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Nuclear Medicine Progress Report for Quarter Ending March 31, 1987

F. F. Knapp, Jr.
K. R. Ambrose
P. C. Srivastava

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Health and Safety Research Division

NUCLEAR MEDICINE PROGRESS REPORT FOR QUARTER ENDING MARCH 31, 1987

F. F. Knapp, Jr.

K. R. Ambrose
P. C. Srivastava

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SUMMARY

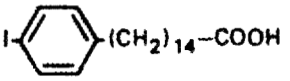
Studies using Langendorff-perfused rat hearts have shown for the first time the formation of a polar metabolite from the methyl-branched fatty acid, BMIPP. Evaluation of the radioactive components in the outflow tract of hearts after administration of the staight-chain analogue [I-131]IPPA and [I-125]BMIPP were pursued. Analysis of lipid extracts by thin-layer chromatography illustrated the presence of a product considerably more polar than BMIPP. These results suggest for the first time that the slow myocardial clearance observed with BMIPP in clinical studies may be associated with the wash-out of an unidentified metabolite.

As a continuation of an evaluation of the effects of tellurium (Te) heteroatom position and the position of alkenyliodide substitution on myocardial uptake and retention properties, several new Te fatty acids have been synthesized and studied in rats. The new agents were prepared by coupling of internal alkenyl iodides prepared from the corresponding boronic acid analogues with sodium alkoxycarbonyl tellurols. Evaluation of the four new analogues (9-I-C_{16}-5-Te-Δ^9, 11-I-C_{18}-7-Te-Δ^{11}, 9-I-C_{18}-5-Te-Δ^9 and 15-I-C_{18}-5-Te-Δ^{15}) demonstrated an unexpected relationship between chain length, and the position of the Te heteroatom and alkenyliodide moiety.

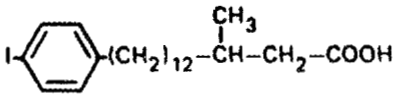
During this period several radioiodinated agents were supplied to collaborators at the University of Michigan, the Brookhaven National Laboratory, and the University of Bonn, West Germany, for collaborative studies.

EVALUATION OF METABOLITES FROM THE RADIOIODINATED β-METHYL-BRANCHED FATTY ACID, 15-(p-IODOPHENYL)-3-R,S-METHYLPENTADECANOIC ACID (BMIPP), USING AN ISOLATED PERFUSED RAT HEART SYSTEM

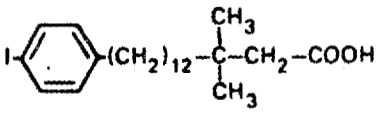
The radioiodinated 3-methyl-branched fatty acid, 15-(p-[1-123]iodphenyl)-3-R,S-methylpentadecanoic acid (BMIPP), shows slow myocardial clearance in experimental animals and also humans. This agent (Figure 1) is thus a good candidate for the evaluation of regional fatty acid uptake patterns by SPECT. The identity of the radioactive component being released from the heart is of interest, however, since it could represent either "back-diffusion" of the unmetabolized BMIPP or the release of a catabolite. Although it was not anticiptaed that BMIPP could be catabolized to short-chain metabolites by the normal β-oxidative process because of the impediment of the 3-methyl group, catabolism through the initial stages of the first cycle of β-oxidation could proceed with the formation of the β-methyl-β-hydroxy product. Alternatively, initial α-hydroxylation followed by decarboxylation could form the racemic 3-methyl fatty acid product which could then proceed through the β-oxidative chain to form the expected short-chain catabolites. Thus, the slow release of radioactivity in vivo could represent back-diffusion of BMIPP, loss of a "partially" catabolized product such as the β-hydroxy-β-methyl product or wash-out of short-chain catabolites resulting from complete β-oxidation. An understanding of this process is important since it will provide a clear picture of the behaviour of BMIPP in vivo and will provide insight into the metabolism of β-methyl-branched fatty acids and may also provide information that can be used to design other agents in which metabolism can be completely inhibited.



15–(p–IODOPHENYL) PENTADECANOIC ACID (IPPA)



15–(p–IODOPHENYL)–3–R,S–METHYLPENTADECANOIC ACID (BMIPP)



15–(p–IODOPHENYL)–3,3–DIMETHYLPENTADECANOIC ACID (DMIPP)

Figure 1. Structures of iodophenyl-substituted fatty acids.

