THE ANTITUMOR AGENT CIS-$Pt(NH_3)_2Cl_2$: DISTRIBUTION STUDIES AND DOSE CALCULATIONS FOR ^{193m}Pt AND ^{195m}Pt

Robert C. Lange, Richard P. Spencer, and Harold C. Harder

Section of Nuclear Medicine, Yale University School of Medicine, New Haven, Connecticut

The radioisotopes of platinum ^{193m}Pt and ^{195m}Pt were produced and compared as radiolabels for the antitumor compound cis-$Pt(NH_3)_2Cl_2$. On the basis of physical characteristics, ^{195m}Pt was the radioisotope of choice. When radiolabeled cis-$Pt(NH_3)_2Cl_2$ (with carrier) was injected into mice bearing sarcoma 180, the tumor/blood ratio of radioactivity varied from 1:3 to 2:0 (4 hr to 5 days after injection). Organ distribution in tumor-bearing mice was similar to that previously noted in control mice. Plasma disappearance data in two patients revealed an initial rapid fall in radioactivity following intravenous injection and then a slower phase. In the two cases, it was estimated that 60–70% of the radiolabel was retained after two days. Most excretion of radioactivity was through the urine.

The compound cis-diamminedichloroplatinum (II), (DDP) is one of the first totally inorganic antitumor agents. The compound is an effective antitumor agent for a number of experimental tumors, including sarcoma 180 (*1*), and it is presently in clinical trials at various medical centers. Because of its component, platinum, the molecule can be radiolabeled with a gamma-ray-emitting radionuclide (*2*). In the present communication we discuss possible platinum radioisotopes that can be used in the radiolabeling, dose calculations, and experiences with the ^{193m}Pt- and ^{195m}Pt-labeled compounds in tumor-bearing animals and patients. We have previously reported preliminary results of distribution studies in normal mice (*2*).

MATERIALS AND METHODS

The platinum isotopes used in this study were ^{193m}Pt and ^{195m}Pt. The ^{193m}Pt was produced by alpha-particle bombardment of natural osmium metal in the Yale Heavy Ion Accelerator (HIA). The nuclear reaction is $^{192}Os(\alpha,3n)^{193m}Pt$. The ^{193m}Pt was radiochemically purified by distilling off OsO_4 after dissolution of the osmium in aqua regia. The carrier-free ^{193m}Pt was then mixed with approximately 10 mg of natural platinum metal so that the DDP could be synthesized as indicated below.

The ^{195m}Pt was produced by neutron irradiation of 70% enriched ^{194}Pt at the Vallecitos reactor of the General Electric Company. About 10 mg of enriched metal were irradiated for each run. The irradiated material was dissolved in aqua regia and the DDP synthesized. The many-step synthesis has the advantage of also serving as a radiochemical purification of the ^{193m}Pt and ^{195m}Pt.

The platinum aqua regia solution was repeatedly evaporated to near dryness with concentrated hydrochloric acid to remove all traces of nitrate ion. The compound K_2PtCl_6 was precipitated by the addition of potassium chloride and reduced to K_2PtCl_4 with hydrazine (*3*). The final synthesis steps to DDP were adapted directly from the Dahra method (*4*). The final product was evaluated for authenticity and purity by biological testing (filament formation in E coli B) and by paper chromatography.

The distribution of DDP was studied in normal white male New Zealand rabbits, in male Swiss white mice with the transplanted tumor sarcoma 180, and in two patients who were in clinical trials with unlabeled DDP.

The adult male rabbits received intravenously 200 μCi of the labeled compound; sequential scintiphotos were obtained with a gamma-ray camera.

The experimental mice received implants of sarcoma 180 in their flanks 10 days before the ^{195m}Pt-

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For reprints contact: Robert C. Lange, Section of Nuclear Medicine, Yale University School of Medicine, New Haven, Conn. 06510.

FIG. 1. Posterior scintiphoto, 3 hr after intravenous injection of cis-$^{195m}Pt(NH_3)_2Cl_2$ into male rabbit (200 μCi, 0.1 mg compound kg body weight). Intense activity is seen in the bladder (at bottom) with less activity in kidneys and liver.

