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Direct Diffusion of *cis*-Diamminedichloroplatinum(II) in Intraperitoneal Rat Tumors after Intraperitonal Chemotherapy: A Comparison with Systemic Chemotherapy[1]

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ABSTRACT

Chemotherapy i.p. is increasingly being tested as a treatment modality for cancer limited to the peritoneal cavity. We have developed a rat tumor model in which penetration and distribution of *cis*-diamminedichloroplatinum(II) into intraperitoneal tumors have been studied. The platinum concentration in intraperitoneal tumor nodules, measured by two techniques, flameless atomic absorption spectroscopy and proton-induced X-ray emission, was always higher after i.p. treatment than i.v. Further, platinum concentrations were higher at the periphery of the tumor after i.p. administration than after i.v., while platinum concentrations in the center of the tumor nodules were identical. No difference was detected in platinum concentrations in s.c. tumors nor in the total area under the curve (plasma) after i.p. and i.v. administration of *cis*-diamminedichloroplatinum(II), suggesting that the higher drug concentration measured in peritoneal tumors after i.p. administration is due to direct diffusion of the drug from the peritoneal cavity.

INTRODUCTION

The aim of cancer chemotherapy is to eradicate all tumor cells. There is increasing recognition that tumors growing within a body cavity are less well supplied by the blood stream, resulting in the establishment of a pharmacological sanctuary (1). Pharmacokinetic modelling for such tumors has suggested that intracavitary administration of chemotherapeutic agents by peritoneal dialysis techniques might result in a significantly greater drug concentration in the peritoneal cavity than in plasma. This concentration difference offers a potentially biomedical advantage in the treatment of malignancies confined to the peritoneal cavity (2). Recent studies have demonstrated that delivery of some anticancer drugs via the intraperitoneal route is feasible and well tolerated (3–9), and that the peritoneal cavity is indeed exposed to higher drug concentrations than the rest of the body (5, 7, 9), as was predicted by Dedrick (2).

cDDP[3] is an important cytotoxic drug in the treatment of a variety of human neoplasms, but serious side effects, like renal, nerve, and intestinal damage, lower its therapeutic index (10, 11). However, the change of route of administration for cDDP from i.v. to i.p. in case of cancers limited to the peritoneal cavity has improved the clinical response (12, 13). cDDP was administered i.p. as a single agent to patients who had residual small volume ovarian cancer which had failed to respond to i.v. cDDP. In these patients impressive clinical results were observed; namely, 30% of the patients achieved a histologically proven complete remission (12).

One reason why intraperitoneal chemotherapy is not 100% effective in these situations may be inadequate drug penetration into tumors. The optimal tumor nodule size for i.p. treatment was not known, but advances in analytical techniques now allow precise measurement of cytotoxic drug concentrations within tumors and plasma. It is thus possible to relate both drug concentrations by means of pharmacokinetic models and to assess penetration but not the pattern of intratumoral drug distribution (14). Ozols *et al.* (15) evaluated intratumoral distribution of doxorubicin by measuring the intensity of intracellular fluorescence in mouse ovarian tumors treated both i.p. and i.v. Only four to six outer cell layers of tumor mass were intensely fluorescent, suggesting high intracellular drug concentrations after i.p. administration. McVie *et al.* (16) calculated platinum content in peritoneal surface tumors of one patient, treated with i.p. cDDP, and found the highest platinum concentrations on the periphery of the tumors.

The present study demonstrates for the first time a detailed topographic distribution pattern of platinum in intraperitoneal tumors after i.p. administration, provides the penetration depth of cDDP into tumors, and indicates important advantages of i.p. chemotherapy over i.v. for cancers limited to the peritoneal cavity.

MATERIALS AND METHODS

Rats. Male WAG/Rij rats, 8 to 12 wk old at the time of the experiments, were obtained from the animal department of the Netherlands Cancer Institute and bred under specific-pathogen-free conditions. The animals were kept in a temperature-controlled room on a 12-h light, 12-h darkness schedule and maintained on standard rat chow and tap water *ad libitum*.

