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Nuclear Medicine Technology Progress Report for Quarter Ending December 31, 1979

F. F. Knapp, Jr.

HEALTH AND SAFETY RESEARCH DIVISION
OAK RIDGE NATIONAL LABORATORY

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NUCLEAR MEDICINE TECHNOLOGY PROGRESS REPORT FOR QUARTER ENDING DECEMBER 31, 1979

F. F. Knapp, Jr.

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SUMMARY

In this progress report, the results of continuing studies with ^{11}C, ^{195m}Pt, ^{75}Se, ^{117m}Sn, and ^{123m}Te-labeled agents are described. Platinum-195*m*-labeled *cis*-dichloro-*trans*-dihydroxy-*bis*-(isopropylamine)-platinum(IV) (CHIP) was prepared for the first time. This second-generation platinum antitumor agent appears superior to the widely used *cis*-dichloro-diammineplatinum(II) (*cis*-DDP) since the dose-limiting nephrotoxicity associated with *cis*-DDP therapy is not encountered. Platinum-195*m*-labeled CHIP is being used to determine the tissue-distribution, excretion, and other pharmacological properties of this new drug and will also be supplied in a Medical Cooperative Program to St. Thomas's Hospital in London, England.

Studies of the heart uptake in rats of ^{75}Se and ^{123m}Te-labeled long-chain fatty acids have continued. The greater heart uptake of ^{123m}Te-9-telluraheptadecanoic acid (ORNL/TM-6916) compared with the selenium analog, ^{75}Se-9-selenaheptadecanoic acid, was confirmed by a dual-labeling experiment in which a mixture of the ^{75}Se- and ^{123m}Te-labeled acids was administered to rats. After 30 min, the excised hearts contained considerably greater ^{123m}Te than ^{75}Se (^{123m}Te:^{75}Se = 3.11:1) compared with all other tissues examined (e.g., blood, 1.77:1; liver, 0.95:1). Although the significance of these results is not fully understood, these studies clearly illustrate the greater uptake of ^{123m}Te-labeled fatty acids by rat heart tissue compared to the analogous ^{75}Se-labeled compounds.

Radiation dose estimates for a new adrenal imaging agent, ^{117m}Sn-23-(trimethylstanna)-24-nor-5α-cholan-3β-ol (23-TSC) have been completed in collaboration with the Radiopharmaceutical Internal Dosimetry Center at the Oak Ridge Associated Universities (ORAU). Tissue distribution and excretion data for ^{117m}Sn-23-TSC (ORNL/TM-7072) were used to extrapolate the radiation dose values to humans. The calculated radiation dose values for ^{117m}Sn-23-TSC are as follows: adrenals, 83 rads/mCi; total body, 0.77 rad/mCi; ovaries, 4.4 rads/mCi. These values are considerably lower than similar estimates determined for a variety of other radio-labeled steroid adrenal imaging agents (ORNL/TM-6958) and suggest that ^{117m}Sn-23-TSC may be an attractive new agent for adrenal visualization

in humans. An additional important result of these studies has been the formulation of a new method of comparing radiation dose values for tissue imaging agents labeled with different radionuclides. Comparison of radiation dose values as rads per 10^6 detectable photons is suggested as a more realistic method of comparison since it accounts quantitatively for both the abundance and detection efficiency of gamma photons.

The diffusion chamber assay system (ORNL/TM-7072) has been further assessed as a technique to determine the toxicity of As_2O_3 administration on the proliferation of cells within chambers implanted in the peritoneal chambers of rats and hamsters. The effects of intravenous and intraperitoneal injection of several doses of As_2O_3 were studied in these two animal species. Both human embryonic lung cells (Flow 2000) and human nasopharyngeal carcinoma cells (KB tumor) were used in the diffusion chamber studies.

In a Medical Cooperative Program with ORAU, the distribution of ^{11}C-labeled amino acids has been assessed in human patients by emission computerized axial tomography. Carbon-11-labeled DL-tryptophan and ^{11}C-1-aminocyclobutanecarboxylic acid (^{11}C-ACBC) were further tested for pancreas and tumor visualization, respectively. In addition, ^{11}C-α-aminoisobutyric acid (^{11}C-AIBA) and ^{11}C-phenethylamine (^{11}C-PEA) were prepared and the brain uptake of these two agents examined in dogs. Carbon-11-labeled 2-methyloctylamine was prepared for the first time, and the lung uptake of this new agent was also determined in dogs. Platinum-195*m*-labeled *cis*-DDP was supplied through a Medical Cooperative Program to the University of California at Los Angeles for nephrotoxicity studies in dogs. In addition, several ^{75}Se and ^{123m}Te-labeled long-chain fatty acids were supplied through Medical Cooperative Programs to determine the uptake and distribution of these new agents in normal and diseased hearts of laboratory animals.

PLATINUM-195*m*

J. D. Hoeschel and T. A. Butler

The synthesis of ^{195m}Pt-labeled *cis*-dichloro-*trans*-dihydroxy-*bis*-(isopropylamine)-platinum(IV) (CHIP) is being investigated in conjunction with a Medical Cooperative Program recently established with the Richard Dimbleby Department of Cancer Research at the St. Thomas's Hospital School of Medicine in London, England. CHIP is a second-generation platinum(IV) antitumor drug, which has been approved for clinical trials in both the United States and Great Britain. CHIP could possibly be a superior antitumor agent compared with the widely used *cis*-dichlorodiammineplatinum(II) (*cis*-DDP) complex, since it is considerably more soluble in aqueous solutions and appears not to have the dose-limiting nephrotoxicity associated with *cis*-DDP therapy.

