rhTSH Stimulation Before Radioiodine Therapy in Thyroid Cancer Reduces the Effective Half-Life of ^{131}I

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Recombinant human thyroid-stimulating hormone (rhTSH) is effectively used for exogenous thyroid-stimulating hormone (TSH) stimulation before diagnostic ^{131}I scintigraphy. It is not yet widely used for preparation of patients receiving a therapeutic amount of radioiodine. **Methods:** The results of 64 consecutive therapeutic applications of rhTSH with regard to clinical tolerance and side effects were evaluated in comparison with 163 radioiodine therapies (RITs) done on patients with hypothyroidism after thyroxine withdrawal during the same period. All therapies—applying 1.1–10 GBq of ^{131}I—used a standardized protocol of patient preparation and activity application. RITs were followed by daily whole-body uptake measurements for 2–6 d, and a biexponential curve fit was used to obtain a short initial and afterward a long effective half-life of ^{131}I. Patients after rhTSH were evaluated as a whole group (group A, $n = 64$) and as a subset of that group with normal thyroglobulin (hTG) levels (group D, $n = 18$). Patients after endogenous TSH stimulation were evaluated as a whole group (group B, $n = 163$), as a subset of that group excluding all ablative RITs (group C, $n = 113$), and as a subset of that subset with normal hTG levels (group E, $n = 87$). **Results:** rhTSH-stimulated patients showed significantly higher TSH values than did endogenously stimulated patients ($P < 0.001$). Furthermore, the effective half-life of ^{131}I was significantly prolonged after endogenous stimulation (e.g., 0.43 d for group A vs. 0. 54 d for group B, $P < 0.001$). All rhTSH applications were tolerated well and without serious side effects. The only side effects were 2 cases of nausea and headache. **Conclusion:** The use of rhTSH for stimulation of TSH before RIT is safe but also significantly reduces the effective half-life of ^{131}I. This is mainly due to a reduced renal iodine clearance in the hypothyroid state, but the bioavailability of radioiodine may be slightly overestimated because of larger amounts of intestinal ^{131}I after endogenous TSH stimulation.

Key Words: thyroid cancer; rhTSH; radioiodine; effective half-life

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Because recombinant human thyroid-stimulating hormone (rhTSH) is readily available, it is increasingly used for the exogenous stimulation of thyroid-stimulating hormone (TSH) incretion in the follow-up of differentiated thyroid cancer (DTC) (*1*,*2*). TSH-stimulated measurements of thyroglobulin (hTG) synthesis serve as a cornerstone for the exclusion of DTC remnants or recidives. Alone or in conjunction with whole-body scintigraphy (WBS) after administration of diagnostic activities of ^{131}I, this approach has been used after endogenous TSH stimulation achieved by withdrawal of thyroxine substitution for several weeks.

Because these investigations are needed frequently during the follow-up of DTC, rhTSH spares the patient the drawbacks of being in a hypothyroid state and thus not only avoids personal discomfort but also significantly reduces the time frame in which the patient will not be able to work or maneuver dangerous or sophisticated equipment. Moreover, patients who, clinically or because of other disease, would not tolerate a hypothyroid phase well can now be investigated more easily.

The potential acceleration of tumor growth under long-term TSH stimulation is a problem that has recently been underlined by the finding of rhTSH-induced, and thus TSH-dependently increased, ^{18}F-FDG uptake in DTC (*3*). A change in renal iodine clearance is also of critical importance. These problems, however, are of greater influence during the therapeutic phase of DTC. Little is known about the feasibility of rhTSH for the treatment of DTC. In 1 study, Berg et al. showed rhTSH to be effective in 11 patients with DTC unable to undergo thyroxine withdrawal (*4*). Also, it is known that hypothyroidism may prolong the bioavailability of iodine or radioiodine because of reduced renal clearance (*5*,*6*). This, in turn, leads to decreased uptake in thyroid remnants and possibly also in tumors in the case of rhTSH stimulation. We retrospectively evaluated 64 radioiodine therapies (RITs) after application of rhTSH versus 163 RITs after endogenous stimulation with special emphasis on the whole-body effective half-life of radioiodine in our patients.

RITs were given according to standardized activities being used according to the clinical situation. Normally, 1.1–3.7 GBq of ^{131}I were given orally for the initial ablation after thyroidectomy, followed by 1 or 2 further RITs with 3.7 GBq of ^{131}I in patients without evidence of further tumor growth. Patients with residual or metastatic disease were treated with activities up to almost 10 GBq ^{131}I.

MATERIALS AND METHODS

The last 265 consecutive RITs administered in our institution were retrospectively evaluated. RITs used standardized activities ranging from 1.1 to almost 10 GBq of ^{131}I adapted to the clinical situation of the patients. ^{131}I was given orally to the patients, who did not eat for at least 6 h beforehand and 2 h afterward. Thirty-eight RITs were excluded because of incomplete data or because of the exclusion criteria (elevated creatinine or hTG antibodies).

