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CHANGES OF MICROELEMENT HOMEOSTASIS WHEN MODELING HIPEC WITH CISPLATINE

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Abstract

HIPEC was simulated on laboratory rats using cisplatin (CP) at a dose of 4 mg/kg. It has been shown that perfusion of a hot and cold solution of CP changes the accumulation of platinum and the concentration of heavy metals in organs (liver, kidney, spleen, blood) in different ways. An acute HIPEC simulation experiment shows that in a fairly short exposure time, critical absorption of platinum into the blood from the abdominal cavity does not occur, although the concentration of platinum in the blood is still growing. At the same time, Pt was found on the surface of parenchymal organs and the peritoneum of rats after the end of the experiment. This platinum is closely related to the surface and is not removed during the washing process. This suggests that the general toxic effect of platinum is less pronounced and delayed than with intravenous administration, but it will certainly occur through further interorgan redistribution.

Keywords: HIPEC, cisplatin, copper, zinc, cadmium, lead, platinum

Introduction

In recent decades, an increase in the number of cancers has been observed in Ukraine and in the world. According to various researchers, the number of cases of local relapses can vary from 25 to 50% [1]. Secondary peritoneal tumor lesions develop in colorectal cancer,

gastric, ovarian, appendix, pancreas, liver, lung, prostate, breast, and skin melanoma cancers. Applied systemic intravenous chemotherapy, as a rule, is rather hard tolerated by patients, has pronounced nephrotoxicity [2, 3] and hepatotoxicity [4, 5], It affects the hematopoietic system and greatly reduces immunity [6, 7]. In the last 15 years in the world and 4 years in Ukraine, hyperthermic intraperitoneal chemoperfusion (HIPEC) has been used to treat peritoneal carcinomatosis. The main advantages of the method are the possibility of using cytotoxic doses of anticancer drugs acting locally on the affected organ, less systemic toxicity compared with standard chemotherapy due to limited absorption from the abdominal cavity into the blood, elevated temperature, which potentiates the effect of cytostatics and itself has an antitumor effect. In the case of platinum preparations, cytotoxicity with increasing temperature is potentiated [8].

Cisplatin (CP) and other platinum derivatives are the cheapest and, in many cases, quite effective anticancer drugs. They are widely used in the world with HIPEC. The general toxic effects of platinum drugs are a logical continuation of their antitumor activity and are well studied by intravenous administration. HIPEC has traditionally been considered less dangerous in terms of side effects. However, a number of factors (elevated temperature, mixing during chemoperfusion, damage to the surface epithelial cells of internal organs) may contribute to somewhat different mechanisms of transport, absorption, and interorganization of the chemotherapeutic drug.

Our clinical observations [9] have shown that after HIPEC, the systemic toxicity of the chemotherapy drug is manifested. The general condition, age, volume of cytoreductive surgery, and the presence of intercurrent non-oncological diseases affect the manifestations of systemic toxicity of CP. A small number of operated patients after HIPEC with cisplatin required to test and refine the observed effects of conducting a model experiment on laboratory animals.

The exchange of trace elements in the modeling of HIPEC has not previously been studied experimentally.

Materials and methods

Studies have been carried out on mature male Wistar rats weighing 180–200 g. Laboratory animals were obtained from the vivarium of the Odessa National Medical University. Animals were kept in vivarium conditions with free access to food and water. The content of Zn, Cu, Hg, Cd, Pb did not exceed the permissible values for food products. The day before the study, the animals were not fed, but access to water was maintained. Before the experiment, we determined the temperature and body mass of animals.

The basis of the HIPEC simulation on laboratory animals was the work [10], but the methodology of the experiment was significantly changed.

The drug Cisplatin "Ebeve" (concentrate) with a concentration of 1 mg / ml was used for perfusion. Prepare a solution for each animal in such a way that the total dose was 4 mg / kg. To do this, in 300 ml of sterile saline was injected (depending on the weight of the animal) 0.8-1.0 ml of concentrate.

