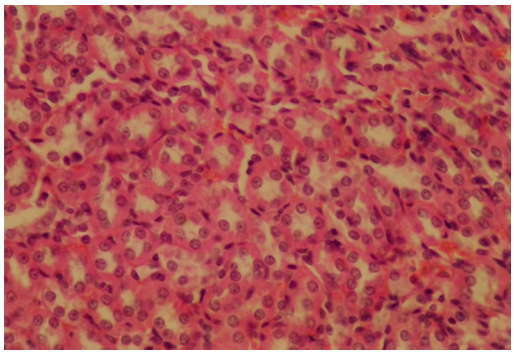

Fig. 2. A kidney tissue section of rats of the control group on day 7

The histological analysis of the kidney structure indicated their damage in the animals of all experimental groups during the first seven days after the end of drug administration. In the animals of the experimental group that received polymer PEG-400, the structure of the kidneys on the 7th day of the experiment showed signs of moderately pronounced vacuolization in the cytoplasm of nephrocytes of the walls of the convoluted tubules and swelling of the perinucleolar zone. Cells with signs of granular dystrophy and paranecrosis were also observed (**Fig. 3**). On the 14th and 21st days of the experiment, rats that received polymer PEG-400 did not have any histological changes in their kidneys. According to the literature (Rafiq *et al.*, 2015), PEG with a molecular weight of 400 Da is optimal for conjugation with antibiotics and does not have an adverse effect on kidney function, nor does it cause morphological changes of their structure in rats.

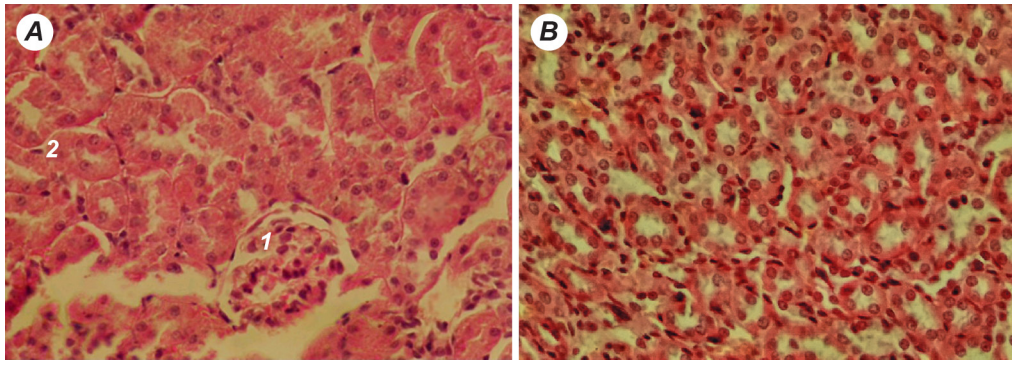

Fig. 3. ***A*** – a kidney tissue section of rats after the administration of PEG-400 on day 7; ***B*** – a kidney tissue section of rats after the administration of PEG-400 on day 14

Notes: *1* – moderate blood filling of the capillaries of the vascular glomerulus; *2* – convoluted tubule nephrocytes with signs of granular dystrophy and paranecrosis

Pathological changes in the kidneys were found on the 7th, 14th and 21st days after the end of administration of the commercial form of antibiotic enrofloxacin to rats. The signs of granular dystrophy, foci of paranecrosis and necrosis of convoluted tubules of nephrocytes were registered in the kidneys of rats of this group. Cytoplasm in 20% of cells had signs of vacuolization (**Fig. 4**). The nephrotoxic effect of the antibiotic enrofloxacin on animal organism was caused (El-Daly, 2013) after the administration of enrofloxacin to experimental animals at a dose of 75 mg/kg for 10 days.

Seven days after the end of the injection, the structure of the kidneys of animals injected with PEGylated antibiotic enrofloxacin was characterized by a slight increase of cell volumes and narrowing of the renal tubules lumens. In separate areas of the cortical zone, nephrocytes of convoluted tubules had vaguely defined contours and their apical part had the appearance of a shapeless mass. In the medulla and cortical zone of the kidneys, vessels are moderately filled with blood cells (**Fig. 5**).

