The Medical Research Center

Brookhaven National Laboratory

Upton, L. I., New York

CIC #12 filed 9/16

725531

V. P. Board

FORM FOR INITIATION OR REVIEW OF CLINICAL

INVESTIGATIVE PROGRAMS

(Submit original only to Department Chairman)

A. Title of the proposal: In-Vivo Measurement of Thorotrast by Whole-Body Gamma Spectroscopy

B. Sponsoring physician(s): Drs. J.S. Robertson, J.E. Jesseph and S.W. Lippincott

C. Responsible investigator(s): Dr. S.H. Cohn

D. Brief description of the study, including its general goals and purpose, and pertinent information on past studies: (Attach additional sheets if necessary.)

The population receiving Thorotrast in the course of diagnostic radiological procedures comprises an important source of clinical data on the late effects of continuous low level ionizing radiation. The dosimetry of Thorotrast is very complex and requires further data on the turnover of Th^{232} and its daughters. The object of this study is to quantify the body burdens of small doses of administered Thorotrast and its turnover in man.

Earlier quantitative studies on the calculation of absorbed dose conducted with Thorotrast-injected patients were not completely successful, owing to the inadequacies of instrumentation and to several complicating circumstances arising from the growth and chemical behavior of the various elements of the Th^{232} chain. The situation, however, has improved considerably due to the development of in-vivo gamma-ray spectrometry and particularly new computer techniques for analysis of complex spectra. In this study, it is proposed to perform such spectral analyses of the gamma-emitting daughters of Th^{232} in patients given small amounts of Thorotrast in order to quantify its uptake and biological turnover, and to determine the resultant tissue dose.

E. Reasons why the investigation(s) are to be performed on human subjects.

Vide supra.

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COLLECTION Committee-Clinical Investigations and Uses of Radioisotop
BOX No. 4
FOLDER CIRC #12

F. Type of patient in which the study is to be done (including approximate number of subjects, if known; special restrictions or requirements; method of obtaining consent; etc.):

Two additional subjects will be required for completion of this study. In order to shorten the period of exposure, it is proposed to utilize only individuals at least 60 years of age, with or without stable disease states, but with essentially normal reticuloendothelial systems. With their full understanding and cooperation, the subjects will be admitted to the Hospital of the Medical Research Center and completely evaluated by standard clinical means. After Thorotrast administration, excretory assays and whole-body counts will be made serially and indefinitely. After the first two to three weeks, the subjects will be followed as outpatients.

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G. 1. Are drugs not in the U. S. Pharmacopoeia (USP) or the NNR being used or contemplated for use? Yes X No ____

2. Is an unusual use of a drug(s) accepted by the USP or NNR contemplated? (An example would be the use of an accepted drug in dosages far exceeding the recommended limits or for purposes distinctly different from the usual indications cited.) Yes ____ No X

3. Are any biological products to be administered that do not bear on their containers or labels notation of approval by the Biological Control Division of the National Institutes of Health? Yes X No ____

4. Is external or internal radiation other than accepted diagnostic or therapeutic procedures to be administered? Yes ____ No X

5. Are any (other) unusual procedures being performed or proposed which in your judgment may entail a special hazard - particularly a hazard above and beyond any imposed by accepted diagnostic and therapeutic measures for that patient? Yes ____ No X

6. Are any radioisotopes to be administered to human beings? Yes X No ____

a. If yes, are the radioisotopes to be used solely within the limits of procedures, specifically described in the USP? Yes ____ No X

Describe the radioisotopic preparation(s):

b. Or are the radioisotopes to be used only in accordance with a project previously approved by the former Radioisotope Committee of this Department? Yes ____ No X

Note the project number: _____

IF ANY OF QUESTIONS 1 THROUGH 5 ARE ANSWERED AFFIRMATIVELY, a detailed analysis of the potential hazards must be appended, including pertinent bibliographic citations and other relevant information.

IF QUESTION 6 IS ANSWERED AFFIRMATIVELY, a completed supplementary form for Radioisotope Administration to Human Beings must be appended. However, this form need not be filed provided that question 6a or 6b is also answered affirmatively. A separate form must be submitted for each radioisotopic species to be administered.