Tumor. CC531 colonic adenocarcinoma was induced by methylazoxymethanol and is well defined (17). The tumor grows subcutaneously, intraperitoneally, and *in vitro*. *In vitro* it is replated at a density of 1×10^5 cells in fresh medium [minimal essential medium (Dulbecco's modification)] with 10% fetal calf serum (Flow Laboratories).

Drugs. cDDP was made by Bristol-Myers, Weesp, The Netherlands. [^{195m}Pt]cDDP (specific activity, 30 μCi/mg) was obtained from the Interfaculty Reactor Institute, Delft, The Netherlands.

Rat Model. Unless stated otherwise, WAG/Rij rats were inoculated i.p. with 2×10^6 CC531 tumor cells in 2 ml of phosphate-buffered saline on Day 0. Four wk later, small tumor nodules were present in 60 to 80% of the rats. Tumor nodules were situated on the diaphragm, peritoneum, and the mesothelium between the intestines, and distant metastases were rare. Treatment with cDDP was started 28 days after inoculation. Tumors and various target tissues were collected at set times to determine platinum concentrations in tissues. Before tissue sampling, animals were sacrificed by ether.

Flameless Atomic Absorption Spectroscopy. A Model 5000 atomic absorption spectrometer (Perkin-Elmer Corp.), with a HGA-500 graphite furnace and an As-40 autosampler, was used for platinum analysis. Platinum concentrations were determined in plasma and peritoneal

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[3] The abbreviations used are: cDDP, *cis*-diamminedichloroplatinum(II); FAAS, flameless atomic absorption spectroscopy; PIXE, proton-induced X-ray emission; AUC, area under the curve.

fluid (total platinum), in ultrafiltrate of plasma and peritoneal fluid (free platinum), and in tumor and target tissues as described by Vermorken *et al.* (18).

Proton-induced X-Ray Emission. The PIXE facility at the Eindhoven University of Technology was used to measure platinum concentrations at different depths within tumors. The technical conditions are described elsewhere (19). For the measurement of spatial distributions, cryostat sections of 40 μm were cut. After drying, the mass thickness was about 0.5 mg/cm^2. The freeze-dried sections were covered with aluminum foil and packed between polystyrene layers (20). Calibration samples were prepared as follows. The polystyrene was loaded with a well-defined solution of cobalt acetylacetonate instead of a section in order to establish quantitatively the ratio of a well-known cobalt peak area and the maximum height of the "bremsstrahlung" which appears at lower energies in the spectra. Furthermore, PIXE spectra were made from tumor sections taken from untreated rats. In these spectra, the germanium K_β fluorescent peak area appeared to be equivalent to a concentration of 1.5 ppm. This background was subtracted from the other values. Platinum concentrations were determined in a line from the periphery to the center of the tumor in areas of 1600-μm^2 beam size (about 40-μm diameter) with a distance of about 500 μm between each point measured.

Comparison of Platinum Concentrations after i.p. or i.v. Chemotherapy. WAG/Rij rats were inoculated with 2×10^6 CC531 tumor cells, and after 4 wk, rats were treated with cDDP (5 mg/kg or 3 times 4 mg/kg) i.v. or i.p. The cDDP was injected i.v. in a volume of 2.5 ml (0.5 mg of cDDP/ml); for the i.p. treatment, cDDP was dissolved in 20 ml of 0.9% NaCl solution prior to injection. Tumor tissue was collected at 4, 24, 48, or 168 h after treatment. Target tissue (liver, kidney, spleen, intestines, and lung) was collected at 168 h after treatment. Platinum concentrations were determined by FAAS. Most tumors at the time of injection were in the range of 3 to 8 mm in diameter.

Absorption of cDDP in Tumors after i.p. Administration. WAG/Rij rats were inoculated i.p. with 2×10^6 CC531 tumor cells. After 4 wk, rats were treated i.p. with cDDP in doses of 5 mg/kg, 10 mg/kg, and 2 times 5 mg/kg with a period of 24 h between injections. At 4, 24, and 48 h, tumors were collected for FAAS platinum determination.

