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Nuclear Medicine Program Progress Report for Quarter Ending June 30, 1992

F. F. Knapp, Jr.

K. R. Ambrose
A. P. Callahan
D. W. McPherson
S. Mirzadeh
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Contract No. DE-AC05-84OR21400

Health and Safety Research Division

NUCLEAR MEDICINE PROGRAM PROGRESS REPORT FOR QUARTER ENDING JUNE 30, 1992

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Work sponsored by
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Date Published—August 1992

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SUMMARY

In this report the results of preliminary studies of pancreatic exocrine function in normal patients and volunteers by a simple urine analysis using a new iodine-131-labeled triglyceride are described. The new ORNL agent, 1,2-dipalmitoyl-3-((15-p-iodophenyl)pentadecan-1-oyl)-rac-glycerol (1,2-Pal-3-IPPA) was radiolabeled with iodine-131 and used in clinical studies in a collaborative program with the Clinic for Nuclear Medicine at the University of Bonn, Germany. The observed rapid urinary excretion of high levels of the orally administered test agent from patients corroborated results from initial studies conducted in laboratory animals (ORNL/TM-12110). In the initial group of normal volunteers and 11 patients with normal pancreatic function an average of 76 ± 13.8% of the administered activity was excreted in the urine in 24 h. Studies will now also focus on evaluation of this agent in patients with pancreatic insufficiency.

The reactor production of dysprosium-166 in the ORNL High Flux Isotope Reactor (HFIR) and the separation of carrier-free holmium-166 have also been pursued. Holmium-166 ($t_{1/2}$ 26.4 h) decays with the emission of high energy beta particles and abundant secondary electrons and is thus of interest for various therapeutic applications. Four-day irradiation of ^{165}Ho in the HFIR resulted in production of ^{166}Ho with a specific activity of 7.25 mCi/mg. The formation of ^{166}Ho by beta-decay of reactor-produced ^{166}Dy was also evaluated. The specific activity of ^{166}Dy for an 8-day HFIR irradiation was 3.5 mCi/mg. Preliminary results indicate that carrier-free ^{166}Ho can be separated from the neutron-irradiated target by HNO_3 elution from di-(2-ethylhexyl)phosphoric acid (HDEHP) impregnated glass beads.

Also during this period a tungsten-188/rhenium-188 generator was supplied to collaborators at the Department of Nuclear Medicine at the University of Massachusetts (D. Hnatowich, Ph.D.) to evaluate the *in vivo* stability and pharmacokinetics of antibodies radiolabeled by both "direct" and "indirect" techniques.

INITIAL CLINICAL STUDIES WITH 1,2-DIPALMITOYL-3-[15-(p-IODOPHENYL)PENTADECAN-1-OYL]-RAC-GLYCEROL (1,2-PAL-3-IPPA) – A NEW CANDIDATE FOR NON-INVASIVE EVALUATION OF PANCREATIC FUNCTION

We described earlier our development of 1,2-dipalmitoyl-3-[(15-p-iodophenyl)pentadecan-1-oyl]-rac-glycerol (1,2-Pal-3-IPPA, Figure 1), as a new radioiodinated triglyceride for the evaluation of pancreatic exocrine function by simple urine analysis (ORNL/TM-12110). Iodine-125-labeled 1,2-Pal-3-IPPA was initially evaluated in rat studies, and we now describe the use of this new agent labeled with iodine-131 for initial clinical studies and evaluation of radioactive hydrolytic products which are excreted in the urine. Oral administration of appropriately radiolabeled triglycerides could offer an attractive simple technique for evaluation of the intestinal hydrolysis catalyzed by pancreatic enzymes, if urinary radioactivity is directly related to the degree of absorption. We have thus re-assessed the use of a radioiodinated fats for the evaluation of pancreatic insufficiency with a new, site-specific triglyceride in which radioiodine is attached to a 15-(p-iodophenyl)pentadecanoic acid (IPPA) residue in a chemically stable position. The metabolism of IPPA is well understood and the final catabolic products from ß-oxidation of IPPA are short chain iodophenyl-substituted acids such as iodobenzoic, 3-(iodophenyl)propionic, and 3-(iodophenyl)propenoic acid. The iodine radiolabel is neither subject to facile deiodination nor released during further catabolism.

