Joslin Diabetes Center

Dedicated to Diabetes Research, Treatment, Education, and Youth Programs

One Joslin Place
Boston, Massachusetts 02215

(617) 732-2608

May 17, 1988

U.S. Nuclear Regulatory Commission, Region I
Nuclear Materials Section A
475 Allendale Road
King of Prussia, PA 19406

Dear Sir,

I am writing to inquire about the procedures necessary to obtain permission to conduct in vivo clinical research studies with certain radionuclides at the Joslin Diabetes Center. I have previously communicated by telephone with Ms. Jenny Johansen (prior to her move to Washington) and with Ms. Judith Jostra concerning this request. Below, I have outlined the background and specific details relevant to this request and have proposed two possible means of accomplishing this objective. I hope that with this information you will be able to advise us as to which approach would be most appropriate and efficacious for achieving this goal.

BACKGROUND: The Joslin Diabetes Center (JDC) is an institute dedicated to administering medical care to patients with diabetes and conducting both clinical and basic research on diabetes and metabolism. Although the JDC is a distinct administrative entity, it is closely affiliated with (and physically adjacent to) the New England Deaconess Hospital (NEDH). All of the medical and clinical research physicians at the JDC are members of the medical staff of the NEDH.

Recently, certain physicians at the JDC have expressed interest in using in vivo radioisotopic techniques during the course of clinical research studies performed at the JDC. Although the JDC is licensed for in vitro use of radionuclides (USNRC License No. 20-15266-01), it does not have approval for the use of radionuclides in human studies. This primarily results from the fact that the JDC does not employ a sufficient number of individuals with the appropriate expertise to establish a full Radiation Safety Committee.

PROPOSAL #1:

One approach to this issue would be to amend or otherwise modify the present license held by the JDC to permit certain physicians on its staff to conduct in vivo clinical research studies with a limited number of radioisotopes (outlined below). It is important to emphasize three basic tenets of this request. First, the radionuclides to be used at the JDC would be for purposes of research and would not involve either diagnostic or therapeutic

use of radioactive byproduct material. Second, all of isotopes and the general investigative nature of the studies to be conducted at the JDC are currently in routine use for the study of intermediary metabolism at several medical centers throughout the United States. Finally, if additional expertise in the area of radiation safety is required, this would be obtained on a consultative basis from appropriately qualified individuals at the NEDH or Harvard University.

Specific Isotopes to be Used:

General Principles: The techniques involving the use of radioisotopic tracers for the study of metabolism in humans have been available since the 1950's. By using either continuous infusions or bolus injections of a trace amount of an isotopically labelled substrate or hormone, important information can be gained regarding the distribution, rates of appearance, synthesis, degradation, clearance, and excretion of substance being traced. Although there is a voluminous literature on the methodology and application of these techniques, a concise review of the principles of radioisotope turnover kinetics can be found in the recent book by Robert R. Wolfe (Tracers in Metabolic Research, Alan R. Liss, Inc., New York, 1984).

The specific isotopes to be utilized in the proposals described below are hydrogen-3, carbon-14, and iodine-125. These isotopes have been the most widely used in human studies since a) they are low energy beta particle or gamma emitters (thus limiting radiation exposure), b) can be easily detected by liquid scintillation counting, and c) are readily excreted from the body.

Hydrogen-3: The chemical forms of hydrogen-3 isotopes to be used will include tritiated derivatives of monosaccharides or their metabolites (e.g., glucose or alanine), non-esterified fatty acids (e.g., palmitate), amino acids (e.g., leucine), hormones (e.g., norepinephrine), and ^3H_2O (for determination of lean body mass). Since all hydrogen-3 is ultimately in equilibrium with the body's water pool (either through specific metabolic degradative pathways or through non-specific proton exchange) and since the turnover time of the body's water pool is several fold slower than the turnover time of the specific metabolites being traced, the most conservative approach to the calculation of radiation dose received from a specific metabolic tracer is based on the half-life of body water.

Thus, assuming that a) the effective half-life is 12 days, b) the total body is the critical organ, and c) total body mass is 70 kg, the total radiation dose delivered per μCi of hydrogen-3 administered can be calculated according to one of several different methods. Using the MIRD method of calculation, $D_{TB} = (A_{TB}) \times (S_{TB})$ = (1.44 X 1 μCi X 12 days X 24 hours/day) X (0.00017 mRem/μCi-hr) = 0.07 mRem per μCi administered. Using the dose equivalent per day method of calculation, the dose per μCi would be 51 X A X E X QF X days ÷ m = 51 X 1 μCi X 0.0057 X 1.7 X 12 ÷ 70000 = 0.08 mRem per μCi. Alternatively, one may obtain the value of 0.13 mRem per μCi directly from tables available in the Handbook of Radioactive Nuclides. Since small differences are obtained depending on the method of calculation used, the most conservative estimate (0.13 mRem per μCi) will be used for subsequent calculations.