Distribution of Platinum in Tumors. WAG/Rij rats were inoculated i.p. with CC531 tumor cells (2×10^6) to detect differences in distribution patterns of platinum in tumors after i.p. or i.v. chemotherapy. After 4 wk, rats received i.v. or i.p. three repeated doses of 4 mg/kg of cDDP, with a delay of 120 h between the different doses. Tumor tissue was collected 168 h after the last administration. The distribution of platinum was quantitatively determined by PIXE.

Contribution of the Blood Supply to the Platinum Tissue Concentration. WAG/Rij rats were inoculated s.c. with 10^6 tumor cells in the interscapular region. After 2 wk, tumors reached a size of 0.75 to 1 cm in diameter, and the rats were treated either i.p. or i.v. with [^{195m}Pt]-cDDP (5 mg/kg) in 0.14 M NaCl. After 24 h, tumors were removed, and ^{195m}Pt-radioactivity was measured with a gamma counter.

Pharmacokinetic Studies. Pharmacokinetic studies were performed in WAG/Rij rats after cannulation of the jugular vein and the carotid artery. cDDP (5 mg/kg) was administered into the cannulated jugular vein or into the peritoneal cavity (5 mg/kg in 20 ml). At different time points after treatment with cDDP, blood samples were taken from the carotid artery. Platinum concentrations in plasma and ultrafiltrate were determined by FAAS.

cDDP clearance from the peritoneal cavity was studied by sampling the peritoneal fluid at the same time points as blood.

Statistics. The Wilcoxon test was used to study the significance (5% level), with P values > 0.05 considered to be not significant.

RESULTS

Concentration of Platinum in Intraperitoneal Tumors after i.p. or i.v. Administration. In Fig. 1, tumor platinum concentrations are shown after i.p. and i.v. administration of cDDP. Platinum concentrations in whole tumors have been measured at different times (4, 24, and 168 h) after administration of a single dose

