ORNL/TM-6410

Nuclear Medicine Technology Progress Report for Quarter Ending March 31, 1978

F. F. Knapp, Jr.

HEALTH AND SAFETY RESEARCH DIVISION
OAK RIDGE NATIONAL LABORATORY

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F. F. Knapp, Jr.

Work sponsored by
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NUCLEAR MEDICINE TECHNOLOGY PROGRESS REPORT FOR QUARTER ENDING MARCH 31, 1978

SUMMARY

Progress is reported for the applications of ^{11}C, ^{195m}Pt, and ^{75}Se. Further human clinical trials with ^{11}C-1-aminocyclobutane carboxylic acid and ^{11}C-DL-tryptophan are reported, and batch production of the ^{11}C-DL-tryptophan has increased twofold to 300 mCi. Detailed studies of the effect of the method of administration of ^{195m}Pt-labeled cis-dichlorodiammine platinum (II) on the tissue distribution and retention of ^{195m}Pt are reported. Selenium-75 labeled β-aminoethyl selenosulfate has been prepared as a potential myocardial imaging agent. The ORIS-11 version Ø1 has been tested successfully on a clinical Gamma-11 nuclear medical imaging system at Vanderbilt University.

CARBON-11

T. A. Butler

The collaborative program with Oak Ridge Associated Universities for the preparation and testing of ^{11}C-labeled amino acids for tumor localization studies continued with only two production runs this quarter due to limited availability of cyclotron beam time. Eight patients were scanned by positron tomography (ECAT) after receiving ^{11}C-labeled amino acids. Six patients were administered ^{11}C-DL-tryptophan and examined for abnormalities in pancreatic uptake. Two patients received ^{11}C-1-aminocyclobutane carboxylic acid (^{11}C-ACBC) and were examined for general tumor localization. Although only five patients have

received ^{11}C-ACBC to date, preliminary results indicate this radiopharmaceutical has some superiority over ^{11}C-ACPC for general tumor localization. Batch production of ^{11}C-DL-tryptophan increased twofold (to 300 mCi) by minor adjustments of the reaction conditions.

PLATINUM-195m

J. D. Hoeschele and T. A. Butler

As part of the continuing medical cooperative program designed to study Pt antitumor compounds, two shipments of ^{195m}Pt-labeled cis-$[Pt(NH_3)_2Cl_2]$ (cis-DDP) were made to the University of Southern California. Three shipments of ^{195m}Pt-labeled Na_2PtCl_6 were made to the University of Kentucky Medical Center. Two shipments of ^{195m}Pt-labeled cis-DDP were made to the University of Arizona Health Sciences Center as a part of a new cooperative program, and one shipment of this agent was made to Mary Hitchcock Memorial Hospital.

Tissue Distribution Studies of Chloroammineplatinum(II) Complexes

Preliminary tissue distribution data for the entire series of chloroammineplatinum(II) complexes were reported in the last Quarterly Progress Report (ORNL/TM-6371), and these studies are continuing. We now report tissue distribution data for ^{195m}Pt-labeled cis-DDP as a function of (1) the dose administered at a fixed drug concentration (1.0 mg/ml), (2) the concentration of cis-DDP at a fixed total dose (8 mg/kg), and (3) the administration of ^{195m}Pt-labeled cis-DDP followed by administration of the diuretic, furosemide (lasix). These studies are not designed to be comprehensive but, rather, are being performed

as an adjunct to the existing medical cooperative programs employing this radiolabeled drug in order to provide insight into the critical pharmacological effects which presumably influence both the efficacy as well as the dose-limiting nephrotoxicity of cis-DDP.

