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EXPERIMENTAL DATA CONCERNING ACTION OF CISPLATIN ON METAL ELEMENTS IN BLOOD

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Abstract

After administration of cisplatin, biochemical homeostasis is affected. Cisplatin has been an important chemotherapeutic agent used in treatment of cancer. This paper is trying to reveal the modification of some elements: Mg, Ca, Fe Na, and K, from blood after intraperitoneal administration of cisplatinum, to Wistar rats. The drug was administrated in doses 2 mg/kg b.w. and 8 mg/kg b.w. The results of these experiment shows that concentration of magnesium and calcium from total blood, and the sodium concentration from blood serum are decreased proportionally with the administrated doses; concentration of iron from total blood and potassium from serum blood are increased.

***Key words**: cisplatin, trace elements, rats blood.*

Introduction

Cancer is a disease characterized by her irreversible evolution, when is untreated or too late treated. This disease is capable to extend all-over the cells and tissues. The cancerous cells can affect the organism entirely, because of some modifications produced by an anabolic process in which is involved the anarchic development of some cells who are dividing improperly.

In antitumoral chemotherapy a various number of drugs are used. Cisplatin (c-DDP, *cis*-diamminedichloroplatinum II), one of the most potent antitumorale drugs, is active against a variety of neoplasms. The

antitumorale action of cis-DDP (cis-diaminodicloroplatina) is attributed to its action on DNA synthesis (Rosenberg, 1995; Gârban, 2000).

Cisplatin (c-DDP, cis-diamminedichloroplatinum) is a planar platinum complex consisting of two chloride leaving groups in the cis-position around platinum. This drug has a broad spectrum of activity against many different solid tumors such as lung, ovary, testis, bladder and head and neck cancers and is also an effective agent in treatment of some hematological malignancies such as refractory lymphomas (Lippert, 1999; Baba, 2002). The adverse effects of c-DDP include nausea and vomiting, nephrotoxicities, ototoxicities, neurotoxicities and myelosupression.

Many nutritional problems in cancer patients are caused by alterations following chemotherapy. During cytostatic therapy the metabolism of carbohydrate, lipid and protein is disturbed. Metal elements are implicated in maintenance of acido-basic balance, osmotic and colloid-osmotic balance. Without an adequate supply of magnesium, iron and potassium the toxic effects cannot be prevented (Ghizdavu, 2000, Ahmadi-Vincu, 2003, Martău, 2003).

The purpose of this study is to evaluate the concentration in blood of some electrolytes after administration of cisplatin.

Experimental

For this experiment adult Wistar strain rats, with an average body weight (b.w.) of 200 ± 20 g were used. The animals were divided in three groups: the control group (C) and two experimental groups E_1 and E_2, each group being consisted of 8 animals (males and females). 2 mg/kg b.w. cisplatin was administrated to animals from the E_1 group, 8 mg/ kg body weight b.w. cisplatin to animals from E_2 group, and saline solution to animals from control group using intraperitoneal (i.p.) administration. Doses have been administrated on the 3^{rd} and 8^{th} day of the experiment. On day 13^{th} of the experiment the animals were killed after anesthesia using Ketanest, and blood samples were taken for analysis. The samples were taken after laparotomy and puncture of vena cava caudalis. The concentration in blood of Ca, Mg, Fe, Na, and K was determined.

The results obtained after this experiment have been proceed by statistic methods, using mean value, ($\overline{X}$), and standards deviation (SD) for each element and also the difference between control group and experimental groups was determined.

Results and Discussions

Macrobioelements and trace elements have a very important role in material and energetic metabolism, and are responsible for biochemical homeostasis (Ghergariu, 1980, Gârban, 1999).

The studies regarding chemotherapy are developed especially using experimental studies on laboratory animals (Ciudin, 1996).

Administration of cisplatin causes changes in some blood serum electrolytes metabolism (sodium, potassium, calcium, magnesium and iron) in Wistar rats. Mean concentration of magnesium, calcium and iron from total blood of Wistar rats (mg/dL) are presented in Table 1.

Table1. Mean concentration of Mg, Ca, Fe in total blood of Wistar rats after cisplatin administration.

Specifications	n	Mg mg/dL	Ca mg/dL	Fe mg/dL
		$\overline{X} \pm SD$	$\overline{X} \pm SD$	$\overline{X} \pm SD$
Group C	8	2.12 ± 0.18	9.77 ± 0.70	0.11 ± 0.02
Group E_1	8	0.93 ± 0.59	9.54 ± 0.56	0.45 ± 0.09
$\Delta \overline{X}$		-1.19	-0.23	+0.35
Grup E_2	8	0.52 ± 0.06	9.20 ± 1.32	0.60 ± 0.07
$\Delta\overline{X}$		-1.60	-0.57	+0.49

n – number of animals per each working group

It might exist the possibility that low serum Mg and Ca levels could be a factor in metastasis. There is evidence that it is contributory to hypercoagulability; possibly, this might participate in neoplastic cell adhesiveness and spread (Seelig, 1993).

Using some literature data, we found that, normal values of magnesium in blood from Wistar rats are 1.46mg/dL; 2.42mg/dL; and calcium values are 10.2 mg/dL, on Wistar rats (Chiricuță, 1982, cited by Ciudin, 1996).

From this data is obviously that mean value of both Ma and Ca in total blood after administration of cisplatin are lower compared to the values of control group (Pollera, 1990, Sartori, 1991). On the contrary, the mean value of iron is increased in experimental group (E_1 and E_2). The mean values of blood iron showed a three, respectively, four fold increase after cisplatin administration compared with the basal mean values. The increasing of iron concentration to experimental groups can be explained by physiological processes of hemo-concentration in case of some microelements that realize stabile binding even if are circulating in body fluids.

Depressions of trace elements can be correlated with some changes of acid - base balance, osmotic and osmotic – colloidal balance (e.g. magnesium and calcium realize stabile combinations with aminoacids).

The variation of concentration of Na and K in blood serum is presented in table 2.

Table 2. Mean concentration of Na and K in blood of Wistar rats after cisplatin administration.

Specifications	n	Na mmol/L	K mmol/L
		$\overline{X} \pm SD$	$\overline{X} \pm SD$
Group C	8	108.8 ± 13.02	4.88 ± 0.31
Group E_1	8	91.80 ± 5.67	6.42 ± 0.63
$\Delta\ \overline{X}$		-17.00	+1.54
Grup E_2	8	86.20 ± 3.49	6.62 ± 0.38
$\Delta\overline{X}$		-22.60	+1.74

n – number of animals per each working group

As could be seen from table 2, cisplatin induced hyponatremia due to renal salt wasting, and it is obviously (Lajer, 2003, 2005). Normal values of sodium in blood of Wistar rats are 152.2 mmol/L and potassium levels are between 5.4 –5.7 mmol/L (Chiricuță, 1982 cited by Ciudin, 1986).

The level of Na in blood serum plasma is lower in experimental groups than control groups. This can be explained by the anorexia and diarrhea during cisplatin treatment that determined the disturbance of homeostasis. Cisplatin cause also an increase in potassium levels from

experimental group blood in comparison with control groups. Potassium has an important role in osmotic equilibrium, in excitability of the muscle; in that case potassium has an antagonist effect with calcium.

Conclusions

Action of cisplatin is characterized by introduction of magnesium and calcium depression in blood in case of experimental group animals. These effects are directly proportional with the administrated doses. In case of iron, his concentration is higher on the experimental groups, because of his presence in the porfirinic structure.

Referring to sodium and potassium, it is observed depression of the sodium level in experimental groups and also the increasing of potassium level at the same groups.

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