Intestinal absorption of dietary triglycerides takes place in the lacteals of the proximal jejunal and distal ileal regions of the small intestine. For triglycerides having long-chain fatty acids (>C-12), hydrolysis takes place before absorption and requires the presence of both bile salts for emulsification and pancreatic lipase for hydrolysis which are specific for the C-1 and C-3 position of the TG. Therefore fatty acid moieties attached to the 1 and 3 positions, for instance, may well have a different specific activity than the 2 position and a site-specific labeling is mandatory. The remaining monoglyceride is also absorbed and then re-esterified prior to transport via the (thoracic) lymph. The TGs are transported in the blood as components of the very low density lipoproteins (VLDL) and the free fatty acids (FFA) are released by tissue lipase hydrolysis at the endothelial surface of the vascular compartment.

A simple non-invasive test for the exocrine function of the pancreas would be attractive for the diagnosis of various diseases of the upper gastro-intestinal tract. An accurate evaluation of fat adsorption can be an indirect measure of pancreatic lipase activity and thus of pancreatic function. Traditional techniques to evaluate steatorrhea are often

unpleasant or impractical and involve chemical fecal fat analysis and the evaluation of blood and fecal radioactivity levels after administration of radiolabeled fats. Iodine-131-labeled olive oil was first used to evaluate intestinal absorption of fat and I-131-labeled triolein was then introduced with the technique of oral administration. Iodine-131-labeled oleic acid was later used to evaluate not only the availability of bile acids for emulsification and hydrolytic enzymes but also patency of the small intestine for absorption. Serum and feces still required analysis, however and the continued use of these substances was not further pursued evidently because of purity and instability problems.

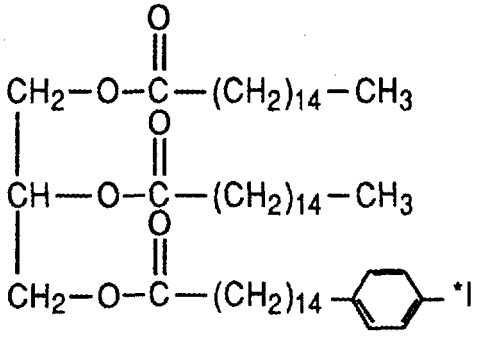

Figure 1.

After oral administration of our new triglyceride (TG) radioiodinated IPPA is released by the action of pancreatic lipases and is then absorped in the intestine. Radioiodinated benzoic acid (IBA) is the expected principle IPPA metabolite which is formed by subsequent metabolism of IPPA after intestinal cleavage and absorption and is excreted in the urine after conjugation. We have prepared the 1,2-Pal-3-IPPA agent in which the iodine label is stabilized by attachment to the para-position of the terminal phenyl ring. With an IPPA-labeled triglyceride, free radioiodide would not be expected to be released by deiodination, the agent would be stable for long-term storage, and the IPPA released has a well defined metabolic fate.

Patient studies at the Clinic for Nuclear Medicine in Bonn, Germany (J. Kropp, M.D. and H. J. Biersack, M.D.) involved five normal volunteers, and six patients without signs of pancreatic disease. A dose of about 30 μCi of iodine-131-labeled 1,2-Pal-3-IPPA was administered orally with subsequent urine collection for two successive 24 h periods. The tracer was administered after an overnight fasting period and a standard breakfast. Blood

samples were drawn 1 h in 11 patients, 3 h (8 patients), 4 h (11 patients), and 6 h (10 patients) after administration. Thin-layer chromatographic (TLC) analysis was performed on the serum lipid extracts. The 24-h urine results are shown in Table 1. An average of 76% (SD: 13.8%) of the radioactive test agent was excreted in the urine of the individual after 24 h. The TLC profiles of blood lipid extracts showed two major radioactive peaks which corresponded to the IBA and the triglyceride standard. The proportion of IBA increased with time which is consistent with the metabolism of IPPA. No difference in the count distribution was observed between the two different solvent systems along with iodobenzoic acid and the unlabeled 1,2-Pal-3-IPPA standard. Solvent system A consisted of petroleum-ether/ether/acetic acid (69:30:1, v/v/v), and solvent system B was composed of benzene/dioxane/acetic acid (80:18:2, v/v/v). After development of the TLC plates in these solvent systems the standards were again visualized with 254 nm U.V. light and then the plate was cut into 15 segments which were counted.

