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## Study of toxicological characteristics of the preparation "Amoxidev 60" in a preclinical experiment on mice

**Sachuk R. M. (ORCID: 0009-0001-0013-416X)**
**Higher Education Institution "Podilskyi State University", Kamianets-Podilskyi, 32316, Ukraine, email: sachukruslan2@gmail.com**

***Abstract.*** *Antibiotics of the β-lactam series, in particular amoxicillin and its derivatives, are widely used in veterinary medicine for the treatment of infectious diseases. Preclinical toxicological evaluation of new dosage forms is necessary to confirm their safety.*
*The aim of the article was to experimentally determine the acute toxicity of the veterinary drug "Amoxidev 60" (based on amoxicillin trihydrate) in laboratory mice and to assign it to the appropriate toxicity class according to modern criteria.*
*The study was conducted on 48 female non-linear white mice aged 3–4 months and weighing 21–22 g, which were kept in standard vivarium conditions. The drug was administered intragastrically in doses of 2000–12000 mg/kg. The animals were observed for 14 days, after which a pathological analysis was performed. Toxicometric indicators ($LD_{10}$, $LD_{16}$, $LD_{50}$, $LD_{84}$, $LD_{90}$, $LD_{100}$) were determined by the probit analysis method.*
*It was established that the median lethal dose ($LD_{50}$) of the drug was 9183,07±887,66 mg/kg body weight. "Amoxidev 60" is classified as toxicity class V (practically non-toxic substances) and hazard class IV (low-hazard substances). At a dosage of 2000–6000 mg/kg, clinical manifestations of intoxication and cases of death of mice were not detected. Higher doses (8000–12000 mg/kg) caused dose-dependent signs of poisoning and lethal consequences.*
*Therefore, the drug "Amoxidev 60" has a wide range of safe doses and can be considered safe for therapeutic use in veterinary medicine. The results obtained are the basis for further pharmacological and clinical studies.*
**Keywords:** amoxicillin trihydrate; "Amoxidev 60"; acute toxicity; laboratory mice; $LD_{50}$; toxicological assessment; veterinary medicine; preclinical studies

Antibacterial drugs of the β-lactam series, in particular amoxicillin and its derivatives, are widely used in veterinary medicine for the treatment of infectious diseases of various animal species (Hahne, 2023; Turner, 2022; Caneschi, 2023). Due to its high effectiveness against gram-positive and gram-negative microorganisms, amoxicillin remains one of the basic drugs in the treatment regimens of respiratory and digestive tract diseases in pigs and poultry (Ledesma, 2018; Fadel, 2022; Kostyshyn, 2022; Masliuk, 2025). However, when creating new dosage forms or improving existing ones, it is mandatory to conduct preclinical studies to confirm their safety (Sachuk, 2025; Katsaraba, 2025). One of the key areas of such research is the assessment of acute toxicity in laboratory animals (Kondratiuk, 2024; Sachuk, 2023; Hunchak, 2020). The study of toxicological characteristics is necessary to determine the range of safe doses, predict possible risks and establish the toxicity class of the drug. Thus, toxicological assessment plays a fundamental role in ensuring the proper quality and safety of veterinary drugs. Significant attention in global veterinary toxicology is paid to the development of standardized methods that allow obtaining reliable and reproducible results (Jacobs, 2024). In accordance with the requirements of European directives and domestic regulatory documents, acute toxicity studies are conducted on laboratory mice, as a universal and highly sensitive model for assessing the effects of drugs on the body. This approach provides the ability to detect clinical manifestations of intoxication, lethal doses and calculate the median lethal dose ($LD_{50}$) (Finch, 2023; Kojima, 2023). The data obtained are important for determining the hazard class of the substance and forming recommendations for its use in practice. In addition, the results of the studies become the basis for further pharmacological and clinical trials. This allows combining experimental results with the practical needs of veterinary medicine.