J. S. Robertson
Sponsoring Physician

Committee on Clinical Investigations and Uses of Radioisotopes

Approval recommended _____ Date _____

Disapproval _____ Date _____

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Chairman, Medical Department

6/25/63
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SUPPLEMENTARY FORM FOR RADIOISOTOPE

ADMINISTRATION TO HUMAN BEINGS

A. Radioisotope

1. Species: (Radioisotope or labeled compound, eg. $Na^{24}Cl$ or 1-C^{14}- glucose)

   Thorotrast ($Th^{232}O_2$)

2. Physical characteristics: (Physical half-life; decay scheme (or type, energy and relative frequency of major emissions)

   See attached decay scheme - Table I.

3. Source: (BNL reactor, cyclotron, hot lab.), commercial supplier, etc.)

   Commercial supplier - Heyden Corp.

4. Preparation: (Target material, quantity, special problems)

   Separated from natural thorium ores.

5. Specific activity and isotopic purity of administered material:

   Amt Th^{232} administered (in 5 ml) gives a liver burden of 1.77×10^{-2} μc in patient 28 days after I.V. injection of Thorotrast (see dose calculation).

6. Radioassay and calibration procedures: (Include validation to be performed at BNL prior to use)

   Thorotrast solution to be used was calibrated against a standardized solution of $Th(NO_3)_4$ in secular equilibrium. Thorotrast also assayed by α pulse analy by the BNL Anal. Chem. group.

7. Vehicle and route of administration:

   5 ml Thorotrast (< 7% of former diagnostic dose).

8. Procedures for control of sterility and pyrogenicity: (Or note that commercially supplied isotopes are certified as ready for administration to human beings.) Sterilized - original solution was prepared for administration to human beings

9. Extraneous effects, if pertinent: (Such as pharmacological or toxic actions of the parent compound or vehicle, etc.) None

B. Radiation Dosage

1. Biological half-life or half-lives, including slow components: Not known, but parent Th^{232} has half-life of 40 years. The daughters Ra^{228} and Ra^{224} turnover much more rapidly, e.g., clinical data in a previous study at BNL indicated a lo of 20% of the injected activity by 28 days.

2. Organ, cellular, or subcellular localization: (Should account for the effects of special drugs or agents on altering the natural distribution of the radioisotope)

   a. Critical or "target" organ(s): Liver

   b. Gonadal exposure:

      The β and γ doses are insignificant as the primary effect is from α particles deposited in R.E. system.

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3. Sample calculations: (Dosage should be calculated for the whole body and for "target" or other separate organs, where indicated) Summary equations are desired; not extensive calculations. Standard dosage equations from references such as Hine and Brownell's Radiation Dosimetry, National Bureau of Standards Handbook 69, and BNL Hospital Form 1167-A should be used where possible and the reference cited. **Dose to liver (critical organ) is calculated from biological data obtained in a previous study at BNL 2 years ago. The patient's body burden was compared to that of a phantom containing a calibrated solution of $Th(NO_3)_4$. See attached sheet for dose calculation. The result dose to liver is calculated to be 0.153 rads/wk.**

C. Radiological Health Aspects

1. Hazards to other patients and to personnel from external or internal radiation: **None**

2. Monitoring procedures, if necessary: **None**

3. Special procedures for handling waste products, excreta, biological samples, etc., where indicated: **None**

4. Plan for isotope accountability, if required: **None**

Questions G1 and 3 are answered affirmatively because of the radiation hazard associated with Thorotrast. The radiation hazard is discussed in the supplementary form above.

