The optimal time interval to increase radioiodine uptake in a multinodular goiter is 24 hours after recombinant human thyrotropin administration

Fast S, Nielsen VE, Grupe P, Bonnema SJ, Hegedus L. Optimizing ^{131}I uptake after rhTSH Stimulation in patients with nontoxic multinodular goiter: evidence from a prospective, randomized, double-blind study. J Nucl Med 2009;50:732-7.

SUMMARY

BACKGROUND Recombinant human thyrotropin (TSH)-(rhTSH) has been undergoing study for the past several years for the preparation of radioiodine (^{131}I) treatment of patients with multinodular goiter, which has not yet been approved by the Food and Drug Administration for this indication. The aim of this study was to determine the optimal time interval between rhTSH administration and ^{131}I administration to enhance radioactive iodine uptake (RAIU).

METHODS This randomized, placebo-controlled, double-blind study was performed on patients referred for ^{131}I treatment of symptomatic multinodular goiter at the Nuclear Department of the Odense University Hospital in Odense, Denmark. Inclusion criteria were a multinodular goiter defined as a thyroid gland with two or more nodules larger than 1 cm determined by ultrasound. Patients routinely had a clinical evaluation, thyroid-function tests and neck ultrasound examination. Goiter volume was estimated by ultrasound except for large goiters that required magnetic resonance imaging (MRI) to estimate goiter volume with or without retroclavicular extension. Fine-needle aspiration biopsy was performed on scintigraphically dominant hypoactive nodules. The exclusion criteria were age younger than 18 years, women of childbearing potential not taking contraceptives, previous ^{131}I therapy, the use of levothyroxine or antithyroid drugs, a history of ischemic heart disease, fine-needle aspiration biopsy cytology that was inconclusive or suggestive of thyroid cancer, or multiple endocrine neoplasia, rapid goiter growth, firm nodules or fixation to adjacent structures, vocal-cord paralysis, regional lymphadenopathy, or an elevated serum calcitonin, urinary incontinence, alcohol or drug abuse, and physical or psychiatric disabilities.

The patients were randomly assigned to receive either a gluteal injection of 0.1 mg of rhTSH (n = 60) or an isotonic saline placebo (n = 30) given 24, 48, or 72 hours before the administration of a ^{131}I tracer, after which an RAIU test was performed at 24 and 96 hours. Four weeks later, RAIU testing was repeated 24 and 96 hours after the administration of rhTSH. Before screening and enrollment, blood tests were obtained for serum thyroxine (T_4), triiodothyronine (T_3), calcitonin, and thyrotropin (TSH). The serum free T_4 index and T_3 index were calculated by multiplying the total T_4 values by the percentage of T_3 resin uptake. Thyroidal RAIU was determined 24 and 96 hours after the oral administration of 24 mCi (0.5 MBq) of ^{131}I. Data were presented as frequencies and medians (range) or as means (±SD or ±SEM), depending on the normality of the data.

RESULTS The study subjects were 90 patients, 78 women (87%) and 12 men (13%), with a median age of 52 years (range, 22 to 83). All patients completed the study. There were no statistically significant differences in age, sex, smoking status, goiter size, number of patients who had undergone hemithyroidectomy, serum TSH, and FT_4 index or baseline RAIU.

The absolute changes in mean 24- hour RAIU: RAIU did not change significantly from baseline in the placebo group. In the study group, the mean (±SD) RAIU increased from 33.8±2.3% to 66.0±1.8% within a 24-hour interval, from 36.8±2.1% to 64.6±2.7% within a 48-hour interval, and from 33.0±2.7% to 49±2.5% within a 72-hour interval (P<0.001 for all within-group changes) (Figure 1). The effect of rhTSH was negatively correlated with the initial RAIU (r = –0.703, P<0.001).

The relative increase in 24-hour and 96 hour RAIU: In the

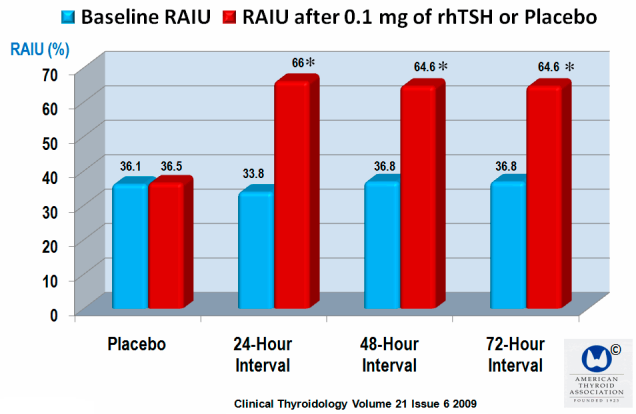

Figure 1. The radioactive iodine uptake (RAIU) did not change significantly from baseline in the placebo subgroups. All within-group changes in RAIU were highly significant as compared with baseline. *P<0.001.