Table 1. Cumulative 24-hour urine levels of radioactivity following oral administration of the 1,2-Pal-3-[^{131}I]IPPA test agent to volunteers and patients who had no evidence of pancreatic insufficiency.

Volunteers	% Dose Day 1	
1	72	
2	93	
3	99	84±12
4	78	
5	72	
Patients without Pancreatic Disease or Malabsorption		
1	71	
2	77	
3	63	70±13
4	92	
5	63	
6	55	

Studies now in progress by our collaborators at the Clinic for Nuclear Medicine at the University of Bonn will evaluate the urinary excretion of radioactivity after oral administration of iodine-131-labeled 1,2-Pal-3-IPPA in a larger group of normal patients and volunteers for data on base-line values. In addition, patients with pancreatic insufficiency from a variety of carriers will also be evaluated to determine the expected decreased urinary release of activity.

HOLMIUM-166 – REACTOR PRODUCTION AND PROCESSING OF AN ATTRACTIVE RADIOISOTOPE FOR THERAPEUTIC APPLICATIONS

Holmium-166 (^{166}Ho) is a potential candidate for various therapeutic applications including chelation to tumor-associated antibodies for radioimmunotherapy (RAIT). Attractive properties include the emission of high-energy β^- particles ($E_{\beta av}$ = 666.0 MeV), an abundance of secondary electrons, an appropriate physical half-life ($t_{1/2}$ = 26.4 h) and decay to a stable daughter isotope (Figure 2). In addition, ^{166}Ho has chemical characteristics (Ho^{+3}; hexadentate) suitable for protein labeling through bifunctional chelates. Due to its chemical similarity with ^{90}Y (+3 oxidation state), the chelating ligands which have been developed for ^{90}Y would be expected to be useful for ^{166}Ho. Holmium-166 also emits a low-intensity and low-energy γ-ray (80 keV, 6%) which would provide the possibility to evaluate organ distribution by gamma camera imaging. Due to lack of high energy γ-ray, ^{166}Ho may be used for outpatient therapy without significant external radiation to other individuals.

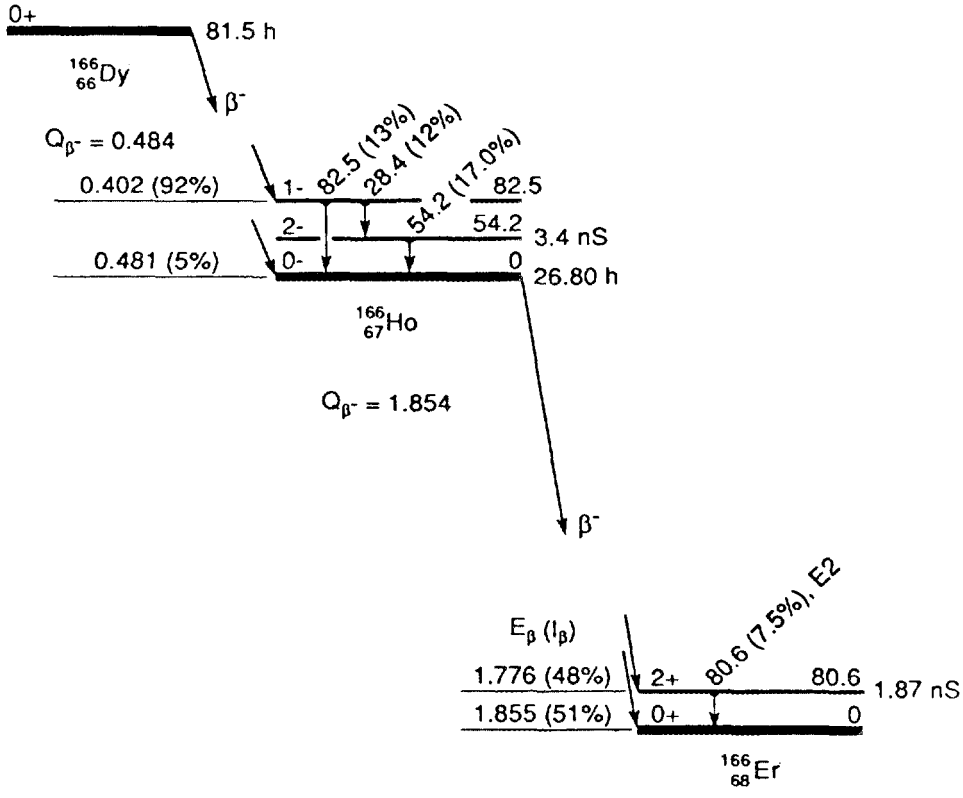

Figure 2. Simplified decay scheme of ^{166}Dy and ^{166}Ho.