On the 14th and 21st days of the experiment, no morphological changes were detected in the kidneys of rats treated with PEGylated antibiotic enrofloxacin, and their structure was identical to that of the control group. Consequently, the use of the PEGylated antibiotic enrofloxacin in experimental rats contributed to the reduction of both the toxicity and duration of the pathological effect in the kidneys. Other researchers point out the positive role of PEGylation for reducing of the toxic effect of antimicrobial drugs on the kidneys (Benincasa *et al.*, 2015). Our previous studies indicate

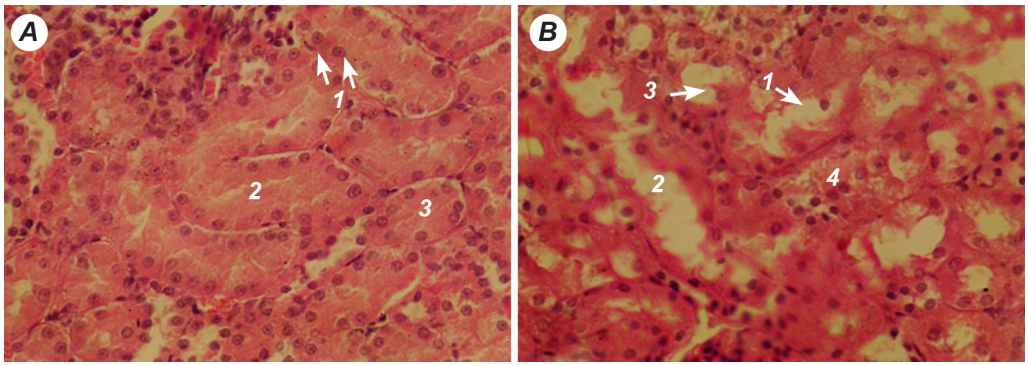

Fig. 4. ***A*** – a kidney tissue section of rats after the administration of commercial form of enrofloxacin on day 7; ***B*** – a kidney tissue section of rats after the administration of commercial form of enrofloxacin on day 21

Notes: ***A***: *1* – convoluted tubule nephrocytes; *2* – primary urine in the tubular lumen; *3* – convoluted tubule nephrocytes with signs of granular dystrophy and paranecrosis; ***B***: *1* – denudation of the basement membrane of proximal tubules; *2* – lumen expansion of the tubules; *3* – formation of cytoplasmic outgrowths of the apical part of nephrocytes; *4* – vacuolization of the cytoplasm of nephrocytes

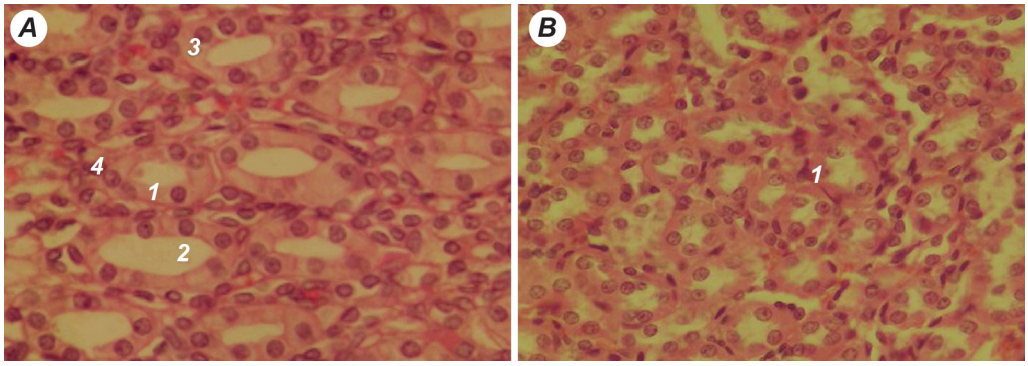

Fig. 5. ***A*** – A kidney tissue section of rats after the administration of PEGylated enrofloxacin on day 7; ***B*** – a kidney tissue section of rats after the administration of PEGylated enrofloxacin, on day 14

Notes: *1* – proximal convoluted tubule; *2* – lumen expansion of the distal tubules; *3* – tubule nephrocytes, *4* – nephrocytes of convoluted tubules with vaguely defined contours

that PEGylation of antibiotic enrofloxacin also decreases its hepatotoxicity (Zelenina *et al.*, 2022). This is explained by the fact that PEGylation leads to the formation of a biphilic macromolecule, which is capable of forming self-stabilized dispersions with nanometer-sized particles of the dispersed phase in aqueous solutions. Stabilization of such particles in an aqueous solution is based on the formation of a structural-mechanical barrier of hydrated polyoxyethylene chains around the nucleus, in which the antibiotic is located. Since the antibiotic enrofloxacin is poorly soluble in water (Yang *et al.*, 2022), its conjugation with PEG leads to the formation of a compound with a good solubility in water and ensured stability, which allows the drug to stay in the organism, penetrate into target tissues or organs without causing negative side effects (Bhattacharya *et al.*, 2019), enhance antibacterial and therapeutic potential (Soultan *et al.*, 2019). Moreover, this may prevent the development of antibiotic resistance (Moen *et al.*, 2021).