TABLE 1. TUMOR/BLOOD RATIO OF RADIOACTIVITY AT TIME INTERVALS AFTER INTRAPERITONEAL INJECTION OF RADIOLABELED cis-$Pt(NH_3)_2Cl_2$ INTO MALE MICE BEARING SOLID SARCOMA 180 (2 ANIMALS AT EACH TIME)

cis-$Pt(NH_3)_2Cl_2$ radionuclide used	Time of sacrifice	Ratio of counts/gm tumor to counts/ml blood	Carrier
^{193m}Pt	4 hr	1.59	8 mg/kg body wt
^{195m}Pt	4 hr	1.95	0.8 mg/kg body wt
	1 day	1.84	
	5 days	1.32	
^{195m}Pt	4 hr	1.89	8 mg/kg body wt
	1 day	1.68	
	5 days	2.00	

labeled compound was injected. The tumored mice received approximately 10 μCi of the labeled compound injected intraperitoneally. To approximate the dosage schedule used in patients, carrier DDP was added at levels of 0.8 mg/kg body weight and 8.0 mg/kg body weight. At various time intervals from 4 hr to 5 days, the mice were sacrificed, and blood, tumor, and organs were counted and compared to standards.

The labeled DDP was administered intravenously to two patients who were receiving the compound in chemotherapeutic amounts.

Patient 1 was a 26-year-old man with a diagnosis of lymphoma. He received 44 μCi of ^{195}Pt-labeled DDP with 2 mg/kg of unlabeled material. Blood samples and quantitative urine collections were obtained. Spot stool samples were also monitored.

TABLE 2. MEAN VALUES (2 ADULT MALE MICE BEARING SARCOMA 180) OF DISTRIBUTION OF ^{195m}Pt 24 HR AFTER INTRAPERITONEAL INJECTION OF cis-$^{195m}Pt(NH_3)_2Cl_2$. CARRIER WAS 0.8 MG/KG OF BODY WEIGHT

Organ	Percent administered dose/gm tissue
Kidneys	2.92
Liver	2.40
Tumor	0.97
Spleen	0.81
Skull	0.78
Small intestine	0.67
Fat	0.63
Blood	0.53
Rib cage	0.50
Heart	0.31
Lungs	0.23
Brain	0.08

Patient 2 was a 35-year-old woman with Stage IV carcinoma of the cervix previously treated with surgery and radiation therapy. She received 500 μCi of labeled DDP with unlabeled carrier at 2 mg/kg body weight. Abdominal and cephalic scintiphotos were obtained with a gamma-ray camera. Blood and a quantitative urine collection were obtained as well as spot stool specimens.

RESULTS

Figure 1 is a scintiphoto obtained 3 hr after injection of ^{195m}Pt-DDP in the rabbit. The compound is concentrated in the liver, kidneys, and by excretion in the bladder.

The tumor/blood ratios obtained in the mice experiments are given in Table 1. The ratio ranges from 1:3 to 2:0 at various time intervals. The organ distribution results of these experiments are given in Table 2. These data were obtained with ^{195m}Pt-labeled DDP and show that the kidneys and liver are the principal sites of localization of the compound.

The distribution of the labeled DDP in Patient 2 is indicated in Fig. 2, which shows early concentration of the compound in the kidneys and the distribution in the head region. A rectilinear scan of the abdominal area of this patient is shown in Fig. 3. The scan was obtained 40 hr after intravenous injection of 500 μCi of ^{193m}Pt-labeled DDP. Organs identifiable by their concentration of radioactivity are the liver and large intestine. Urinary excretion data for Patients 1 and 2 are shown in Fig. 4, and blood plasma levels of Patient 2 are shown in Fig. 5.