The Effect of Varying the Dose of cis-DDP

The results of varying the dose of cis-DDP over the range of 1.0 to 8.0 mg/kg and the potential clinical implications of these results are as follows:

1. The percent dose retained per gram of tissue is approximately constant over the entire dose range for all tissues studied with the possible exception of the lungs and testes (see Table 1). This means that a constant fraction of the injected dose is retained in all tissues (nominally < 15%) for a single intravenous injection and hence proportionally greater amounts of Pt are retained by the kidney at the higher doses.
2. The ideal drug regimen for cis-DDP is one which would maintain or potentiate the effectiveness of the drug and minimize the dose-limiting kidney toxicity. If kidney damage (impairment) is related proportionally to the amount of Pt retained, there would appear to be no particular advantage in replacing a single-dose regimen by a divided- dose schedule since the amount of Pt retained is likely to be the same for a given total dose. This premise of course assumes that a constant fraction of Pt would be retained for each successive dose of the divided-dose regimen and that the rat is a good pharmacokinetic model for the human. Recent work reported by

our collaborators at the University of Southern California has indicated that the rat indeed appears to represent such a model.

The Effect of Varying the Concentration of cis-DDP

We also wished to evaluate whether kidney retention (damage) of Pt could be altered by varying the concentration of cis-DDP that was administered at a total dose of 8.0 mg/kg. Experiments were performed which involved injection of animals with ^{195m}Pt-labeled cis-DDP at concentrations of 0.5, 1.0, and 1.5 mg/ml. The results of these experiments (Table 1) indicated essentially no difference in the tissue distribution of radioactivity at the three different concentrations of cis-DDP. It would appear, therefore, that kidney retention is not likely to be diminished by varying the drug concentration. Apparently the in vivo dilution of the drug is so rapid that kidney exposure is the same regardless of the concentration of the drug solution which is administered. It is possible, however, that kidney retention of Pt may be diminished by the administration of a very dilute formulation of cis-DDP or by a much slower intravenous administration of the drug. We hope to initiate experiments which will investigate the distribution of ^{195m}Pt after the implantation of a minipump (ALZET) containing ^{195m}Pt-labeled cis-DDP. The use of such a minipump will allow the very slow release of cis-DDP.

The Effect of Simultaneous Administration of cis-DDP and a Diuretic

We have initiated a study to determine the effect on tissue distribution/retention of injecting furosemide immediately following cis-DDP administration. Furosemide (lasix) is a specific diuretic and

mannitol is a general diuretic. Both of these agents are being used clinically in conjunction with cis-DDP cancer chemotherapy for the purpose of decreasing kidney toxicity, particularly in the case of high-dose platinum therapy ($\sim$ 3.5 mg/kg). It has been presumed that these agents decrease kidney toxicity by enhancing urinary excretion of Pt. Our preliminary results qualitatively confirm the refuting data reported by Coupal and co-workers at the University of Kentucky, which indicate that the use of cis-DDP plus furosemide actually leads to enhanced retention in all organs, particularly the kidney, 24 hr after injection. At a dose of 2 mg/kg of cis-DDP followed by furosemide treatment, the average increase in retention in the blood, liver, spleen, testes, and brain is $\sim$ 26% and for the kidney, 60%, compared with levels for animals treated with cis-DDP only at this same dose. Essentially identical results were obtained with a cis-DDP dose of 4 mg/kg.

Brain Uptake Studies of ^{195m}Pt-Labeled $[PtA_4]Cl_2$ Complexes

It was reported earlier (ORNL/TM-6371) that intravenous administration of the ^{195m}Pt-labeled dipositive cation complex, $[Pt(NH_3)_4]Cl_2$, resulted in a five-fold greater accumulation of radioactivity in the rat brain than that detected with the ^{195m}Pt-labeled neutral complex, cis-DDP. These results are interesting since multiply charged species are thought to be selectively excluded from transport across the blood-brain barrier. Also, these results suggest the possibility that ^{195m}Pt-labeled $[PtA_4]Cl_2$ complexes (where A represents a generalized amine) might be useful as brain imaging agents. We have pursued this possibility by determining whether $[Pt(NH_3)_4]Cl_2$, the parent compound