To study the release of products from BMIPP and to provide a system for the isolation of sufficient amounts of the unknown component, an isolated Langendorff-perfused rat heart system has been used. Hearts from fasted rats were removed and perfused in a retrograde fashion through the aorta in the usual manner with oxygenated Krebs-Henseleit buffer at a flow rate of 10 ml/min using a peristaltic pump. The special modifications for these studies includes the jacketed chamber in which the heart was enclosed to insure the temperature was maintained at 37°C. The buffer temperature was also maintained by a coiled chamber. The partial pressures of O_2 and CO_2 were maintained at 450-550 mm and 42-45 mm, respectively, by using a 5% O_2-95% CO_2 gas mixture. The frequency of the heart beats was from 180-200 contractions/minute. The radioactive fatty acids, dissolved in albumin, were administered through the injection port and effluent samples collected each minute over a 15 min period. In this fashion the release of metabolites could be assessed independent of flow.

In Figure 2 the release of [I-125] and [I-131] products from normoxic rat hearts administered [I-131]IPPA and [I-125]BMIPP is illustrated. The clearance curve for IPPA increases rapidly to peak at about 5 min and then

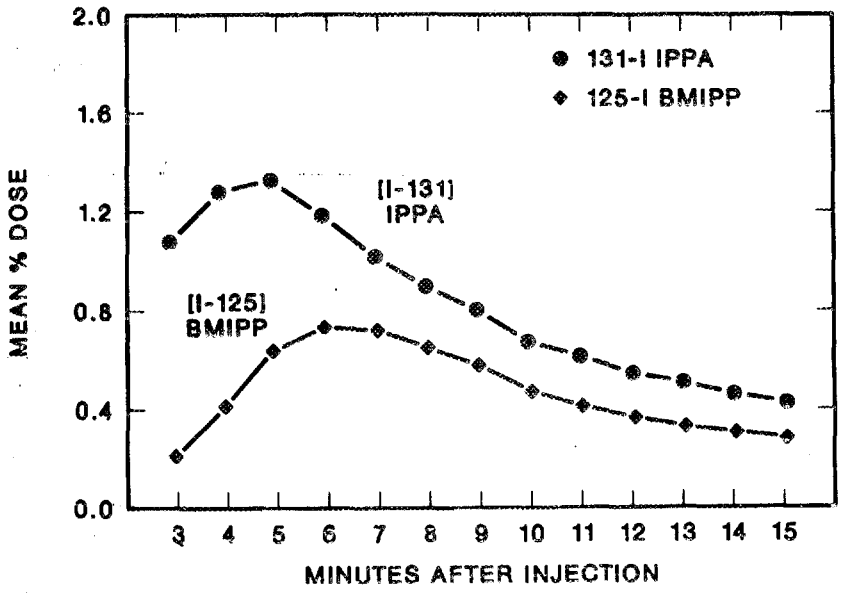


Figure 2. Time-course of radioactivity in the outflow from rat hearts (n=5) administered with a mixture of [I-131]IPPA/[I-125]BMIPP.

decreases with an apparent monoexponential or biexponential curve over the 15 min period. The release curve for BMIPP has a similar shape but a major difference is the release of significantly decreased levels of radioactivity which is consistent with the longer retention observed in vivo. In addition, the BMIPP release curve consistently peaked later (6-7 min) in all studies. To gain some insight into the identity of the components released in the outflow, representative samples were acidified and extracted with chloroform-methanol and the organic extracts dried, concentrated and analyzed by thin-layer chromatographic analysis. Since the initial perfusate sample collected during the first minute following adminstration of the radioiodinated fatty acids into the aortic inflow represents the injected agents cleared from the coronary circulation, this sample serves as a control. Analysis of samples for the first minute, as expected, showed the presence of [I-131]IPPA and [I-125]BMIPP (Figure 3). In contrast, analysis of the lipid extracts in samples 3, 5, 7, 10 and 15 showed levels of polar products from both IPPA and BMIPP increasing rapidly with time (Figure 4). Even after 3 min,