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Carbon-14: The specific chemical forms of carbon-14 isotopes to be used will include monosaccharides and their metabolic derivatives (e.g., glucose, lactate, or alanine for the determination of glucose recycling and Cori cycle activity, gluconeogenesis, or glycolytic activity), non-esterified fatty acids (e.g., palmitate for the measurement of free fatty acid oxidation and turnover), amino acids (e.g., leucine for the determination of leucine turnover and oxidation), and $H^{14}CO_3$ (for priming the body's bicarbonate pool which allows more rapid isotopic equilibration). The principal route of excretion of carbon-14 is through entry into the plasma bicarbonate pool and subsequent elimination as expired $^{14}CO_2$.

Thus, assuming that a) the effective half life is 10 days, b) the total body is the critical organ, and c) total body mass is 70 kg, the total radiation dose delivered per μCi of carbon-14 administered can be calculated according to the methods noted above. Using the MIRD method, $D_{TB} = (A_{TB}) \times (S_{TB}) = (1.44 \times 1\ \mu Ci \times 10\ days \times 24\ hours/day) \times (0.0015\ mRem/\mu Ci\text{-}hr) = 0.52$ mRem per μCi administered. Using the dose equivalent per day method, total dose per μCi = 51 X A X E X QF X days ÷ m = 51 X 1 μCi X 0.0493 X 1.0 X 10 ÷ 70000 = 0.36 mRem per μCi. Finally, one may obtain the value of 0.57 mRem per μCi from tables in the Handbook of Radioactive Nuclides. Since small differences are obtained depending on the method of calculation used, the most conservative estimate (0.57 mRem per μCi) will be used for subsequent calculations.

Iodine-125: The specific chemical from of iodine-125 to be used is ^{125}I-iothalamate (for measurement of glomerular filtration rate). The isotope is widely used for determining changes in renal function during the progress of certain diseases (e.g., diabetes) or following therapeutic interventions.

All patients are pretreated with SSKI so that thyroid uptake of ^{125}I is negligible. The iothalamate is administered subcutaneously or intravenously and is rapidly excreted from the body in the urine (generally within 4 hours). During a typical study involving the administration of 35 μCi of ^{125}I-iothalamate, whole body radiation exposure is 0.25 mRem. Organ specific doses include 0.84 mRem to the kidney, 0.30 mRem to the ovaries, 0.06 mRem to the testes, and 30 mRem to the bladder. (It should be noted that the bladder dose is a theoretical maximum and generally represents a 4 to 7 fold overestimate of the actual dose received under the conditions of the study.)

Summary: It is important to emphasize that the radiation doses delivered during research applications with all of these isotopes is extremely small. In the course of numerous studies performed by Dr. Simonson and his colleagues at other institutions during the past 8 years, the largest single dose of hydrogen-3 administered during a single study was less than 200 μCi (26 mRem). In the case of individuals being studied on repeat occasions, the total lifetime dose did not exceed 1000 μCi (130 mRem). In a similar manner, maximum radiation exposure for carbon-14 was 200 μCi (114 mRem) per single dose and 500 μCi (285 mRem) for total lifetime exposure. For iodine-125, whole-body single dose exposure from 35 μCi is approximately 0.25 mRem while maximum lifetime exposure would not exceed 2 mRem. These doses are all well within the guidelines of 5 Rems per single dose and 15 Rems total dose

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commitment established by the FDA (Code of Federal Regulations, 4-1-86 edition, Volume 21, Chapter 1, part 361.1).

PROPOSAL #2:

The second possible approach to this issue would be to conduct the aforementioned clinical research studies at the JDC under the NRC license and the Radiation Safety Committee of the NEDH. The members of the Radiation Safety Committee and the Radiation Safety Officer at the NEDH have indicated in principle that they are willing to administer the ordering, handling, storage, and disposal of the radionuclides used for in vivo studies at the JDC. The studies would be performed within the discretely defined clinical research unit at the JDC. However, it is important to emphasize that this approach would mean that another licensee (the NEDH) would be responsible for the administration of the in vivo use of radionuclides at the JDC (which holds an independent NRC license for in vitro use only). It is not clear to us whether this would represent an administrative conflict or in any other way violate the regulations of the NRC.

SUMMARY:

We hope that this letter provides sufficient information on the background and specific purposes for which we seek approval to conduct in vivo clinical research studies with radionuclides at the JDC. We would appreciate receiving further specific information as to whether either (or both) of these approaches is feasible and, if so, what procedures are necessary to enact one of these proposals. Please address all correspondence to Donald C. Simonson, M.D., Joslin Diabetes Center, One Joslin Place, Boston, MA 02215. Thank you.

Yours truly,

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