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PRELIMINARY PROGRESS NOTE[1]

Comparison of the Resin Uptake of I^{131} Labeled Triiodothyronine and Thyroxine in Hyperthyroidism and Other Conditions[2]

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Alteration in the binding capacity and degree of saturation of the thyroxine-binding serum proteins have provided the basis for certain tests of thyroid function since the red cell uptake of I^{131} labeled L-triiodothyronine (T_3-I^{131}) was first described by Hamolsky (1). Subsequent improvements, the most notable of which was the replacement of human erythrocytes by an anion exchange resin (2), and the simplicity of the technique, have led to wide acceptance of the competitive binding of T_3-I^{131} between the resin and plasma carriers as an index of thyroid function (3-9).

Considering the alterations in binding states of both thyroxine-binding protein carriers, thyroxine-binding globulin (TBG) and thyroxine-binding prealbumin (TBPA) and their degree of saturation in thyroid and non-thyroidal illness (10), it appeared that the use of labeled L-thyroxine (T_4-I^{131}) instead of T_3-I^{131} in the resin uptake test might be of greater value by giving an indication of total availability of unbound, or the presumed biologically active, thyroxine. L-thyroxine is bound by both TBG and TBPA, whereas L-triiodothyronine is bound only by TBG (10). Consequently, alterations in the binding capacity of TBPA would not be expected to be reflected directly in the resin uptake of T_3-I^{131} (T_3-RU), except when available TBG binding sites are reduced by an increased thyroxine pool, as evidenced by a high PBI. If T_4-I^{131} were used in the resin uptake test (T_4-RU), alterations in the TBPA binding capacity should greatly influence the uptake in certain conditions. In hyperthyroidism the T_4-RU should yield better separation from normal than T_3-RU not only because of increased TBG and TBPA saturation (increased total thyroxine pool) but also by the decreased binding capacity of the latter (10, 11). In some conditions no difference between T_3-RU might be expected: (a) hypothyroidism with slightly increased binding capacity of TBG (10, 11) but decreased TBPA capacity (10, 11) and a reduced thyroxine pool; (b) pregnancy where TBG capacity is greatly increased (12). In chronic debilitated states (with TBPA binding reduction) (10) T_4-RU might not be as diagnostic as T_3-RU. Although the use of T_4-I^{131} in

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the resin uptake technique has been mentioned (5, 7, 13), no relative diagnostic improvement was noted compared to the use of T_3-I^{131} in contradistinction to the findings in this preliminary study.

MATERIALS AND METHODS

The clinical material consisted of patients on the medical services of the various hospitals of the Indiana University Medical Center and normal volunteers. In the group were 18 normal individuals, 10 hyperthyroid and 3 hypothyroid patients, 4 pregnant individuals and 5 patients with chronic debilitating illness. The diagnosis of thyroid disease was made on the basis of clinical findings, serum protein-bound iodine determination and thyroidal uptake of radioiodine. Serum was stored at −20° C. until used. A control serum pool (400 ml.) was prepared from samples obtained from 50 normal subjects; small aliquots were stored at −20° C. for subsequent use in each run and the preliminary studies for incubation time and temperature effects.

The procedure used was essentially that described by Mitchell, *et al* (3) with certain modifications noted below.[1] Preliminary studies indicated that equilibration was completed at about 120 minutes for both T_3-RU and T_4-RU. In a number of hyperthyroid and hypothyroid sera, the separation from normal appeared to be similar in varying the incubation time from 30-120 minutes. Varying the temperature from 21° C. to 36° C. for the 120 minute incubation showed a linear increase in resin uptake for both iodinated amino acids of about 1 per cent per degree. All subsequent runs were performed at room temperature (24-28° C.) corrected to 25° C. with a 120 minute incubation. All the above studies and determinations on 9 normal sera were performed in duplicate. Since in these studies a 2 percentage point mean difference in duplicate determinations for T_3-RU and 1.4 for T_4-RU were noted, in subsequent runs duplicate determinations were discontinued.