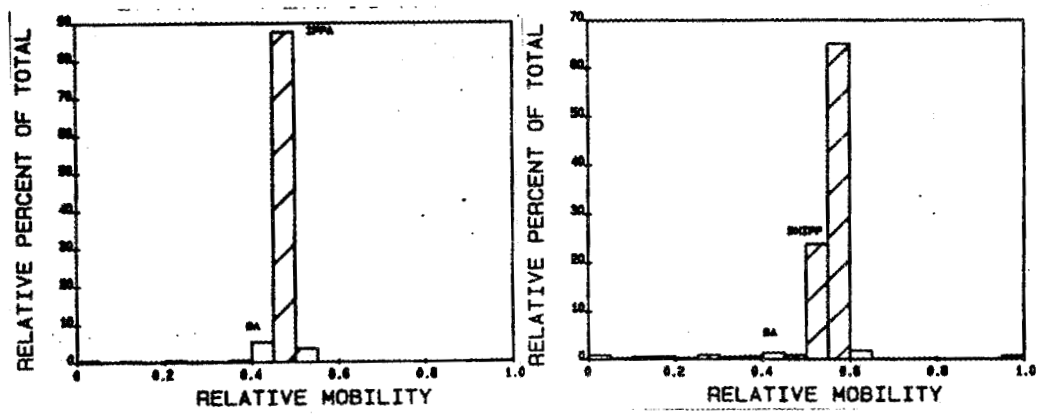


Figure 3. Thin-layer chromatographic (TLC) mobility of radioactive components in the initial perfusate (1 min) from hearts administered [I-131]IPPA/[I-123]BMIPP (solvent system, petroleum ether with ether-ether-acetic acid, 70:30:1).

radioactivity from IPPA had the expected mobility of p-iodobenzoic acid, the established metabolite from IPPA resulting from β-oxidation. Analysis of radioactivity released from BMIPP exhibited mobility much more polar than the administered BMIPP (Figure 4). The radioactive component was soluble in basic solution and could be re-extracted from acidified sample, demonstrating the presence of an acidic group, presumably a carboxylic acid.

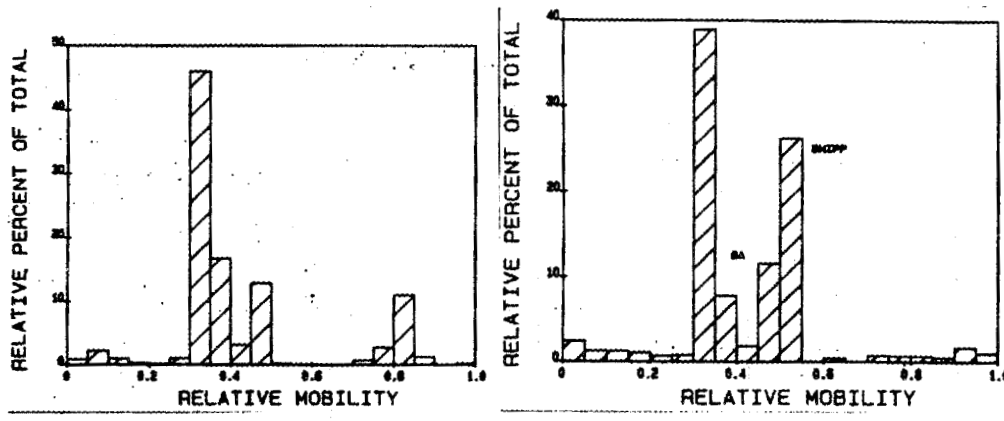


Figure 4. TLC mobility of radioactive components in the later perfusate (5 min) from hearts administered with [I-131]IPPA/[I-125]BMIPP (same solvent system as for Figure 3).

The modified fatty acid, BMIPP, was designed to inhibit β-oxidation resulting in increased retention which would facilitate evaluation of regional myocardial fatty acid uptake patterns by SPECT using the iodine-123-labeled agent. The clearance could represent back-diffusion of unaltered methyl-branched fatty acid, or the loss of a metabolite. Differentiation of these two possibilities could not be assessed in vivo except by the use of cardiac catheterization. The current studies were designed to evaluate the release kinetics of radioiodinated BMIPP from isolated rat hearts. The polar component released from BMIPP in these isolated rat heart studies (Figure 4) contains a carboxyl group and from the relative chromatographic polarity, it would appear to be a hydroxy acid. One possibility is the presence of 15-(p-iodophenyl)-3-hydroxy-3-methyl-pentadecanoic acid (β-hydroxy BMIPP or BHMIPP). Studies are now in progress to synthesis BHMIPP and to isolate sufficient levels of the unknown metabolite for mass spectral analysis.