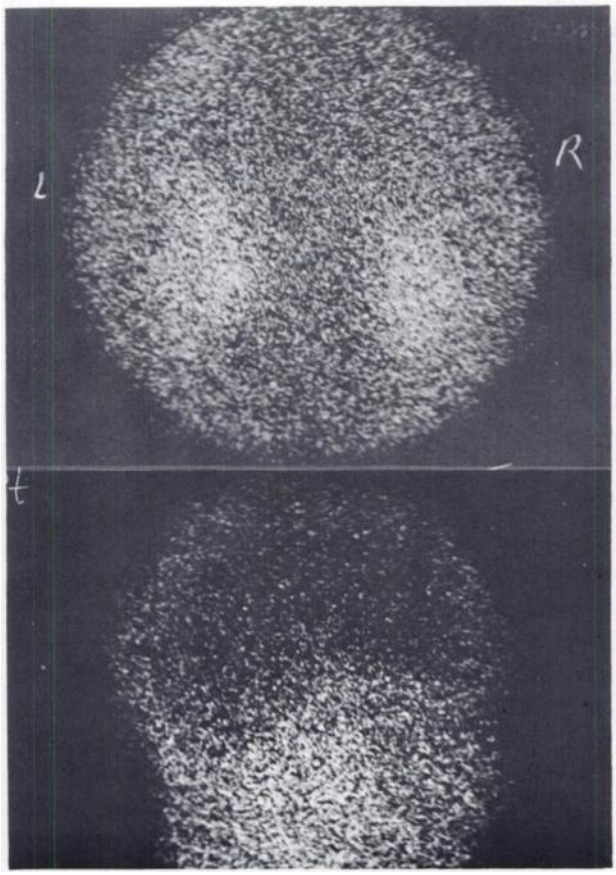

FIG. 2. Top view is frame from posterior dynamic study following intravenous injection of 500 μCi of cis-$^{193m}Pt(NH_3)_2Cl_2$ in 35-year-old woman with metastatic carcinoma of cervix. Note activity in kidney. Bottom is lateral view of head (nose to the right) 9 hr after injection of compound. Brain area is relatively devoid of activity.

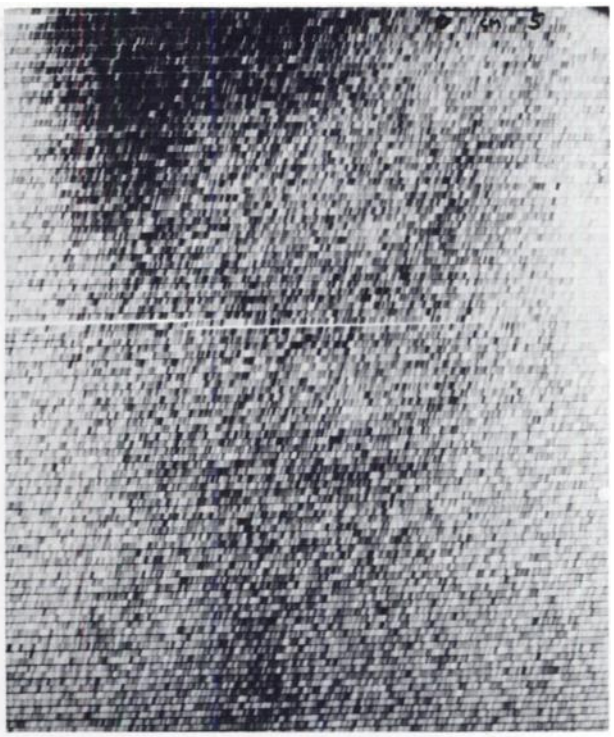

FIG. 3. Anterior abdominal scan in 35-year-old woman with carcinoma of cervix 48 hr after administration of 500 μCi of cis-$^{193m}Pt(NH_3)_2Cl_2$. Initial diagnosis of patient's disease had been made 3 years previously, and she had been treated with radiation therapy. Evidence of distant metastases had recently appeared, including nodule in left neck (which on excision revealed tumor tissue). Note liver and bowel-radioactivity.

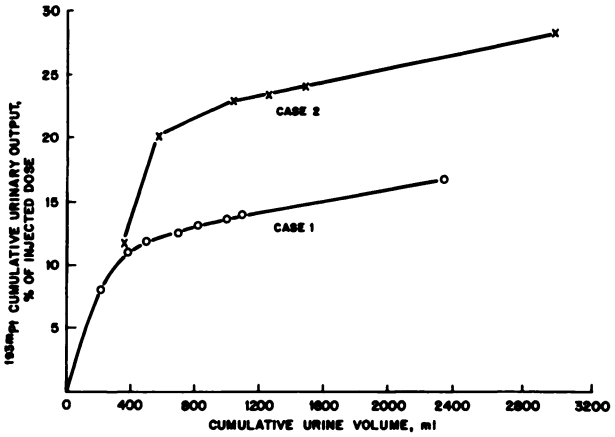

FIG. 4. Cumulative urinary excretion of ^{193m}Pt following intravenous injection of cis-$^{193m}Pt(NH_3)_2Cl_2$ in Patients 1 and 2.

Whole-body retention of labeled DDP in mice (daily counting above a scintillation detector) has been reported (*2*). When such counting was performed with mice bearing sarcoma 180, retention was higher than in controls. In each case, however, the extra retained radioplatinum could be related (at autopsy) to activity in the tumor (approximately 1%/gm tumor on Day 1; Table 2).