of such a generic series, exhibits selective uptake within the various anatomical regions of the brain and, therefore, whether it might have potential as such an imaging agent. We have also prepared ^{195m}Pt-labeled $[Pt(CH_3NH_2)_4]Cl_2$ and $[Pt(i\text{-}C_3H_7NH_2)_4]Cl_2$ in an effort to determine what ligand structural features of $[PtA_4]Cl_2$-type complexes might lead to increased brain uptake. Tissue distribution experiments were performed with these compounds to determine whether there would be increased uptake of radioactivity in the brain compared with data obtained for ^{195m}Pt-labeled $[Pt(NH_3)_4]Cl_2$. A further point of interest is that $[Pt(NH_3)_4]Cl_2$ might be a good candidate as a radiosensitization agent since it is taken up in the brain at higher levels than either cis- or trans-DDP. Both of the latter compounds are radiosensitization agents while only cis-DDP demonstrates antitumor activity. An additional and important fact is that $[Pt(NH_3)_4]Cl_2$ is much less toxic (LD_{50} > 200 mg/kg) than cis-DDP (LD_{50} ~ 13 mg/kg).

Our preliminary results with these ^{195m}Pt-labeled $[PtA_4]Cl_2$ complexes have shown the following:

1. Radioactivity is uniformly distributed within the brain following administration of ^{195m}Pt-labeled $[Pt(NH_3)_4]Cl_2$ and exhibits no selective uptake in any one anatomical region.
2. Autoradiographic studies of brain slices following in vivo administration of the ^{195m}Pt-labeled complex have demonstrated the localization of radioactivity principally within the extravascular spaces rather than within the cells.
3. Rectilinear scans of a female rat at both 4 and 24 hr after administration of ^{195m}Pt-labeled $[Pt(NH_3)_4]Cl_2$ clearly showed

brain uptake. Upon computer enhancement of the data, the anatomical features of the brain could be seen.

4. Tissue distribution data (Table 2) for the ^{195m}Pt-labeled $[Pt(CH_3NH_2)_4]Cl_2$ and $[Pt(i\text{-}C_3H_7NH_2)_4]Cl_2$ analogs show generally reduced uptake in all organs after 24 hr compared to the data for ^{195m}Pt-labeled cis-DDP and brain uptake is reduced by nearly a factor of ten. Increasing the alkyl character of the A substituent of the $[PtA_4]Cl_2$ complexes presumably increases the lipophilicity of the complex but does not increase the uptake of such complexes by the rat brain.

SELENIUM-75

D. V. Woo, K. R. Ambrose, T. A. Butler, and F. F. Knapp

Taurine Analogs Labeled with ^{75}Se for Potential Myocardial Imaging

Taurine is a naturally occurring sulfonic acid ($H_2N\text{-}CH_2CH_2\text{-}SO_3H$) that plays a pivotal role in the final stages of sulfur amino acid catabolism and in the conjugation with and subsequent excretion of bile acids. Taurine also accumulates in the heart tissue of several animal species suggesting that structurally related analogs labeled with suitable γ-emitting nuclides may have potential as heart imaging agents. Such agents could conceivably serve also as tools to investigate the pharmacokinetics and binding of taurine to heart tissue and the metabolism of taurine bile acid conjugates. The selenium isostere of taurine, selenotaurine, has been prepared and found to be unstable. Consequently, we have prepared β-aminoethyl selenosulfate ($H_2N\text{-}CH_2CH_2\text{-}SeSO_3H$) labeled with ^{75}Se as a taurine analog.

Selenium-75 was reacted with an aqueous solution of a stoichiometric amount of potassium sulfite (K_2SO_3) to form ^{75}Se-labeled selenosulfate ($^{75}Se\text{-}K_2SeSO_3$). This simple yet useful preparative method actually involves an interesting net oxidation of sulfur from S(+4) to S(+6) with a concomitant net reduction of selenium from Se(0) to Se(-2). As a result, the selenium becomes bonded directly to sulfur with the potassium cation associated with the selenium (e.g., $KO_3\text{-}S\text{-}Se\text{-}K$). The selenium can thus be alkylated with the appropriate reagent, and in the present case, reaction of $^{75}Se\text{-}K_2SeSO_3$ with 2-chloroethylamine hydrochloride resulted in the formation of ^{75}Se-β-aminoethyl selenosulfate ($^{75}Se\text{-}H_2N\text{-}CH_2CH_2\text{-}Se\text{-}SO_3H$). Following removal of the reaction solvents, the product was dissolved in water and applied to a mixed-bed anion-cation exchange column. Elution with water removed a homogeneous product and thin-layer radiochromatographic analysis indicated that the majority of the radioactivity co-chromatographed with the expected mobility of β-aminoethyl selenosulfate. The microscale synthesis of ^{75}Se-labeled β-aminoethyl selenosulfate has also been optimized to the 500 micromole level. The maximum yield has been about 50%, and specific activities have varied from 20 to 40 mCi per millimole.