SYNTHESIS AND EVALUATION OF NEW TE FATTY ACID ANALOGUES CONTAINING INTERNAL IODOALKENES

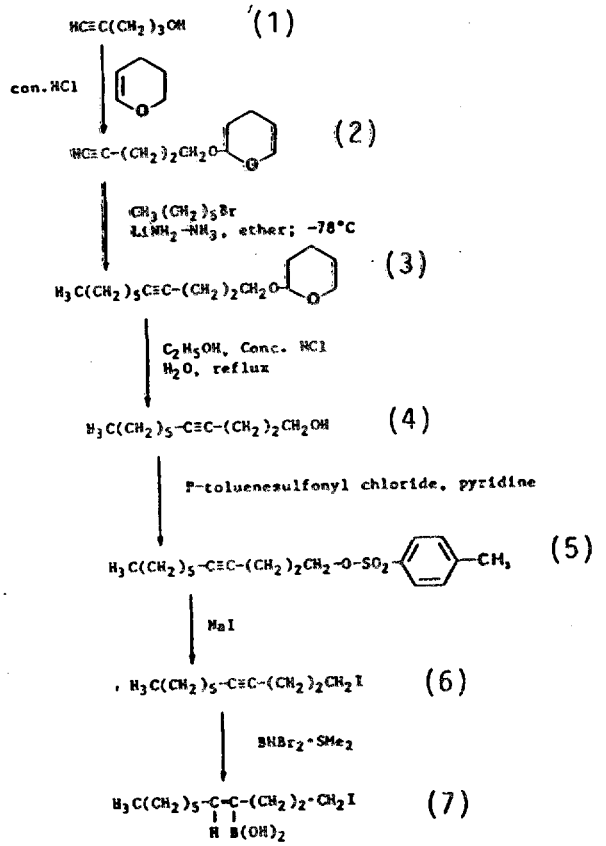
Development of radiolabeled long-chain fatty acids as tools to evaluate myocardial physiology and perfusion is of interest. Tellurium can be readily incorporated in the fatty acid chain while maintaining the linearity of the fatty acid molecule. The presence of tellurium is a unique structural feature that results in the prolonged retention or "trapping" of the modified fatty acids in the myocardium. Radioiodinated tellurium fatty acids have been investigated to take advantage of the attractive properties of nonradioactive Te in the fatty acid chain for prolonged myocardial retention and of ^{123}I for imaging. Radioiodide has been successfully stabilized as an iodophenyl moiety on 15-(p-iodophenyl)-6-tellurapentadecanoic acid (ORNL/TM-8186), and as a terminal vinyliodide on 18-iodotellura-17-octadecenoic acid (ORNL/TM-7918) with Te in the different positions (ORNL/TM-8746). These agents show high heart uptake and high myocardial retention in rats and excellent myocardial images after injection in dogs. New radioiodinated internal iodoalkenyl

tellurium fatty acid analogues have now been prepared in conjunction with collaborators at the University of Tennessee (G. W. Kabalka et al.) to investigate further the effects of internal alkenyliodide on myocardial uptake and retention. The general synthetic route is shown in Scheme I and Scheme II. The procedure involves protection of the hydroxyl group of a terminal acetylenic alcohol (1) by reaction with dihydropyran with subsequent coupling with the requisite alkyl bromide to form the internal alkyne (2). Following acid cleavage of tetrahydropyranyl ether (3), the free alcohol (4), was converted to the tosylate (5) by the new procedure developed during this work (Varma et al, 1986). The tosylate (5) was converted to the iodide (6) by treatment with KI and the iodide then converted to the isomeric mixture of the internal alkenyl boronic acid (7). In this way a series of substrates were prepared for the preparation of Te fatty acids 12a-12d (Fig. 5).