The synthesis of CHIP entails the same general reaction scheme reported earlier for the preparation of *cis*-DDP (ORNL/TM-5936) to the stage of the *cis*-PtA_2Cl_2 intermediate (A=isopropylamine). The final step in the synthesis of CHIP involves the oxidation of the Pt(II) precursor, *cis*-PtA_2Cl_2, with 30% H_2O_2 as shown below.

$$cis\text{-}PtA_2Cl_2 + H_2O_2 \xrightarrow[5\text{-}10\ \text{min}]{85^\circ C} \text{CHIP}$$

The conditions for the final oxidation step and the subsequent purification of the product by recrystallization are critical for obtaining CHIP in significant yields. Preliminary syntheses of ^{195m}Pt-labeled CHIP performed on the 0.2 millimole scale indicate that several minor products are produced when the reaction time with H_2O_2 is increased to 30 min or if the oxidation product is treated with water during the recrystallization step. Purification is presently achieved by crystallization from water and first crop yields are on the order of 25%. Thin-layer chromatographic analysis of CHIP indicate that aqueous solutions of the complex do not undergo further decomposition at 37°C for up to 24 h. In contrast, detectable decomposition of CHIP in saline solution was detected within 1-2 h at 37°C, suggesting that replacement of the hydroxyl groups of the complex with the chloride ions (anation

reaction) is occurring. The instability of CHIP in concentrated aqueous solutions at temperatures required for crystallization (>100°C) indicated that crystallization from dilute H_2O_2 is required. In addition, purification of CHIP by absorption column chromatography will be assessed. Platinum-195*m*-labeled CHIP will be supplied to St. Thomas's Hospital for studies involving the potentiation of x-ray therapy of tumors by CHIP.

BIOHAZARDS FROM ENERGY TECHNOLOGIES-ARSENIC TOXICITY

K. R. Ambrose

The effect of arsenic trioxide (As_2O_3) on human cell growth in diffusion chambers has been further investigated using different administration routes, an alternate cell line and a second animal species. In these studies, the toxicity or growth inhibition induced by As_2O_3 was measured by a comparison of the mean target cell numbers in the diffusion chambers within the peritoneal cavities of arsenic-treated and control (saline or water treated) rats at various days after treatment. Five to ten chambers per treatment group were used to assay cell growth at each time period.

In a previous report (ORNL/TM-7072), a preliminary experiment was described in which an aqueous solution of As_2O_3 administered orally to rats induced a temporary inhibition in the growth of human embryonic lung cells (Flow 2000) within the intraperitoneally implanted chambers. The dose levels of As_2O_3 employed were 5, 10, and 15 mg/kg body weight, a range encompassing the 96 h LD_{50} (dose lethal to 50% of the population) for the rat (15 mg/kg) and the reported "no effect" level (<10 mg/kg).[1] Data on the growth inhibition of the lung cells observed 24 h after oral administration of these doses of As_2O_3 are listed in Table 1. Within the three dose levels administered, the dose response appears to be linear, although several additional dose levels must be investigated to confirm this apparent relationship. In other studies, the effects of orally administered As_2O_3 on the growth of the KB tumor target cells (human nasopharyngeal carcinoma, ORNL/TM-6639) were investigated. The results of these experiments were inconsistent since a dose of 10 mg/kg of As_2O_3 resulted in 49% inhibition of KB cells in one experiment, whereas in a repeat study, no growth inhibition was observed in the arsenic-treated animals (Table 1).

Table 1. Inhibition of KB or Flow 2000 cell growth in implanted chambers 24 h after administration of As_2O_3

Administration (animal species)	Dose (mg/kg)	Inhibition of cell growth[a] (%)	
		Flow 2000 cells	KB tumor cells
Oral intubation (rat)	15.0	48[b]	
	10.0	32[c]	49[b], 0
	5.0	18[b]	25[b]
Intravenous injection (rat)	5.0	35[c]	
	2.5	14[b]	
Intraperitoneal injection (rat)	10.0		(lethal dose)
	5.0 (2X)		51[c]
	5.0		46[b], 25[b], 45[c]
Intraperitoneal injection (hamster)	7.5	92[c]	
	5.0	52[c], 52[c]	

[a]Percent inhibition cell growth = (1 - mean cell count in test group/mean cell count in control group X 100) with 5-10 chambers in each test or control group.

[b]Mean cell counts from chambers of arsenic-treated animals were statistically lower than mean cell counts from chambers of control animals at the 95-99% confidence level (Wilcoxon test).

[c]Mean cell counts from chambers of arsenic-treated animals were statistically lower than mean cell counts from chambers of control animals at the 99-99.9% confidence level (Wilcoxon test).

Oral administration of a test substance results in a variation between animals as to the amount of substance (in this case, arsenic) that gets into the serum and thus into the peritoneal fluid. Since intravenous (i.v.) and intraperitoneal (i.p.) injection have less inherent variation, these two routes of administration were employed in determining the effects of As_2O_3 on KB or Flow 2000 cell growth in diffusion chambers. The choice of the target cells for each study depended primarily on the availability of the respective target cells. In studies where As_2O_3 was administered intraperitoneally, a sterile aqueous solution of As_2O_3 was injected in volumes ranging from 0.40 to 0.91 ml, depending on the rat's weight and the concentration of the As_2O_3. For i.v. injections, the aqueous solution was mixed 1:1 with isogenic rat serum, and filter-sterilized; volumes of 0.40 to 0.85 ml (dependent on the animal's weight and the dosage level) were injected in the lateral tail vein of anesthetized rats.