One ml. samples of serum were placed in duplicate plastic test tubes. One ml. T_3-I^{131}-buffer solution was added to one, while 1.0 ml. T_4-I^{131}-buffer solution was added to the other tube, followed in about 1 minute by the addition of the resin sponge to each tube. Following incubation the solution was drawn off the sponges and the sponges were washed 4 times with equal volumes of distilled water. The T_3-RU and the T_4-RU were calculated by dividing the residual activity (sponge radioactivity after washing) by the initial activity (radioactivity added) and multiplying by 100, followed by correction for incubation temperature. Control sera for T_3-RU and T_4-RU were processed simultaneously by the same method. The results were expressed as a percentage of control serum value

[1]The T_3-I^{131} in tris-maleate buffer solution, 0.1 M, pH 5.2, contained 0.10 to 0.12 μc and 0.0033 to 0.0051 μg. per ml., while the labeled thyroxine in identical buffer solution contained 0.10 to 0.13 μc and 0.0026 to 0.0064 μg per ml. On arrival concentrated human serum albumin was added to the isotope solutions to make a final concentration of 0.5%; the solution was stored at 10° C. The resin used was Amberlite CG-400 in the chloride cycle imbedded in a polyurethane sponge (Triosorb). The resin sponge specifications were essentially those previously published (3). The resin and labeled hormones were kindly supplied by Dr. Howard Glenn of Abbott Laboratories.

for the particular run. All radioactive counting was done in duplicate in a scintillation well counter for a sufficient period of time to keep the probable error below 1 per cent.

RESULTS

The average T_3-RU and T_4-RU on control serum for 7 different runs with 3 different shipments of T_3-I^{131} and T_4-I^{131} were 42 per cent and 12 per cent, respectively.