High specific activity ^{166}Ho can be obtained directly by the irradiation of ^{165}Ho via the $^{165}Ho[n,\gamma]$ reaction or indirectly from β^- decay of ^{166}Dy ($t_{1/2}$ = 81.4 h, $E_{\beta max}$ = 400 keV), as shown in Figure 3. The later route yield to carrier-free preparations of ^{166}Ho. In this case, the ^{166}Dy parent nuclei is produced in a fission nuclear reactor with double neutron capture on ^{164}Dy. The goals of this project are to measure the production yields of ^{166}Ho and ^{166}Dy in the hydraulic tube of the ORNL High Flux Isotope Reactor (HFIR) and to develop techniques for separation of carrier-free ^{166}Ho from neutron irradiated Dy targets.

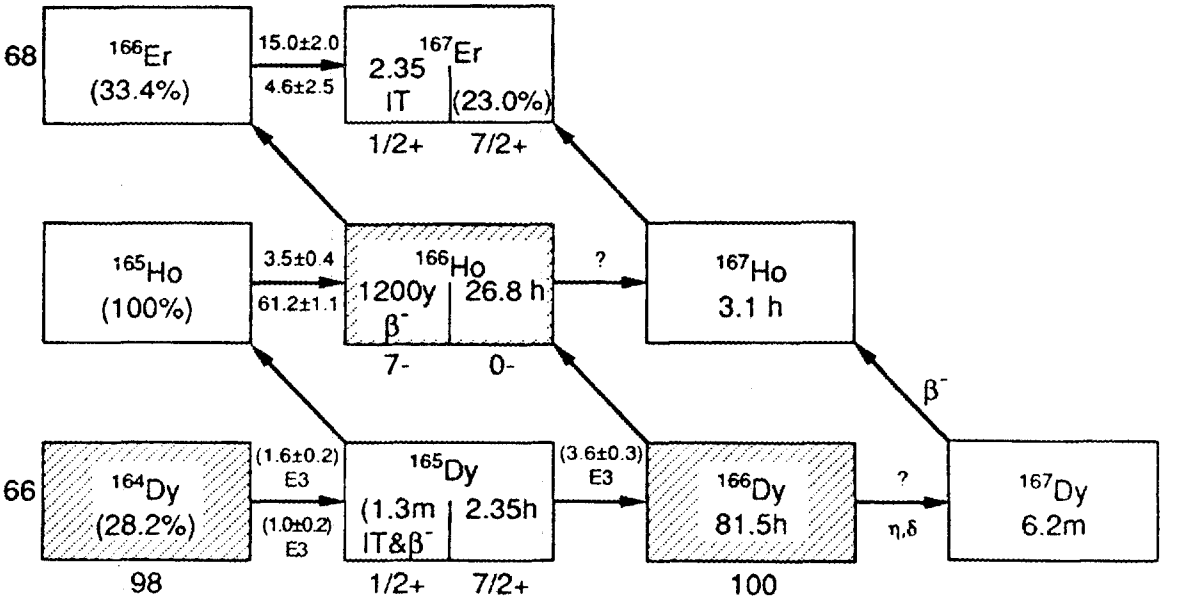

Figure 3. Reactor production of ^{166}Ho.

For a four-day irradiation of 13.3 mg of natural Ho (monoisotopic) as Ho_2O_3 at the hydraulic tube (HT) position 5, the experimental yield of ^{166}Ho is 96.5 mCi, in comparison to the theoretical yield of 75.7 mCi. The increased experimental yield is attributed to the contribution from resonance integrals at the epithermal neutron flux region. The specific activity of ^{166}Ho at saturation at the end of bombardment (EOB) would therefore be expected to be ~10 Ci/mg of ^{165}Ho. The experimental yields of ^{166}Dy were 3.5 and 2.2 Ci/mg of ^{166}Dy for 8 and 1 days of irradiation in positions 5 and 6 of HT, respectively. Although, the yield by the indirect route is lower than the direct route by a factor of three, the specific activity of the ^{166}Ho from the decay of ^{166}Dy would be much higher and would approach the theoretical value.

