EXPERIMENTAL SUBSTANTIATION OF THE USE OF XENOBIOTICS IN MAMMALS

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Abstract. Xenobiotics are foreign substances that are not part of the cycle. Many synthetic surfactants entering the body of mammals, including humans, cause a number of allergic reactions, and also cause infectious diseases, acting as contaminants acting on the body through food. **Purpose of the research.** Conduct a study of the metabolism of xenobiotics and drug-drug interactions under experimental conditions. **Methods and materials:** To achieve this goal, the results of these 20 experimental animals (mice of the Vistar genus, weight - 14-18 g, both sexes) were analyzed. As a material for the study, a biopsy of liver tissue was performed after exposure to drugs (doxirubicin) on days 3, 5, 10 of the experiment. Hepatocytes were stained with hematoxylin-eosin, standard wiring was used. We used iron (II) sulfate, potassium ferrocyanide, acetic acid, potassium phosphate, hydrochloric acid, sodium chloride, sodium hydroxide. Statistical processing was performed using the Student-Fisher test, the nonparametric Mann-Winney test, and the Kraskes-Wallis test. **Results.** The effect of ferrocyanide oxidation on the substrate activity of hepatocytes showed that at the beginning of the experiment (0-5 min) the content of this substance was at the level of 9.5 ± 0.05 μmol / L, while the content of HIF and peptide (4.1 ± 0.05 and 6.3 ± 0.05, p≤0.05, μmol / L). Within 30 minutes, the content of ferrocyanide increased to 12.0 ± 0.05 (p≤0.05), while the content of HIF and peptide did not increase (p≤0.05). When evaluating the effect of iron (II) sulfate on the metabolic activity of macrophages of hepatocytes, it was found that the state of these cell organelles when exposed to iron (II) sulfate without an enzyme at 0-5 minutes and 25-30 minutes was the same and amounted to 4.5 ± 0.05 (p≤0.05) μmol / L, while in the state without an inhibitor in a time interval of 5-10 minutes it reached values of 4.5 ± 0.05 (p≤0.05) μmol / L, and at 15-20 minutes reached values of 1.8 ± 0.05 (p≤0.05) μmol / l and was the minimum value for the entire period of the influence of iron (II) sulfate. **Conclusion:** Summarizing the above, we can conclude that dcosirubicin has an ambiguous isoforms of cytochrome P450, since different classes of this monooxygenase react differently with this drug.

Key words: hypoxia-inducible factor; xenobiotics; doxirubicin; experiment; mouse

I. Introduction

Xenobiotics are foreign substances that are not part of the cycle. Many synthetic surfactants entering the body of mammals, including humans, cause a number of allergic reactions, and also cause infectious diseases, acting as contaminants acting on the body through food [1-5].

Cytochrome P450 is a hemoprotein and belongs to group b cytochromes. As you know, the cytochrome P450 system is the main environment in which xenobiotics are neutralized.

The neutralization of almost all xenobiotics occurs in the liver under the influence of 2 phases. In phase 1, cytochrome P450 is of primary importance, in phase 2 - UDP-glucoronyltransferase [6-9]. Five isoforms of cytochrome P450 are key, since it is thanks to them that the metabolism of xenobiotics is carried out. These are 3A4, 2C9, 2C19, 2D16, 1A2 and carry out aromatic hydroxylation, aliphatic hydroxylation, N-dealkylation, N-demethylation, C-oxidation with the formation of aldehydes, ketones, carboxylic acids [10-15].

After analyzing a large amount of works [16-22], it can be concluded that experimental modeling of the metabolism of xenobiotics and drug-drug interactions was not carried out, which was the relevance of the study.

II. Purpose of the research

Conduct a study of the metabolism of xenobiotics and drug-drug interactions under experimental conditions.

III. Materials and methods

To achieve this goal, the results of these 20 experimental animals (mice of the Vistar genus, weight - 14-18 g, both sexes) were analyzed. As a material for the study, a biopsy of liver tissue was performed after exposure to drugs (doxirubicin) on days 3, 5, 10 of the experiment. Hepatocytes were stained with hematoxylin-eosin, standard wiring was used. We used iron (II) sulfate, potassium ferrocyanide, acetic acid, potassium phosphate, hydrochloric acid, sodium chloride, sodium hydroxide.

