In antitumoral chemotherapy a various number of drugs are used. Among them, cis - dichlorodiammineplatinum (abbreviated cis-platinum, cis-DDP or cDDP) has been widely used in chemotherapy [1-3].

From the chemical point of view cis-platinum is a heavy metal complex containing a central platinum atom surrounded by two ammonia molecules and chloride atoms arranged in the cis - position. Cis-platinum, as a compound, was the first time described by Peyrone in 1845, and the separation of its cis and trans isomers was elucidated in 1895 by Alfred Werner [4-6]. In 1960s, Rosenberg and his team research discovered that the electrolysis products from a platinum electrode inhibited mitosis in Escherichia coli bacteria. It is generally accepted that the major target in the interaction of cis - platinum with biological system is represented by deoxyribonucleic acid (abbreviated DNA) which is the carrier of genetic information.

Experimental part

For the experimental part, we used tumor free adults Wistar rats, supplied by the Animal Breeding Facility of the University of Agricultural Sciences and Veterinary Medicine of Timisoara. The animals were maintained on pathogen-free conditions, at 22-25°C room temperature, at 55-65% relative air humidity, and fed on normal rhythm and standard breeding food and water. All animals manipulation were performed according to the ethical principles for animal care.

The antineoplastic drug called cis-platinum used for this study was the commercially available Sin-Platin (Sindan, Romania).

The animals were randomly divided in five groups: one control (C) and four experimental groups (E1, E2, E3 and E4) and injected intraperitoneally (i.p.) with cis-platinum (the drug called Sin-Platinum) in study days 3 and 8. The animals from control group were injected with saline solution (placebo), also in study days 3 and 8. The results showed that the concentration of metal ions in liver is modified proportionally with administrated doses.

Results and discussions

Cis-platinum synthesis starts from the tetrachloro-platinate compound PtCl4⁻ (fig. 1). In case of the first NH₃ ligand, the addition is made to any of the four equivalent positions of the complex, but the second NH₃ ligand could be added cis or trans to the amine. Platinum can have different possible oxidation states, but especially two dominant oxidation states, +2 and +4. In case of platinum complexes in which platinum was in the +2 oxidation state the complexes are octahedral, and when platinum is in the +2 oxidation state, it forms square planar complexes [7,8,9]. The platinum complexes, having platinum with either the +2 or +4 oxidation state, are shown in figure 2.

Because of the several side effects, over the years, many platinum complexes have been studied, some are shown in figure 3.

From all platinum compounds the most antitumoral agent has proved to be cis-platinum.
Because of the planar geometry, after the penetration into the blood, the two labile ligands 2 (Cl)− are released during the hydrolysis. The process of hydrolysis has two steps, and at the end of each step a mono-, respectively a diaquated species are resulting (fig. 4). The aquated species of cis-platinum can form several types of covalent adducts with DNA.

The binding of cis-platinum to DNA can affect the structure of DNA and also the protein synthesis. The citotoxic activity of cis-platin correlates with the quantum of platinum that is bound to DNA macromolecule [10].

Previous studies revealed that cis-platinum caused DNA interstrand cross-links and DNA – protein cross – links [11].

In double - stranded DNA the major site of platination (65%) is represented by the intrastrand cross-links between two adjacent bases deoxyguanosines (GG). Another 20% of DNA platination derives from intrastrand cross-links between adenosine and guanosine, and no adducts were realised between the nucleosides in opposite places. Other platinum derivates (9%) derives from a cross-link between
two deoxyguanosines separated by a third nucleoside [12, 13]. In all situations, platinum was bound to the N7 atom of purine bases (fig. 5).

These results revealed that the 1,2 - intrastrand cross-links are the major adducts formed by cis-platinum. Also, the high selectivity N atom of guanine in the major groove of double stranded DNA is common to cis-platinum and its analogues [14].

Our experiments performed on laboratory rats revealed that the distribution of cisplatinum in the organism lead to the c-DDP - DNA adducts formation [15]. As a consequence of interaction with proteins, some modifications regarding some metal concentration can be mentioned. Metal elements are implicated in biochemical homeostasis, which is very important for the normal development of chemical and biochemical processes from organism [16, 17].

In our study the concentrations of some trace elements were determined in liver after cis-platinum administration. The obtained data are presented in table 1.

Zinc plays a role in stabilizing the biomembrane structure, and polynucleotides conformation. The modifications of these metals concentrations are related to the lesions produced by cis-platinum on DNA macromolecule. Also it is a cofactor for many enzymes. Zinc values are higher in experimental groups compared to control groups, and in case of experimental group (E₄) these difference are significant (p< 0.01), (fig. 6).

Table 1

<table>
<thead>
<tr>
<th>Specification</th>
<th>n</th>
<th>Zn (µg/g) w.t.</th>
<th>Cu (µg/g) w.t.</th>
<th>Fe (µg/g) w.t.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group C</td>
<td>10</td>
<td>32.93 ± 5.48</td>
<td>9.26 ± 1.52</td>
<td>195.05 ± 27.50</td>
</tr>
<tr>
<td>Group E₁</td>
<td>10</td>
<td>34.57 ± 5.76</td>
<td>9.38 ± 1.64</td>
<td>189.87 ± 26.53</td>
</tr>
<tr>
<td>ΔX</td>
<td></td>
<td>+1.64</td>
<td>+0.12</td>
<td>-5.18</td>
</tr>
<tr>
<td>Group E₂</td>
<td>10</td>
<td>35.18 ± 5.93</td>
<td>9.59 ± 1.90</td>
<td>184.79 ± 24.31</td>
</tr>
<tr>
<td>ΔX</td>
<td></td>
<td>+2.25</td>
<td>+0.33</td>
<td>-10.26</td>
</tr>
<tr>
<td>Group E₃</td>
<td>10</td>
<td>35.76 ± 6.21</td>
<td>9.97 ± 2.16</td>
<td>178.33 ± 24.76**</td>
</tr>
<tr>
<td>ΔX</td>
<td></td>
<td>+2.83</td>
<td>+0.71</td>
<td>-16.72</td>
</tr>
<tr>
<td>Group E₄</td>
<td>10</td>
<td>36.89 ± 6.75*</td>
<td>10.37 ± 2.30*</td>
<td>171.71 ± 23.90*</td>
</tr>
<tr>
<td>ΔX</td>
<td></td>
<td>+3.96</td>
<td>+1.11</td>
<td>-23.34</td>
</tr>
</tbody>
</table>

n = number of animal for each group  *p< 0.01  **p< 0.05
Iron concentration is lower in experimental groups in comparison with control groups. The decreasing is significant in experimental groups E₂ and E₃. In case of E₄ iron concentration is lower with 16.72 mg/dL, meaning 8.57%, and in case of E₅ with 23.34%, meaning 11.96%.

Our results revealed hepatic damages caused by cisplatinum administration. Metal elements zinc, copper and iron are implicated in biochemical homeostasis, which is very important for the normal development of several processes from organisms, such as: acido-basic balance, osmotic and colloid-osmotic equilibrium.

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