Of the remaining 227 RITs, 163 in 103 patients were done after endogenous TSH stimulation and 64 in 38 patients were done after exogenous stimulation using rhTSH. Endogenous stimulation consistently comprised complete thyroxine withdrawal for 4 wk before the intended RIT. For the first 2 wk, 40 μg of triiodothyronine were given for compensation, but 2 wk before RIT this medication was withdrawn as well. rhTSH was stimulated through 2 consecutive intramuscular 0.9-mg doses of rhTSH (Thyrogen; Genzyme Corp.) and application of the radioiodine on day 3. Human hTG was measured on the day of radioiodine administration in patients who had undergone endogenous stimulation and on day 5 in patients who had received rhTSH. For all hTG measurements, an immunoradiometric assay (DYNOtest; Brahms) that included a recovery test was used. The analytic sensitivity of this test is 0.05 ng/mL, and the functional assay sensitivity (20% interassay variation coefficient) is 0.3 ng/mL.

rhTSH was not used for ablative RIT of a thyroid remnant. In the other cases, a decision was made as to the compassionate use of rhTSH or endogenous stimulation according to the clinical situation of the patient. Patients with metastatic disease were pretreated with rhTSH if tumor progression under long-term TSH stimulation was feared. Other patients who would not tolerate endogenous stimulation, such as those who had severe secondary diseases or whose treatment had additional diagnostic aspects, also underwent rhTSH-stimulated RIT.

The patients were divided into 5 groups. Group A was the complete group of patients undergoing rhTSH-stimulated RIT, group B was the whole group of patients receiving RIT after thyroxine withdrawal, and group C was a subset of this group excluding all first ablative RITs. Group D consisted of patients with rhTSH stimulation but normal values of hTG (less than 2 ng/mL), and the same held true for group E, with the difference of endogenous TSH stimulation. Details of the patients in each group are shown in Table 1. In group A, 59% of the tumors were papillary, 21% were follicular, 10% were Hürthle cell, and 8% were insular DTC (2% were of unknown histopathology). Of the 163 RITs performed on group B, 72% were for papillary tumors, 24% were for follicular tumors, and 2% each were for insular and Hürthle cell carcinomas. Regarding the size of the primary tumors in group A, 8% were Tx, 11% were T1, 29% were T2, 6% were T3, and 46% were T4. These percentages compare with 10% Tx, 25% T1, 34% T2, 4% T3, and 27% T4 in group B. No evidence of DTC on the posttherapeutic WBS was found for 25% of group A; a local recidive was found for 6%; lymph node metastasis, for 26%; bone metastases, for 11%; parenchymal (lungs, liver) metastases, for 8%; and multifocal tumor, for 24%. These percentages compare with the 78% of group B for whom a widely normal WBS was found (which included all RITs done for the ablation of thyroid remnants), the 2% for whom a local recidive of DTC was found, the 11% for whom lymph node metastases were found, the 1% for whom bone tumors were found, the 5% for whom parenchymal tumors were found, and the 3% for whom multifocal tumor growth was found. Overall, the patients in group A thus showed a trend toward more aggressive tumor types and more advanced tumor stages than did the patients in group B.

With a calibrated sodium iodide multichannel analyzer probe (Westmeier Corp.), the remaining activity within the whole body was measured daily for at least 2 d and up to 6 d, and a standardized factor of 2 was used for compensation of intracorporal attenuation. Whole-body uptake was measured with operation of the probe in lifetime mode for compensation of dead time. A standardized distance of 3.5 m was maintained between the patients and the probe. From the data obtained, a biexponential curve-fit was used and a short and long effective half-life, in days, was calculated. TSH values and short effective half-lives for endogenous and exogenous stimulation were tested for the whole collectives and their subgroups with normal tumor marker hTG using the unpaired *t* test.

RESULTS

Age and sex did not markedly differ between the subgroups (Table 1). Reflecting the larger number of patients with advanced DTC, group A on average was treated with higher radioiodine activities than was group B (mean, 4.9

TABLE 1
Characteristics of Patient Groups

Characteristic	Group A	B	C	D	E
No. of RITs	64	163	113	18	87
Sex (M:F)	27:37	48:115	33:80	6:12	25:62
Age (y)	57	50	52	53	48
Weight (kg)	72	76	76	74	74
Height (cm)	169	168	168	169	167
Body surface (m^2)	1.84	1.87	1.88	1.86	1.84
Body mass index	25	26	27	26	26

