SUMMARY

Objective: The authors report in a large series the use of radio-probe-guided surgery (RGS) in non radioiodine-avid, well-differentiated thyroid cancer (DTC).

Design: Thirty-seven patients with loco-regional recurrent, non radioiodine-avid DTC were studied with $^{99m}$Tc-sestamibi directed RGS using a handheld gamma probe as an intra-operative detector.

Outcome: Twenty-three women and 14 men were followed after RGS for 35.4 ± 12.5 months (range 9-57). There were 33 papillary (one “tall” cell variant), 2 follicular, and 2 Hürthle cell cancers. In 7 patients, thyroid cancer recurred in the neck while cervical lymph node metastases were found in 31 patients (one patient had papillary cancer both in the thyroid bed and cervical lymph nodes). Sixty-six discrete nodules ranging from 6 to 45 mm (mean tumor diameter: 18.4 ± 8.5 mm) were identified by both high-resolution ultrasound and $^{99m}$Tc-sestamibi probe guided RGS. After RGS, Tg (thyroglobulin) fell in 33 of 37 patients and mean target/non target sestamibi uptake ratios decreased in all 37 patients ($P < 0.0001$).

Conclusion: These data confirm the earlier observations by the same group of authors that a $^{99m}$Tc-sestamibi intra-operative gamma probe can be used to identify and guide resection of recurrent tumor and involved lymph nodes in loco-regional metastases of non radioiodine-avid thyroid cancer.

COMMENT

The ability of differentiated thyroid cancer (DTC) to concentrate radioiodine can be lost in as much as 30-40% of cases (especially in older patients, as well as in more aggressive and less well differentiated types of carcinomas), for instance after the repeated administration of radioiodine to treat local recurrences or loco-regional and distant metastases. Although such lesions do not concentrate RI$^{131}$, they maintain some differentiated functions such as the ability to produce Tg, which is highly useful to help diagnose their presence. High resolution ultrasound has also proven useful in the identification of small lymph nodes, but alone it cannot discern the presence of metastases. Scintigraphy with radio-pharmaceuticals (with avidity for thyroid cancer cells) has also been demonstrated to be useful in the diagnosis of such lesions. Combined with high resolution ultrasound, $^{99m}$Tc-MIBI scintigraphy can be used to diagnose the presence and localization of loco-regional metastases in patients with thyroid cancer that no longer concentrate radioiodine. One of the few therapeutic options left for such cases is surgical removal of the lesions. Surgical intervention can be facilitated by the use of RGS (Radio-guided intra-operative Probe for Surgery) with the ability to positively identify involved lymph nodes.
The present study expands the previous experience of this group, reported originally on 8 patients, and now concerning 37 patients, who all had their recurrent thyroid cancer successfully localized and extirpated using this combined approach and surgical technique. Twenty-eight of 37 patients were considered to be disease-free during the follow up. The present study does not allow to directly assess the efficacy of RGS in the overall treatment of thyroid cancer, nor does it allow to compare RGS with other existing modalities for the intra-operative localization of thyroid cancer. This study, however, demonstrates the applicability of this approach in the treatment of loco-regional recurrence of non radiiodine-avid thyroid cancer. (Daniel Glinoer, M.D.; Ph.D.)

See Figures below

**FIG. 1.** Pre- and post-RGS radioactivity ratios. L, lesion; B, background; OS, operative site.

**FIG. 2.** Pre- and post-RGS thyroglobulin levels. Dotted line, thyroglobulin level of 2 mg/mL.
**Topic:** THYROID CANCER

**Title:** Trend in thyroid carcinoma size, age at diagnosis, and histology in a retrospective study of 500 cases diagnosed over 20 years.

**Authors:** Trimboli P, Ulisse S, Graziano FM, Marzullo A, et al. (Roma, Italy)

**Reference:** Thyroid 16: 1151-1155, 2006

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**SUMMARY**

**Background:** Recently, the Italian Network of Cancer Registries analyzed 5101 cases of thyroid carcinoma showing a reduction of mortality rate of 4% per year. This prompted the authors to evaluate the temporal trend in tumor size, age at diagnosis, and histology in a retrospective analysis of 500 thyroid cancers diagnosed over a 20-year period.

**Analysis:** Thyroid cancers were divided in two groups. The first included 193 cases diagnosed from 1985 to 1994, and the second 307 from 1995 to 2004. The size of all tumors was significantly reduced from $40 \pm 6$ mm to $17 \pm 5$ mm. Age at diagnosis of carcinomas increased significantly from 40 years in the first group to 48 years in the second group. Analysis of the histological types revealed a significant increase of PTC (papillary) rate in the second decade from 82% to 92%, and a concomitant reduction of anaplastic thyroid cancer (ATC) from 3.7% to 1.0%. Moreover, a significant increase in micro-PTC rate from 3.7% to 36.4% was observed.