The study of the toxicity of the drug "Amoxidev 60, created on the basis of amoxicillin trihydrate, has both scientific and practical significance. The drug is intended for the treatment of infectious

diseases of pigs caused by microorganisms sensitive to amoxicillin, and therefore requires careful confirmation of its safety. The use of laboratory mice in toxicological experiments allows you to determine the clinical manifestations of poisoning, characteristic pathological changes and critical dosage levels. Calculation of toxicometric parameters, in particular $LD_{50}$, allows to attribute the drug to the appropriate toxicity and hazard class. This is important not only for substantiating the possibility of its use, but also for predicting the potential impact on the environment. As a result, the results obtained will contribute to ensuring the effectiveness and safety of "Amoxidev 60" in veterinary practice.

**The aim of the study** was to experimentally determine the acute toxicity of the drug "Amoxidev 60" in laboratory mice, assess its safety during intragastric administration, and assign the drug to the appropriate toxicity class according to modern toxicological criteria.

**Materials and methods of research.** Preclinical study of a medicinal product based on amoxicillin trihydrate – an antibacterial veterinary drug for systemic use – was conducted on the basis of the laboratory for quality control, safety and registration of veterinary medicinal products and feed additives of LLC «DEVIE». 1 g of the drug contains the active substance: amoxicillin – 500 mg (in terms of amoxicillin trihydrate – 573 mg). Excipient: citric acid anhydrous. The drug is used to treat pigs with diseases of the digestive tract and respiratory organs caused by microorganisms sensitive to amoxicillin.

Pharmacological tests were carried out in accordance with officially approved methodological approaches, with strict adherence to international standards and ethical principles, which made it possible to obtain results that are characterized by a high degree of reliability, reproducibility and scientific validity (Honcharuk, 1995; Datsenko, 2001; Kotsiumbas, 2006).

The experiment was conducted on 48 female non-linear white mice (3-4) months old and weighing (21-22) g. Laboratory animals were kept in standard cages (8 units), measuring 40×60 cm, which provided sufficient space for free movement. For special conditions, two cages measuring 20×40 cm with a limited area were also used. The vivarium is equipped with an isolated room for conducting different stages of experiments and is equipped with a monitoring system that allows you to track the health of animals in a constant control mode (Voroniak, 2023).

Complete mixed feed for rodents was used for feeding mice. Animals had free access to water and food.

Before the start of the studies, each animal was weighed, and a solution was prepared from the drug in distilled water. The doses of the drug "Amoxidev 60" administered were calculated individually, according to the weight of each mouse. At the same time, the volume of the drug suspension administered intragastrically did not exceed 1,0 $cm^3$. The determination of the dose range for the main experiment was carried out in a preliminary experiment.

For this purpose, in the preliminary experiment, a control and three experimental groups of 4 animals each (n=4) were formed according to the principle of analogues. The drug "Amoxidev 60" in the form of a solution was administered in doses of 2000,0; 7000,0 and 12000,0 mg/kg of body weight, by absolute weight of the drug, once orally using an esophageal-gastric tube. Animals of the control group were administered distilled water.

The clinical condition of the experimental animals was observed for 14 days, noting the appearance and development of clinical signs of poisoning, the time of death or recovery to physiological norm. During the clinical examination of the mice, attention was paid to behavior, reaction to external stimuli, the presence of appetite, skin condition, color of mucous membranes, frequency of breathing and defecation, changes in color and consistency of feces, etc.

After the death of the animals, a pathological autopsy was performed. To establish pathological changes, a macroscopic method of research was used (Sentyurin et al., 2005). The pathological autopsy was performed according to the following scheme:

– at the first stage, an external examination was performed, noting the condition of the fur coat and mucous membranes;

– on the second – an autopsy and examination of body cavities and internal organs, such as the pharynx, trachea, larynx, heart, lungs, liver, spleen, kidneys, stomach, intestines were performed, noting changes in color, consistency, pattern and shape of the organs.

Based on the results of death, the $LD_{10}$, $LD_{16}$, $LD_{50}$, $LD_{84}$, $LD_{90}$, $LD_{100}$ and the $LD_{50}$ error were calculated using the probit analysis method modified by V. B. Prozorovsky.

