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COLLECTION Protocols - Clinical
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Dr. G. C. Cotzias, Chairman
Comm. on Use of Isotopes in Patients

Drs. S. H. Cohn and J. E. Jasseph

Proposed Clinical Investigation - "In-Vivo Measurement of Thorotrast (ThO_2) by Whole-Body Gamma Spectrometry."

Objective

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 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 and particularly due to the development of in-vivo gamma-ray spectrometry and 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} as distributed in the whole body of patients given small amounts of ThO_2 as "Thorotrast."

Investigators

Drs. S. H. Cohn, J. E. Jasseph and S. W. Lippincott.

Isotope

The decay chain of Th^{232} is rather complicated and a summary of the pertinent energies of its daughters is included in Table 1.

In the past, the administered dose has usually been 75 ml (15 gm Th^{232}) for hepatosplenography. We propose to give only 10 ml (2.0 gm) intravenously, to the three patients who will comprise the study group. Thus the accumulated tissue dose will be greatly lower (by a factor of at least 7) than that absorbed when the agent was used diagnostically.

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Past Experience

Thousands of patients in the United States and abroad have received Thorotrast in diagnostic radiology between 1930-1945 (1,7). Its use has since been largely curtailed because of the recognition that Th^{232}, being a member of a radioactive chain, might, after many years, be carcinogenic, similar to the action of radium in bone.

In his detailed study of 33 patients, Looney (1) was unable to establish a causal relationship between Thorotrast administration and later development of malignant lesions of the reticuloendothelial system. Furthermore, his cumulative review of approximately 3000 patient studies did not establish that the incidence of malignancies was different from that of the general population. These studies are tabulated in Table 2.

In spite of the extensive use of Thorotrast since 1931, only comparatively few cases have been reported where a carcinogenic effect could be demonstrated. While it is certainly possible that malignant tumors can be produced, the latent period is long (15-20 years) and large doses are required - 300 mg/kg (12). This dose is tenfold greater than the dose contemplated in our study.

Radiation Dose

The radiation dose to tissues from Thorotrast has not been worked out completely because of its complexity. The self-absorption of its α's in Thorotrast aggregates, the degree of "washout" of daughters, the degree of radioactive equilibrium of the parent Th^{232} and its daughters and their metabolic turnovers are some of the unknowns in the dosimetry (1-6). Estimates of the radiation dose from radiochemical and autoradiographic approaches have been made and are summarized by Looney (2). The estimates of the average dose to the liver by a combination of methods vary widely, from 1-9 rad/week following deposition of 75 ml of Thorotrast. The average accumulated dose to the liver, the primary organ of Thorotrast deposition, in 30 years was calculated to be 3500 rad (2). The average dose to bone marrow over 30 years is 1/10 of the average accumulated dose to the liver, or 350 rads.

Subjects

A previous study has been carried out at BNL in which 12 ml of Thorotrast was administered to 3 patients. Other medical centers are studying Thorotrast and have administered doses up to 60 and 75 ml to patients (1).

Only three 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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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} γ	3.98	1.00	--	--	--	--
Ra^{228}	6.7 γ	--	--	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 γ	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	0.013
		5.622	0.005			0.720*	0.126
		5.765	0.0068			0.800*	0.109
		6.047	0.238			1.03	0.037
		6.086	0.092			1.34	0.034
						1.61	0.047
						1.81	0.047
						2.20	0.018
Po^{212}	3.04×10^{-7} s	8.78	0.66	--	--	--	--
TI^{208}	3.1 m	—	—	1.8	0.36	0.277	0.035
						0.510	0.087
						0.582*	0.28
						0.859	0.05
						2.62	0.347

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

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CLINICAL FINDINGS FOLLOWING THOROTRAST ADMINISTRATION*

Table ~~VIII~~ II

Thorotrast Follow-Up Studies

Year Reported	Total No. of Patients	Results	Investigator	Comments
1935	175	No deleterious effects found	Rigler, Koucky and Abraham[8]	3.5 year follow-up, 100 patients dead from primary disease. 32 patients not traced. 43 patients living and apparently unaffected.
1942	286	No deleterious effects found	Yater and Coe[9]	10 year follow-up. 189 patients dead. 67 patients not traced. 30 patients examined.
1951	2,235	2 malignant tumors of liver, and 1 leukemia	Thomas, Henry and Kaplan[7]	Questionnaires sent to 132 radiologists
1953	235	4 anemias and 2 leukemias	Johansen, Backer, Rundo and Faber[10,11,12]	
1955	35	1 hemangioendothelioma of liver. Induration at site of injection in 4 patients. Minor hematologic changes.	Looney, Hursh, Colodzin and Stedman[13,14]	Retention approximately 15 years. 14 patients dead. Mean age at death, 62 years
1956	21	1 endothelial cell sarcoma of liver. 1 primary hepatoma of liver. 1 carcinoma of maxillary sinus. 9 of 12 patients studied had less than 4 million erythrocytes per mm.[3]	Fruhling, Gross Batzenschlager and Dorner[15]	Mean retention approximately 10 years. 12 patients dead
1958	136	3 patients dead from malignant disease other than that for which thorotrast was given (i.e., carcinoma of stomach, mouth and lung). None considered to be related to thorotrast. Hematologic studies on 26 patients showed only low lymphocyte counts in 2 patients.	Berrett and MacRae[16]	Follow-up of 136 patients who had caroti arteriographies between 1934 and 1950. Evaluation of 134. 66 now dead. None attributable to complications of thorotrast

*From:

Looney, W. B.
An investigation of the late clinical findings following Thorotrast (Thorium Dioxide) administration.

Am. J. Roentgenol. 83:163, 1960

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