We are currently investigating three routes for separation of carrier-free ^{166}Ho from neutron irradiated Dy targets, which are separation based on the hot atom chemistry of ^{166}Dy-DTPA complex, separation by extraction column chromatography and separation by reversed phase ion-exchange chromatography. The separation based on the hot atom chemistry takes advantage of the decay energy to break the complex apart and free the daughter atom. In contrast to our expectations, the DTPA complex strongly binds the energetic ^{166}Ho which is produced from decay of ^{166}Dy. In extraction chromatography, an equilibrium mixture of $^{166}Dy/^{166}Ho$ in 0.1 M HNO_3 is applied to a column containing glass powder impregnated with di-(2-ethylhexyl)-phosphoric acid (HDEHP). Separation was achieved with 1.3 M HNO_3, as shown in the chromatogram of Figure 4.

The third separation scheme utilizes reversed phase ion exchange chromatography in which the partition properties of Ho and Dy between the cation-exchange resin and weakly complexing ligands are taken advantage of with α-hydroxyisobutyric acid (α-HIBA) in slightly acidic media (pH ~4.3-4.6). The chromatograms obtained under several conditions are shown in Figure 5. The later two processes using AG50W-X4 at pH 4.28 are promising and their applicability for large scale production will be explored. Both techniques will require metal free HPLC.

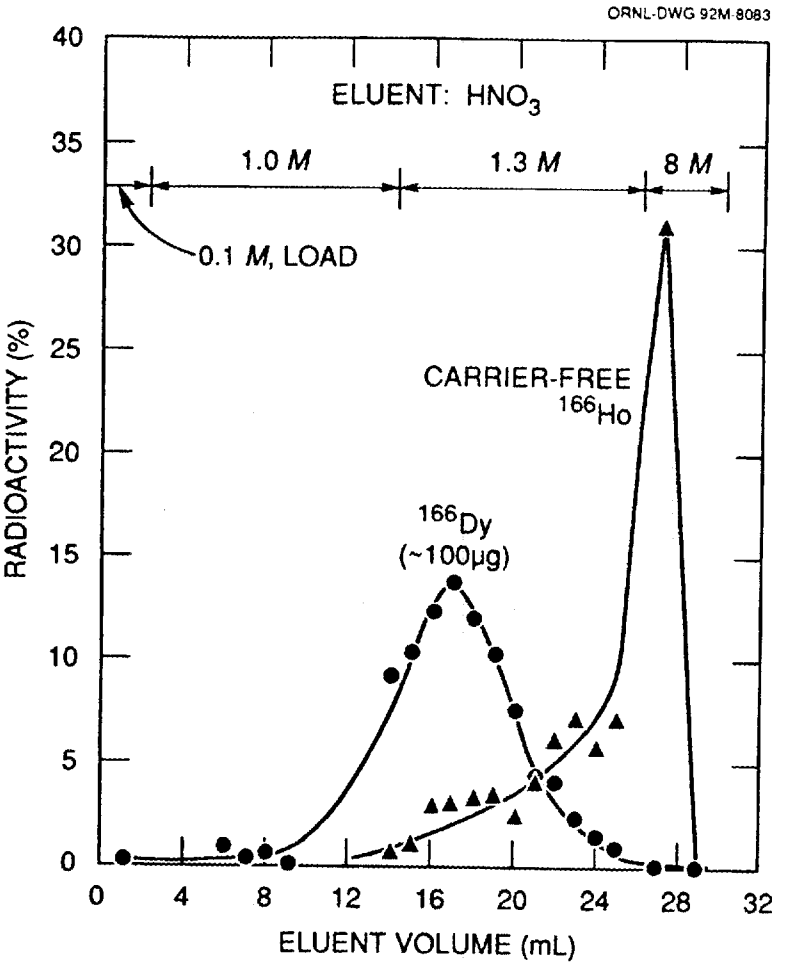

Figure 4. Separation of ^{166}Ho from ^{166}D on HDEHP-impregnated glass powder eluted with HNO_3.