The results in the patient group and volunteers are shown in Figure 1. It

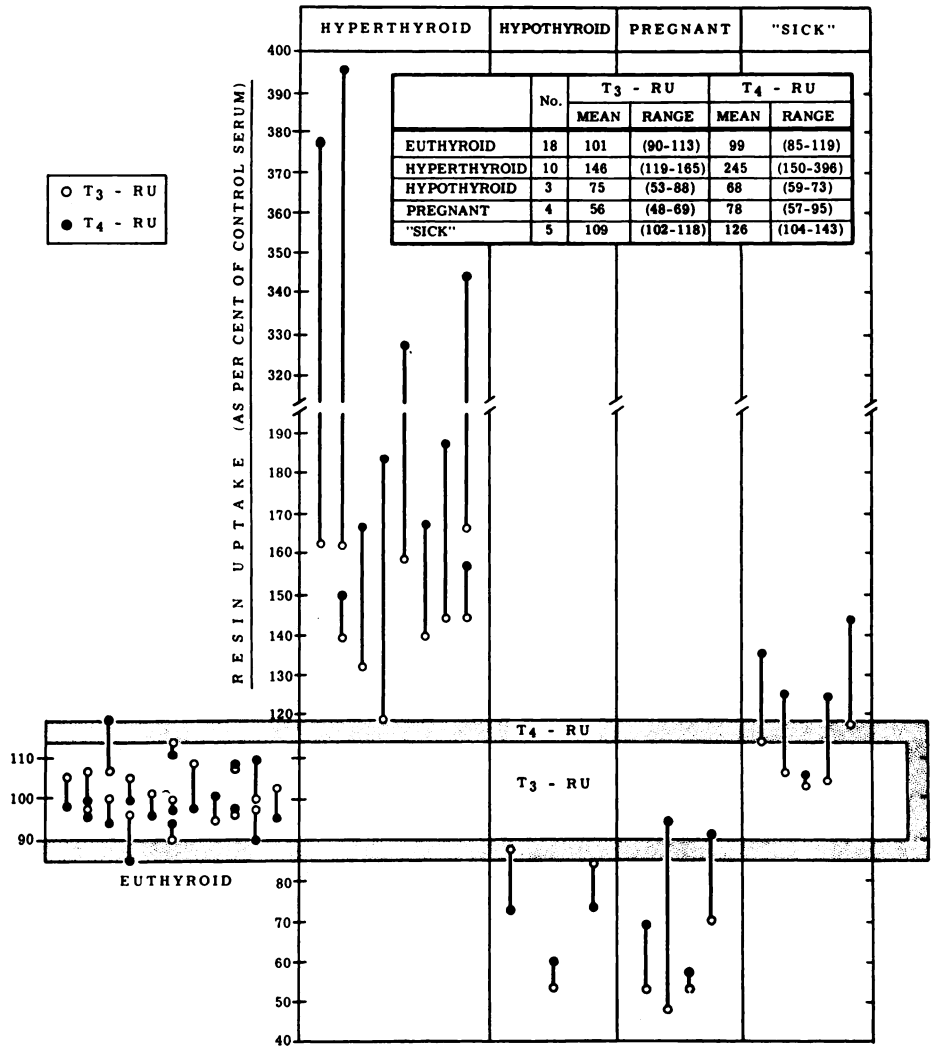

Fig. 1. Comparison of resin-sponge uptake of I^{131} labeled triiodothyronine and thyroxine in various conditions, expressed as percent of pooled control serum.

can be seen that the normal range for the T_3-RU was 90 to 113 per cent of normal control serum with a mean of 101 per cent, while that for the T_4-RU was 85 to 119 per cent with a mean of 99 per cent. The uptake values in the hyperthyroid group for both the T_3-RU and the T_4-RU showed no overlap with the normal group. The much higher results with a marked improvement in separation from normal with T_4-RU in the hyperthyroid group is readily apparent. Separation from the normal range was less definite in the small number of hypothyroid patients but the T_4-RU appeared to be more reduced than the T_3-RU.

The pregnant subjects all had low T_3-RU values, while the T_4-RU values on the same subjects were less strikingly decreased. The "sick" or chronically debilitated subjects showed a slight elevation of the T_4-RU values in four of the five subjects and of the T_3-RU values in two of the subjects. The findings in this group and in pregnancy appear to be as predicted above.

COMMENTS

The use of labeled thyroxine in the resin uptake test for diagnosis of thyroid disease has received little attention. T_4-RU studies, without concommitant comparison with T_3-RU, have been reported on sera of pregnant and non-pregnant women (2), and in thyroid disease (13), the latter at 3° C. incubation temperature. No relative differences in group discrimination from what had been obtained previously with T_3-RU using the sponge technique and room temperature were noted by the same authors (3). Brief comments on comparison of T_3-RU and T_4-RU have been made (5, 7); about equal discriminating ability with the two tests were reported. Possible sources for the previous failure of T_4-RU to yield relatively better diagnostic discrimination in thyroid disease, may be due to a combination of factors, such as lack of a stable resin preparation, suboptimal pH and temperature conditions, insufficient dilution of the binding carriers to accentuate the resin uptake, and failure to use control serum. More extensive studies in various conditions will be required to substantiate that the T_4-RU tests is superior to the currently used T_3-RU in the diagnosis of hyperthyroidism, and of equal value in other thyroid conditions. The concomitant performance of both tests in any given case may eventually result in a specific "Resin Profile" for various conditions. Simultaneous electrophoretic determinations of the thyroxine-serum protein carrier binding state are in progress to substantiate the basis for the various "Resin Profiles".

SUMMARY

The resin uptake of L-triiodothyronine-I^{131} (T_3-RU) and L-thyroxine-I^{131} (T_4-RU) were performed on 18 normal subjects and 22 patients with thyroid disease and non-thyroidal illness. In hyperthyroid subjects, the T_4-RU data are much higher than the T_3-RU data with marked improvement in the separation from normal. The T_4-RU is felt to be superior to the T_3-RU in the diagnosis of hyperthyroidism; its relative value in other conditions has yet to be established.

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