Animals were divided into 3 groups of 7 individuals. The animals of the first group were simulated with HIPEC, the second with chemoperfusion with a solution of room temperature (cold CP solution). The animals were anesthetized with sodium thiopenate at a dose of 35 mg/kg. Rats were fixed on the operating table and 2 catheters were installed - inlet and outlet. For the first group, a container with a solution of cisplatin was placed in a water bath with a temperature of 48 °C so that the solution was infused with a temperature of 43-44 °C. For the second group, the solution temperature was 20 °C. The control animals were perfused with 0.9% NaCl. The temperature of the animals and the solutions were checked with a non-contact thermometer. The temperature of the rats did not rise above 40.1 ° C (39.2-39.5 for control). The solution was applied using a peristaltic pump at a rate of 5 ml/min.

Quantitative elemental analysis was performed by the atomic emission method at an EMAS-200 CCD NPP spectrometer.

Results and its discussion

In intact rats, trace amounts of platinum in the kidneys are determined at the level of the measurement method error. Platinum concentration in the liver, spleen, peritoneum and blood is lower than the sensitivity of the method (0.01 μg/g) (Fig. 1).

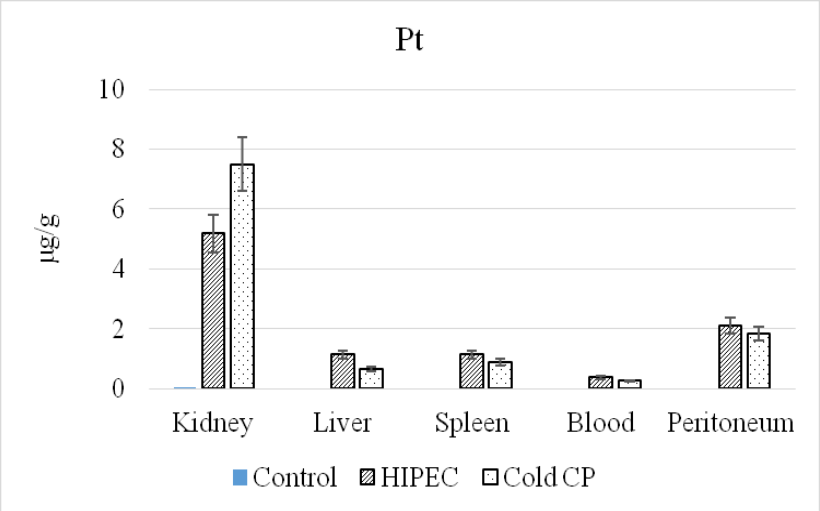

Fig. 1. Concentration of platinum in organs and tissues after perfusion of cold CP solution or HIPEC, μg/g of damp tissue or blood.

Table 1

Total content of platinum in organs and tissues after the perfusion of a solution of cold CP and HIPEC, μg (estimated value taking into account organ morphometry)

Organ/tissue	**Pt, μg**	
	HIPEC	Cold CP
Kidney	8,3 ± 1,2	11,9 ± 1,9
Liver	9,0 ± 1,3	5,2± 0,7
Spleen	0,94 ± 0,09	0,74± 0,08
Blood	3,3 ± 0,4	2,4 ± 0,3

From tabl. 1 and Fig. 1 It can be seen that despite the relatively low concentration of platinum in the liver, the total amount of Pt in the liver with HIPEC even slightly exceeds that in the kidneys. Perfusion cold and warmed (HIPEC) solution CP, despite the short duration of exposure, causes significant accumulation of platinum in the kidneys, and the absolute value is higher when perfusion of cold solution. Perhaps the reason for this lies in the field of thermodynamic characteristics of cellular processes - increasing entropy with increasing temperature reduces the efficiency of simple diffusion processes when transporting the CP to the target organs. Another reason may be a change in cellular metabolism with hyperthermia.

The content of platinum in the liver, peritoneum and spleen is slightly different in the experimental groups and between the organs, which suggests the predominant role of platinum sorption on the surface of organs when the CP solution is introduced into the abdominal cavity. The temperature affects the processes of accumulation of platinum in the target organs. With increasing temperature, a large amount accumulates in the liver, and when perfusion of cold solution - in the kidneys. Maximum accumulation of platinum occurs in the kidneys. There is also accumulation of platinum in the spleen, which is slightly dependent on the temperature of the solution being introduced.

