THE MICROSCOPIC EVALUATION OF HEPATOTOXIC EFFECTS OF TIRAPAZAMINE IN COMBINED ADMINISTRATION WITH CISPLATIN

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In search of an effective antineoplastic therapy new substances with anticarcinogenic effects are used in preclinical studies, simultaneously strategies are devised to use a combination therapy comprising two drugs or more. A common problem is a therapy failure caused by cell resistance to the standard therapeutic agents. In recent years there have been studied the effects of cisplatin combined with bioreductive drugs such as tirapazamine. The study was aimed at the microscopic evaluation of hepatotoxicity indicators and basic biochemical parameters associated with metabolism in rats receiving cisplatin combined with tirapazamine.

In the experiment male rats of WAG strain, Wistar breed were randomly divided into 6 groups, each containing 8 rats. The animals with the body mass of 160 ± 20 g received two preparations: tirapazamine – TP (ADVANCED TECH. & IND. CO., LTD., China) and cisplatin – CP (Cefarm, Poland) according to the following schedule: control group – intraperitoneal physiological saline; 2 mg cisplatin/kg b.m. (CP); 5 mg tirapazamine/kg b.m. (5TP); 10 mg tirapazamine/kg b.m. (10TP); 5 mg tirapazamine/kg b.m. + 2 mg cisplatin/kg b.m. (5TP+CP); 10 mg tirapazamine/kg b.m. + 2 mg cisplatin/kg b.m. (10TP+CP). The two preparations were administered six times at weekly intervals. Samples for examination, i.e. liver sections, were collected one week after the last administration of the drugs. The liver sections underwent microscopic evaluation according to the standard procedure. In the sera stored at the temperature of 4°C the activity of aspartate transaminase and alanine transaminase was examined immediately.

The microscopic examination revealed hepatocyte focal necrosis surrounded by scarce inflammatory infiltrations from mononuclear cells around necrotic foci. There was observed vacuolar degeneration and necrosis of single hepatocytes. The sinusoids were dilated. The study demonstrated hepatotoxic effects of tirapazamine in rats receiving cisplatin indicated by a significant increase in the activity of both transaminases which only occurred in the rats receiving the lower TP dose combined with cisplatin.

It cannot be excluded that during the presence of the examined drugs in tissues there occur disorders of the oxidation-reduction equilibrium or even oxidative stress. The available information on the causes of redox equilibrium disorders leading to oxidative stress implies that the mechanisms of that phenomenon are different for CP and TP. In consequence, the evaluation of oxidative stress should be extended by including the examinations of DNA oxidative damage.