The studies were conducted in the vivarium of DEVIE LLC. The room has a total area of 50 $m^2$ and is intended for keeping a limited number of laboratory animals for scientific purposes under the

constant supervision of the company's specialists. Feeding was carried out in accordance with the species, physiological state and needs of the animals, observing the principles of a balanced diet. The composition of the granulated feed included optimal amounts of proteins, fats, carbohydrates, vitamins and minerals. The storage conditions of the feed ensured their safety and excluded the possibility of spoilage.

Manipulations on rats were carried out in accordance with existing regulatory documents (European convention for the protection of vertebrate animals used for experimental and other scientific purposes, 1986; Stattia 26 Zakonu Ukrainy No. 5456-VI, 2012; Council Directive 86/609/EEC, 1986), which regulate the organization of work with the use of experimental animals and compliance with the principles of the «European Convention for the Protection of Vertebrate Animals Used for Experimental and Other Scientific Purposes» (EC, 1986).

The results obtained were processed by methods of variational statistics, using the StatPlus 7.6.5.0 program package. The data were presented as mean values with standard deviation at a confidence level of 95%.

**Results.** After taking into account the results of the previous experiment, 6 experimental groups were formed in the main experiment, the mice of which were administered the drug “Amoxidev 60” in the form of a solution in doses (by absolute mass of the drug) – 2000,0; 4000,0; 6000,0; 8000,0; 10000,0 and 12000,0 mg/kg of body weight, as well as a control group, the animals of which were administered distilled water in a volume of 0,2 $cm^3$, according to a similar regulation. There were 6 animals in each group (n=6).

In the previous experiment, the mice were administered the drug “Amoxidev 60” in doses of 2000.0; 7000,0 and 12000,0 mg/kg of body weight. Clinical observations showed that intragastric administration of the drug to mice of the I experimental group (2000,0 mg/kg body weight) did not cause a picture of acute poisoning: the mice were mobile, responded well to external stimuli, actively consumed food and water. No deaths of mice in this group were observed during the 14-day observation period (Table 1).

*Table 1*

**Dynamics of mouse mortality in a preliminary experiment to determine the acute toxicity of the “Amoxidev 60” preparation (n=16)**

| **The time of death of mice, through** | **Mice groups and doses, mg/kg body weight** | | | |
|---|---|---|---|---|
| | Control | Experiment | | |
| | | I (2000,0) | II (7000,0) | III (12000,0) |
| **1-7 hours** | – | – | **–** | **4** |
| **8 hours-1 day** | – | – | **1** | **–** |
| **2-3 days** | – | – | **–** | **–** |
| **4 – 14 days** | – | – | **–** | – |
| **Total deaths** | – | – | **2** | **4** |

In mice of the II experimental group (7000,0 mg/kg body weight) within an hour after the administration of the drug, excitement was registered, which over the next 3 hours turned into depression. The animals reluctantly moved around the cage, bent their pelvic limbs under the abdomen, and breathed heavily. In one mouse, diarrhea and more pronounced clinical signs of poisoning were observed after 4 hours: the animal sat in one place and almost did not react to external stimuli, refused food and water. This condition in this mouse was observed during the first day after administration; clonic convulsions, comatose state and death were added after (8-10) hours (Table 1). The clinical condition in the remaining 3 mice gradually recovered and did not differ from the control on the (5-6) day of the experiment.

In mice of the III experimental group, which were administered the drug at a dose of 12000,0 mg/kg of body weight, a more pronounced clinical picture of poisoning was observed: within (10-15) minutes after the administration of the drug, excitement was recorded, which turned into pronounced depression, the animals refused food and water, slowly moved around the cage, bending their limbs under the stomach. The reaction to external stimuli was reduced, then impaired coordination of movements was observed. Then the animals sat in one place and almost did not react to external stimuli, refused food and water. Within (4-6) hours after the administration, all mice were observed to

be depressed, the animals lay on their sides, clonic convulsions were observed, and then a comatose state and death (Table 1).

In the main experiment, mice were administered the “Amoxidev 60” preparation at doses of 2000,0; 4000,0; 6000,0; 8000,0; 10000,0 and 12000,0 mg/kg body weight. During observation of animals of the I-III experimental groups (2000,0-4000,0 mg/kg body weight), no signs of acute poisoning were observed: mice were mobile, responded well to external stimuli, actively consumed food and water, and in mice of the III experimental group, slight depression and liquefaction of feces were observed within 2 days after administration. Death of mice in these groups was not observed during the 14-day observation period (Table 2).