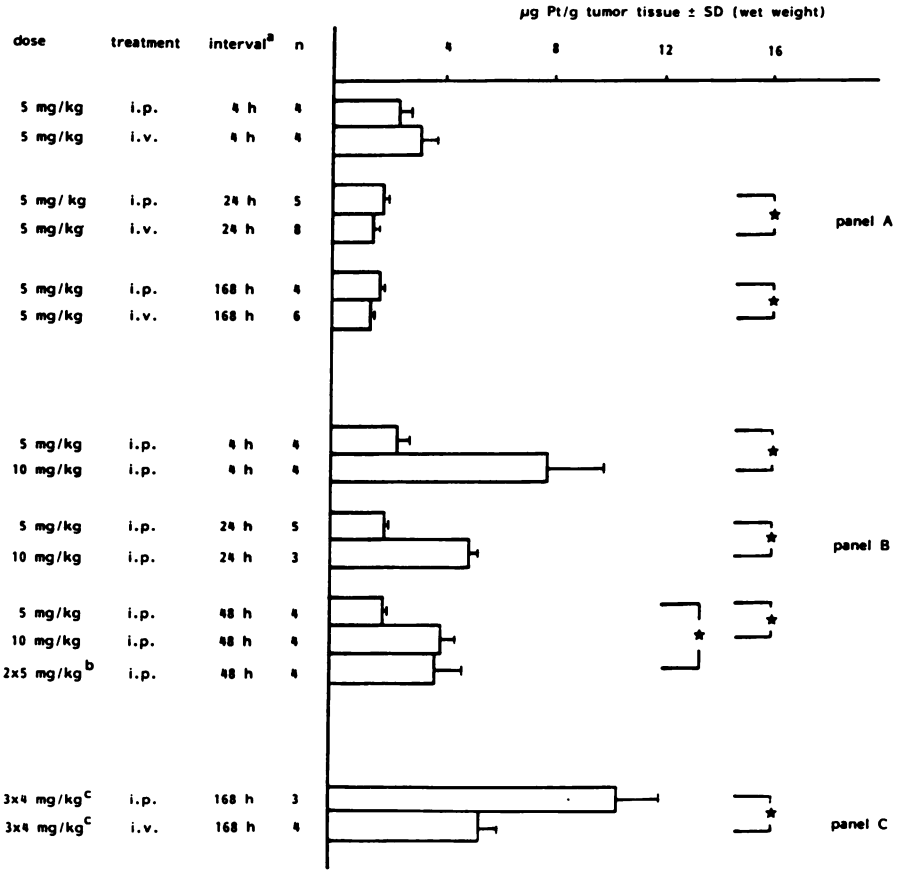

Fig. 1. cDDP concentrations in intraperitoneal tumors after i.p. or i.v. administration of 5, 10, 2 times 5, or 3 times 4 mg/kg of body weight of cDDP at 4, 24, 48, and 168 h after treatment. *, levels of significance ($P < 0.05$); *n*, number of rats; *a*, interval between last administration and tissue collection; *b*, interval between administration (24 h); *c*, interval between administrations (120 h).

of the drug (Fig. 1*A*). Comparing the i.p. and i.v. treated animals, no significant difference in platinum concentration could be detected after 4 h. However, a clear difference has been detected at 24 h. This difference still existed after 168 h. The highest platinum concentrations were always found after i.p. administration except after 4 h, indicating that higher platinum levels can be reached in intraperitoneal tumors after i.p. administration.

Further, Fig. 1 shows that doubling the dose at least results in a doubling of the platinum tumor concentration (Fig. 1*B*). This indicates that, after two doses, the absorption capacity of the tumor was not reduced. This observation is confirmed by the fact that platinum concentrations in tumors of i.p. and i.v. treated animals are markedly increased after repeated doses (3 times 4 mg of cDDP/kg of body weight; Fig. 1*C*). Important is the fact that the difference in platinum concentration between i.v. and i.p. treated animals is accentuated ($p < 0.05$). This means in terms of therapeutic implication that i.p. chemotherapy for tumors of this size (3 to 8 mm in diameter), situated in the peritoneal cavity, is probably the best option.

Distribution of Platinum in Tumors after i.p. and i.v. Chemotherapy. Platinum levels were determined quantitatively in tissue by PIXE. Measurements have been performed in line from the periphery of the tumor to the center, on thick (40 μm) sections cut at right angles through peritoneal tumor nodules of rats, using a microbeam of 40 μm in diameter. As shown in Table 1, a big difference between the distribution of platinum in the tumors treated i.v. or i.p. could be detected. The i.p. treated tumor has the highest concentrations on the periphery, presumably caused by penetration of platinum from the peritoneal cavity. The advantage extends up to 1.5 mm inward from the periphery of the tumor. A considerable concentration is present in the center of the tumor treated i.v., but on the periphery the concentration decreased compared to the center.

Role of the Blood Supply in Delivering cDDP to the Tumor. Platinum concentrations were measured in s.c. tumors to determine the exposure of the tumor to the drug via the circulation after i.p. and i.v. therapy. Fig. 2 shows no significant difference in platinum tissue concentration between the two routes of administration. This means that both after i.p. as well as after i.v. administration of cDDP the tumor is exposed to the same amount of drug. These data are confirmed by pharmacokinetic studies (Figs. 3 and 4; Table 2).

As shown in Figs. 3*A* and 4*A* and in Table 2, the AUCs in plasma and plasma ultrafiltrate, as a measure for the exposure of the tumor by the drug, do not differ significantly between i.p. and i.v. treated animals. The plasma/plasma ultrafiltrate ratio is 4.6 in both cases, indicating that only part of the administered cDDP is therapeutically active, while the tumor is equally exposed to cDDP after both i.v. and i.p. treatment. Figs. 3*B* and 4*B* and Table 2 show also that the AUC for bound and free platinum in the peritoneal cavity after i.p. treatment is

Table 1 *Platinum distribution in intraperitoneal tumors after i.v. and i.p. administration of cDDP*

There were three rats, each with one tumor.