DISCUSSION

Because the synthesis of labeled cis-diamminedichloroplatinum (II) requires the better part of a working day, we are obliged to consider platinum radionuclides that have a half-life of 1 day or longer. In addition, the label must be simple to produce by charged-particle bombardment or neutron irradiation, and it must emit radiation detectable outside the body. Both ^{193m}Pt and ^{195m}Pt meet these criteria and are probably the only platinum radionuclides that are useful for distribution and localization studies. These isotopes both have half-lives of about 4 days and decay by highly internally-converted gamma-ray transitions. Thus, the only externally detectable emissions from the radionuclides are the 67 keV characteristic K x-rays of platinum.

Presented in the appendix are radiation absorbed dose calculations for ^{193m}Pt and ^{195m}Pt. The absorbed radiation dose is higher with ^{195m}Pt (0.985 mrad/μCi for ^{195m}Pt as compared to 0.603 mrad/μCi for ^{193m}Pt). However, the photon yield (principally K x-rays) is four times greater than ^{195m}Pt (0.842

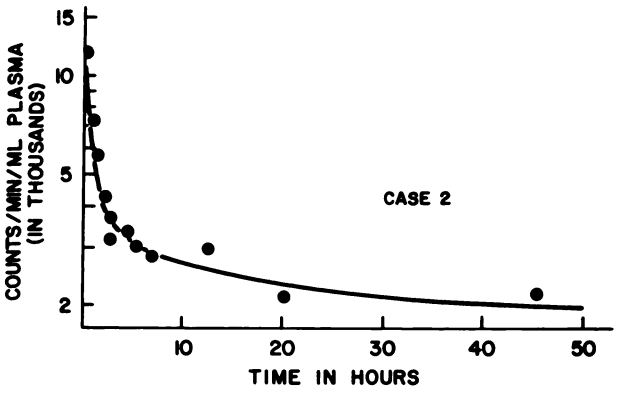

FIG. 5. Plasma radioactivity following intravenous injection of cis-$^{193m}Pt(NH_3)_2Cl_2$ in Patient 2.

K x-rays per disintegration for ^{195m}Pt as compared to 0.202 K x-rays per disintegration for ^{193m}Pt). Hence, microcurie for microcurie, at the same specific activity, ^{195m}Pt is probably the platinum radionuclide of choice.

The distribution of the labeled DDP in the tumored mice was essentially the same as previously reported for control mice (*2*). However, the tumor/blood ratio of radioactivity was greater than one at all times from 4 hr to 5 days. The ^{195m}Pt-labeled DDP distribution in the rabbit was the same as previously noted for the ^{193m}Pt-labeled compound.

The same metabolic pathways observed in animals for DDP may well be followed in humans. Specifically, some material is excreted rapidly through the kidneys, and there is little (if any) accumulation in the brain (Fig. 2). The labeled compound is concentrated in human liver, and an additional portion is apparently excreted in the bowel (Fig. 3). The major excretory pathway is in the urine as indicated in Fig. 4. Blood disappearance of the radiolabel showed at least two parts to the curve (Fig. 5), with a slower component in addition to the rapid disappearance phase. Based on the radioactivity excreted in the urine and spot stool samples, it is estimated that 60–70% of the labeled DDP is retained after 48 hr.

Even though there was no evidence of active tumor in Patient 2, there was also no apparent concentration of the labeled DDP in the region of the original cervical carcinoma.

ACKNOWLEDGMENT

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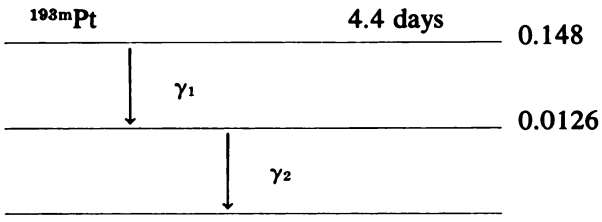
APPENDIX: DOSE CALCULATIONS

DOSE CALCULATIONS FOR ^{193m}Pt

Decay scheme:



Decay parameters.

γ_1: $E_\gamma = 0.135$ MeV. Completely converted in K, L, and M shells. $K/L_I/L_{II}/L_{III} = 48/58/15/100$. $L/M = 0.333$.

γ_2: $E_\gamma = E_\gamma = 0.0126$ MeV. Completely converted in M shell.

The ^{193m}Pt was assumed to be uniformly distributed throughout the body. The effective half-life was taken to be equal to the physical half-life of 4.4 days.

