EVALUATION OF THE STATE OF THE CARDIOVASCULAR SYSTEM OF RABBITS UNDER INFLUENCE OF FREE AND BOUND FORM OF THE CYTOSTATIC AGENT DOXORUBICIN

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Relevance: Targeted drugs, which significantly reduce the toxic effects of cytostatic drugs, are widely used in clinical practice for the treatment of cancer. The Institute of Bioorganic Chemistry of the Academy of Sciences of the Republic of Uzbekistan has developed a polysaccharide-conjugated form of doxorubicin (DOX), PGA-DOX, which has promising medical implications.

Purpose of the study: to evaluate the functional state of the cardiovascular system of rabbits when exposed to free and bound forms of DOX with the introduction of equivalent doses of the cytostatic.

Materials and methods: Rabbits weighing 2-2.5 kg (4 per group) were administered a single intravenous injection of DOX at a dose of 2.0 mg/kg (Group 1), PGA-DOX at a dose of 23.5 mg/kg (Group 2), and control animals (Group 3) were given water for injection in an equivalent volume. Blood pressure (systolic, SBP, and diastolic, DBP) and heart rate (HR) were measured for 2 hours.

Results: In the control group of animals, the blood pressure and heart rate indicators in the experimental rabbits remained within the range of initial values throughout the observation period, with some decrease in all three indicators 30 minutes after the intravenous injection. Similar dynamics of the decrease in blood pressure and heart rate indicators 30 minutes after administration are observed for both cytostatic drugs, however, with varying degrees of effect. 30 minutes after a single intravenous administration of PGA-DOX to rabbits at a dose of 23.5 mg/kg, a statistically significant decrease in SBP relative to the control is observed (up to 126.0±3.02 mmHg, $p=0.0035$), however, the indicators are restored to the initial and control levels by the end of the observation (2 hours after drug administration). DBP readings drop below control values within 10 minutes ($p=0.026$) of drug administration and do not recover after 30 minutes ($p=0.008$) and 120 minutes ($p=0.04$) of observation. Pulse rate also does not normalize—it remains below control values after 30 minutes ($p=0.037$) and 120 minutes ($p=0.008$) of drug administration.

Administration of the free form of DOX at a dose of 2 mg/kg resulted in a more pronounced suppression of the cardiovascular system function in rabbits. Thus, a significant decrease in SBP to 139.0±3.2 mmHg was observed already 10 min after intravenous administration of the drug ($p=0.045$). By 30 min of observation, SBP dropped to 107.0±4.7 mmHg ($p=0.0007$) with some recovery 2 hours after administration, but the indicator did not reach the control values ($p=0.0024$). DBP was also significantly lower than the control throughout the entire observation period after

administration ($p<0.006$). HR dropped significantly by 30 min of observation ($p=0.04$) and did not recover by 120 min of the experiment ($p=0.004$).

When comparing the two forms of the drugs, it was found that the drug DOX (2 mg/kg) has a greater inhibitory effect on the cardiovascular system: after 30 and 120 minutes of observation, the SBP ($p<0.008$) and DBP ($p<0.04$) indicators were statistically significantly lower than with PG-DOX (23.5 mg/kg).

Conclusions: A single intravenous administration of DOX and PG-DOX to rabbits at a therapeutic dose resulted in a toxic effect on cardiovascular function. A comparison of the two drugs revealed a significantly greater inhibitory effect on the cardiovascular system for 2 hours after administration for DOX (2.0 mg/kg) compared to PG-DOX (23.5 mg/kg) ($p < 0.05$).