CONCLUSIONS

After intramuscular injection of PEGylated antibiotic enrofloxacin, commercial antibiotic enrofloxacin and PEG-400 to laboratory rats, serum creatinine content was within the physiological range. Histological analysis of the kidneys of animals that were intramuscularly injected with PEGylated antibiotic enrofloxacin showed minor changes in the structure within the first seven days of the experiment. The administration of the commercial form of antibiotic enrofloxacin caused morphological changes in the structure of kidneys 21 days after the end of the injections. Thus, PEGylation of the antibiotic enrofloxacin leads to a decrease of its nephrotoxicity.

COMPLIANCE WITH ETHICAL STANDARDS

Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Human Rights: This article does not contain any studies with human subjects performed by any of the authors.

Animal Rights: All international, national and institutional guidelines for the care and use of laboratory animals were followed.

AUTHOR CONTRIBUTIONS

Conceptualization, [V.V.; D.O.]; methodology, [O.Z.; M.K; M.S]; investigation, [V.V.; D.O.; V.S.]; data analysis, [M.K.]; writing – original draft preparation, [O.Z.]; writing – review and editing, [O.Z.; M.K.; V.V.]; visualization, [V.S.]; supervision, [V.V.; V.S.]; project administration, [V.V.; D.O.; V.S.]; funding acquisition, [–].

All authors have read and agreed to the published version of the manuscript.

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ВМІСТ КРЕАТИНІНУ У КРОВІ ТА СТРУКТУРА НИРОК У ЩУРІВ У РАЗІ ВНУТРІШНЬОМ'ЯЗОВОЇ ІН'ЄКЦІЇ ПЕГЕЛЬОВАНОГО АНТИБІОТИКА ЕНРОФЛОКСАЦИНУ

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Обґрунтування. Поліетиленгліколь (ПЕГ) може впливати на проникність мембран, збільшуючи надходження антибактеріального препарату клітинами

мікроорганізмів, тому пегілювання підвищує ефективність антибіотиків за допомогою хімічної модифікації їхніх молекул. Важливим є встановити токсичність новоствореного препарату на організм. Метою досліджень було вивчити функціональний стан і структуру нирок лабораторних щурів за внутрішньом'язового введення їм пегельованого антибіотика енрофлоксацину, а також традиційного антибіотика енрофлоксацину та полімеру ПЕГ-400, які використовували для створення пегельованого антибіотика енрофлоксацину.

Матеріали та методи. Пегельований антибіотик енрофлоксацин одержували за реакцією взаємодії хлорангідриду енрофлоксацину з полімером ПЕГ-400 (поліетиленгліколь молекулярною масою 400 Да). Дослідження проведено на чотирьох групах щурів: контрольній і трьох дослідних, по 12 тварин у кожній. Контрольним щурам внутрішньом'язово вводили фізіологічний розчин, а дослідним групам: першій – традиційний антибіотик енрофлоксацин, другій – полімер ПЕГ-400, третій − пегельований антибіотик енрофлоксацин.

Результати. Проведені дослідження не встановили суттєвої різниці між вмістом креатиніну в сироватці крові лабораторних щурів контрольної та дослідних груп через 7, 14 та 21 доби після останнього введення препаратів. Показники креатиніну у крові всіх груп тварин перебували у межах фізіологічних коливань. Гістологічних змін у структурі нирок у контрольних щурів не було виявлено за час проведення експерименту. За внутрішньом'язового введення дослідним тваринам полімеру ПЕГ-400 і пегельованого антибіотика енрофлоксацину гістологічні зміни структури нирок встановлювали протягом перших 7 днів після закінчення введення препаратів. Ін'єкції дослідним щурам традиційної форми антибіотика енрофлоксацину спричиняло гістологічні зміни структури нирок протягом 21 доби експерименту.

Висновки. Чотириразове внутрішньом'язове введення щурам пегельованого та традиційного антибіотиків енрофлоксацину встановило, що пегілювання знижує нефротоксичну дію та скорочує тривалість негативного впливу на нирки.

Ключові слова: щури, полімер ПЕГ-400, пегельований антибіотик енрофлоксацин, креатинін, структура нирок

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