Both i.p. and i.v. administration of As_2O_3 to rats appeared to induce greater growth inhibition of target cells within the chambers than that observed when the arsenic was administered orally (Table 1). This was not surprising since even the gross toxicity of As_2O_3 was increased when this agent was administered by either the i.p. or i.v. route. A 10 mg/kg dose of As_2O_3 was lethal in two separate experiments after i.p. injection, although a dose of As_2O_3 as high as 15 mg/kg was not lethal to rats when administered orally. Three separate experiments using a 5 mg/kg As_2O_3 dose gave 46%, 25%, and 45% growth inhibition. The only factor that could possibly account for the lower toxicity (25% inhibition) observed in the one experiment is the greater (2X) dilution of As_2O_3 in that particular experiment.

Most of the arsenic toxicity data reported in the literature are based upon studies with rats. Since the metabolism of arsenic in the rat is unique and unlike that of other mammals including man, it has been suggested that another animal species such as the hamster may be a better candidate for arsenic toxicity studies.[2] The toxicity of As_2O_3 on the proliferation of Flow 2000 cells in diffusion chambers implanted intraperitoneally in hamsters has therefore been examined. All of the methods used in these studies were similar to those described for the

rat (ORNL/TM-6639) except that only three chambers were implanted per hamster, and six to nine chambers comprised each test or control group. Although i.p. injection of 5 mg/kg As_2O_3 to rats caused a temporary diarrhea in most of the animals, hamsters tolerated well both the 5.0 and 7.5 mg/kg As_2O_3 dose levels. The aqueous solution of As_2O_3 administered to the hamsters induced a 52% growth inhibition of target cells in those animals receiving 5 mg/kg and 92% inhibition in animals receiving 7.5 mg/kg As_2O_3 (Table 1). A second study employing only the 5 mg/kg dose level again resulted in 52% growth inhibition in cells counted one day after administration of As_2O_3.

Hamsters will be used in future studies to investigate a broader range of acute dose levels of As_2O_3 and also the effect of chronic exposures. The ability to implant and remove chambers without sacrificing the test animals will make it possible to test a chronically exposed animal at several time points during exposure.

TIN-117*m*

F. F. Knapp and T. A. Butler

In a recent report, the synthesis of a series of ^{117m}Sn-labeled steroids containing structural modifications of both the nucleus and sidechain was described (ORNL/TM-6958). Tissue distribution studies in rats indicated that the structural features required for optimal adrenal uptake included an equatorial C-3-hydroxyl group, an all *trans*-ring structure and a sidechain of moderate length (ORNL/TM-7072). Tin-117*m*-labeled 23-(trimethylstanna)-24-nor-5α-cholan-3β-ol (23-TSC) encompasses these structural features and showed the highest adrenal uptake in rats of the ^{117m}Sn-labeled steroids that were investigated. The pronounced adrenal uptake, relatively rapid excretion of radioactivity and the attractive radionuclidic properties of ^{117m}Sn suggest that ^{117m}Sn-23-TSC should be considered as a potential new agent for adrenal visualization in humans.

In conjunction with J. L. Coffey of the Radiopharmaceutical Internal Dosimetry Information Center at the Oak Ridge Associated Universities, the radiation dose values to human organs from ^{117m}Sn-23-TSC have been estimated. The radiation dose values were calculated by the general formalism adopted

by the Medical Internal Radiation Dosimetry Committee of the Society of Nuclear Medicine using tissue distribution and excretion data determined for this agent in rats (ORNL/TM-7072). The total body retention of ^{117m}Sn-23-TSC follows a single exponential elimination component with a 4.2 day half-time (Fig. 1). The retention of radioactivity in the adrenals and ovaries also exhibited single exponential elimination components (Fig. 2) with half-times of 4.2 days and 5.5 days, respectively. The