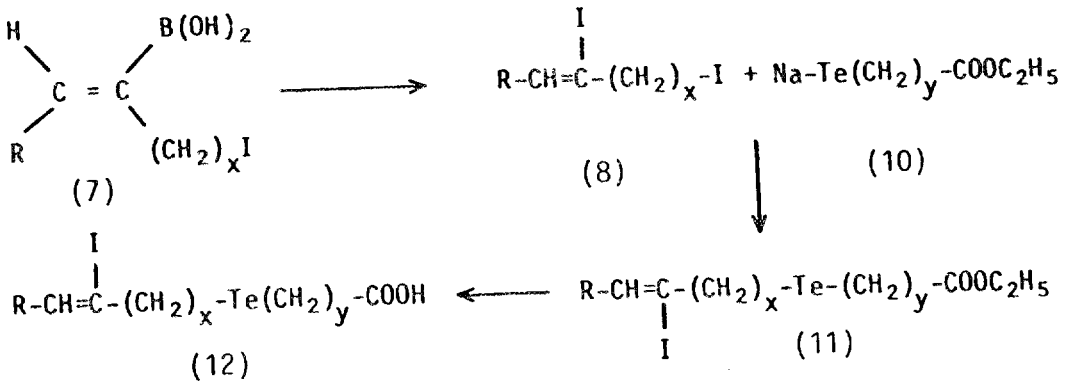
The approach summarized in Scheme II was used to prepare the three new internal iodoalkenyl tellura fatty acids. The structures of these three new analogues are shown in Figure 5.

Compound	Structure
12a 9-I-C_{16}-5-Te-Δ^{9}-	$H_3C-(CH_2)_5-C(H)=C(I)-(CH_2)_3-Te-(CH_2)_3-COOH$
12b 11-I-C_{18}-7-Te-Δ^{11}-	$H_3C-(CH_2)_5-C(H)=C(I)-(CH_2)_3-Te-(CH_2)_5-COOH$
12c 9-I-C_{18}-5-Te-Δ^{9}-	$H_3C-(CH_2)_7-C(H)=C(I)-(CH_2)_3-Te-(CH_2)_3-COOH$
12d 15-I-C_{18}-5-Te-Δ^{15}-	$H_3C-CH_2-C(H)=C(I)-(CH_2)_9-Te-(CH_2)_3-COOH$

Figure 5. Structures of iodoalkenyltellurium fatty acids.



Scheme I



Scheme II

The new analogues were designed to permit an evaluation of the effects of several structural features on myocardial uptake and clearance kinetics in fasted rats. These include fatty acid chain length, the position of the tellurium heteroatom, and the position of the iodoalkenyl moiety. The goal of such structure-activity studies is to optimize the properties of these interesting molecules to show the most attractive in vivo properties. In addition, the availability of structure-activity data will permit the design of the most useful agent for further investigations.

The iodine-125-labeled fatty acid analogues were prepared by the same approach shown in Scheme II by radioiodination of the borono intermediates (7), followed by silicic acid column purification of the radioiodinated iodoalkenyl iodide intermediates and subsequent coupling with the methylcarboxyalkyl sodium tellurides (10). The esters of the fabricated fatty acids (11) were purified by column chromatography, hydrolyzed with base to the free acids (12) and then complexed with bovine serum albumin in the usual manner and administered to fasted Fischer rats. The results of these tissue-distribution studies are shown in Table 1 and demonstrate an unexpected relationship between fatty acid structure and myocardial uptake and clearance properties. Although the factors effecting the in vivo properties are not clear, these studies have shown that a combination of chain length, Te position and the relative position of the internal iodoalkenyl substitution are important factors. The most interesting observation is the clearance of analogues 12c and 12d which has not been demonstrated with other analogues.

