725213 The Medical Research Center

Brookhaven National Laboratory

Upton, L. I., New York

Project H-60:

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Permission is requested from the Isotope Committee to administer I^{131} labeled human thyroglobulin to clinically investigated normal subjects and to individuals with a variety of thyroid disorders.

Investigators: W.Wolins, G.Terres, C.Shellabarger and S.Cohn

Objective:

The purpose of this investigation is to study the turnover of I^{131} labeled human thyroglobulin in man. It has been stimulated by reports of antithyroglobulin in the serum of patients with Hashimoto's struma and myxedema (1,2,3). The presence of such antibodies should appreciably alter the rate of degradation of the antigen (thyroglobulin) and permit quantitation of the antibodies present (4). Since thyroglobulin does not ordinarily appear in the circulation, its turnover in the normal individual is of interest when related to the turnover of other globulins and is a necessary prelude to the interpretation of turnover studies of the antigen in thyroid disease.

Methodology:

a). Choice of Patients.

It is proposed to use as controls individuals hospitalized at Brookhaven National Laboratory for diseases not related to abnormalities in thyroid function whose thyroid function has been investigated by the usual means and found to be normal.

Individuals with thyroid disease will be admitted prior to diagnosis and after a specific diagnosis has been made. Investigation at BNL will establish or confirm the diagnosis. In each case the presence of circulating antithyroglobulin will be established by the use of the Boyden technique (10). Prior to the study of the turnover of thyroglobulin, skin and conjunctival tests for sensitivity will be performed as will tests to assure the sterility of the preparation used (filtration and culture).

b). Source of thyroglobulin.

The protein is to be obtained from thyroid glands removed surgically or from fresh post-mortem material and the thyroglobulin extracted by the method of Derrien et al (5,6). The preparation will be purified by repeated precipitation and dialysis. The final fraction to be used will be isolated by electrophoresis. Degradation will be hindered by procedures performed at low temperatures.

c). Iodination of thyroglobulin

This will be accomplished by either the method of Hughes or that of McFarlane (7,8,9).

d). Specific activity of the Preparation. It is anticipated that this will be 1 μc per mgm of thyroglobulin. This will permit whole-body counting after administration of 1 mgm of thyroglobulin I^{131} to each patient.

e). Counting

By means of whole-body counting the rate of degradation of the administered protein will be determined.

f). Lugol's solution - will be administered prior to and during the course of the experiment.

g). Pharmacological activity of the administered thyroglobulin. These calculations are made on the assumption that 1 mgm of thyroglobulin will be administered and that all of its iodine will be available as l-thyroxine.

M.Wt. Thyroglobulin 675,000
Content iodine in thyroglobulin 1% = 6750
M.W. Iodine 126

$\frac{6750}{126}$ = 54 atoms iodine per molecule thyroglobulin

$\frac{54}{4}$ = 13.5 = molecules thyroxine per molecules thyroglobulin.

M.Wt. thyroxine = 1000

If

$$\frac{.001}{6.75 \times 10^{5}} \times 6 \times 10^{23} = \text{(Molecules Thyroglobulin 1 mgm)}$$

13.5 = Molecules Thyroxin per molecule thyroglobulin

$\frac{1000}{6 \times 10^{23}}$ = Wt. Thyroxine per molecule

$$\frac{.001}{6.75 \times 10^{5}} \times 6 \times 10^{23} \times 13.5 \times \frac{1000}{6 \times 10^{23}}$$

$$\frac{= 13.5}{6.75 \times 10^{5}} = 2 \times 10^{-5} \text{ g thyroxin per mgm thyroglobulin}$$

Thus 20 µg l-thyroxine will be the maximal dose of hormone available from 1 mgm of thyroglobulin. This is equal to 1/20 the daily maintenance dose. Except under very unusual circumstances, such a dose should be innocuous. These unusual circumstances may be anticipated and patients who might develop some difficulty avoided.

h). Sterilization:
The thyroglobulin will be sterilized by filtration and its sterility tested by culture.

i). Pyrogens:
Will be removed by filtration during sterilization.

j). Route of Administration:
The thyroglobulin will be administered intravenously.

k). Calculation of radioactivity of iodinated I^{131} preparation:
Since the efficiency of the counter for I^{131} is known (33%)

the quantity to be administered can readily be calculated by counting an aliquot of a dilute solution of the radioiodinated thyroglobulin.

Dosimetry

In view of the sensitivity of the whole-body counter which can follow the degradation of 1 μc of I^{131}, it is our intent to approximate this quantity of protein-bound radioactivity in our study. A calculation based on the administration of 5 μc of I^{131} indicates that the total dose would be 2 milliroentgens and the total dose to blood will be 3.4 milliroentgens. The following is the calculation of the dose:

I. A. Dose to blood (d_β)

$$d_{(\beta)} = \frac{3.7 \times 10^4 \times 60 \times 60}{6.24 \times 10^7} \bar{E}_\beta = C_b = \text{rad/hr}$$

$$= (2.12)\ (0.187)\ C_b = 0.4\ C_b \quad \text{rad/hr}$$

$d_{(\gamma)}$ = (depends on concentration in whole body)

assume C_t = 1/2 Cb

C_t = I^{131} concentration in whole body

C_b = I^{131} concentration in blood

$$= 10^{-3}\ T\ \bar{g}\ C_t$$

T = r/mc/hr at 1 cm from source (See Hine and Brownell) p 594

$\bar{g}$ = geom.factor for γ dose calcul. (See Hine and Brownell) for 70 Kg man p 256

$$= (10^{-3})\ (2,18)\ (120)\ \left(\frac{Cb}{2}\right) = 0.13\ Cb \quad \text{rad/hr}$$

Thus total dose to blood = 0.40 Cb

+0.13

0.53 Cb rad/hr

B. Dose to whole body $d_{(\beta+\gamma)}$

Assume: Beta dose to whole body outside blood vessels assumed to be 1/2 of that to blood. $C_t = \frac{Cb}{2}$ but γ dose is same throughout body.

1 mgm., depending on its specific activity and the quantity of radioactivity administered will approximate 1 μc.

4. The calculated dose from the disintegration of 1 mc of I^{131} in a kilo human is 400 milliroentgens. This is equivalent to 2 milliroentgens per 5 μc of injected dose to tissue or 3.4 milliroentgens per 5 μc of injected dose to the blood.
5. The maximal dose of l-thyroxine following administration 1 mgm of thyroglobulin is 20 μg.

Donald C. Borg, M.D.

Walton W. Shreeve, M.D., Ph.D

John L. Bateman, M.D.

Elmer E. Stickley, Ph. D.

James S. Robertson, M.D., Ph.D.
Ex Officio

Lee E. Farr, M.D., Ex Officio

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McGavack