Tissue distribution studies have been performed with both male and female Fischer strain rats after intravenous administration of the ^{75}Se-labeled agent (10 μCi per animal). Groups of animals were sacrificed at time intervals varying from 30 min to 24 hr after injection of the labeled agent. The resulting percent dose per gram of tissue data indicate that maximal uptake in most tissues occurred within two hours after injection. After two hours, the highest percent dose per gram values

were found in the following organs: liver (4.1 ± 0.16) > kidney (2.2 ± 0.11) > heart (1.4 ± 0.14) > lungs (0.7 ± 0.03). The hearts of rats have been imaged using a rectilinear scanner at 2, 6, and 24 hr after administration of ∿100 μCi of the ^{75}Se-labeled agent.

During the next quarter we hope to identify the form in which ^{75}Se is found in the heart, liver, and lung tissues of rats after administration of the ^{75}Se-labeled agent. It is possible that the ^{75}Se-labeled β-aminoethyl selenosulfate is concentrated intact in the heart tissue. Alternatively, metabolites of the administered agent may be the radioactive species that accumulate in heart tissue, and one of these could be elemental ^{75}Se. If it is the intact ^{75}Se-labeled β-aminoethyl selenosulfate that accumulates in the heart tissue, our studies could be of importance since the ^{75}Se-labeled agent might thus be used as a tool to study the binding of this taurine analog to the myocardium. Such studies could help delineate the properties of taurine binding. In addition, if ^{75}Se-labeled bile acid conjugates are detected in liver extracts of these animals, such data may suggest that β-aminoethyl selenosulfate forms conjugates with bile acids in a manner similar to the conjugation of taurine with these steroids. If we find ^{75}Se-labeled bile acid conjugates, one could envision the use of the ^{75}Se-labeled β-aminoethyl selenosulfate as a tool to study the conjugation, metabolism and excretion of such bile acid conjugates.

If the intact ^{75}Se-labeled agent does indeed concentrate in heart tissue, we feel additional experiments with ^{75}Se-labeled β-aminoethyl selenosulfate and analogous studies with related compounds will be warranted. These include competitive heart uptake studies which will

involve determining the effect of taurine pretreatment on the heart uptake of ^{75}Se-labeled β-aminoethyl selenosulfate in rats. Additional studies will also be conducted to define those pharmacokinetic parameters that affect optimal heart uptake of this agent, and the preparation of high specific- activity material will allow us to investigate the effect of carrier on the uptake and distribution of this radiolabeled agent. We have found β-aminoethyl selenosulfate to be toxic at low dosages in the rat and this observation will be further investigated. There are no toxicity problems apparent, however, with the moderate to high specific-activity preparations that have been used to image rat heart tissue. Tissue distribution experiments with other β-aminoalkyl selenosulfates will allow us to study structure-activity properties of this interesting class of compounds. The potential preparation of ^{123m}Te-labeled β-aminoethyl tellurosulfate will also be investigated.