*Table 2*

**Dynamics of mouse mortality in the main experiment to determine the acute toxicity of the “Amoxidev 60” preparation (n=42)**

| Mice groups and doses, mg/kg body weight | | The time of death of mice, through | | | | |
|---|---|---|---|---|---|---|
| | | 1-7 hours | 8 hours-1 day | 2-3 days | 4-14 days | Total deaths |
| Control | | – | – | – | – | – |
| Experiment | I (2000,0) | – | – | **–** | – | – |
| | II (4000,0) | – | **–** | **–** | – | – |
| | III (6000,0) | – | **–** | – | – | – |
| | IV (8000,0) | – | **1** | **–** | – | **1** |
| | V (10000,0) | **1** | **3** | **–** | – | **4** |
| | VI (12000,0) | **6** | – | – | – | **6** |

A more pronounced clinical picture of poisoning was observed in mice of the IV-V experimental groups (8000,0 and 10000,0 mg/kg of body weight). Within an hour after the administration of the drug, excitement was recorded, which turned into depression over the next 4 hours. The animals reluctantly moved around the cage, bent their pelvic limbs under their stomachs, and breathed heavily. In some mice, diarrhea and a more pronounced clinical picture of poisoning were observed after (5-6) hours: the animals sat in one place and almost did not react to external stimuli, refused food and water. This condition was observed in one mouse from IV and 4 mice from V experimental groups during the first day after administration. In addition, clonic convulsions, a comatose state, and death were observed after (9-11) hours (Table 2). The clinical condition of the surviving mice gradually recovered and did not differ from the control on the (7-9) day of the experiment.

In a larger number of mice of the VI experimental groups (12000,0 mg/kg body weight) within (10-15) minutes after the administration of the drug, excitement was recorded, which turned into pronounced depression. The animals refused food and water, slowly moved around the cage, bending their limbs under the stomach, the reaction to external stimuli was reduced, then impaired coordination of movements was observed. Then the animals sat in one place and almost did not react to external stimuli, refused food and water. Within (3-5) hours after the administration, all mice from the group showed pronounced depression, the animals lay on their sides, clonic convulsions were observed, and then a comatose state and death.

After the death of the mice, a pathological autopsy was performed. During the external examination of the corpses of the experimental animals, it was found that the fur was disheveled; minor discharges were observed from the oral and nasal cavities, while the anus area was heavily soiled with feces; pallor of the visible mucous membranes was noted.

At autopsy in mice:

- pallor of the mucous membranes of the oral cavity, trachea, pharynx and esophagus was recorded;
- the stomach with food and drug residues, in some animals it was swollen, the mucous membrane was severely hyperemic;
- the heart was enlarged in volume, the atria were filled with blood;
- the blood was not clotted;
- the liver was not significantly enlarged in volume, unevenly colored, of elastic consistency;

- the lungs, spleen and pancreas were unchanged; the bladder was full of urine, the kidneys were light brown in color, enlarged in volume;

- catarrhal inflammation of the mucous membrane was detected in the digestive tract.

The next stage of studying the toxicological characteristics of the “Amoxidev 60|” preparation was the determination of the median lethal dose and its standard error ($LD_{50}$, $LD_{10}$, $LD_{16}$, $LD_{84}$, $LD_{90}$, $LD_{100}$).

The median lethal dose $LD_{50}$ was calculated using the probit analysis method according to Prozorovsky V. B.

The toxicometric parameters of the drug were calculated using the least squares method for probit analysis of lethality curves.

The percentage of lethality, probits (Y), and weight coefficients of probits (Z) were determined.

To construct a graph, the values of drug doses (mg/kg) were plotted on the abscissa axis, and the effect values (%) were plotted on the ordinate axis.

A graphical representation of the curve reflecting the "dose-effect" dependence for mice is presented in Fig. 1.