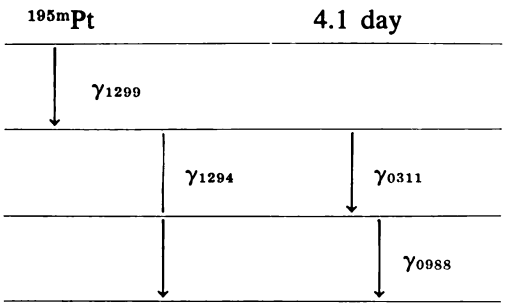
Radiation$_i$	N_i	$\bar{E}_i$ (MeV)	$\Delta_i \left(\frac{gm - rad}{\mu Ci\text{-}hr}\right)$
γ_1	0	0.135	—
e_K, γ_1	0.213	0.057	0.0258
e_L, γ_1	0.597	0.123	0.1567
e_M, γ_1	0.188	0.132	0.0529
γ_2	0	0.0126	—
e_M, γ_2	1.000	0.0092	0.0196
$K_{\alpha 1}$, x-rays	0.102	0.0668	0.0145
$K_{\beta 2}$, x-ray	0.0562	0.0651	0.0078
$K_{\beta 1}$, x-rays	0.0348	0.0757	0.0056
$K_{\alpha 2}$, x-ray	0.0091	0.0778	0.0015
KLL Auger	0.0062	0.0530	0.0007
KLX Auger	0.0040	0.0640	0.0005
KXY Auger	0.0004	0.0730	—
L x-rays	0.278	0.010	0.0059
LXY Auger	0.494	0.007	0.0074
M x-rays	2.494	0.0026	0.0138

The total-body dose was calculated from data in the above table and information contained in MIRD Pamphlet 5, 1969.

$\bar{D} = 0.000603$ rad/μCi administered.

DOSE CALCULATIONS FOR ^{195m}Pt

Decay scheme:



Decay parameters.

γ_{0311} ($e_L = 320$), γ_{0988} ($e_K = 230$, $K/L_I + L_{II}/L_{III} = 18/10/0.8$). γ_{1299} ($e_K = 100$), $K/L_I + L_{II}/L_{III} = 2.0/10/17$.

γ_{0311} ($e/\gamma > 7$), γ_{0988} ($e/\gamma = 9$) γ_{1299} (e/γ very large), $K/L = 0.26$.

Further information provided from decay scheme of ^{195}Au, which undergoes electron capture to ^{195}Pt.

The ^{195m}Pt was assumed to be uniformly distributed throughout the body. The effective half-life was taken as the physical half-life (worst case): $(T_{1/2})_{eff} = 4.1$ days. The total-body dose was calculated from data in the above table and information contained in MIRD Pamphlet 5, 1969.

Radiation$_i$	N_i	$\bar{E}_i$ (MeV)	$\Delta_i \left(\frac{gm - rad}{\mu Ci\text{-}hr}\right)$
γ_{1299}	<0.001	0.1299	—
e_K, γ_{1299}	0.0526	0.0515	0.0058
e_L, γ_{1299}	0.710	0.1169	0.1768
e_M, γ_{1299}	0.237	0.1269	0.0640
γ_{1294}	0.0164	0.1294	0.0045
e_K, γ_{1294}	0.0069	0.0510	0.0007
e_L, γ_{1294}	0.0158	0.1164	0.0039
e_M, γ_{1294}	0.0054	0.1264	0.0014
γ_{0311}	0.0181	0.0311	0.0012
e_L, γ_{0311}	0.705	0.0181	0.0272
e_M, γ_{0311}	0.235	0.0281	0.0014
γ_{0988}	0.1059	0.0988	0.0223
e_K, γ_{0988}	0.635	0.0204	0.0276
e_L, γ_{0988}	0.162	0.0858	0.0296
e_M, γ_{0988}	0.054	0.0958	0.0110
$K_{\alpha 1}$	0.425	0.0668	0.0605
$K_{\alpha 2}$	0.234	0.0651	0.0324
$K_{\beta 1}$	0.145	0.0757	0.0234
$K_{\beta 2}$	0.038	0.0778	0.0063
KLL Auger	0.0260	0.0530	0.0029
KLX Auger	0.0166	0.0640	0.0022
KXY Auger	0.0017	0.0730	0.0002
L x-rays	0.836	0.0100	0.0178
LXY Auger	1.487	0.0070	0.0221
M x-rays	4.652	0.0026	0.0258

$\tilde{D} = 0.000985$ rad/μCi administered.