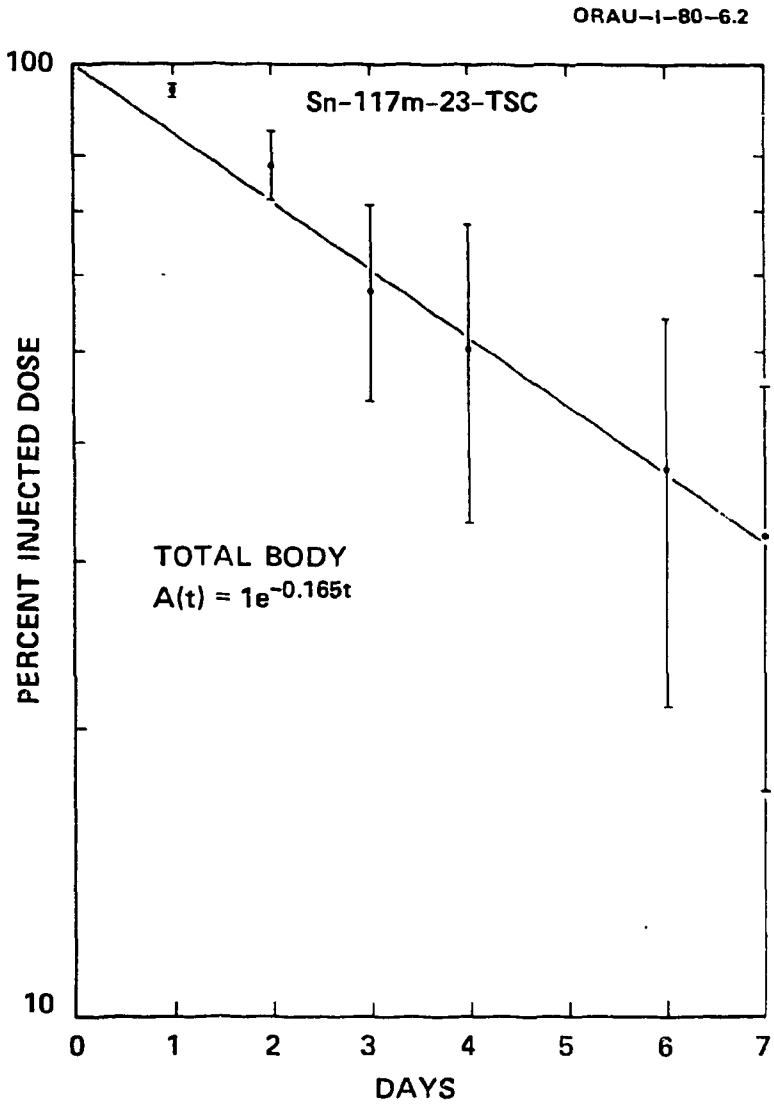

Fig. 1. Total body retention in female Fisher rats following administration of ^{117m}Sn-labeled 23-(trimethylstanna)-24-nor-5α-cholan-3β-ol (Sn-117*m*-23-TSC). Source: Radiopharmaceutical Internal Dosimetry Information Center, Oak Ridge Associated Universities.

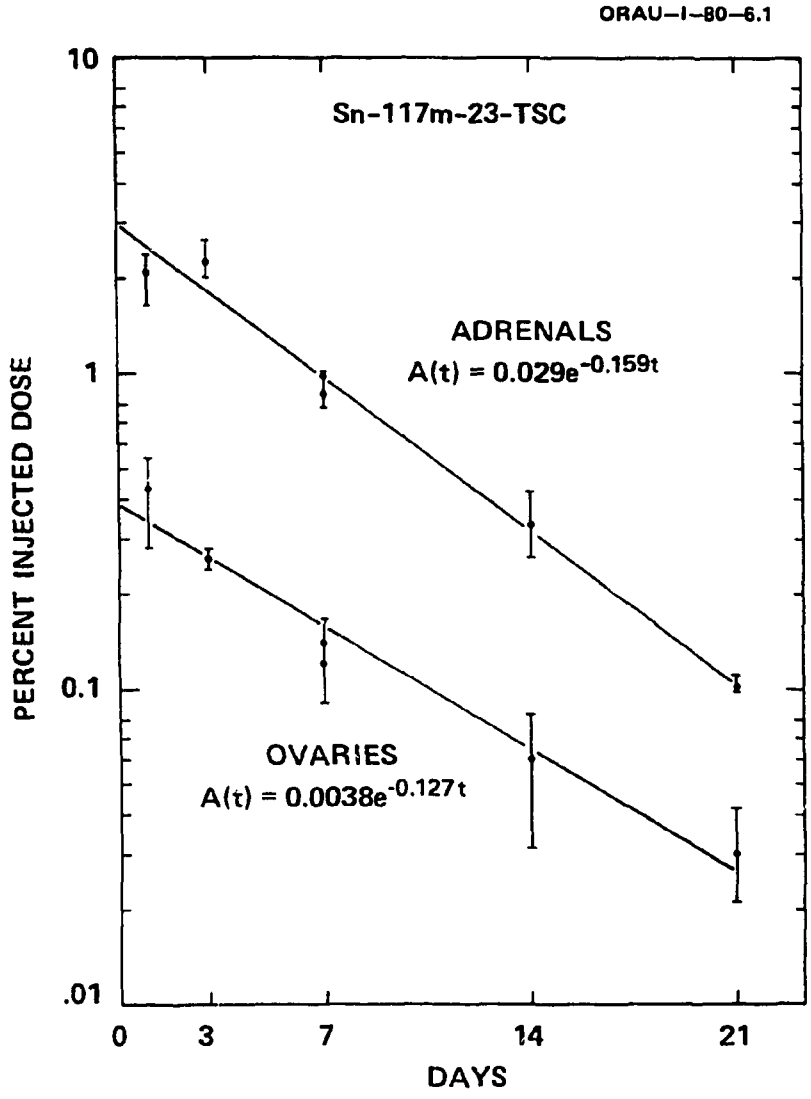

Fig. 2. Elimination of radioactivity from the adrenals and ovaries of female Fisher rats following administration of ^{117m}Sn-labeled 23-(trimethylstanna)-24-nor-5α-cholan-3β-ol (Sn-117*m*-23-TSC). Source: Radiopharmaceutical Internal Dosimetry Information Center, Oak Ridge Associated Universities.

estimated radiation dose values to humans calculated from these rat data are as follows (rad/mCi): adrenals, 83; ovaries, 4.4; total body, 0.77.

