Cancer Chemother Pharmacol (1982) 10: 51–54

Cancer Chemotherapy and Pharmacology

Human Tissue Distribution of Platinum after cis-Diamminedichloroplatinum

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Summary. *Using X-ray fluorescence spectrometry, platinum concentrations were determined in autopsy tissue samples from 12 patients who had received cis-diamminedichloroplatinum (DDP) 20–120 mg/m² up to 6 months antemortem. Tissue platinum concentrations were highest in liver (0.5–3.7 μg/g wet weight), prostate (1.6–3.6 μg/g), and kidney (0.4–2.9 μg/g), somewhat lower in bladder, muscle, testicle, pancreas, and spleen, and lowest in bowel, adrenal, heart, lung, cerebrum, and cerebellum, Platinum concentrations in tumors were generally somewhat lower than the concentration in the organ in which the tumor was located, with the exception of intracerebral tumors. Different metastatic sites in the same patient had substantially different platinum concentrations and hepatic metastases had the highest concentrations. Intra-arterial administration of drug may augment tissue concentrations of platinum. In a patient undergoing therapeutic abortion 4 days after treatment, the platinum concentration was 0:5 μg/g in the placenta and 0.3 μg/g in the fetus. The data suggest that for in vitro sensitivity testing, DDP concentrations of ≦ 7 μg/ml should be used.*

Introduction

The tissue distribution of platinum after administration of the drug *cis*-diamminedichloroplatinum (DDP) has been defined in a number of animal species. Generally, it is found in the greatest concentrations in kidney, liver, muscle, and skin within the first hour after drug administration, and is still readily detectable in kidney, liver, skin, and lung after 4 weeks [8]. Some investigators have also noted high concentrations in ovary, testis, uterus [14], and fat [7]. Limited human data exist that show maximum concentrations in kidney 3 days after drug administration and in liver 24 days after drug administration [6].

Defining tissue concentrations may be of importance, since it may help provide a pharmacologic explanation for organ-specific toxicity or for antitumor activity. In addition, it is known that DDP is a radiosensitizer [4, 5], and knowledge of its tissue distribution could help forewarn against enhancement of radiation-induced toxicity by platinum. Of great potential importance are recently developed techniques of testing in vitro sensitivity of human tumor cells to various antineoplastic agents [9]. Tissue distribution studies of these drugs will provide an estimate of what drug concentrations should be tested in vitro.

This study was undertaken to determine the tissue distribution of platinum in autopsy specimens from patients who had received DDP antemortem.

Materials and Methods

Autopsies were monitored and tissue samples were collected from 12 patients who had received DDP up to 6 months antemortem.

In addition, the products of conception were collected during a therapeutic abortion on a patient who had received DDP 4 days earlier, and serial biopsies of cutaneous malignant melanoma nodules were obtained from a patient undergoing treatment with DDP. Samples were frozen until analysis.

Platinum concentration was determined using X-ray fluorescent spectrometry. Some tissues were analyzed by macerating them, drying a standard amount on mylar film cemented onto non-pigmented 35 mm slide mounts, and comparing the results with standard curves generated by adding variable amounts of CDDP to control tissues. Other tissue samples were lyophilized resuspended in a standard zirconium solution, air-dried on mylar film, and assayed using the zirconium as an internal standard.

Once dried, samples were excited with an X-ray beam from an Ag anode X-ray tube (40 kV, 20 mA) filtered with 200 μm Ag plus 50 μm Al. Samples were counted for 600 s (live time). A Kevex Model 0600 Ultra trace X-ray tube subsystem equipped with a 2 kW X-ray generator, Mark AAA Si (li) detector cryostat, and a Model 7000 Micro-X Universal Spectrometer (Kevex Corporation, Foster City, CA, USA) was used.

Quantitative measurements of Pt were performed using the Pt Lα emission (9.43 KeV, weighted average). To correct for the interfering Zn Kα emission (9.57 KeV, weighted average) the spectrum of pure Zn was normalized to the Zn Kα peak (8.63 KeV, weighted average) of the sample spectrum and the normalized pure Zn Kα peak was subtracted from the sample spectrum. The area of the Pt Lα peak (Pt window = 9.20–9.72 KeV) was then mass-normalized by dividing it by the area of an arbitrarily defined window (17.74–20.28 KeV) on the inelastic scatter peak of the exciting Ag Kα emission. This inelastic scatter is proportional to the mass of the sample, and therefore by determining the ratio of the area of the Pt Lα

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0344-5704/82/0010/0051/$ 01.00

peak to this scatter peak, the area is mass-normalized and is a measure of the concentration of Pt in the sample. The lower limit of detection for platinum was 0.24 μg/g tissue. The correlation coefficients for the standard curves were > 0.99.