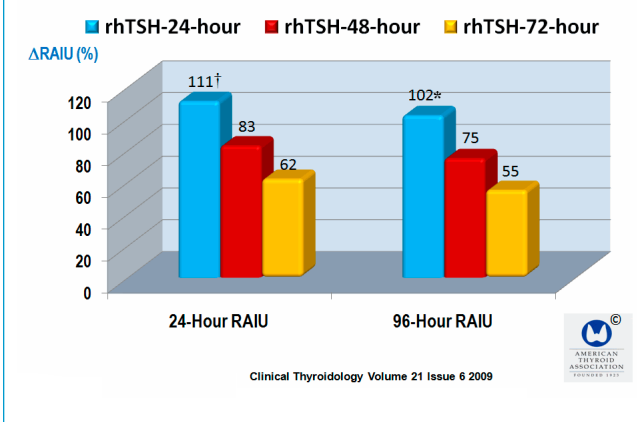

Figure 2. The increase in the 24-hour and 96-hour RAIUs was significantly higher in the rhTSH-24-hour group (*P = 0.023) than it was in the rhTSH-72-hour group (†P = 0.0012). ΔRAIU is the percent change in RAIU after rhTSH stimulation.

rhTSH-24-hour group, the mean (±SD) RAIU increased from 33.8±9.8% to 66.0±7.7% (mean relative increase, 111.2±15.5%) and the rhTSH-96-hour RAIU increased from 33.5±10.5% to 62.5%±9.3% (mean [±SEM] relative increase, 102.±13.9% [SEM]). In the rhTSH-48-hour group, the mean 24-hour RAIU increased from 36.8±9.3% to 64.6±12% (mean relative increase, 83.3±11.0%) and the rhTSH 96-hour RAIU increased from 37.5±9.8% to 63.7±13.6% (SEM) (mean [±SEM] relative increase, 74.9±8.7%). In the rhTSH-72-hour group, the mean 24-hour RAIU increased from 33.0±11.9 to 49.6±11.3% (mean elative RAIU increase 62.4±10.5%] and the 96-hour RAIU increased from 33.9±11% to 49±11.6% (mean [±SEM] relative increase, 55±10.3%; all changes in RAIU and rhTSH subgroups were significant (P<0.001) (Figure 2). There was a strong correlation between baseline 24-hour RAIU and the increase in 24-hour RAIU after rhTSH stimulation.

A post hoc analysis found that the mean relative increase in 24- and 96-hour RAIU in the rhTSH-24-hour group was significantly higher than the increase in the rhTSH-72-hour group (P = 0.023 and 0.012, respectively.

CONCLUSION In patients with MNG the optimal time interval to increase radioiodine uptake is 24 hours after rhTSH injection.

COMMENTARY

Administering rhTSH to prepare patients with multinodular goiter (MNG) for ^{131}I therapy is a significantly different clinical scenario than administering the drug to patients with thyroid cancer who have undergone total or near-total thyroidectomy. The problem, of course, is that rhTSH stimulates the release of thyroid hormones in patients with MNG. Only 0.1 mg of rhTSH was administered in this study by Fast et al. This small amount of rhTSH is required for patients with goiter being prepared for ^{131}I therapy.

In one of the earliest studies, Huysmans et al. (1) tested 15 patients with nontoxic goiter after being given 0.01 or 0.03 mg of rhTSH before a ^{131}I tracer of 20 to 40 mCi. After 0.01 mg, FT_4 increased from 16.0±2.6 to 18.5±3.7 pmol/L (P<0.0001) and T_3 increased from 2.10±0.41 to 2.63±0.66 nmol/L (P<0.0001). After 0.03 mg, FT_4 increased from 15.2±1.5 to 21.7±2.9 pmol/L (P<0.0001), and T_3 increased from 1.90±0.43 to 3.19±0.61 nmol/L (P<0.0001). FT_4 and T_3 levels peaked 8 to 96 hours after rhTSH injection. Administering 0.01 mg 2 hours before ^{131}I increased the 24-hour RAIU from 30±11% to 42±10% (P<0.02), and administering the same dose of ^{131}I mg 24 hours before ^{131}I, the 24-hour RAIU increased from 29±10 to 51±10% (P<0.0001). Administering 0.03 mg of rhTSH 24 hours before ^{131}I increased 24-h RAIU from 33±11% to 63±9% (P<0.0001), and after giving 0.01 mg of rhTSH 2 hours before ^{131}I, the 24-hour RAIU did not increase in 1 patient, and increased to less than 10% in 2 other patients. However, administering rhTSH 24 hours before ^{131}I increased 24-hour RAIU by more than 10% in all 14 patients, increasing to >20% in 10 and >30% in 6 patients.

In subsequent studies (1-6), differing amounts of rhTSH were administered to patients with MNGs, raising the question about whether different doses of rhTSH might have a major effect on outcome. A study by Nieuwlaat et al. (4) that compared the use of 0.01 mg with 0.03 mg of rhTSH in patients with MNG found an 87% increase in mean RAIU using 0.01 mg, as compared with a significantly higher rate of 145% when 0.03 mg was administered. Still, other studies find no differences between the two doses (7). For example, an open label study by Braverman and Kloos (5) designed to assess the safety, adverse effects, and RAIU in response to rhTSH tested 0.03, 0.1 mg, and 0.3 mg doses in 29 patients with small nodular goiter. After evaluating the patients at 6, 24 and 48 hours, that RAIU doubled at each time point as compared with baseline uptake. Small increases in serum thyroxine and triiodothyronine occurred in some patients, along with mild symptoms of hyperthyroidism in a few patients, especially after 0.3 mg. There was a flat dose–response curve over the range of rhTSH doses tested, each of which approximately doubled thyroidal RAIU.

The study by Fast et al. clearly demonstrates that the effect of rhTSH on thyroidal RAIU is time-dependent, with a steady decline over time. However, the authors suggest that the lack of a statistically significant difference between the effects observed in the 24-hour and 48-hour subgroups are likely due to the lack of study power. The finding of a negative correlation between the increase in 24-hour RAIU and the baseline serum TSH concentration is a novel and potentially clinically important finding. The findings of this study clearly indicate that the optimal time interval that maximally increases ^{131}I therapy is 24 hours after the administration of rhTSH. However, the authors nonetheless caution that whether this time interval is optimal for goiter reduction is yet to be established.

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