The presence of platinum in the spleen after HIPEC may be another factor in the overall toxicity of the CPU. It is believed that the normal functioning of the immune system is a major factor in the natural protection against the appearance of malignant neoplasms. This fact is proved by clinical observations of patients with weakened immune system, in which the tumors are found tens times more often than people with normal functioning immune system [11, 12].

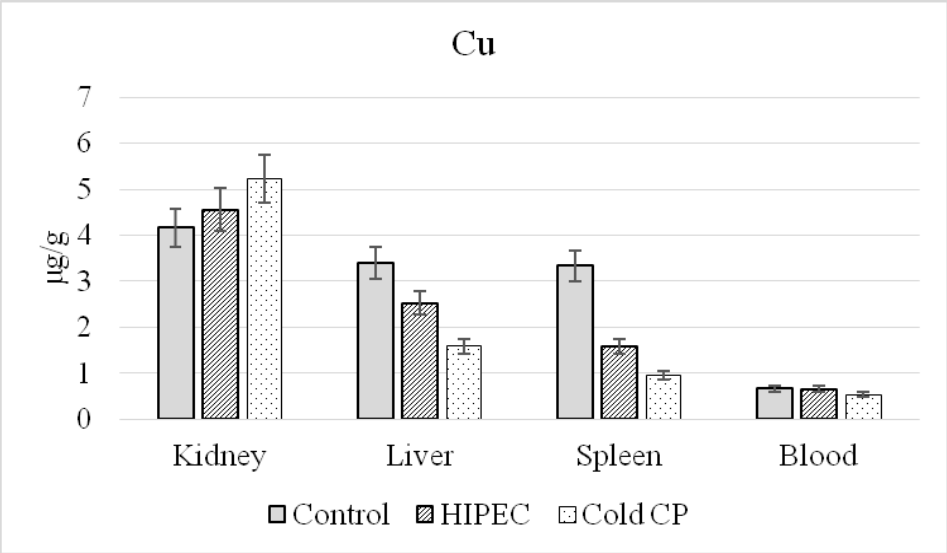

Fig. 2. Concentration of Cu in organs and tissues after perfusion of cold CP solution or HIPEC, µg/g of damp tissue or blood.

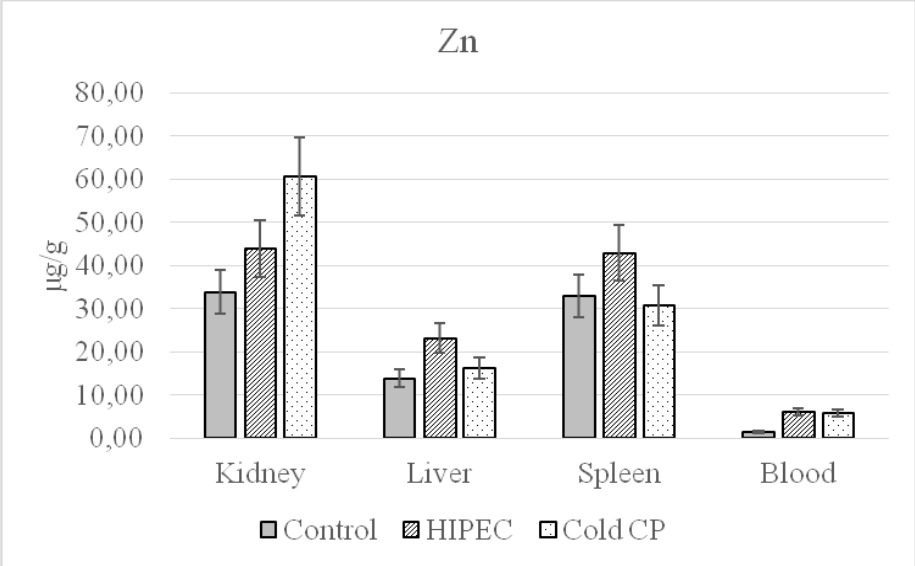

Fig. 3. Concentration of Zn in organs and tissues after perfusion of cold CP solution or HIPEC, µg/g of damp tissue or blood.