Distance inward from the periphery (mm)	Platinum concentration (ppm) after the following cDDP administrations	
	3 × 4 mg/kg i.v.	3 × 4 mg/kg i.p.
0.1	11 ± 3[a]	36 ± 2
1.0	19 ± 7	37 ± 3
1.5	24 ± 6	29 ± 4
2.2	25 ± 6	25 ± 2

[a] Mean ± SD.

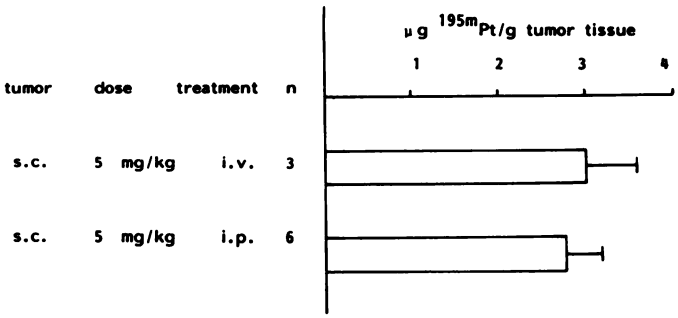

Fig. 2. Platinum concentration in s.c. tumors after i.v. or i.p. treatment with [^{195m}Pt]cDDP (5 mg/kg). Tumors were removed after 24 h, and radioactivity was determined. *n*, number of tumors.

about 6 times higher than the AUCs in the peritoneal cavity after i.v. treatment. Thus, the exposure of the tumor in the peritoneal cavity by cDDP after i.p. administration is considerably greater than in i.v. treated animals. The effects of these differences were shown in Table 1.

Biodistribution of cDDP. Lung, liver, kidney, spleen, and small intestines were sampled after 3 doses of 4 mg/kg (Table 3). No major difference in platinum concentration could be detected in lung or intestinal tissue between i.v. and i.p. treated animals; however, significantly higher platinum concentrations were found in the kidney of the i.v. treated rats compared to the i.p. treated rats (i.v./i.p. ratio, 0.59).

A small difference in concentration is also present in the liver. In this case, a higher drug concentration is achieved after i.p. administration (i.v./i.p. ratio, 1.23). This can possibly be explained by direct absorption of cDDP from the peritoneal cavity via the portal vein. The major advantage of i.p. chemotherapy in terms of possible toxicity is a lower platinum concentration in the kidney.

DISCUSSION

The rationale for i.p. drug administration in patients with ovarian cancer is that even in advanced stages of the disease the tumor remains localized in the peritoneal cavity (1). Preclinical data, pharmacokinetic modelling, and recent clinical investigations have demonstrated an increased tumor exposure to a number of antineoplastic agents (cDDP, cytarabine, doxorubicin, 5-fluorouracil, melphalan, methotrexate, and mitoxantrone) when administered i.p. as opposed to i.v. administration (3–9, 21). The critical question regarding i.p. administration of chemotherapeutic drugs is whether a greater concentration of the cytostatic drug is achieved in the tumor and whether the increased drug concentration will depend on the degree of absorption and penetration of the cytostatic drug into tumor deposits in the peritoneal cavity. To study this question, an animal model which resembles the anatomical features and cDDP sensitivity of ovarian cancer closely (22) and showed great similarities to other, intraperitoneal xenograft tumor models (23–25), was developed. The results from this present study do indeed demonstrate that i.p. chemotherapy led not only to higher drug concentrations in the tumor than i.v. administration but also to a more favorable drug distribution pattern in the tumor.

Extensive pharmacokinetic studies after i.p. administration of cDDP have been performed (3, 12), but to our knowledge no correlation between cDDP exposure and platinum concentrations in the tumor has been reported. Data in this paper demonstrate that a high exposure of the tumor after i.p. chemo-