**Conclusion:** It may be speculated that the above decreased mortality rate for thyroid carcinoma could be related to the significant reduction with time of cancer size, to the progressive increase of PTC rate and to the reduction of ATC rate. These data, if confirmed in other series, underscore the importance of evaluating thyroid nodules smaller than 10 mm and corroborate recent findings suggesting that age be reconsidered as an independent prognostic factor for differentiated thyroid cancers.

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**COMMENT**

This retrospective study has a main interest, which is to show (or rather confirm to us) that the pattern of diseases changes with time and progress in diagnostic methodologies. When I was a young doctor (a long time ago!), thyroid cancers were mainly diagnosed among palpable nodules, shown to be solitary and ‘cold’ on thyroid scintigraphy. Nowadays, one half of confirmed thyroid cancers are discovered in multinodular goiters (and not as a single nodular lesion) and they are often non palpable (i.e. ‘seen’ by ultrasound). Also, anaplastic thyroid cancers have become exceedingly rare in our daily endocrine practice, probably as a result of the surgical removal of thyroid nodules before anaplastic tissue can form. It was quite striking in the study of our Italian colleagues that micro-cancers of the papillary type (less than 10 mm in diameter) represented 36% of all their cases in the more recent years. Many of these were presumably thyroid cancers diagnosed in multinodular goiters, operated for various reasons.

Despite such favourable prognostic factors (smaller tumors, mainly of the papillary type), is it to say that the disease has
become “less malignant”? The answer is NO, since we know that even micro-
cancers can produce distant metastases. Therefore, the conclusion should be that
thyroid ultrasonography (performed by experienced radiologists), followed by fine
needle aspiration cytology (performed by experienced cytologists) have nowadays
become the mainstay of the preoperative diagnosis of thyroid nodular lesions. Our
attention must focus on small nodules that

need to be investigated, aspirated, and
followed up (when not removed by the
surgeon). Also, there is now good worldwide consensus on the management
of thyroid cancer after surgery and, using
these guidelines, one can hope that the
morbidity and mortality rates related to
thyroid cancer (despite an increase in the
prevalence, seen everywhere) will continue
to decrease in the coming years.

(Daniel Glinoer, M.D.; Ph.D.)

See Figures below

**FIG. 1.** Median size at diagnosis of papillary thyroid carcinoma (PTC), follicular thyroid carcinoma (FTC), and anaplastic thyroid carcinoma (ATC) cases diagnosed from 1985 to 1994 (■) and from 1995 to 2004 (▲).

**FIG. 2.** Papillary thyroid carcinoma (PTC), follicular thyroid carcinoma (FTC), and anaplastic thyroid carcinoma (ATC) rate in the two groups; 1985–1994 (■), 1995–2004 (▲).
**SUMMARY**

**Background:** Sunitinib malate is an oral tyrosine kinase inhibitor recently approved for the treatment of gastrointestinal stromal tumors and renal carcinoma. Because the ret proto-oncogene is also inhibited by this agent, clinical evaluation of thyroid function was performed.

**Objective:** To describe the prevalence and clinical presentation of thyroid dysfunction related to Sunitinib therapy.

**Design:** Prospective, observational cohort study.

**Setting:** Tertiary care hospital.

**Patients:** 42 patients treated for a median of 37 weeks (range: 10-167 weeks).

**Measurements:** Following analysis of serial TSH measurements collected prospectively during a clinical trial of sunitinib, the proportion of patients with thyroid dysfunction was determined.

**Results:** Abnormal serum TSH concentrations were documented in 26 of 42 patients (62%); 15 (36%) developed persistent, primary hypothyroidism; 4 (10%) developed isolated TSH suppression; and 7 (17%) experienced transient, mild TSH elevations. The risk for hypothyroidism increased with the duration of sunitinib therapy. Six of 15 (40%) hypothyroid patients had suppressed TSH concentrations before developing hypothyroidism, suggesting thyroiditis. Two hypothyroid patients evaluated with thyroid ultrasonography had no visualized thyroid tissue despite normal baseline thyroid function.

**Limitations:** The exploratory nature of this study precluded more frequent biochemical and ultrasonographic analysis that may better define the mechanisms of sunitinib-associated thyroid dysfunction.