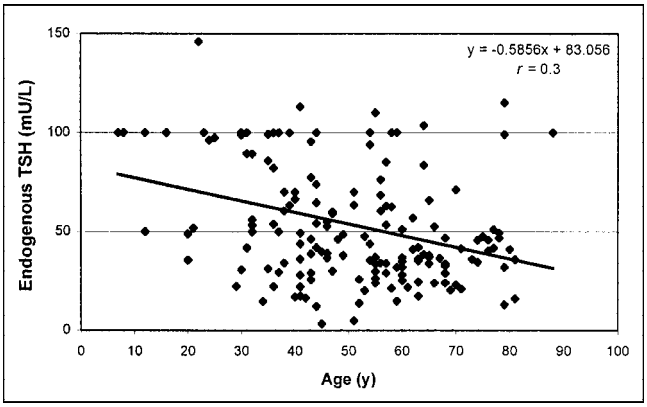

FIGURE 1. Age dependency of endogenous TSH incretion.

GBq vs. 3.1 GBq). The use of rhTSH was tolerated well by all our patients, with only 2 experiencing minor side effects. Both patients complained of nausea and headache on the second day of rhTSH application. Neither needed symptomatic treatment.

Figure 1 shows that there was a slight trend toward less extensive TSH stimulation after thyroid hormone withdrawal in elderly patients. TSH stimulation after rhTSH, in contrast, was not related to age and was significantly higher than after endogenous stimulation (unpaired *t* test for groups A or D vs. B, C, or E, respectively; $P < 0.001$). All patients received the stimulus under TSH-suppressive doses of thyroxine. The mean TSH after rhTSH was 90 mU/L, and the lowest increase was found at a TSH of 33 mU/L (Fig. 2). As also demonstrated in Figure 2, the hTG levels did differ significantly between groups A and B, consequent to a major criterion used to select candidates eligible for rhTSH therapy—namely, metastatic tumor growth.

Although there was considerable overlap between the groups, the mean effective half-life of the radioiodine was 0.43 ± 0.11 d for patients after rhTSH stimulation (group A). For patients after endogenous TSH stimulation (group B), the mean effective half-life was 0.54 ± 0.11 d. The results were different on a highly significant level ($P < 0.001$, unpaired *t* test). To evaluate the influence of thyroid remnants or metastases, 3 additional subgroups were evaluated. When the evaluation included only those patients who presented with a normal hTG value under TSH stimulation ($n = 18$, group D), the mean effective half-life after rhTSH was 0.45 d (± 0.11 d). This value compares with a mean effective half-life of 0.54 d (± 0.14 d) for the 87 patients who fulfilled the criteria of a normal hTG level and at least 1 prior RIT (group E). The difference remained significant ($P < 0.05$, unpaired *t* test). As also demonstrated in Figure 3, the longer half-life for the patients who underwent endogenous stimulation was not due to remaining thyroid remnants (group C vs. E).

DISCUSSION

rhTSH was used to induce TSH stimulation followed by RIT in patients who were known, or suspected, not to tolerate endogenous TSH stimulation. Compared with other patients, more of these patients had a more severe tumor burden. There were also patients treated with rhTSH who could not tolerate long-term endogenous TSH stimulation for other causes. The rhTSH was tolerated well by all our patients, and no serious side effects occurred. Only 2 patients complained of nausea and headache after administration of the substance, and neither needed treatment.

Physiologic iodine clearance is significantly influenced by thyroid and kidney function. Because all patients underwent thyroidectomy, there remain only small thyroid remnants, tumor recurrences, and metastases to influence iodine clearance apart from renal function. Hypothyroidism is known to change the renal and enteral clearance of iodine. To measure the degree to which endogenous versus exogenous TSH stimulation would change the clearance, we obtained the effective half-life of the therapeutic ^{131}I and found it to be significantly lower after exogenous TSH stimulation both in the main groups A and B and in the subgroups without relevant thyroid remnants or tumor tissue (groups D and E).

Earlier studies on the kinetics of radioiodine have referred mainly to intravenously administered test activities of iodine isotopes. Because the intestinal absorption of iodine

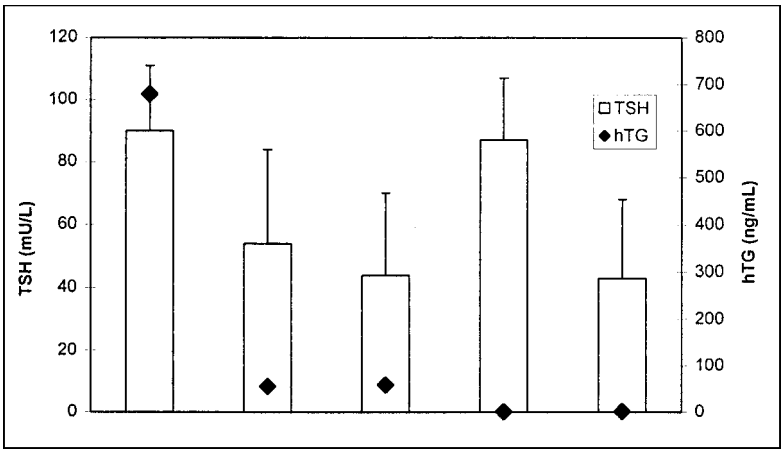

FIGURE 2. Comparative evaluation of mean TSH values (plus 1 SD) for different groups with and without rhTSH stimulation and corresponding mean hTG levels. From left to right, bars represent groups A, B, C, D, and E.