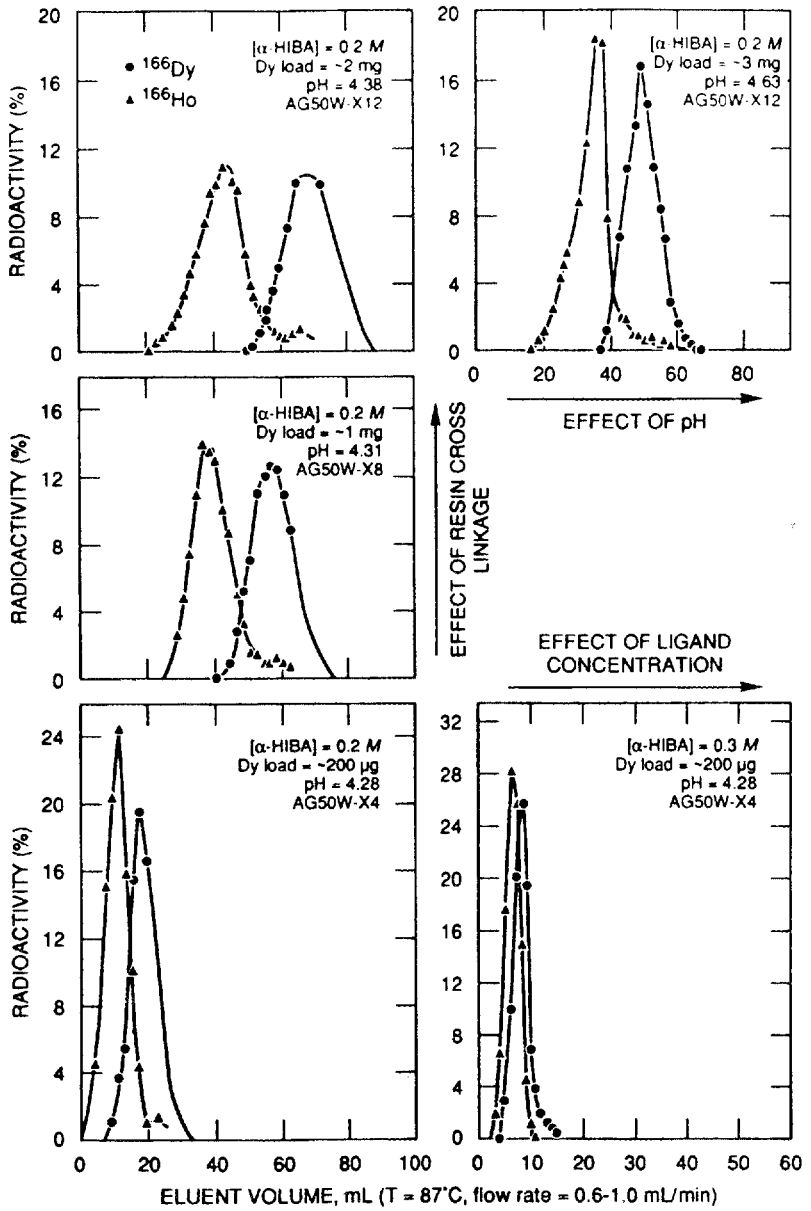

Figure 5. Examples of partitioning of ^{166}Ho and the ^{166}Dy partition cation exchange resin by elution with α=HIBA.

Our goals are to continue the refinement and further development of extraction column chromatography and reverse phase ion-exchange chromatography for separation of carrier-free ^{166}Ho from neutron irradiated Dy targets. The effects of the target mass and radiolysis are two crucial parameters which will be addressed. Based on the present data, the use of a metal free HPLC seems unavoidable for large scale production, and this route will also be pursued.

AGENTS FOR MEDICAL COOPERATIVES

Iodine-125-labeled 15-(p-iodophenyl)-3-R,S-methylpentadecanoic acid (BMIPP) was shipped to the University of Bonn, Germany (Dr. J. Kropp) for continuing metabolic studies in an isolated rat heart model system. A tungsten-188/rhenium-188 generator was shipped to the University of Massachusetts for antibody labeling studies (D. Hnatowich, Ph.D).

OTHER NUCLEAR MEDICINE GROUP ACTIVITIES

Publications

Hasan, A., and Srivastava, P. C. "Synthesis and Biological Studies of Unsaturated Acyclonucleoside Analogues of *S*-Adenosyl-L-homocysteine Hydrolase Inhibitors," J. Med. Chem. *35*, 1435-1439 (1992).