The biomass after exposure to the xenobiotic was collected by centrifugation, washed with a solution of 50 mM Tris-HCl buffer, pH-7.0 and destroyed by ultrasound. All subsequent stages of purification were carried out in buffer solutions. The resulting biomass was used to isolate a soluble fragment using chromatography.

Statistical processing was carried out using the Student-Fisher test, the nonparametric Mann-Winney test, and the Kraskes-Wallis test.

IV. Results

The ferrocyanide is used to ensure the circulation of ferrous iron. Ferrocyanide can directly reduce oxoferryl and is an alternative substrate for mono-oxygenases, we used this phenomenon to develop continuous catalytic activity of the enzyme.

In the absence of reducing agents and in the presence of ferrocyanide, the enzyme catalyzes its oxidation using HIF as a cofactor. Oxoferryl, formed during the oxidation of ketoglutarate, oxidizes ferrocyanide to ferricyanide and is the result of HIF prolyl hydroxylase activity (Figure 1).

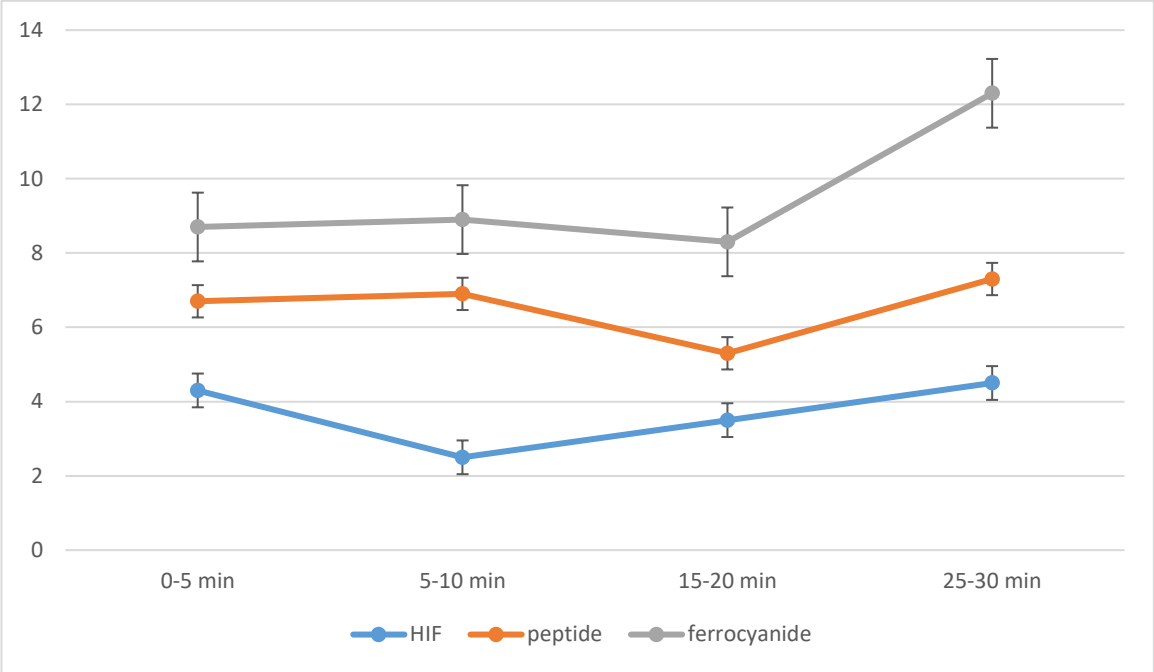

Figure: 1. The effect of ferrocyanide oxidation on the substrate activity of hepatocytes.

