BRIEF REPORT

Serum Thyrotropin (TSH) Levels after Recombinant Human TSH Injections in Children and Teenagers with Papillary Thyroid Cancer

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Context: In preparation for whole body radioactive iodine scanning, recombinant human TSH (rhTSH) is usually administered as 0.9-mg im injections on 2 consecutive days without regard to age, body size, or other comorbid conditions.

Objective: Our objective was to determine whether the usual adult rhTSH dosing regimen would result in excessive elevations of serum TSH in children and teenagers with thyroid cancer.

Design/Setting/Patients/Interventions: A retrospective review identified 53 children and teenagers with thyroid cancer who underwent whole body radioactive iodine (RAI) scanning over a 12-yr period at two major medical centers (34 after thyroid hormone withdrawal). Peak TSH levels were correlated with age, serum TSH after rhTSH administration and/or hypothyroid withdrawal was examined. Peak TSH levels were correlated with age, weight, and body surface area.

Results: The mean serum TSH at the time of RAI administration was similar in patients undergoing hypothyroid preparation (138 ± 118 mIU/liter; range, 110–452 mIU/liter) and those treated with rhTSH (134 ± 75 mIU/liter; range, 32–290 mIU/liter; P = 0.07). Serial determinations after rhTSH injections revealed a mean serum TSH of 268 ± 76 mIU/liter (range, 87–628) at 6 h and 130 ± 58 mIU/liter (range, 67–250) at 24 h after the initial injection, and 361 ± 78 mIU/liter (range 161–524) at 6 h and 134 ± 44 mIU/liter (range, 32–290) at 24 h after the second injection.

Conclusions: The mean TSH levels achieved in children after rhTSH injections are remarkably similar to values previously reported in adults despite marked differences in clinical characteristics between children and adults. These data suggest that dose adjustments are not generally required in children and teenagers undergoing rhTSH stimulation for RAI scanning or serum-stimulated thyroglobulin determinations. (J Clin Endocrinol Metab 90: 6553–6555, 2005)

IN NOVEMBER 1998, the U.S. Food and Drug Administration issued approval for the use of recombinant human TSH (rhTSH; Thyrogen, Genzyme Corp., Cambridge, MA) as an adjunctive diagnostic tool for serum thyroglobulin testing with or without radioactive iodine imaging in the follow-up of well-differentiated thyroid cancer.

The standard dose of rhTSH can be administered either as two 0.9-mg injections 24 h apart or three 0.9-mg injections at 72-h intervals (1). In healthy volunteers, pharmacokinetic studies after a single im 0.9-mg injection of rhTSH demonstrate a peak serum TSH of approximately 280 mIU/liter within 6–8 h of injection, which then falls to approximately 140 mIU/liter at 24 h and 25 mIU/liter at 48 h after rhTSH administration (2). Serious adverse effects after rhTSH were uncommon, but nausea and headache were seen more frequently with the highest rhTSH doses tested in the initial phase I/II trial of healthy adult volunteers (3).

In general, this standard dosing regimen is routinely used regardless of age, gender, size of the patient, or other comorbid conditions. A recent study by Vitale et al. (4) demonstrated a significant influence of body surface area on peak serum TSH levels after two consecutive daily injections of 0.9 mg rhTSH. In multivariate analysis, body surface area (BSA) was negatively correlated with peak TSH levels. The lowest peak TSH of 22 mIU/liter was documented in the patient with the highest BSA (120 kg, female, with a body mass index (BMI), 41.5 kg/m²; BSA, 2.44 m²), whereas the two highest peak TSH values (~260 and ~280 mIU/liter) were seen in two of the three children included in this study (age, 10 and 11 yr; BMI, 22.3 and 22.5 kg/m², respectively; BSA, 1.23 and 1.32 m², respectively). These observations suggest that alterations in dosing may be necessary in patients with either a very low or a very high BSA.

Over the last several years, an extensive body of literature has documented the safety and clinical efficacy of rhTSH in the follow-up of adults with thyroid cancer (5, 6). Because of this track record of safety in adults, we began to offer rhTSH preparations for radioactive iodine (RAI) scanning and thyroglobulin stimulation initially to teenagers, and then to younger children with thyroid cancer. As with our previous studies (7, 8), rhTSH was used with the full consent of the patients and their parents in a clinical setting, with the ex-
pectation of clinical benefit and to avoid the clinical symp-
toms of hypothyroidism.

In this manuscript we retrospectively review our clinical
experience in children and teenagers undergoing diagnostic
RAI whole body scanning over the last several years, with
particular emphasis on serum TSH levels at the time of testing
after either hypothyroid withdrawal or rhTSH stimulation.