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June 25, 1963

TABLE I

Radioactivity of Thorium 232 Decay Series

Isotope	Half-Life	Alpha Energy (MeV)	Alpha Abundance $\alpha/Th^{232}\alpha$	Beta Energy (MeV)	Beta Abundance $\beta/Th^{232}\alpha$	Gamma Energy (MeV)	Gamma Abundance $\gamma/Th^{232}\alpha$
Th^{232}	1.39×10^{10} Y	3.98	1.00	--	--	--	--
Ra^{228}	6.7 Y	--	--	0.012	1.00	--	--
Ac^{228}	6.12 h	--	--	0.46	0.13	0.058	0.003
				0.66	0.08	0.129	0.034
				0.15	0.53	0.209	0.04
				1.72	0.07	0.270	0.03
				1.85	0.09	0.328	0.032
				2.18	0.10	0.338	0.092
						0.779	0.008
						0.790	0.045
						0.831	0.016
						0.908*	0.25
						0.963*	0.19
Th^{228}	1.9 Y	5.339	0.28	--	--	0.084	0.02
		5.423	0.72				
Ra^{224}	3.64 d	5.194	0.004	--	--	0.241	0.046
		5.448	0.046				
		5.681	0.95				
Rn^{220}	54.5 s	6.282	1.00	--	--	--	--
Po^{216}	0.158 s	6.775	1.00	--	--	--	--
Pb^{212}	10.6 h			0.331	0.88	0.115	0.02
				0.569	0.12	0.176	0.01
						0.239*	0.80
						0.300	0.05
Bi^{212}	60.6 m	5.603	0.0037	2.250	0.64	0.040	0.01
		5.622	0.005			0.720*	0.12
		5.765	0.0068			0.800*	0.10
		6.047	0.238			1.03	0.03
		6.086	0.092			1.34	0.03
						1.61	0.04
						1.81	0.04
						2.20	0.01
Po^{212}	3.04×10^{-7} s	8.78	0.66	--	--	--	--
Tl^{208}	3.1 m	—	—	1.8	0.36	0.277	0.03
						0.510	0.08
						0.582*	0.28
						0.859	0.05
						2.62	0.34

* Measured by whole body counter -
(The ratio of the daughters give a measurement of the radioactive equilibrium)

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PRIVACY ACT MATERIAL REMOVED

CALCULATION OF RADIATION

Dose from Thorotrast

1. 0.266 μc of a calibrated solution of $Th(NO_3)_4 \cdot 4H_2O$ was placed in the liver of the REMAB phantom and counted in the whole-body counter. This is a 40-year-old solution of $Th(NO_3)_4$ and therefore is in secular equilibrium with its daughters.

2. In a previous study, patient ( ) was injected with 12 ml of Thorotrast and her gamma spectrum at 28 days post injection was compared to that of the above phantom. It was found that patient had approximately 16% of the activity of the above phantom, or .0426 μc (.16 x 0.266) in the liver.

3. In the contemplated study, 5 ml of Thorotrast will be administered instead of 12 ml; therefore, only 1.77×10^{-2} μc ($\frac{5}{12} \times 4.26 \times 10^{-2}$) will be expected to be retained by the liver (the critical organ).

4. Using the standard equation - Hine and Brownell, p. 824.

$$D_\alpha = 51.2 \text{ CE rads/d}$$

$$C = \frac{\mu c}{gm} \text{ and}$$

where 1.7×10^3 g (wt. of liver)

E = effective α energy for liver for 7 α's of Th^{232} chain

= 41 Mev (see ICRP, p. 139)

$$D_\alpha = 51.2 \left(\frac{1.77 \times 10^{-2}}{1.7 \times 10^3}\right) 41 \text{ rads/d}$$

$$= 2.18 \times 10^{-2} \text{ rads/d}$$

$$= 1.53 \times 10^{-1} \text{ rads/wk}$$ to liver (critical organ)

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PRIVACY ACT MATERIAL REMOVED

This is the dose that the patient will receive following injection of 5 ml of the Thorotrast solution. The α dose is considered to be the limiting radiation dose. The beta and gamma doses received are at least an order of magnitude lower than the α radiation dose.

Assumed in the above calculation:

1. Thorotrast and Thorium daughters remain indefinitely in body after 28 days.
2. No self-absorption of α particles occurs in the large Thorotrast aggregates formed in the liver.
3. Daughters are in equilibrium with parent Th^{232} and there is no differential turnover or "wash-out" of daughters.

Since all of these assumptions are conservative, the above computed dose based on these assumptions will maximize the estimate of potential radiation hazard.

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