In an effort to more realistically compare the radiation doses from adrenal agents labeled with different radionuclides, a method has been developed to calculate radiation dose values in units of rads per 10^6 detectable photons. The traditional method of calculation of radiation

dose (rads per microcuries) may give similar radiation dose values for agents labeled with different radionuclides. Actually, it may often be necessary to administer considerably more of the agent radiolabeled with a radionuclide that emits photons in low abundance or which are inefficiently detected. In such an instance the actual radiation dose will be considerably higher since more radioactivity must be injected for optimal organ visualization. These differences in emission properties can be accounted for by calculating the radiation dose values in units of rads per 10^6 detectable photons. Such calculations are straightforward and include terms for the photon abundance values and the efficiency of a 1/2-in sodium iodide crystal detector as a function of photon energy. Although other factors such as tissue attenuation have not been considered, this method of calculation does account for differences in detection efficiency and abundance of photons for different radionuclides. Calculation of radiation dose values as rads per 10^6 detectable photons should be of general applicability for intercomparison of radiation dose values for many other tissue-imaging agents. The radiation dose values as rads per 10^6 detectable photons for ^{117m}Sn-23-TSC and several other adrenal imaging agents were determined in this manner (Table 2). As an example, the ratio of radiation dose values (rads per millicuries) for ^{117m}Sn-23-TSC and ^{131}I-NP-59 is 83:150. In contrast, the ratio of radiation dose values in units of rads per 10^6 photons is 2.9:19. This comparison demonstrates the much higher radiation dose from the ^{131}I-labeled agent since it takes considerably more radioactivity to detect the same number of photons that are detected with a much smaller dose of the ^{117m}Sn-labeled agent.

SELENIUM-75 and TELLURIUM-123*m*

F. F. Knapp, Jr., T. A. Butler, and K. R. Ambrose

An important aspect of the results of tissue distribution studies reported earlier for various ^{123m}Te and ^{75}Se-labeled long chain fatty acids was the significantly greater heart uptake in rats of radioactivity following intravenous administration of ^{123m}Te-9-telluraheptadecanoic acid compared to that observed with ^{75}Se-9-selenaheptadecanoic acid (ORNL/TM-7072, 6958, and 6916). This was an unexpected and interesting finding

Table 2. Comparison of estimated radiation dose values to human tissues for ^{117m}Sn-23-TSC and several other radiolabeled steroid adrenal imaging agents

Compound	Radiation dose			
	Adrenals		Ovaries	
	rad/mCi	rad/10^6 photons	rad/mCi	rad/10^6 photons
Sn-117*m*-23-(trimethylstanna)-24-nor-5α-cholan-3β-ol (23-TSC)	83	2.9	4.4	0.15
Te-123*m*-(isopropyltelluro)-24-nor-5α-cholan-3β-ol (23-ITC)	98	3.6	8.0	0.29
Se-75-23-(isopropylseleno)-24-nor-5α-cholan-3β-ol (23-ITC)	24	0.86	2.3	0.082
I-131-6β-iodomethyl-19-nor-cholest-5(10)-en-3β-ol (NP-59)	150	19	7.3	0.93
Se-75-6β-[methylseleno)methyl]-19-nor-cholest-5(10)-en-3β-ol (Scintidren)	93	3.3	14.0	0.50

since the only difference in the structures of the two fatty acids is the presence of either selenium or tellurium in the C-9 position. Since the tissue distribution of the two fatty acids was expected to be similar, a dual labeling experiment was designed to substantiate the apparent greater heart uptake of the ^{123m}Te-labeled fatty acid that was observed in the studies described above.

To avoid any potential variations in tissue distribution that could possibly result from differences in specific activities, the two fatty acids were prepared with similar specific activities. The ^{123m}Te-9-telluraheptadecanoic acid had a specific activity of 24 mCi/millimole and ^{75}Se-9-selenaheptadecanoic acid was prepared with a specific activity of 27 mCi/millimole. The two radiolabeled fatty acids were combined and the mixture complexed with a 6% solution of delipidated bovine serum albumin. The ^{123m}Te:^{75}Se ratio of the final solution was 0.74:1 after filtration through a 0.22 micron Millipore filter. Female rats were each injected intravenously with 0.5 ml of this solution containing 4.35 μCi of the ^{123m}Te-labeled fatty acid and 5.85 μCi of the ^{75}Se-labeled fatty acid. After 30 min the animals were sacrificed, the organs removed, and the ^{123m}Te and ^{75}Se contents of the various tissues determined. These results are summarized in Table 3 and agree well with similar tissue distribution results determined earlier in experiments with the individual fatty acids (ORNL/TM-6638, 6639, 6671, and 6916). The ^{123m}Te:^{75}Se ratios were also calculated for each tissue (Table 3) and clearly indicate a selective uptake of the ^{123m}Te-labeled fatty acid by the heart compared with the other tissues. In fact, the ^{123m}Te:^{75}Se ratio of the heart was nearly two-fold greater than the blood ratio, which closely parallels the ratio calculated from the results of studies with the individual agents. These results also illustrate that all of the tissues examined retained considerably higher levels of ^{123m}Te than ^{75}Se since the ^{123m}Te:^{75}Se ratios for the tissues were significantly greater than the ratio of the injected mixture. Excretion studies with female rats following administration of ^{75}Se-9-selenaheptadecanoic acid (ORNL/TM-7072) indicate that approximately 50% of the injected activity is excreted within 24 h, primarily in the urine. In contrast, a much slower rate of excretion is observed following administration of ^{123m}Te-9-telluraheptadecanoic acid and significant

Table 3. Distribution of radioactivity in tissues of female rats following intravenous administration of a mixture of ^{123m}Te-9-telluraheptadecanoic acid and ^{75}Se-9-selenaheptadecanoic acid[a]