BETA-ADRENERGIC MYOCARDIAL AGENTS

D. V. Woo

Chloropractolol was iodinated with stable iodine in a preliminary study to determine the optimal reaction conditions for maximal labeling efficiency and to obtain sufficient material for preliminary chromatographic analyses. The chloropractolol (10 micromoles) and NaI (10 micromoles) were dissolved in phosphate buffer (pH 7.6) and the reaction initiated by the addition of the chloramine-T oxidant (20 micromoles). After one-half hour the reaction was terminated by the addition of an excess of sodium metabisulfite. The entire reaction mixture was loaded on a DEAE sephadex column and the column eluted with TRIS buffer (pH 8.3). The

absorbance of the eluate was continuously monitored at 254 and 280 nm. Fractions 0.5 ml in volume were collected and the resulting elution profile indicated two major peaks. The elution position of the parent compound was determined by chromatographic analysis of the chloropractolol standard on the same column. The standard was eluted in fractions 10-12 indicating that the first peak eluted upon chromatographic analysis of the crude reaction mixture (fractions 10-12) may be unreacted starting material. The second peak (fractions 24-34) presumably represents the iodinated product and exhibits the expected polar chromatographic behavior. The fractions containing the iodinated product were combined and extracted with carbon tetrachloride until the final extract contained no ultraviolet absorbing material. An aliquot from the combined extracts was taken for analysis. Following evaporation of the solvents, the residue was redissolved in methanol and applied to a high-pressure liquid chromatographic column (Silica A, Perkin-Elmer). Methanol was used as the eluent, and only one major peak was detected suggesting that the product was homogenouus. The remaining extract was re-chromatographed on the DEAE sephadex column, and only one major peak absorbing at 254 nm was eluted in the same region as the original sample (fractions 24-34). These results indicate that the iodinated chloropractolol can be purified by DEAE sephadex chromatography and that this material is relatively stable.

Larger amounts of the iodinated chloropractolol will be prepared in the next quarter to make available sufficient material for mass spectral and nuclear magnetic resonance spectral analyses. In this way the general chemical and physical properties of this new and potentially

useful agent can be studied and the position(s) that the iodine is introduced into the aromatic ring can be determined. Our eventual goal is the preparation of radioiodinated chloropractolol and the investigation of the potential usefulness of this agent as a myocardial imaging agent. The results of tissue distribution experiments in rats will determine if this is a realistic goal.

The ability of chloropractolol to displace ^{3}H-alprenolol from the purified membranes from the aortas and myocardia of rats has been investigated in collaboration with Dr. N. Revis of the Biology Division. A displacement constant (K_D) of $\sim 5 \times 10^{-9}$ mole has been determined for the chloropractolol which indicates that this agent appears to be selective for the β_1-adrenergic receptors in heart tissue. Further studies designed to test the potential irreversible binding of chloropractolol to such membranes will be examined during the next quarter.

IMAGING AND INSTRUMENTATION

P. R. Bell and J. M. Dougherty

Translation of ORIS

The first phase of the translation of the Oak Ridge Imaging System (ORIS) from the PDP-8 language to the PDP-11 language has been completed.

The resulting system ORIS-11 version Ø1 has been tested successfully on a clinical GAMMA-11 nuclear medicine imaging system at the Vanderbilt University Medical Center. This version of ORIS-11 is not a stand-alone system but is used to process raw-data images accessed and stored on disk by the GAMMA-11 system, which is a clinical imaging system supplied by the Digital Equipment Corporation. The ORIS-11 enhances

the limited data processing capabilities of the GAMMA-11 system by providing a number of image processing procedures.

Procedures available in ORIS-11/VØ1 are

1. Nonlinear least-squares polynomial smoothing and bounding.
2. Quickbound, a procedure to remove grossly aberrant data points.
3. Antiscatter and antipenetration correction to remove the effects of gamma ray scattering in the patient and gamma ray penetration of the walls of the camera collimator.
4. Two-dimensional Fast Fourier transform processing for image filtering and also for detection of imaging system defects which otherwise may grow unnoticed for a long time.
5. An adaptive filter disk. A nonlinear smoothing applied in the spatial frequency domain of the Fourier transform.
6. Time smoothing for dynamic study sequences. Essentially a Hanning filter applied in the time domain to the sequence to improve the statistical strength of the sequence without affecting its spatial resolution. As dynamic studies are of lone counts per picture element, this is often quite helpful.
7. The NTMAX functional images for brain perfusion studies. Time relationship and maximum perfusion images are summarized from the whole study.
8. Symmetry images produced from static images or from sums of frames from dynamic studies. These enhance any contralateral dissymmetry.

