Correlations of biochemical parameters of blood serum in swine during anti-parasitic treatment with Ivermin followed by pharmacocorrection

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Abstract. The control of endo- and ectoparasites of animals takes an important place in the complex of medical and preventive measures carried out on farms and livestock enterprises of industrial type. Considering the risk of adverse effects of anti-parasitic drugs, we analyzed the changes of biochemical parameters of blood serum in swine (commercial hybrid) with a single subcutaneous injection of Ivermin (A.D. Ivermectin) at a dose of 0.2 mg/kg with subsequent introduction of a double Azoxivet immunostimulator (A.D. Azoximer bromide) in a dose of 0.5 mg/kg and the carbon enterosorbent Zoocarb at a dose of 0.2 g/kg 2 times a day for 3 days. In 14 days after the start of the experiment, biochemical analysis of blood serum was performed using the Screen Master Analyzer and a set of reagents from the company "Human" (Germany). Statistical data processing was performed using the Student's parametric T-Test for independent samples. The correlations between variables were evaluated using Spearman's Rank Correlation Coefficient. It turns out that Ivermin, when administered in a single therapeutic dose causes changes in the biochemical parameters of blood serum, indicating a high risk of hepatotoxic and nephrotoxic effects. The number of correlations of symptoms with the introduction of Ivermin increases. Pharmacocorrection allows minimizing the marked changes. Statistically significant correlations of variables disappear, and this indicates a decrease in adaptive stress.

1. Introduction
Currently, more than 10 billion doses of medicines are administered to animals daily around the world. There are practically no cows, swine, sheep and other animals in livestock complexes and farms that are not administered certain medications. Millions of animals are subjected to therapeutic and preventive treatments for endo- and ectoparasites every year. The studies all over the world have confirmed the high anti-parasitic effectiveness of Ivermectin-containing drugs and their widespread use in many countries [1]. At present, there is a lot of information about the toxic effects of anti-parasitic drugs of different chemical groups [2-4]. However, their undesirable effects when introducing therapeutic doses and the possibility of pharmacocorrection of side effects have not been sufficiently studied.

In this regard, the research was aimed to establish changes in the biochemical parameters of blood serum in swine with subcutaneous administration of Iverm, followed by pharmacocorrection of
undesirable effects and the analysis of correlations of individual parameters before and after anti-parasitic treatment.

2. **Materials and methods**
The object of the study was 30 swine (commercial hybrid) at the age of 130 days. The animals were divided into 3 groups of 10 heads each: group 1 – control animals that were not subjected to anti-parasitic treatment; group 2 – animals that were injected with Ivermin (A.D. Ivermectin, JSC "Drvalevskiy enterprises of bioveterinary industry", Poland) at a single subcutaneous dose of 0.2 mg/kg; group 3 – animals that were injected intramuscularly with Azoxivet (A.D. Azoximer bromide, "AVZ S-P", Russia) at a dose of 0.5 mg/kg once a day, as well as the animals received the carbon enterosorbent Zoocarb (Institute of Hydrocarbon Processing SB RAS, Russia) at a dose of 0.2 g/kg 2 times a day for 3 days with food. 14 days after the beginning of the experiment, blood was taken from all the animals for biochemical research. For this purpose, a Screen Master Biochemical Analyzer and a set of reagents from the company “Human” (Germany) were used.

The experiment was performed following the requirements of the European Convention for the Protection of Vertebrates used for experiments or other scientific purposes (Strasbourg, 1986). Statistical processing of the obtained data was made using the program STATISTICA V. 12 (StatSoft Inc., USA) through the Student's parametric T-Test for independent samples. The results are presented as the arithmetic mean (M) and standard error of the mean (SEM). The differences were considered statistically significant at p<0.05. The correlations between variables were evaluated using Spearman's Rank Correlation Coefficient R, which was considered statistically significant at p<0.05.

3. **Results and discussion**
Comparative analysis of biochemical parameters of animal blood serum indicates that a single administration of Ivermin in a therapeutic dose causes an increase in the total protein content, urea and creatinine concentrations, as well as the levels of AST and ALT (Figure 1).

The concentration of total protein in blood serum depends mainly on the synthesis and breakdown of two main protein fractions – albumins and globulins [5; 6]. In this case, it is possible to activate immunological processes with an increased formation of immunoglobulins.