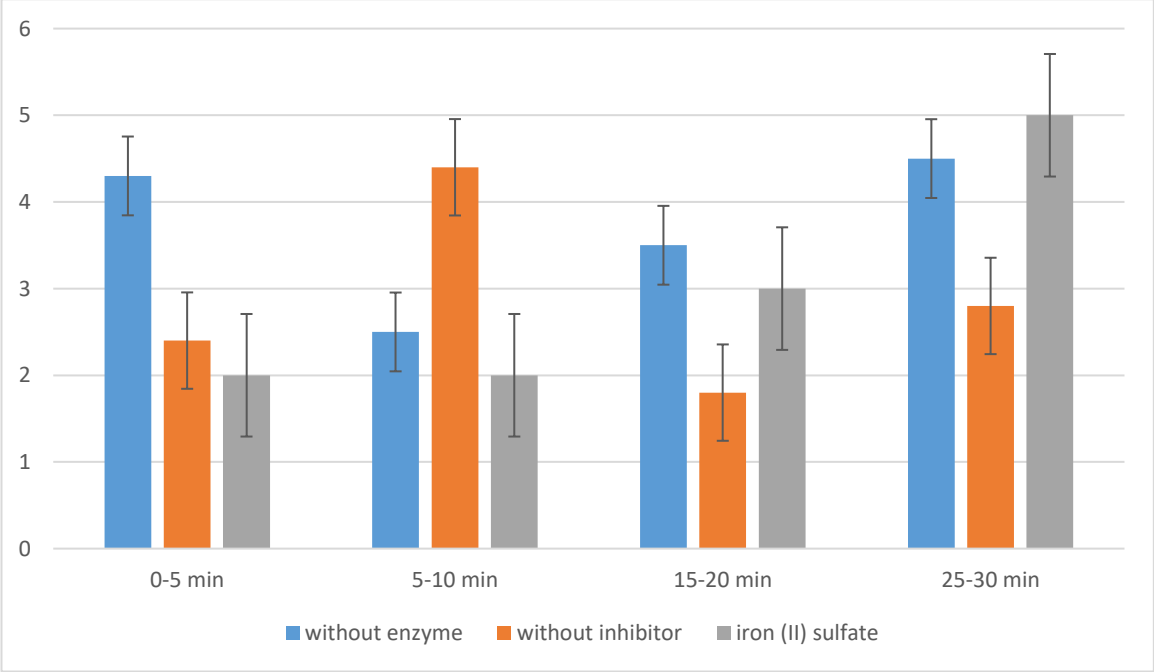

Figure: 2. Assessment of the effect of iron (II) sulfate on the metabolic activity of hepatocyte macrophages.

Doxirubicin was used as a substrate; its main source of biotransformation in the liver is the cytochrome P450 2B6 isoform. Its main route of drug inactivation is N-dechlorethylation, which is catalyzed mainly by cytochrome 3A4. Since 4-hydroxylation is the most important metabolic pathway that occurs with the

participation of the electron donor NADP, it becomes clear the importance of this cytochrome isoform in the reactions of biotransformation of drugs in the liver.

Calibration curves of the effect of doxirubicin on the state of macrophages of hepatocytes were determined.