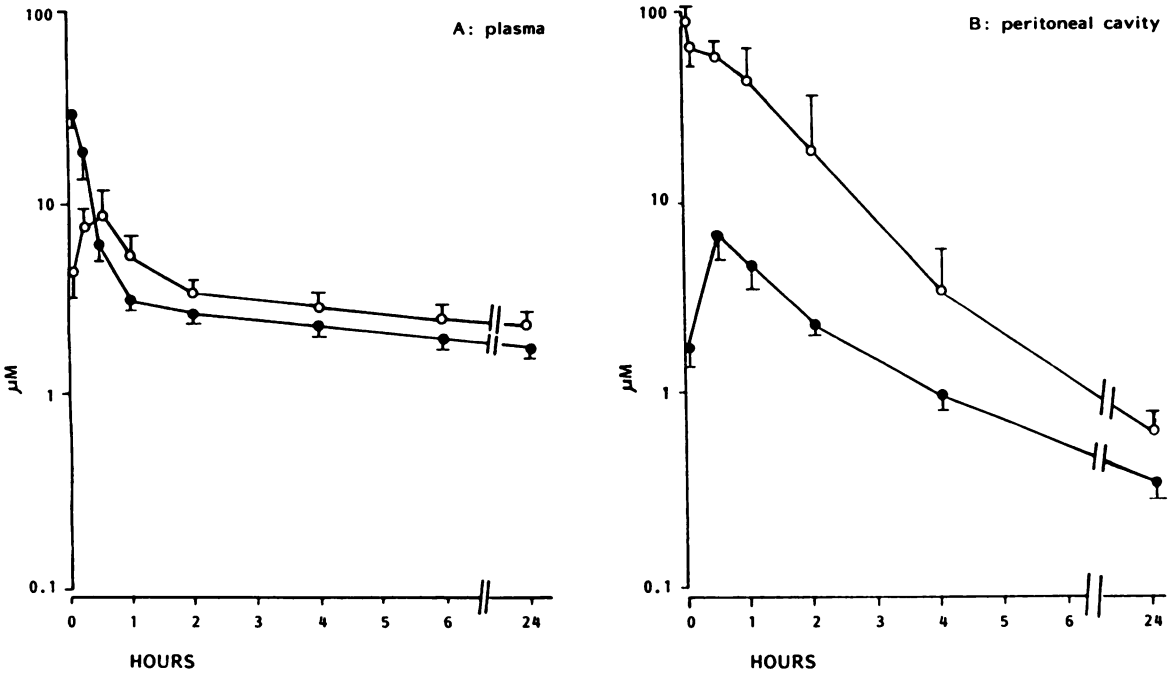

Fig. 3. Semilogarithmic concentrations *versus* time plot of total platinum in plasma (*A*) and in peritoneal fluid (*B*) after i.v. (●) and i.p. (○) administration of cDDP (4 mg/kg). *Bars*, SD.

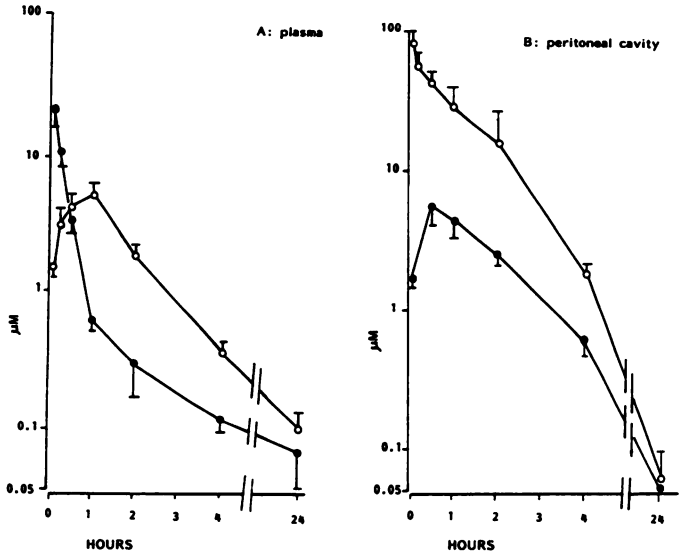

Fig. 4. Semilogarithmic concentrations *versus* time plot of ultrafiltrable platinum in plasma (*A*) and in peritoneal fluid (*B*) after i.v. (●) and i.p. (○) administration of cDDP (4 mg/kg). *Bars*, SD.

Table 2 *Areas under the concentration × time curve (μm·m) in plasma and peritoneal fluid after i.v. and i.p. administration*

There were three rats.