Knapp, F. F., Jr., and McPherson, D. W. "Development of New Radioiodinated Receptor Ligands for Cerebral Imaging by Single Photon Emission Tomography," In, Brain Diagnosis with Radionuclides – Current Status and Future Aspects. G. S. Limouris and S. K. Shukla, editors, Mediterra Publishers, Athens (ISBN 960-85227-0-6), pp. 37-52 (1992).

Mirzadeh, S., Rice, D. E., and Knapp, F. F., Jr. "Carrier-Free Iridium-194 from an Osmium-194/Iridium-194 Generator – A New Candidate for Radioimmunotherapy," Applied Radioisotopes and Technology, Part A, 43, 689-692 (1992).

Recent Clinical Trials with ORNL Agents

Clinical studies have been recently initiated in hospitals in Belgium and the Netherlands with two iodine-123-labeled cardiac imaging agents developed in the ORNL Nuclear Medicine Program. The agents, based on the ORNL concept of "metabolic trapping," permit the evaluation of fatty acid uptake in the heart muscle in relation to various types of heart disease by tomographic imaging techniques. Studies are in progress with "DMIPP," in the Department of Cardiology at the Free University Hospital, in Amsterdam, the Netherlands, by Frans Visser, M.D.. These human studies were preceded by detailed collaborative studies in laboratory animals to evaluate the metabolism and *in vivo* behavior of this agent. A similar agent, "BMIPP," is now also being used in the Nuclear Medicine Department at the Free University Hospital in Brussels, Belgium, by P. R. Franken, M.D., and colleagues for the evaluation of coronary artery disease.

Meeting Presentations

Several papers were presented or co-authored by members of the Nuclear Medicine Group at the recent Annual Meeting of the Society of Nuclear Medicine held in Los Angeles, California, on June 7-12, 1992:

Griffiths, G., Knapp, F. F., Jr., Callahan, A. P., Hasen, H. J., and Goldenberg, D. "The Generation of Rhenium-188-Labeled Antibodies by Direct Labeling Methods."

Knapp, F. F., Jr., Kropp, A., Ambrose, K. R., Callahan, A. P., Lambert, C. R., and Biersack, H.-J. "Site-Specific/Stable Radioiodination of 1,2-Palmitoyl-3-[15-(p-iodophenyl)pentadecan-1-oyl]-rac-glycerol (1,2-Pal-3-IPPA) for Evaluation of Pancreatic Insufficiency by Urine Analysis."

Kropp, J., Koehler, U., Zierz, St., Knapp, F. F., Jr., Briele, B. V., Smekal, A., Biersack, H.-J. "Evaluation of Myocardial Involvement in Patients with Systemic Myopathies with 15-(p-Iodophenyl)pentadecanoic Acid (IPPA) SPECT."

McPherson, D. W., and Knapp, F. F., Jr. "Synthesis of Iodoaltanserine – A Potential New Ligand for SPECT Imaging of Serotonin-s_2 Cerebral Receptors."

Lisic, E. C., Mirzadeh, S., and Knapp, F. F., Jr. "Facile Synthesis of Re-188-Labeled Re(V)-DMSA by Room Temperature Triphenylphosphine (O_3P) Reduction of Perrhenate."

Srivastava, P. C. and Hasan, A. "Synthesis and In Vivo Metabolism Studies of [I-125]-Iodoacycloadenosin-4'-ene – A Potential Inhibitor of S-Adenosyl-L-Homocysteine Hydrolase."

Recent Patents

The U.S. Patent Office has made a notice of allowance for the ORNL patent describing the tungsten-188/rhenium-188 generator system which provides carrier-free rhenium-188 as perrhenic acid for radiolabeling of therapeutic agents. In addition, a patent describing new radioiodinated agents specific for the cerebral muscarinic receptors for nuclear medicine imaging studies has also been filed by the Department of Energy.

Knapp, F. F., Jr., Lisic, E. C., Mirzadeh, S., and Callahan, A. P. "Tungsten-188/Carrier-Free Rhenium-188 Perrhenic Acid Generator System."

McPherson, D. W. "Radiopharmaceuticals for the *In Vivo* Imaging of Muscarinic Receptor Populations."

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