**Subjects and Methods**

Clinical records were retrospectively reviewed to identify children
and teenagers less than or equal to 18 yr of age undergoing routine
diagnostic whole body RAI scanning at two medical centers between

BSA (square meters) was calculated using the following formula:

\[ \text{BSA} = 0.20247 \times \text{height (m)}^{0.725} \times \text{weight (kg)}^{0.425} \]

BMI was calculated using the following formula:

\[ \text{BMI} = \text{weight (kg)} / \text{height (m)}^2 \]

Patients pretreated with rhTSH (Thyrogen, Genzyme Corp.) received
0.9 mg im, into the gluteus maximus on 2 consecutive days according
to the standard adult regimen.

In each patient prepared with traditional hypothyroid withdrawal
(discontinuation of levothyroxine for 3–6 wk before diagnostic
scanning), serum TSH was available at the time of administration of the
diagnostic dose of RAI. Because most patients undergoing rhTSH stim-
ulation were having full dosimetry studies, blood samples were avail-
able just before the initial 0.9-mg rhTSH injection and 6, 10, 24, 30, and
48 h after the initial rhTSH injection. Because this was a retrospective
study, not all patients had sampling performed at all time points.

The serum TSH levels were measured using a variety of assays over the
last 10 yr, with normal reference ranges that have generally ranged from
0.5–5 mIU/liter. No attempt was made to correct for minor differ-
ences in TSH assays either within institution or between institutions.
The data are presented as the TSH value clinically reported in the
patient’s record.

Data are analyzed based on the TSH level at the time of RAI admin-
istration and on the peak TSH level achieved before RAI administration.
In the hypothyroid withdrawal group, the peak TSH was the TSH level at
the time of RAI administration. All data are presented as the mean ±
se, with medians and ranges given as appropriate. ANOVA was used
to analyze mean values between multiple groups. \( P < 0.05 \) was con-
sidered significant. Associations between individual BSA and peak TSH
and TSH levels at the time of RAI administration were analyzed by
correlation analysis.

**Results**

A total of 53 children and teenagers underwent routine
RAI diagnostic scanning as part of their follow-up for thyroid
cancer at our institutions over a 12-yr period (1990–2002). All
patients included in this analysis had previously undergone
total thyroidectomy and radioactive iodine remnant ablation
for papillary thyroid cancer.

The majority of the patients (n = 34) underwent traditional
thyroid hormone withdrawal; 19 patients received rhTSH
injections in preparation for RAI scanning. With regard to the
patients seen at each institution, 23 of the patients were seen
at the Hospital de Pediatría, Buenos Aires (including 12
patients prepared with rhTSH with an age range of 9–18 yr,
and 11 patients prepared with thyroid hormone withdrawal
with an age range of 4.6–15 yr). Thirty of the patients were
evaluated at Memorial Hospital, New York (including seven
patients prepared with rhTSH with a mean age of 15–18 yr,
and 23 patients prepared with thyroid hormone withdrawal
with a mean age of 6–18 yr). A summary of the clinical
characteristics of these patients is given in Table 1.

The mean serum TSH levels after two 0.9-mg rhTSH injec-
tions were 268 ± 76 mU/liter (range, 87–628) 6 h and 130 ± 58
mU/liter (range, 67–250) 24 h after the initial injection and 361 ±
78 mU/liter (range, 161–524) at 6 h, and 134 ± 44 mU/liter
(range, 32–290) 24 h after the second injection (see Fig. 1, left
panel). As shown in Fig. 1, the initial 24-h serum TSH values
were very similar to values previously reported by Torres et al.
in a cohort of six normal adults (2).

The mean serum TSH level at the time of RAI adminis-
tration appeared to be slightly higher in patients undergoing
hypothyroid preparation (188 ± 118 mU/liter; range, 110–
452 mU/liter) than in those prepared with rhTSH (134 ± 75
mU/liter; range, 32–290 mU/liter), although this difference
did not reach statistical significance (\( P = 0.07 \)).

Because our cohort included a wide range of ages, rhTSH-
stimulated patients were divided into three groups, based on
age at the time of diagnostic scanning, to compare children
less than 13 yr of age with young teenagers (13–15 yr old,
inclusive) and older teenagers (>15–18 yr old, inclusive).
No significant differences were seen in the mean serum TSH
levels at the time of RAI administration after two consecutive
rhTSH injections in children (187 ± 107 mU/liter), young
teenagers (88 ± 71 mU/liter), and older teenagers (130 ± 76
mU/liter). Likewise the serum TSH values over time after
rhTSH injections were quite similar among the three groups,
although the younger children tended to have higher peak
TSH values after each injection than the older teens, and this
difference did not reach statistical significance (see Fig. 1,
right panel).