Results

Figure 1 shows the concentration of platinum in various organs. Patients are arranged in order of length of time from the first day of their last treatment. Generally the highest platinum concentrations were found in liver, prostate, and kidney. Somewhat lower concentrations were found in bladder, muscle, testicle, pancreas, and spleen, and still lower concentrations were found in bowel, adrenal, heart, lung, cerebrum, and cerebellum. Relatively low platinum concentrations were found in the single samples of ovary and uterus that were collected. Platinum was found in all tissues tested as long as 180 days after last DDP administration.

Tumor platinum concentrations varied with the site of the tumor, and the route of DDP administration. Based on our limited data, it appeared that hepatic metastases may have had a higher platinum concentration than metastases to other sites in the same patient. In addition, intra-arterial administration of drug may have resulted in higher tissue concentration of drug, since patient 4, who received a hepatic artery infusion of DDP, had by far the highest tumor platinum concentration and was the only patient with a higher concentration of platinum in intrahepatic tumor than in the liver. However, this patient also received a relatively high dose of DDP and had a relatively short time interval between treatment and autopsy. Patient 10, who received an intracarotid infusion of DDP, was the only one of the three patients with intracerebral tumors who had a higher concentration of platinum in tumor than in kidney.

Table 1 demonstrates tissue and plasma concentrations of platinum as a function of time in cutaneous metastases from patient 13, who had malignant melanoma and received DDP 40 mg/m^2 per week. The first sample was obtained just prior to his second DDP injection. Tissue platinum concentration was higher 1 week after the second than 1 week after the first DDP treatment, and was higher in tissue than in concurrent or peak plasma concentrations after the second treatment. In addition, tumor platinum concentration was similar 2 days and 7 days after the second treatment.

Patient 14 underwent a therapeutic abortion 3 days after her third weekly IV treatment with DDP 40 mg/m^2. The platinum concentration in the placenta was 0.52 μg/g and in combined parts of the 8-week-old fetus it was 0.31 μg/g.

Table 1. Concentrations of platinum in cutaneous malignant melanoma metastases immediately before and after second weekly IV injection of DDP 40 mg/m^2

Time (h)	Tissue platinum (μg/g)	Plasma platinum (μg/ml)
Pretreatment	0.2	0.2
Posttreatment		
0	2.9	1.1
45	1.7	0.5
166	2.0	0.7

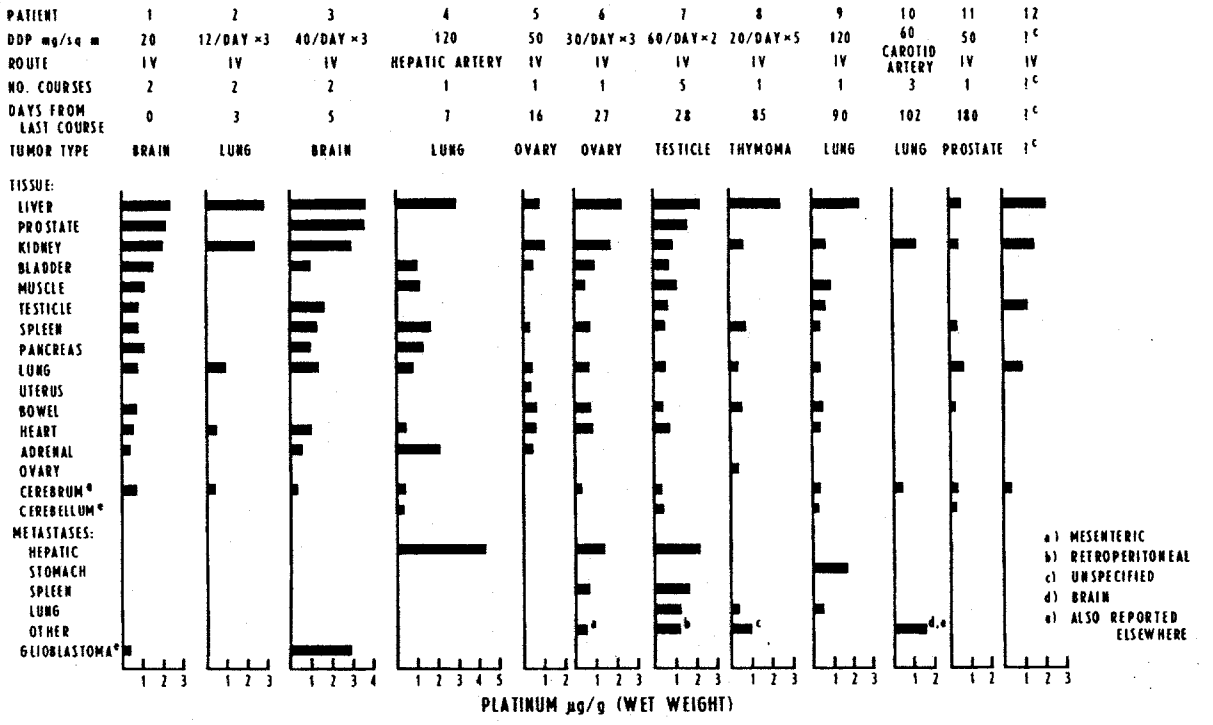

Fig. 1. Postmortem human tissue concentrations of platinum after DDP therapy. Tissues were obtained at autopsy examination of 12 patients who had received DDP antemortem. Tissue platinum concentration was measured using X-ray dispersive fluorescent spectrometry. Platinum was detectable in all tissues tested. Where no value appears, no tissue was obtained. Patients 1, 2, 3, 7, 9, 10, 11, and 12 were males and patients 4, 5, 6, and 8 were females