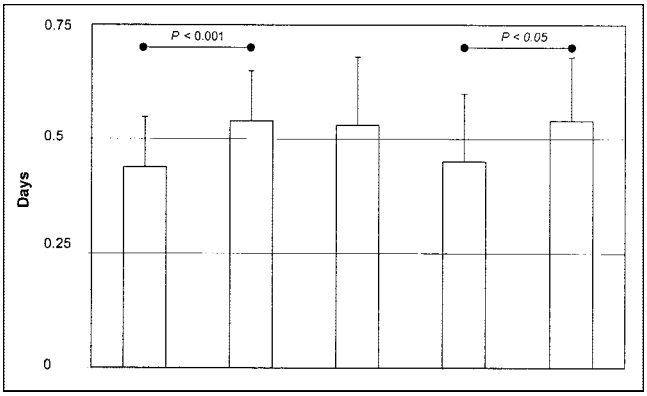

FIGURE 3. Effective half-life of therapeutic activities of radioiodine in patients after rhTSH stimulation (groups A and D) and after endogenous TSH stimulation (groups B, C, and E). From left to right, bars represent groups A, B, C, D, and E.

is rapid and nearly complete, one can assume that the conclusions of these data are also applicable to a model using oral administration of radioiodine. The International Commission on Radiological Protection (ICRP) has published data on ^{131}I showing it to have a biologic half-life of 0.3 d for patients with blocked thyroid uptake and excluding activity within the bladder (*7*).

Data on the effective half-life as presented in this study show a slightly prolonged mean half-life of 0.43 d (group A) for those patients after rhTSH stimulation who can be considered comparable to the ICRP collective. Uptake within residual or metastatic tissue could be a reason for this difference but does not seem to be of major influence since the mean effective half-life in subgroup D was even longer (0.45 d). Apart from clinical causes, this difference may be attributed to the technique of uptake measurement and, here, to the inclusion of activity within the bladder and to the rather robust application of a standard factor of 2 for attenuation correction to all acquired data. However, as this factor does influence all acquired data equally, the bladder activity remains a potential source for the differences found. Still, a highly significant difference toward prolongation of the effective half-life of radioiodine in patients with endogenous TSH stimulation can be noted. The prolongation ranged from a 20% to a 25% increase in effective half-life for the studied patients. This is less than what was reported for other studies, which found that a prolongation of approximately 50% was associated with a higher tumor uptake (*6*). In contrast, the current data were obtained under therapy conditions and in a relatively large group of patients. The basic findings, however, are the same regardless of the diagnostic or therapeutic use of radioiodine. If the amount of activity per dose is individually estimated pretherapeutically, then the dose may be adjusted for the shorter effective half-life if the use of rhTSH is intended. A drawback of our study is that we could not provide some direct insight into the efficacy of rhTSH-stimulated RIT. Because we did not do a dosimetry of tumor lesions in rhTSH-stimulated patients versus endogenously stimulated patients, only the long-term hTG could be used to follow the efficacy of RIT. For this purpose, however, our 2 main study groups were too heavily influenced by our selection modus, as the rhTSH stimulation was justified mainly by aggressive tumor growth or metastatic disease. A post-therapeutic increase of hTG would therefore not necessarily represent an RIT failure.

Another question is whether the longer effective half-life in hypothyroidism does in fact represent biologically available radioiodine. Even though intraindividual comparisons of larger groups of patients are difficult to obtain, we believed that post-therapeutic whole-body scintigrams after rhTSH showed better contrast between the tumor or thyroid remnant and the background, at least in part because of a higher fraction of ^{131}I in the large bowels in patients with endogenous stimulation. This issue, however, warrants further evaluation.

CONCLUSION

Because there were no relevant side effects, the use of rhTSH can be expected to be feasible and safe for therapeutic purposes in the setting of RIT. This finding confirms the results of earlier studies on a limited number of patients (*4,8–10*). Under therapy conditions, a significantly shorter effective half-life of ^{131}I can be expected after exogenous stimulation with rhTSH, compared with hypothyroidism after hormone withdrawal.

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