Platinum	Administration	
	i.v.	i.p.
In plasma	3466 ± 365[a]	3915 ± 305
In ultrafiltered plasma	746 ± 37	842 ± 34
In peritoneal fluid	1497 ± 81	9561 ± 325[b]
In ultrafiltered peritoneal fluid	921 ± 54	6402 ± 421[b]

[a] Mean ± SD.
[b] Significantly different ($P < 0.05$).

therapy actually leads to higher platinum concentrations in the tumor (Fig. 1). The difference in platinum concentration in tumor tissue after i.p. and i.v. administration could be increased by giving repeated doses (Fig. 1). An explanation for this

Table 3 *Platinum concentrations (μg/g of tissue, wet weight) after i.v. and i.p. administration of cDDP (3 × 4 mg/kg)*

Tissue[a]	i.v.	i.p.	i.p./i.v. ratio
Kidney	22.7 ± 4[b]	13.4 ± 2	0.59
Liver	7.2 ± 0.5	8.9 ± 0.8	1.23
Intestines	3.8 ± 1.5	3.7 ± 1.0	0.97
Lung	8.5 ± 1.2	6.9 ± 1.7	0.81
Tumor	5.5 ± 0.7	10.9 ± 1.5	1.98

[a] Number of rats, 4.
[b] Mean ± SD.

phenomenon could be the general property of tissue to accumulate platinum (26).

The toxicity of cDDP has been well documented (11, 27). Nephrotoxicity and neurotoxicity are dose limiting for cDDP when standard regimens are used. The major site of toxicity in the rat kidney is the P3 segment of the proximal tubule (28) in which also the highest levels of cDDP-DNA adducts are detected (29). The development of nephrotoxicity appears to correlate with elevated plasma cDDP levels (30). Despite the fact that this study was not performed to study the toxic effects of cDDP on the kidney, it seems that the concentration of platinum in the kidney correlates with the site of lesions causing nephrotoxicity.

Few data are available describing intratumoral drug distribution after i.p. drug administration (15, 16). In this paper, a topographic study of platinum distribution in tumors, after i.p. and i.v. administration, has been performed for the first time. Platinum concentrations have been measured in very small areas of frozen tissue sections. After treatment with the same regimen, higher platinum concentrations were found in the periphery of the tumor after i.p. administration than i.v., while in the center of the tumor equal concentrations were found. These data suggest that the advantage of i.p. over i.v. therapy is maximal in the first 1.5 mm of the peritoneal surface of the tumor, equivalent to 50 to 75 cell layers. From data obtained in i.v. treated animals (Table 1), it is reasonable to assume that the center of an i.p. treated tumor gets its cDDP via the blood circulation. This was confirmed by the fact that AUCs of

platinum in plasma (Table 2) and the platinum concentration in s.c. tumors (Fig. 2) were comparable after i.p. and i.v. administration of cDDP. This implies that the higher platinum concentrations in the outer region of intraperitoneal tumors obtained after i.p. administration are caused by direct diffusion.

In some cases of ovarian cancers, the change to i.p. administration has led to clinical responses in patients resistant to i.v. cDDP (12, 13). Comparing this with data obtained in our animal model, a correlation between intratumoral concentrations and the antitumor response is suggested.

The results of this study demonstrate that i.p. chemotherapy compared to i.v. administration does lead to higher drug concentrations and to a different distribution pattern within the tumor. The advantage of i.p. chemotherapy is probably based on the fact that high drug concentrations can be reached on the periphery of the tumor. From these data and work of Dedrick *et al.* (2), it is likely that intraperitoneal chemotherapy will completely remove only small tumor nodules. However, the outer parts of large nodules will be exposed to higher drug concentrations than can be achieved by by i.v. treatment, and if penetration characteristics of the drug could be improved, even these tumors might be susceptible. This might be achieved by changing the molecular weight or the lipophilicity of the drug, or by prolonging the duration of the drug exposure, for example, by influencing the blood flow in the tumor or by increasing the drug peak levels in the peritoneal cavity.

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