Table 1. Distribution of radioactivity in tissues of Fischer 344 female rats following intravenous administration of E-[^{125}I]iodotellurium fatty acids.[a]

Fatty acid,	minutes after injection	Percent injected dose/gm Tissue: Heart (H)	Blood (B)	Liver	Lungs	Kidneys	Thyroid	Mean H:B ratio
12a	5	5.11	0.33	14.23	0.67	...	10.44	15.5
	30	5.76	0.48	11.51	0.57	...	17.19	12.0
	60	6.52	0.32	9.24	0.50	...	28.78	20.4
12b	5	4.17	0.65	15.6	2.29	2.41	10.3	6.4
	30	4.76	0.67	12.1	1.95	2.41	11.7	7.1
	60	5.66	0.49	9.3	1.84	2.23	13.9	11.2
12c	5	2.07	1.66	9.83	2.45	2.47	21.8	1.3
	30	1.11	1.20	5.12	1.14	2.17	65.5	0.9
	60	0.66	0.89	3.39	0.78	1.26	118	0.7
12d	5	2.83	1.02	10.08	2.89	2.14	14.2	2.8
	30	1.39	0.95	5.35	1.22	2.15	47.8	1.5
	60	0.80	0.82	4.39	0.84	1.67	69.7	0.9

[a] Five fasted female rats for each time period were used.

AGENTS FOR MEDICAL COOPERATIVE PROGRAMS

Osmium-191

Several shipments of osmium-191 were made during this period. Two of the new activated carbon osmium-191/iridium-191m radionuclide generators were supplied to collaborators at the UCLA Medical Center, Torrance, California (Dr. I. Mena). One shipment of osmium-191 was made to Children's Hospital, Boston, Massachusetts (Dr. S. Treves). One shipment of osmium-191 as potassium perosmate was supplied for geochemical research to the Massachusetts Institute of Technology, Cambridge, Massachusetts (Prof. S. Hart).

Copper-64

Two shipments of copper-64 were made to the Oak Ridge Associated Universities (Dr. J. Crook) during this period to study the heart uptake of Cu-citrate by PET in a canine model.

Radioiodinated Agents

Two shipments of iodine-125 labeled agents were made to collaborators. One shipment of [I-131]BMIPP was supplied to BNL, Upton, New York (Dr. P. Som), for evaluation of fatty acid uptake patterns in experimental cardiomyopathy using autoradiography. In addition, [I-125] N-(p-iodophenyl)malemide was supplied to University of Michigan, Ann Arbor, Michigan (Dr. D. J. Buchsbaum) for antibody labeling studies. A sample of [I-131]DMIPP was supplied to the University of Bonn, West Germany (Drs. A. Kropp and H. J. Biersack).

OTHER NUCLEAR MEDICINE GROUP ACTIVITIES

Publications

K. R. Ambrose, B. A. Owen, M. M. Goodman, and F. F. Knapp, Jr. "Evaluation of the Metabolism in Rat Hearts of Two New Radioiodinated 3-Methyl-Branched Fatty Acid Myocardial Imaging Agents," European Journal of Nuclear Medicine, 12(10), 1987.

F. F. Knapp, Jr., M. M. Goodman, Ambrose, K. R., P. Som, A. B. Brill, K. Yamamoto, K. Kubota, Y. Yonekura, R. Dudczak, P. Angelberger, and R. Schmoliner "The Development of Radioiodinated 3-Methyl-Branched Fatty Acids for Evaluation of Myocardial Disease by Single Photon Techniques," In, Noninvasive Measurement of Cardiac Metabolism, E. E. van der Wall, Editor, Martinus Nijhoff Publishers, Amsterdam, pp. 159-202 (1987).

Visitors

Dr. L. A. O'Tuama, a neurologist and fellow in nuclear medicine at the Johns Hopkins Medical Institutions, visited the Nuclear Medicine Group on January 26, 1987. A group of East Tennessee High School students visited on March 6, and several nuclear medicine technology students from Vanderbilt University toured the facilities on March 13, 1987.

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108. J. W. Thiessen, M.D., DOE-OHER, ER-71, Washington, DC 20545

109. F. Visser, M.D., Cardiology Dept., Free University Hospital, De Boelelaan 117, Amsterdam, The Netherlands
110. H. N. Wagner, Jr., M.D., Div. of Nuclear Medicine, Johns Hopkins Medical Institutions, Baltimore, MD 21205
111. L. C. Washburn, Medical and Health Sciences Division, ORAU, Oak Ridge, TN 37830
112. A. P. Wolf, BNL, Upton, NY 11973
113. D. V. Woo, Hahnemann University, Philadelphia, PA 19102
114. R. W. Wood, Jr., DOE-OHER, Washington, DC 20545