Although ORIS-11 VØ1 is not a stand- alone system, future versions were planned to be complete systems. The ORIS-11 VØ1 depends upon GAMMA-11 to perform all data acquisition for the clinical patient studies. The

ORIS-11 VØ1 is then run as a separate task under the RT-11 monitor. The user manipulates and processes the GAMMA-11 images, then replaces the processed data or functional images created where desired in the GAMMA-11 data files.

The ORIS-11 VØ1 has been implemented and tested in the Department of Radiology, Division of Nuclear Medicine of the Vanderbilt University Medical Center, Nashville, Tennessee. The group headed by Dr. A. B. Brill, currently on leave, is led by Dr. Ron Price and Jon Frickson. Actual clinical testing of ORIS-11 VØ1 will be performed by the Nashville group.

A technical report for ORIS-11 VØ1 is currently being finished. The report will contain the general system organization, a brief users' guide, the program listings, and information on expansion of ORIS-11 VØ1. This report will be distributed by and supported by the Biomedical Computing Technology Information Center (BCTIC) along with the PDP-8 version of ORIS.

ORIS Report

Volume 3 of ORNL/TM-5875 has been published and will be available through BCTIC shortly.

The PDP-8 version of ORIS has been brought fully up to date with incorporation of some minor improvements. In addition, the tape version running on the TC-8 or TD8E DECtape units has been brought up to date, as well as a tape version of ORIS using a VC8E display. Support for further development of ORIS will terminate at the end of April. The ORIS program and associated equipment will continue to be used to study

the behavior of new radiopharmaceuticals in laboratory animals as a part of the continuing Nuclear Medicine Technology Program.

MISCELLANEOUS

Ten shipments of ^{43}K were made this quarter. Three shipments were to the University of Mississippi for coronary disease studies including a comparison with similar images obtained using ^{201}Tl. Four shipments went to the National Institute for Environmental Health and three shipments went to the V.A. Center, Wood, Wisconsin.

Two shipments of ^{64}Cu were sent to ORAU for their study of tumor localization in animals using ^{64}Cu citrate administered in vivo.

One shipment of ^{165}Er was made to ORAU for further evaluation of its potential for tumor localization using a proportional counter camera. It was found that a 1.0 wt % Dy (principally ^{164}Dy) impurity in the ^{164}Er neutron target material resulted in the production of ^{166}Dy by double neutron capture in an amount equaling ~60% of the ^{165}Er yield at a reference time of 6 hr post- reactor discharge time. Factors such as the half-life of ^{166}Dy (81.5 hr, vs 10.34 hr for ^{165}Er), decay energies, and retention time in the human body lead to the conclusion that the ^{166}Dy contamination must be greatly reduced before human applications could be considered.

Visitors for this period included Dr. K. J. Irgolic from the Chemistry Department at Texas A & M University, who discussed the synthesis of organotellurium compounds of biological interest. He also presented a HASRD seminar on February 19, 1978, describing the effects of arsenic on biological systems. Dr. David Schurr from the Nuclear

Medicine Department of the Kaiser Permanente Medical Group in Oakland, California, visited on January 2, 1978 to discuss the ORIS system. Henry Kramer, the manager of Nuclear Products Technology at Union Carbide Corporation, visited on March 15 to discuss radiopharmaceutical development.

J. D. Hoeschele attended the Middle Atlantic Regional Meeting of the American Chemical Society at Hunt Valley, Maryland, on April 5-7. F. F. Knapp, J. K. Poggenburg, and D. V. Woo attended the 1st Annual Meeting of the Radiopharmaceutical Science Council of the Society of Nuclear Medicine at Atlanta, Georgia, on January 22.

PAPERS AND PUBLICATIONS

Papers

N. D. Johnson, J. D. Hoeschele and R. O. Rahn, "Comparative Binding of Pt-195m Radiolabeled cis- and trans-Dichlorodiammine Platinum(II), DDP, to DNA," Middle Atlantic ACS Meeting, Hunt Valley, Maryland, April 6, 1978.