Discussion

Human tissue drug concentration data are extremely difficult to obtain. Of necessity, great heterogeneity exists in the patient population, in that drug dose, schedule, and number of courses varied markedly. Adding to the difficulty is the fact that we were able to quantitate only total platinum concentration and were not able to determine whether it was in the form of parent drug or metabolite. Hence, our results must be interpreted very cautiously. Nevertheless, the information is useful and a number of tentative conclusions can be drawn.

As previously noted by others [6], we found that platinum persists in tissues in high concentrations for several months after treatment with DDP.

Despite the fact that higher concentrations of platinum were found in liver than in kidney, hepatic toxicity from DDP is far less common than nephrotoxicity [3]. Therefore, it should not be assumed that the nephrotoxicity of DDP is only a drug-concentration effect. Knowledge of the biochemical factors that render the kidney relatively sensitive and the liver relatively resistant to DDP toxicity might suggest additional measures that could be taken to reduce DDP nephrotoxicity. It is possible that the drug present in liver was complexed in an inactive non-toxic form before it was taken up by the liver.

We have previously noted that infusion of DDP into the hepatic artery results in a lower peak peripheral plasma concentration of platinum, area under the concentration X time curve, and urinary excretion, and higher volume of distribution and clearance than does infusion of DDP into other arteries or IV [10]. These data and the observed high liver platinum concentrations suggest that the liver may be capable of sequestering DDP. It has previously been suggested that DDP undergoes enterohepatic recirculation [13], despite there being no known hepatic metabolism of the drug. In light of our data, it would be reasonable to study the feasibility of administering higher doses of DDP into the hepatic artery for hepatic metastases than are tolerable by other routes, since less may escape into the systemic circulation when hepatic artery infusion is used.

Besides being present in high concentrations in liver, platinum was also present in higher concentrations in hepatic metastases than in metastases to other sites in both the patients who had both hepatic and other metastases. The reasons for tissue platinum variability between different metastatic sites in the same individual are not clear, although the observed differences could be artefactual or could be due to differences in blood flow, differences in amount of necrotic tissue or protein, or differences in biological properties of tumor cells capable of surviving in liver vs. other metastatic sites. If the observation of higher platinum concentrations in hepatic vs. other metastatic sites is confirmed, it would be reasonable to study the preferential use of DDP in patients who have hepatic metastases.

We have previously demonstrated that intra-arterial administratioin of DDP results in augmentation of local peak plasma platinum concentration and concentration X time [10], and intra-arterial administration of DDP has been shown to be highly effective in the treatment of localized malignancies [2, 11]. Tissue data obtained from patients 4 and 10 are consistent with the postulate that local tissue uptake of DDP is enhanced by intra-arterial drug administration, although these data are too limited to be taken as proof. It is possible that patient 4 had higher platinum concentrations in her intrahepatic tumor than in the liver, because intrahepatic tumor derives most of its blood supply from the hepatic artery, which was infused with drug in this patient, whereas the normal liver derives 80% of its blood supply from the portal venous system [1].

We have previously reported concentrations of platinum in intracerebral tumors after IV and intracarotid DDP that are potentially cytotoxic and radiosensitizing [12]. There is no indication from our data that platinum attains any higher concentrations in extracerebral than in intracerebral tumors. In addition, our data do not indicate that tumor platinum concentrations are generally any higher than concentrations achievable in some normal tissues, although higher concentrations are found in intracerebral tumor than in brain [12].

The molecular weight of DDP is approximately 50% higher than that of platinum. Therefore, since we found 0.5–4.5 μg platinum/g in tumor samples, it would be reasonable to study DDP concentrations of ≤ 7 μg/ml in in vitro sensitivity testing systems.

No appropriate lower level can be assigned for testing since our method did not determine the molecular species of the measured platinum. It is possible that very little of it was in a cytotoxic form. On the other hand, it is reasonable to offer an estimate of the upper limit to be tested since the molar concentration of DDP in the tissue can be no higher than the molar concentration of platinum detected.

Acknowledgements. This work was supported by grant CA-14528 from the National Cancer Institute, National Institute of Health, Bethesda, Maryland.

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