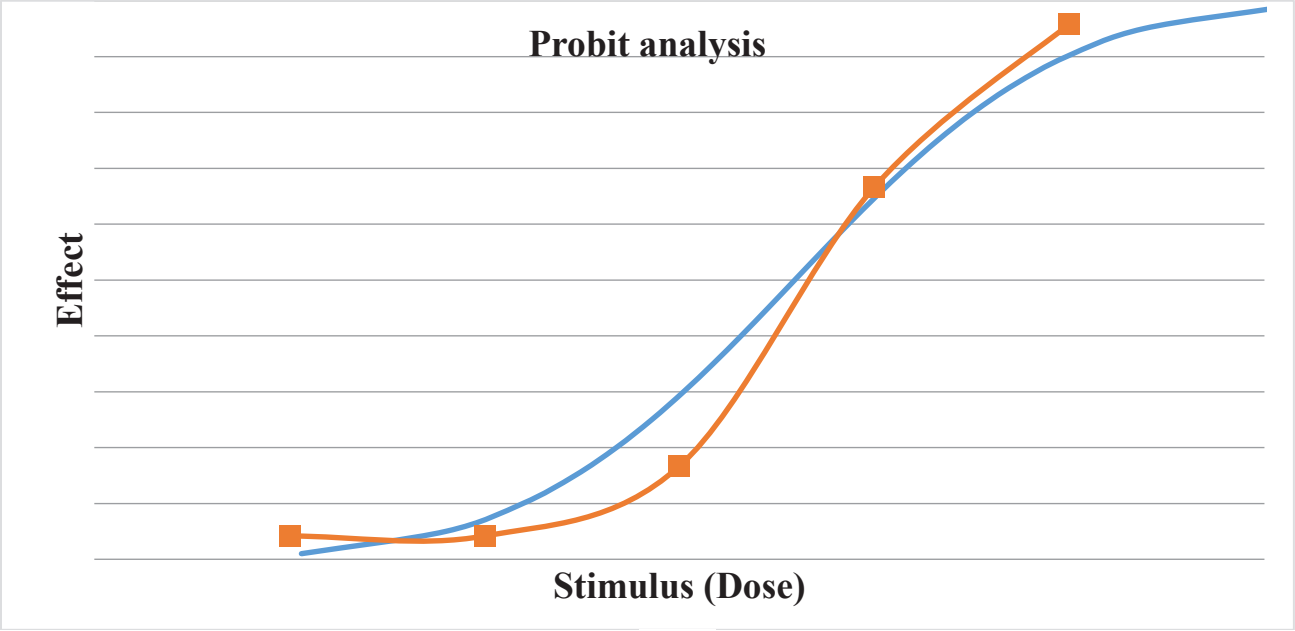


**Fig. 1. Mortality curve of female mice under conditions of a single intragastric administration of the “Amoxidev 60” preparation**

The results of calculating the median lethal dose of the drug for mice under conditions of intragastric administration are given in table 3.

*Table 3*

**Results of calculation of lethal doses of the “Amoxidev 60” preapration, under conditions of a single intragastric administration to female mice**

| Stimulus (Dose) | Percentage (%) | N | Probit (Y) | Weighting Factor (Z) |
|---|---|---|---|---|
| 2000 | 4,1667 | 6 | 3,2680 | 1,5359 |
| 4000 | 4,1667 | 6 | 3,2680 | 1,5359 |
| 6000 | 4,1667 | 6 | 3,2680 | 1,5359 |
| 8000 | 16,6667 | 6 | 4,0326 | 3,5653 |
| 10000 | 66,6667 | 6 | 5,4303 | 4,5697 |
| 12000 | 95,8333 | 6 | 6,7320 | 1,5359 |
| **Regression Statistics** | | | | |
| **$LD_{50}$** | **9183,07** | **$LD_{50}$ Standard Error** | | **887,66** |
| *$LD_{10}$* | 6396,20 | *$LD_{16}$* | 7008,76 | |
| *$LD_{84}$* | 11357,38 | *$LD_{90}$* | 11969,94 | |
| *$LD_{100}$* | 12444,53 | | | |

According to the results of the studies, it was established that the LD50 of the “Amoxidev 60” preparation, under the conditions of its single intragastric administration to female mice, is 9183,07±887,66 mg/kg, $LD_{10}$ – 6396,20 mg/kg, $LD_{16}$ – 7008,76 mg/kg, $LD_{84}$ – 11357,38 mg/kg, $LD_{90}$ – 11969,94 mg/kg, $LD_{100}$ – 12444,53 mg/kg of body weight, respectively.