Tissue	Mean percent dose/gram		
	^{123m}Te	^{75}Se	^{123m}Te:^{75}Se[c]
Heart	5.6 (3.3)[b]	1.8 (1.9)	3.11:1
Blood	0.5 (0.5)	0.3 (0.5)	1.66:1
Liver	6.0 (12.1)	6.3 (7.9)	0.95:1
Kidneys	1.8 (1.9)	1.6 (1.7)	1.13:1
Lungs	1.6 (1.1)	1.3 (1.6)	1.23:1
Spleen	0.6 (0.5)	0.4 (0.3)	1.50:1
Pancreas	1.2 (0.7)	0.7 (0.9)	1.71:1
Small intestine	0.8 (0.9)	0.4 (0.7)	2.00:1
Large intestine	0.08 (0.09)	0.05 (0.11)	1.60:1
Brain	0.1 (0.1)	0.1 (0.2)	1.00:1

[a]Mean values for three animals sacrificed 30 min after injection.

[b]The numbers in parentheses are the mean percent dose/gram of tissue values determined in parallel studies in animals injected with the individual agents.

[c]The ^{123m}Te:^{75}Se ratio of the injected mixture was 0.74:1.

levels of radioactivity are detected in both the urine and feces (Fig. 3). With the ^{123m}Te-labeled fatty acid only 15% of the administered radioactivity is excreted within one day after injection. Furthermore, even after five days only approximately 50% of the administered radioactivity is excreted. These elimination kinetics are considerably slower than observed with the analogous ^{75}Se-labeled agent and explain the greater tissue retention of ^{123m}Te observed in the dual labeling study (Table 3). The results of thin-layer radiochromatographic analysis of lipid extracts from rat hearts following administration of the ^{75}Se- and ^{123m}Te-labeled fatty acids further illustrate differences in the metabolism of these two agents. Attempts to demonstrate the incorporation of radioactivity into glycerides of rat heart tissue following administration of ^{123m}Te-9-telluraheptadecanoic acid have been unsuccessful. In contrast, chromatographic analysis of lipid extracts from rat hearts following injection of ^{75}Se-9-selenaheptadecanoic acid clearly demonstrated radioactive components that cochromatographed with both the diglyceride and triglyceride standards (ORNL/TM-7072).

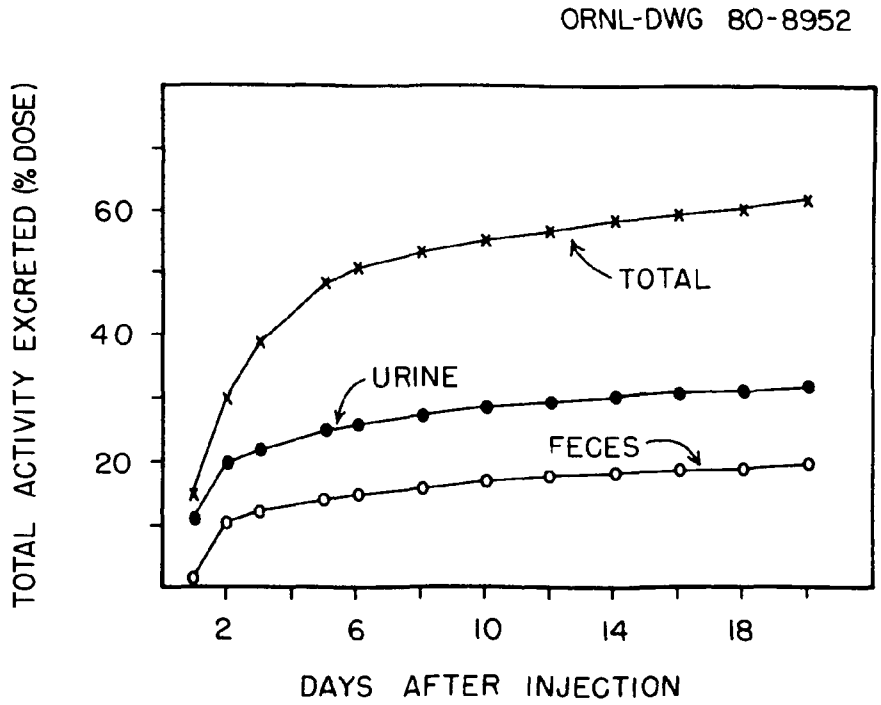

Fig. 3. Excretion of radioactivity in urine and feces from female rats following administration of ^{123m}Te-9-telluraheptadecanoic acid.