Changes in the content of zinc and copper are also maximal in the kidneys. Very interesting is the change in the copper content in the organs when exposed to the CPU. The copper content in the kidneys increases, and in the liver and spleen decreases (changes are significant compared with the control, $p < 0.05$, but for the spleen unreliable in the perfusion groups of the CP solution and HIPEC, $p > 0.05$). These data correlate well with the maximum nephrotoxicity of CP associated with the possible involvement of the Ctr1 copper transporter in platinum cellular transport. [132, 14]. It is known that tumor cells differ in the fastest possible metabolism, which requires an increased intake of substances, including ions of

essential metals (zinc, copper). That is why there is a selective accumulation of platinum ions in tumor tissues compared with other tissues. However, epithelial cells of the nephron also belong to fast-growing cells with an active metabolism. That is why epithelial cells of the nephron are so sensitive to platinum compounds and other cytostatics.

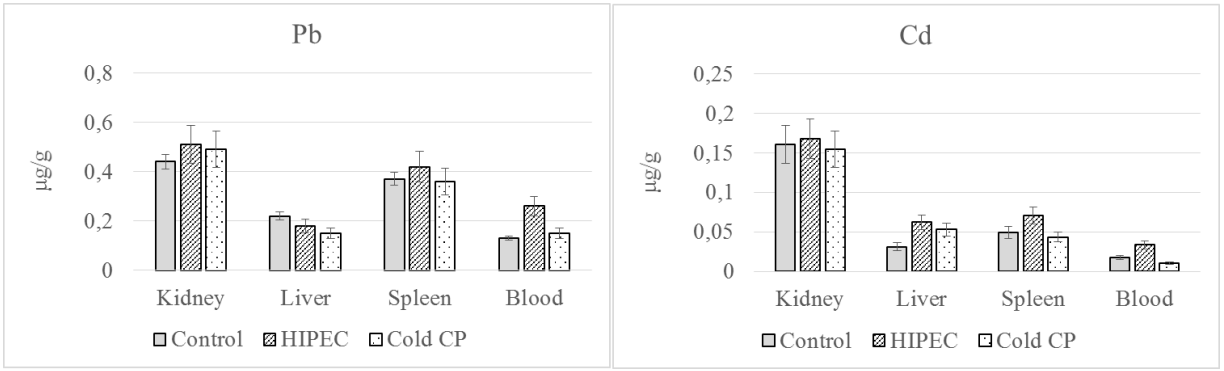

Fig. 4. The content of toxic metals in organs and tissues after perfusion of cold CP solution or HIPEC, µg/g of damp tissue or blood.

As can be seen from fig. 4, the maximum concentrations of lead and cadmium are found in the kidneys. Sufficiently high concentrations of toxic metals are determined in the spleen. By the concentration of TM, the organs were distributed as follows: Cd kidneys> spleen = liver> blood; Pb kidney> spleen> liver> blood. Differences in the content of TM in the organs between the groups are not significant.

The development of nephrotoxicity after administration of platinum drugs is associated with a whole cascade of processes, including DNA damage, oxidative stress, impaired protein synthesis, reduced mitochondrial function, apoptosis and necrosis of epithelial tubule cells. It is believed that the toxic effect of platinum drugs is associated with impaired mechanisms of basolateral transport [15, 16].

The development of nephrotoxicity after the introduction of platinum preparations is associated with an entire cascade of simultaneous or sequential processes, which include DNA damage, oxidative stress, protein synthesis, decreased function of mitochondria, apoptosis, and necrosis of the epithelial cells of the tubules. It is believed that the toxic effect of platinum preparations is also associated with violation of the mechanisms of basolateral transport [16, 17].

Due to the enormous compensatory abilities of the kidneys, aimed at ensuring homeostasis, the exclusion from the active action of even half of the nephrons does not

significantly affect their functions for a certain time [18].This applies not only to metal nephropathy, but also to most other kidney diseases of various etiologies. [19, 20].

Conclusion

An acute HIPEC simulation experiment shows that in a fairly short exposure time, critical absorption of platinum into the blood from the abdominal cavity does not occur, although the concentration of platinum in the blood is still growing. At the same time, Pt was found on the surface of parenchymal organs and the peritoneum of rats after the end of the experiment. This platinum is closely related to the surface and is not removed during the washing process. This suggests that the general toxic effect of platinum is less pronounced and delayed than with intravenous administration, but it will certainly occur through further interorgan redistribution.

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