A comparison of either peak serum TSH or TSH at the time of
RAI administration with BSA, weight, or age failed to
demonstrate any significant correlation in patients stimu-
lated with rhTSH.

No significant adverse side effects were reported in the
patients undergoing rhTSH stimulation. As would be ex-
pected, chart review did reveal mild nausea and headaches in
a few of the patients. In no case did the nausea or headache
require treatment or admission to the hospital. Although
RAI-avid pulmonary metastasis were present in 25% of the
patients, and one patient had an RAI-avid skull metastasis,
one experienced pain or swelling sufficient to result in
pulmonary compromise or neurovascular compromise.

**Discussion**

Contrary to what we expected, the serum TSH profile after
two consecutive daily doses of 0.9 mg in children and teen-
agers was very similar to that previously reported in studies
of normal adults, as shown in Fig. 1 (2, 3). Furthermore, the

<table>
<thead>
<tr>
<th>Gender</th>
<th>BSA (m²)</th>
<th>rhTSH</th>
<th>Thyroid hormone withdrawal</th>
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<tr>
<td>Female</td>
<td>15</td>
<td>1.55 ± 0.2</td>
<td>1.24 ± 0.3</td>
</tr>
<tr>
<td>Male</td>
<td>4</td>
<td>0.8–1.9</td>
<td>0.7–1.7</td>
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TABLE 1. Clinical characteristics of patients

<table>
<thead>
<tr>
<th>n</th>
<th>Age (yr)</th>
<th>rhTSH</th>
<th>Thyroid hormone withdrawal</th>
</tr>
</thead>
<tbody>
<tr>
<td>19</td>
<td>Mean 13.6 ± 3.4</td>
<td>13.6 ± 3.7</td>
<td></td>
</tr>
<tr>
<td>34</td>
<td>Median 13</td>
<td>14</td>
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<tr>
<td></td>
<td>Range 7–18</td>
<td>4.6–18</td>
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<tr>
<td></td>
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<td>Female</td>
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<td>Male</td>
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Fig. 1. In the left panel, serum TSH levels after 0.9-mg rhTSH im injections on 2 consecutive days in children and teenagers with thyroid cancer compared with serum TSH values measured after a single 0.9-mg im injection of rhTSH in six healthy adult volunteers in the study by Torres et al. (2). Despite significant differences in age and body size between children and adults, the serum TSH curves show remarkable overlap in the first 24 h after rhTSH administration. In the right panel, serum TSH levels after rhTSH administration (0.9 mg, im, on 2 consecutive days) analyzed by age of the patient at the time of injection. Children refers to patients less than 13 yr of age, early teenagers were 13–15 yr old (inclusive), and late teenagers were more than 15–18 yr old (inclusive). Although there is a trend toward higher peak serum TSH levels in the youngest children, these differences did not reach statistical significance (by ANOVA).

TSH level at the time of RAI administration in this cohort of children and teenagers (mean TSH, 134 ± 75 mIU/liter) was very similar to that previously reported by Robbins et al. (9) in 45 adults with thyroid cancer (mean TSH, 105 ± 43 mIU/liter), and by Haugen et al. (1) in 117 adults with thyroid cancer (mean TSH, 124 ± 59 mIU/liter). These data would suggest that dose alterations may not be necessary when rhTSH is used in children and teenagers with thyroid cancer.

In our cohort of children and teenagers, no correlation was detected among BSA, the age of the patient, and either the peak TSH or the TSH level at the time of RAI administration. As in the study of Vitale et al. (4), the peak TSH levels in children in our cohort also was in the 250–260 mIU/liter range. The BSA values for most patients in our cohort were normal to low, making it impossible to directly compare peak TSH values with those seen in the largest patients in the Vitale study (4).

Fortunately, rhTSH was very well tolerated by all of the patients, with only minimal nausea and occasional headaches as would be expected in a typical adult thyroid cancer cohort. There were no serious or unexpected side effects.

It should be noted that this manuscript does not address the sensitivity or specificity for disease detection in these children. Although there is no reason to suspect that rhTSH would not be a useful adjunct to disease detection in children with thyroid cancer, additional studies are needed to verify the clinical utility of rhTSH for the detection of recurrent disease in children with thyroid cancer.

In summary, our data demonstrate that rhTSH can be safely administered to children and teenagers without significant unexpected side effects. Furthermore, the serum TSH pharmacokinetic profiles after two consecutive daily doses of 0.9 mg rhTSH are very similar in adults and children, making dose adjustments unnecessary in all but the very youngest children.

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