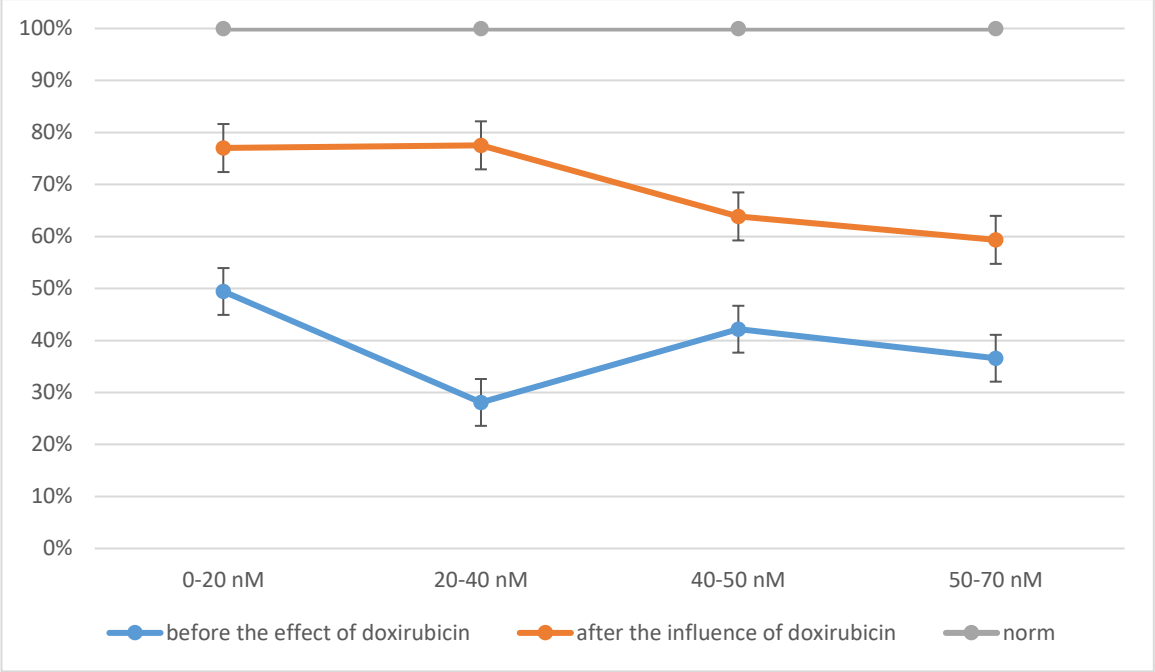

Figure: 3. Evaluation of the effect of doxirubicin on the state of cytochrome P450

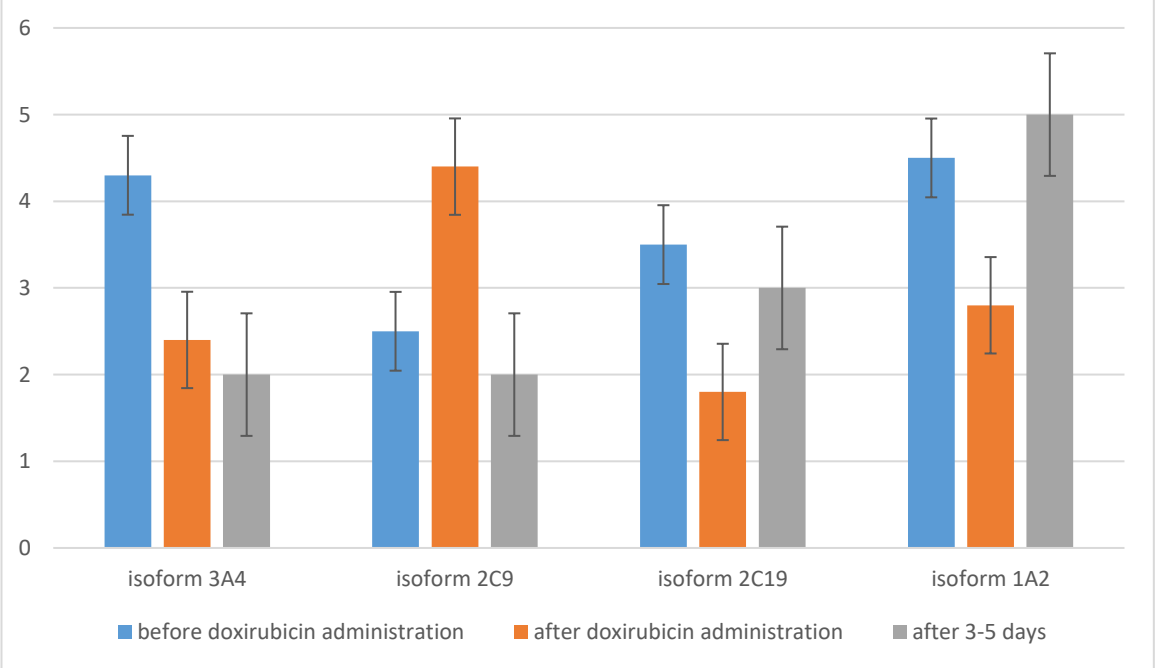

Figure: 4. Assessment of the nature of the biotransformation of cytochromes P450 in the presence of doxirubicin.

V. Conclusion

Summarizing the above, we can conclude that dcosirubicin has an ambiguous effect on various isoforms of cytochrome P450, since different classes of this monooxygenase react differently with this drug. However, in general, it can be noted that this antitumor antibiotic has a positive effect on the state of oxidative dealkylation, as one of the most important oxidation reactions of xenobiotics, since the process induced in the sarcoplasmic reticulum of hepatocytes improves the water solubility of this drug and excretion through the kidneys by means of aquaporins (1, 2), which undoubtedly plays a huge role in the metabolism of this drug compound.

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