Therefore, the “Amoxidev 60” preparation can be classified in terms of toxicity as class V - practically non-toxic substances ($LD_{50}$ 5001-15000 mg/kg), and in terms of the degree of danger as class IV – low-hazard substances ($LD_{50}$> 5000 mg/kg) (Kotsyumbas I.Ya., 2005).

**Conclusions.** According to the results of the studies, it was established that the median lethal dose ($LD_{50}$) of the “Amoxidev 60” preparation, under the conditions of a single intragastric administration to laboratory mice, is 9183,07±887,66 mg/kg of body weight, which indicates a low level of toxicity.

The drug is classified as class V toxicity (practically non-toxic substances) and class IV hazard (low-hazard substances), according to modern toxicological criteria. At a dosage of 2000–6000 mg/kg, clinical manifestations of poisoning and cases of death of mice were not observed, which indicates a relatively wide range of safe doses.

Higher doses (8000–12000 mg/kg) caused a violation of the general condition of animals, characteristic clinical signs of intoxication and lethal consequences, depending on the level of load. The obtained data indicate the safety of the “Amoxidev 60” preparation when used therapeutically in pig farming, and justify the possibility of its further pharmacological and clinical study.

**Prospects for further research**. Further scientific research will be aimed at studying the subacute and chronic toxicity of the “Amoxidev 60” preparation, involving various types of laboratory and farm animals. This will allow assessing its cumulative properties, impact on the functional state of internal organs and possible long-term consequences of use.

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## Вивчення токсикологічних характеристик препарату «Амоксидев 60» у доклінічному експерименті на мишах

**Сачук Р.М.**
Заклад вищої освіти «Подільський державний університет», м. Кам'янець-Подільський, Україна, sachukruslan2@gmail.com

***Резюме.*** *Антибіотики β-лактамного ряду, зокрема амоксицилін та його похідні, широко застосовуються у ветеринарній медицині для лікування інфекційних хвороб. Проведення доклінічної токсикологічної оцінки нових лікарських форм є необхідним для підтвердження їхньої безпечності.*

*Метою статті було експериментально визначити гостру токсичність ветеринарного препарату «Амоксидев 60» (на основі амоксициліну тригідрату) у лабораторних мишей та віднести його до відповідного класу токсичності за сучасними критеріями.*

*Дослідження проведено на 48 самках нелінійних білих мишей віком 3–4 місяці та масою 21–22 г, яких утримували у стандартних умовах віварію. Препарат вводили внутрішньошлунково у дозах 2000–12000 мг/кг. За тваринами спостерігали протягом 14 діб, після чого проводили патологоанатомічний аналіз. Токсикометричні показники ($LD_{10}$, $LD_{16}$, $LD_{50}$, $LD_{84}$, $LD_{90}$, $LD_{100}$) визначали методом пробіт-аналізу.*

*Встановлено, що середньолетальна доза ($LD_{50}$) препарату становила 9183,07±887,66 мг/кг маси тіла. «Амоксидев 60» віднесено до V класу токсичності (практично нетоксичні речовини) та IV класу небезпечності (малонебезпечні речовини). При дозуванні 2000–6000 мг/кг клінічних проявів інтоксикації і випадків загибелі мишей не виявлено. Вищі дози (8000–12000 мг/кг) спричиняли дозозалежні ознаки отруєння та летальні наслідки.*

*Отже, препарат «Амоксидев 60» має широкий діапазон безпечних доз і може розглядатися як безпечний, при терапевтичному застосуванні у ветеринарній медицині. Отримані результати є підґрунтям для подальших фармакологічних та клінічних досліджень.*

**Ключові слова:** амоксицилін тригідрат; «Амоксидев 60»; гостра токсичність; лабораторні миші; $LD_{50}$; токсикологічна оцінка; ветеринарна медицина; доклінічні дослідження

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