Urea is the final product of protein metabolism in the body. It is removed from the body by glomerular filtration [7]. Increasing in urea concentration in the blood is associated with an impairment of the excretory function of the kidneys when Ivermin is administered. The nephrotoxic effect is confirmed by an increased level of creatinine. This indicator is widely used in the diagnosis of kidney diseases since it reflects the degree of impairment of their excretory and filtration functions [8]. Moderate hyperfermentemia (increased levels of AST and ALT at 1.5-2 times) indicates the possibility of cardio - and hepatotoxic effects of the drug [9]. These changes may be caused by the development of oxidative stress, which triggers the mechanisms of cell membrane damage [10; 11].

The development of adaptive tension during anti-parasitic treatment is evidenced by an increase in the number of statistically significant correlations of biochemical indicators compared to the control group (table 1, 2).

When correcting these undesirable effects of Ivermin using Azoxivet and Zoocarb, there was a tendency to normalize the metabolic status of animals with minimizing differences compared to the control group (Figure 1). The absence of statistically significant correlations after pharmacocorrection indicates a decrease in adaptive stress (table 3).
Figure 1. The changes in the biochemical parameters of blood serum in swine: (a) - total protein; (b) - urea; (c) - AST; (d) - ALT; (e) - creatinine.

Table 1. The correlations of biochemical parameters of blood serum in swine of the control group, n=10

|          | Total protein | Urea  | Creatinine | AST  | ALT  |
|----------|---------------|-------|------------|------|------|
| Total protein                     | -    | -0.304 | -0.248     | -0.164 | 0.359 |
| Urea     | -0.304        | -     | 0.742b     | -0.267 | -0.073 |
| Creatinine | -0.248    | 0.742b | -          | -0.370 | -0.158 |
| AST      | -0.164        | -0.267| -0.370     | -     | 0.304 |
| ALT      | 0.359         | 0.073 | -0.158     | 0.304 | -    |

a Spearman's Rank Correlation Coefficient.
b p<0.05.
Table 2. The correlations of biochemical parameters of blood serum in swine after administering Ivermin, n=10

|       | Total protein | Urea | Creatinine | AST | ALT |
|-------|---------------|------|------------|-----|-----|
| Total protein | -             | 0.927<sup>c</sup> | 0.952<sup>c</sup> | -0.345 | 0.188 |
| Urea    | 0.927<sup>c</sup> | -    | 0.976<sup>c</sup> | -0.503 | 0.406 |
| Creatinine | 0.952<sup>c</sup> | 0.976<sup>c</sup> | -    | -0.370 | 0.224 |
| AST     | -0.345        | -0.503 | -0.370 | -    | -0.745<sup>a</sup> |
| ALT     | 0.188         | 0.406 | 0.224     | -0.745<sup>a</sup> | - |

<sup>a</sup> Spearman's Rank Correlation Coefficient.
<sup>b</sup> p<0.05.
<sup>c</sup> p<0.001.

Table 3. The correlations of biochemical parameters of blood serum in swine after administering Ivermin and providing pharmacocorrection<sup>d</sup>, n=10

|       | Total protein | Urea | Creatinine | AST | ALT |
|-------|---------------|------|------------|-----|-----|
| Total protein | -            | -0.321 | -0.188 | 0.055 | -0.394 |
| Urea    | -0.321        | -    | 0.455     | -0.503 | 0.018 |
| Creatinine | -0.188        | 0.455 | -        | -0.212 | -0.285 |
| AST     | 0.055         | -0.503 | -0.212 | -    | 0.370 |
| ALT     | -0.394        | 0.018 | -0.285    | 0.370 | - |

<sup>a</sup> Spearman's Rank Correlation Coefficient.
<sup>d</sup> Statistically significant correlations are missing.

4. Conclusion
Thus, the results of the research indicate that the anti-parasitic treatment of animals with Ivermin causes changes in the biochemical parameters of blood serum with an increase in their correlation relationships.

Twofold administration of Azoxivet which has immunostimulating and antioxidant properties [12], on the background of the three-day course of enterosorption with the use of the carbon enterosorbent Zoocarb eliminates the signs of nephro- and hepatotoxic effect of Ivermin and reduces the level of adaptive tension in the body.

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