ANTIRHEUMATOID GOLD COMPLEXES

J. D. Hoeschele and T. A. Butler

Gold (Au) complexes have been used clinically for over five decades as an effective and sometimes spectacular cure for arthritis. Nonetheless, the biochemical basis of gold therapy remains obscure. The mechanism of action has been postulated to involve interaction of the gold complexes with specific proteins leading to enhanced stability of macroglobulin or collagen. An additional effect may be inhibition of the hydrolytic action of lysosomal enzymes. Clinically effective complexes such as the Au(I) thiolates are administered intramuscualarly. More recently, a new class of orally active antirheumatoid gold complexes have been developed, which can be represented by the general formulae, R_3PAuX or Ar_3PAuX. Optimal antirheumatoid activity is exhibited by Auranofin, an agent composed of the triethylphosine gold moiety (Et_3PAu) attached to the 3-position of β-D-thioglucose tetraacetate (X). Auranofin also exhibits limited but useful antitumor activity. Detailed investigations of the biological fate and disposition of the Et_3PAu-moiety have not been reported, although this unit appears essential for the antirheumatoid response elicited by Auranofin. By radiolabeling Auranofin and related complexes with ^{195}Au, ^{199}Au, ^{32}P, ^{33}P, or ^{35}S, the stability, reaction with sera, tissue distribution and excretory properties in rats of these agents can be studied. The in vivo displacement of the ligands bound to gold is likely to be a key factor in determining the differences in biological activity and tissue distribution properties of these agents. The use of the radiolabeled agents will provide an effective means of obtaining useful structure activity data which may, in turn, be helpful in understanding and predicting differences in activity of the various complexes. Biological studies with the radiolabeled agents could also provide insight into the mechanism of action of this important class of clinically useful agents.

Preliminary studies have included the development of spectrophotometric method of analysis for Au(III) in 1 *M* HCl solution and the synthesis of the ϕ_3PAuCl complex. The spectrophotometric assay of Au(III) is important for the determination of the specific activity of ^{195}Au(III)

solutions during the synthesis of the radiolabeled gold complexes. In an initial analysis, Au^0 metal was dissolved in aqua regia and the nitrates removed by repeated evaporation from 12 *M* HCl. Samples of Au(III) obtained in this manner were dissolved in 1 *M* HCl and ranged in concentration from 1 to 20 μg/ml. In such solutions, the Au(III) exists as $AuCl_4^-$ and exhibits two major absorption bands at 226 and 313 nm. Beer's Law is obeyed in the concentration range studied as well as for the less intense absorption band at 360 nm.[3] Measurement of the more intense absorption band at 226 nm (ε=3.82 x 10^4 M^{-1} cm^{-1}) permits sensitive detection of the $AuCl_4^-$ species. As an example, a solution of $AuCl_4^-$ with a concentration of 1 μg/ml exhibits 0.192 absorbance units. With expanded scale capabilities, the limit of direct spectrophotometric detection of $AuCl_4^-$ at 226 nm is within 10 ppb. A summary of the absorption properties of $AuCl_4^-$ is shown in Table 4.

Table 4. Spectral properties of $AuCl_4^-$ in 1 *M* HCl at 25°C[a]

Wavelength (nm)	Molar absorptivity, ε[b] $M^{-1}cm^{-1}$	Absorbance value/ μg Au/ml
313	5.48 x 10^3	2.79 x 10^{-2}
226	3.82 x 10^4	1.92 x 10^{-1}

[a]Determined using a Cary 219 ultraviolet-visible spectrophotometer.

[b]Based on a linear regression analysis.

Chlorotriphenylphosphinegold(I) (ϕ_3PAuCl) was snynthesized as a model complex of the general formula, Ar_3PAuX. This complex was obtained in approximately 80% yield by direct combination of ϕ_3P with $HAuCl_4 \cdot 3H_2O$ in ethanol at 0°C. The Ar_3PAuX is an intermediate for the synthesis of an analog of Auranofin and will be used in preliminary ^{31}P-nuclear magnetic resonance studies to determine the chemical shift values for the Ar_3PAu moiety using $(CH_3)_3OP$ as the internal standard. The syntheses of the β-D-thioglucose tetraacetate substrate and several other intermediates have been initiated.

RADIONUCLIDES FOR MEDICAL COOPERATIVE PROGRAMS

F. F. Knapp, Jr., J. D. Hoeschele, and T. A. Butler

Carbon-11

Five production runs were made for the Medical Cooperative Program with Oak Ridge Associated Universities (ORAU) to study the application of ^{11}C-labeled amino acids for tumor localization and pancreas imaging in human patients. Five batches of ^{11}C-DL-tryptophan and five batches of ^{11}C-1-aminocyclobutanecarboxylic acid (^{11}C-ACBC) were prepared and tested in patients at the ORAU Medical Division for tomographic visualization of tumors and pancreatic disorders. A total of 6 patients at ORAU were examined with these amino acids. A current objective of the ORAU Medical Division is to perform repetitive examinations of individual patients to determine if the progress of therapy can be followed. Two preparations of ^{11}C-α-aminoisobutyric acid (^{11}C-AIBA) were utilized in preclinical studies to determine the potential application of this agent for brain function studies. In conjunction with the University of Kentucky and ORAU, four batches of ^{11}C-phenethylamine (^{11}C-PEA) were prepared for preclinical studies to determine the potential usefulness of this new agent for brain function studies. In addition, ^{11}C-2-methyloctylamine was prepared for the first time and its lung uptake assessed in dogs.

Platinum-195*m*

Platinum-195*m* labeled *cis*-dichlorodiammineplatinum(II) was supplied under the Medical Cooperative Program to the Medical School at the University of California at Los Angeles (Dr. E. Petrilli) for preclinical nephrotoxicity studies in dogs in anticipation that the agent will be utilized in future clinical investigations.

Selenium-75 and Tellurium-123*m*

Collaborators in the Medical Cooperative Program investigating a unique class of radiolabeled selenium and tellurium fatty acids as potential myocardial-imaging agents were supplied compounds to amplify and extend the preclinical studies. A new member of the cooperative program, Medical Products Division of Union Carbide Corporation (Dr.

