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BERKELEY: DEPARTMENT OF NUTRITIONAL SCIENCES

June 22, 1971

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TO: Radiation Safety Subcommittee
Environmental Health & Safety
481 Cowell Hospital

FROM: Sheldon Margen, M.D., Professor of Human Nutrition and Chairman of the Department of Nutritional Sciences

RE: Application for use of 10μCi. ^{14}C labelled glycerol in studies of glyceride kinetics in six female obese human volunteers.

SUMMARY

Application is made to use two 10μCi doses of 1-3 ^{14}C - glycerol for glyceride kinetic studies in each of six obese individuals. These subjects are female volunteers between the ages of 21-50 years, and each is motivated by a desire to lose weight during the course of the experiment. It is planned to undertake this experiment between July 19th and September 21st, 1971.

PURPOSE OF STUDY

It is intended to determine the rate of secretion from the liver into the plasma of endogenous plasma glycerides before and after dietary restrictions of protein and calorie intake.

Individuals become obese because the rate of deposition of triglycerides into the adipose tissue exceeds their rate of removal. We are interested in determining whether the rate of supply of endogenous glycerides, secreted as lipoproteins from the liver, is greater in obese individuals than in normal subjects, and whether the rate of glyceride secretion in obese subjects can be altered by dietary manipulation and by loss of weight.

There are a number of ways in which glyceride kinetics can be studied, but all those available for human experimentation involve the use of radioactive isotopes (1,2,3). We consider that in general the method published by Farquhar et al. (3) provides the most satisfactory method for measuring the glyceride secretion rate yet available.

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JUSTIFICATION FOR THE USE OF ^{14}C LABELLED GLYCEROL

At the present time it has not been found possible to procure ^{13}C labelled glycerol for the kinetic studies proposed. Farquhar (3) used either ^{3}H or ^{14}C labelled glycerol in his initial studies, but subsequently used only ^{14}C on the basis that translocation of ^{3}H from the glycerol might occur. Although this is a possibility with ^{14}C, LeRoy (4) states that formate-^{14}C given to mice in single doses equivalent to 300-500 mCi in man produces ^{14}C labelling in liver and brain purines, but would disintegrate at such a rate as to produce maximum mutation rates less than the spontaneous rate of gene mutation.
In view of the great sensitivity with which ^{14}C disintegration can be measured in a liquid scintillation counter, it has been estimated from published data (3) that 10μCi is sufficient to give reliable estimates for each experiment.

DETAILS OF TECHNIQUE

When glycerol is injected intravenously into human subjects, 50% is immediately oxidised to CO_2 and water, (5) some is converted to glucose and a proportion is converted to a-glycerophosphate in the liver cells, and thence incorporated into the glycerol moiety of hepatic glycerides. From the liver some glyceride is secreted into the plasma, circulates to the adipose tissue and there is hydrolysed to fatty acids and glycerol. The glycerol component is not incorporated into the adipose tissue as such, but recirculates to the liver and is there recycled (6). In the technique of Farquhar et al. (3), ^{14}C labelled glycerol is injected intravenously and the incorporation of the label into the plasma glycerides is measured. From the subsequent decay in glyceride specific activity a value for the glyceride secretion rate in the steady state can be calculated.
Farquhar et al. (3) have used 15μCi of glycerol-1-3-^{14}C in their studies on humans, which have included some obese subjects (personal communication). From their data the biological half-life of glycerol-1-3-^{14}C appears to be between 4 and 8 hours. This is confirmed by some preliminary studies by Paul and Bortz (5), from which a mean biological half life of about 8 hrs. is calculated.

DOSAGE CALCULATION

ASSUMPTIONS

a) 10μCi of ^{14}C glycerol is to be given to each subject on two occasions at least 40 days apart.
b) The maximum biological half-life of glycerol-1-3-^{14}C is 12 hours - 0.5 days.
c) All the ^{14}C is concentrated in the critical organs of the body, namely adipose tissue and bone.
d) The minimum body weight of the obese subjects is 70 Kg, and fat and bone together contribute at a minimum 18 Kg.

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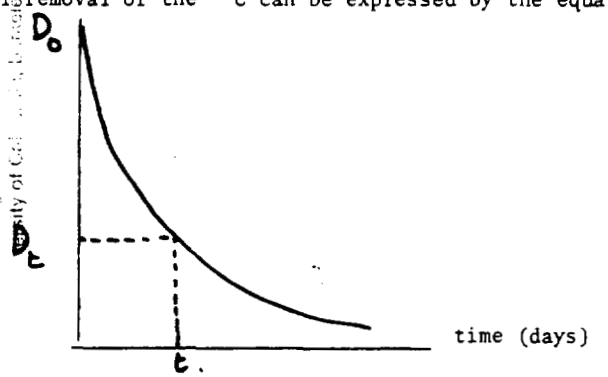
The biological removal of the ^{14}C can be expressed by the equation:



$D_t = D_o\, e^{-\kappa t}$ where κ is the decay coefficient.

Therefore, the total μCi.days dose equals

$$\int_{t=0}^{t=\infty} D_t = \int_{t=\infty}^{t=0} D_o\, e^{-\kappa t} = \frac{D_o}{\kappa}$$

Now $\kappa = \dfrac{\log_e 2}{\text{half-life}} = \dfrac{0.693}{0.5} = 1.386/\text{day}$

$\therefore$ μCi.days $= \dfrac{10}{1.386} = 7.215$ μCi.days

equivalent to a constant dose of 7.215 μCi for 1 day.

Fraction of ^{14}C disintegrating in 1 day $= \dfrac{4}{10^7}$

$\therefore$ μCi.disintegrating $= \dfrac{7.215 \times 4}{10^7} = \dfrac{2.886}{10^6}$ μCi.

When 1μCi completely disintegrates in 1 g tissue = 9×10^6 reps.

$\therefore$ When 1μCi completely disintegrates in 18 Kg tissue $= \dfrac{9 \times 10^6 \text{ reps.}}{18 \times 10^3}$

$\therefore$ When $\dfrac{2.886}{10^6}$ μCi disintegrates dose

$$= \frac{9 \times 10^6}{18 \times 10^3} \times \frac{2.886}{10^6} \text{ reps.} = \underline{\underline{1.443}} \text{ millireps}$$

Since the experiment is to be repeated, the total maximum dose is 2.886 millireps.

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The dosage may be considered in two other ways.

(1) Paul and Bertz (5) state that 50% of the injected glycerol is immediately oxidized to carbon dioxide and water. Therefore, at a maximum, 50% of the glycerol is converted to glucose. From the published data, at a maximum, one-fifth of the glucose will be incorporated into the glycerol moiety of the adipose tissue triglyceride. Hence 1 μCi might end up at this site. The half-life of adipose tissue triglyceride is about six days (6). Calculating the total adipose tissue irradiation for a 70-kg individual gives a value of 3.26 millireps.

(2) Skipper et al. (7) have studied bicarbonate excretion and localization in the rat. If their data are extrapolated to a 10 μCi injection of $H^{14}CO_3$ into a 70-Kg man, the radiation in the bone, where long-term retention will occur, would be 0.03 millireps per day at one to two weeks (8). Hence, even assuming that 50% of the injected glycerol immediately enters the bicarbonate pool the bone radiation at one to two weeks will be only 0.015 millireps per day.

SOURCE:

Glycerol 1:3 ^{14}C in aqueous solution can be obtained commercially in sterile, pyrogen-free form suitable for intravenous injection into human subjects. Schwartz/Mann and ICN (Chemical and Radioisotope Division) would be able to provide this.

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