F. F. Knapp, K. R. Ambrose, and A. P. Callahan, "Te-123m Labeled Telluro Amino Acids — A New Class of Potential Pancreas Imaging Agents," Annual Meeting, Radiopharmaceutical Science Council, Society of Nuclear Medicine, Atlanta, Georgia, January 22, 1978.

Journals

S. Huntoon, B. Fourcans, B. N. Lutsky, E. J. Parish, M. Emery, F. F. Knapp, Jr., and G. J. Schroepfer, Jr., "Sterol Synthesis. Chemical Synthesis, Spectral Properties, and Metabolism of 5α-Cholest-8(14)-en-3β,15β-Diol and 5α-Cholest-8(14)-en-3β,15α-Diol," J. Biol. Chem. 253(3):775-782, February, 1978.

Lee C. Washburn, Bruce W. Wieland, Tan Tan Sun, Raymond L. Hayes, and Thomas A. Butler, "[1-^{11}C] DL-Valine, A Potential Pancreas-Imaging Agent," J. Nucl. Med. 19(1):77-83, January, 1978.

Reports

J. K. Poggenburg, Nuclear Medicine Technology Progress Report for Quarter Ending December 31, 1977, ORNL/TM-6371.

Table 1. The distribution of radioactivity in rat tissues after intravenous administration of various doses of ^{195m}Pt-labeled cis-DDP[a]

Dose (mg/kg)	Percent dose per gram tissue					Av ± S.D. (all doses)
	1	2	5	6	8	
Tissue						
Blood	0.23	0.21	0.24	0.19	0.19	0.21 ± 0.02
Liver	0.31	0.33	0.38	0.31	0.34	0.33 ± 0.03
Spleen	0.24	0.26	0.30	0.24	0.23	0.25 ± 0.03
S. Intestine	0.10	0.11	0.11	0.070	0.11	0.10 ± 0.02
Kidneys	1.87	1.56	1.84	1.40	1.62	1.66 ± 0.20
Testes	0.045		0.12	0.032	0.036	0.058 ± 0.04
Brain	0.012	0.015	0.012	0.011	0.012	0.012 ± 0.001
Heart	0.084	0.068	0.079	0.061		0.073 ± 0.01
Lungs	0.21	0.21	0.23	0.11		0.19 ± 0.05
Carcass					0.13	
(Percent dose)					(24.7%)	

[a]Concentration of ^{195m}Pt-labeled cis-DDP = 1.0 mg/ml saline solution. The data reported in Tables 1 and 2 were obtained using Fischer 344 male rats, 10-14 weeks old. A saline solution of the ^{195m}Pt-labeled agent was injected via the tail vein and the tissues were removed 24 hr later and radioassayed.

Table 2. The distribution of radioactivity in rat tissues 24 hr after the intravenous administration of ^{195m}Pt-labeled $[PtA_4]Cl_2$ agents

	Percent dose per gram tissue x 10^2		
A:	NH_3	CH_3NH_2	$(CH_3)_2CHNH_2$[a]
Tissue			
Blood	0.66	0.75 ± 0.20	1.6 ± 0.3
Liver	13.7	3.5 ± 0.3	20.7 ± 1.6
Spleen	6.3	2.1 ± 0.2	3.4 ± 0.01
Pancreas		1.2 ± 0.2	2.1 ± 0.2
Stomach	4.2	0.32 ± 0.03	1.5 ± 0.2
S. Intestine	7.6	1.9 ± 0.6	4.8 ± 1.2
Kidneys	24.6	12.3 ± 1.0	97.2 ± 4.8
Fallopian tubes, ovaries & uterus	6.9	1.2 ± 0.1	1.3 ± 0.2
Muscle		0.31 ± 0.04	0.31 ± 0.01
Heart	3.3	0.40 ± 0.11	0.64 ± 0.10
Brain	4.8	0.50 ± 0.10	0.65 ± 0.17
Cecum		58 ± 16	63.2 ± 0.1
(Percent dose)		(2.3 ± 0.8%	4.0 ± 0.3

[a]This preparation probably also contains ^{195m}Pt-labeled $[PtA_3Cl]Cl$.

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