J. K. Poggenburg), was supplied with ^{75}Se-methyl-9-selenaheptadecanoate, ^{123m}Te-methyl-9-telluraheptadecanoate and ^{75}Se-methyl-13-selenaheneicosonate. The Nuclear Medicine Division of Massachusetts General Hospital (Dr. H. William Strauss) was supplied with ^{75}Se-methyl-13-selenaheneicosonate.

LIST OF REFERENCES

1. J. W. E. Harrison, E. W. Packman, and D. D. Abbott, "Acute Oral Toxicity and Chemical and Physical Properties of Arsenic Trioxides," *A.M.A. Arch. Ind. Health* 17:118-123 (1958).
2. Committee on Medical and Biological Effects of Environmental Pollutants, *Arsenic*, National Academy of Sciences, Washington, D.C., pp. 121-172 (1976).
3. F. H. Fry, G. A. Hamilton and J. Turkevich, "The Kinetics and Mechanism of Hydrolysis of Tetrachloraurate(III)," *Inorg. Chem.* 5:1943-1946 (1966).

OTHER NUCLEAR MEDICINE TECHNOLOGY GROUP ACTIVITIES

Two shipments of ^{43}K were supplied on a cost recovery basis to the University of Mississippi Medical Center for their clinical application of the radionuclide in heart disease studies.

K. R. Ambrose and F. F. Knapp, Jr., attended the Annual Meeting of the Southeastern Chapter of the Society of Nuclear Medicine which was held in Orlando, Florida, on October 31-November 3, 1979.

Visitors for this period included a group of graduate students in a radiation biology course at the University of Tennessee who visited on November 13 and were given an overview of the Nuclear Medicine research program. On November 15, a group of physicians, nurses, and physician assistants attending an ORAU course entitled *Medical Planning and Care in Radiation Accidents* visited the facilities.

PAPERS AND PUBLICATIONS

Papers

Four papers were presented at the Southeastern Chapter Meeting of the Society of Nuclear Medicine which was held in Orlando, Florida, on October 31-November 3, 1979:

J. L. Coffey, F. F. Knapp, Jr., K. R. Ambrose, and A. P. Callahan, "Dosimetry of Some Potential Heart Imaging Agents."

F. F. Knapp, Jr., K. R. Ambrose, A. P. Callahan, R. A. Grigsby, and K. J. Irgolic, "The Preparation of Tin-117*m*-Labeled 12,12-Dimethyl-12-Stannahexadecanoic Acid: The Initial Member of a Potential New Class of Radiopharmaceuticals."

F. F. Knapp, Jr., T. A. Butler, and A. P. Callahan, "The Preparation of 24-(Trimethylstanna)-Chol-5-en-3β-ol: A New Potential Adrenal Imaging Agent."

F. F. Knapp, Jr., K. R. Ambrose, A. P. Callahan, R. A. Grigsby, and K. J. Irgolic, "Potential Myocardial Imaging with the Se-75-Labeled Isostere of Oleic Acid: 9-Selenaheptadecanoic Acid."

Publications

P. A. DeSimone, R. S. Yancy, J. J. Coupal, J. D. Butts, and J. D. Hoeschele, "Effect of Forced Diuresis on the Distribution and Excretion (Via Urine and Bile) of ^{195m}Platinum When Given as ^{195m}Platinum *cis*-dichlorodiammineplatinum(II)," *Cancer Treatment Reports* 63, 951, 1979.

S. J. Lippard and J. D. Hoeschele, "Binding of *cis*- and *trans*-dichlorodiammineplatinum(II) to the Nucleosome Core," *Proc. Natl. Acad. Sci. U.S.A.* 76, 6091, 1979.

L. C. Washburn, T. T. Sun, B. L. Byrd, R. L. Hayes, and T. A. Butler, "DL-[Carboxyl-^{11}C]tryptophan, a Potential Agent for Pancreatic Imaging: Production and Preclinical Investigations," *J. Nucl. Med.* 24, 857, 1979.

L. C. Washburn, T. T. Sun, B. L. Byrd, R. L. Hayes, and T. A. Butler, "1-Aminocyclobutane[^{11}C]carboxylic Acid, a Potential Tumor-Seeking Agent," *J. Nucl. Med.* 20, 1055, 1979.

Four papers were published by the Society of Nuclear Medicine in *Radiopharmaceuticals II: Proceedings of the 2nd International Symposium on Radiopharmaceuticals.*

J. D. Hoeschele, T. A. Butler, and J. A. Roberts, "Microscale Synthesis and Biodistribution of Pt-195*m*-Labeled *cis*-Dichlorodiammineplatinum(II), *cis*-DDP," pp. 173-183.

F. F. Knapp, Jr., K. R. Ambrose, A. P. Callahan, R. A. Grigsby, and K. J. Irgolic, "Tellurium-123*m*-Labeled Isosteres of Palmitoleic and Oleic Acids Show High Myocardial Uptake," pp. 101-108.

L. C. Washburn, T. T. Sun, B. L. Byrd, R. L. Hayes, T. A. Butler, and A. P. Callahan, "High-Level Production of C-11-Carboxyl-Labeled Amino Acids," pp. 767-777.

D. V. Woo, F. F. Knapp, Jr., T. A. Butler, and A. P. Callahan, "An Efficient Microscale Preparation of Tin-117*m*-Tin Tetrachloride - A Pivotal Intermediate for the Synthesis of Tin-117*m*-Labeled Radiopharmaceuticals," pp. 147-154.

Reports

F. F. Knapp, Jr., *Nuclear Medicine Technology Progress Report for Quarter Ending September 30, 1979*, ORNL/TM-7072.