**Conclusion:** Hypothyroidism is a frequent complication of sunitinib therapy. Regular surveillance of thyroid function is warranted in patients receiving this drug. Although the mechanism by which this complication occurs is unknown, the observations of preceding TSH suppression and subsequent absence of visualized thyroid tissue in some patients suggest that sunitinib may induce a destructive thyroiditis through follicular cell apoptosis. This provides a rationale for further investigation of sunitinib treatment in patients with advanced thyroid cancer.
COMMENT
Tyrosine kinase inhibitors are molecules belonging to new lines of treatment in oncology and have been shown to be beneficial for the treatment of numerous malignant conditions. These molecules have been pharmaco-modeled to block the activity of selected kinase signalling enzymes, but it is increasingly evident that their effects may overlap the ‘theoretical’ selectivity and, in turn, have undesirable effects on several kinase pathways. Sunitinib (SUTENT®) has recently been approved in USA and Europe for the treatment of patients with metastatic or surgically unresectable disease. After the identification of 2 index cases who developed primary hypothyroidism, the authors of the present study expanded their original observations to a large group of patients treated with Sunitinib. They show herein that 36% of the patients developed hypothyroidism after an average of 50 weeks of therapy. Patients in this study had a normal thyroid function before therapy and the data suggest that this kinase inhibitor induced some sort of destructive thyroiditis by a yet unknown mechanism associated with the drug. The article does not give details about a possible thyroid function recovery after stopping the drug, but it mentions TSH normalization after combined l-thyroxine administration.
Primary hypothyroidism is a rare complication of therapeutic drugs, but has been described with several agents, such as Lithium, interferon-alpha and interleukins, amiodarone and other iodine-containing agents, phenytoin, carbamazepine, rifampicine, etc.
Finally, the implication of the present study is the need to monitor thyroid function regularly in patients treated with this (and other) tyrosine kinase inhibitors and obviously also treat those patients who develop hypothyroidism with l-thyroxine. (Daniel Glinoer, M.D.; Ph.D.)

See Table below

### Table. Serum Thyroid-Stimulating Hormone Concentrations in 15 Patients Who Developed Hypothyroidism during Sunitinib Therapy for the Treatment of Gastrointestinal Stromal Tumors

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age, y</th>
<th>Duration of Sunitinib Therapy, wk</th>
<th>Time to Persistent Elevation of TSH Levels, wk</th>
<th>TSH Concentrations during Sunitinib Therapy, mU/L</th>
<th>Evidence of Thyroiditis†</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
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<td>98</td>
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<td>37</td>
<td>31</td>
<td>1.4</td>
<td>7.2</td>
</tr>
</tbody>
</table>

* TSH = thyroid-stimulating hormone.
† TSH concentration less than 0.5 mU/L before elevation of TSH levels and initiation of l-thyroxine therapy.
GOITROUS CONGENITAL HYPOTHYROIDISM

Title: Goitrous congenital hypothyroidism in a twin pregnancy causing respiratory obstruction at birth: implications for management.

Authors: Reynolds BC, Simpson JH, Macara L, Watt AJB, et al. (Glasgow, UK; & Mainz, Germany)


SUMMARY

Objective: The authors report a twin pregnancy complicated by fetal goitrous hypothyroidism secondary to dyshormonogenesis caused by thyroglobulin deficiency.

Patients: Antenatal treatment with intra-amniotic thyroxine was considered but not performed, given the late gestational age at diagnosis and the multiple nature of the pregnancy. Both twins developed airway obstruction at delivery, requiring intubation and ventilation for 2 to 12 days.

Context: The authors review the literature and describe the practical issues relating to the antenatal assessment and perinatal management of fetal goiter.

COMMENT

A dichorionic twin pregnancy was confirmed at 12 weeks gestation in a healthy primiparous woman. At 18 weeks of gestation, fetal ultrasonography revealed no abnormality. A subsequent ultrasonography, at 24 weeks gestation, identified a neck mass in one of the twins, assumed to be a fetal goitre. At 31 weeks gestation, the goiter was enlarging (antero-posterior diameter: 43 mm) and was highly vascular, raising concern about a possible teratoma. One week later, ultrasound examination showed that the second twin also had a neck mass. MRI was performed (33 weeks gestation), allowing to confirm that the neck masses were goiters (tracheal compression was not reported at this stage). The mother had a normal thyroid function status, with slightly positive TPO-Ab titers. In the absence of maternal thyroid disease, the diagnosis was goitrous congenital hypothyroidism due to dyshormonogenesis. In view of the late gestational age and presence of twins, therapeutic thyroxine intra-amniotic administration was not performed. At 36 weeks gestation, one twin developed polyhydramnios. Delivery by caesarian section was carried out at 37 weeks gestation. Twin N°1 was intubated at 2 min of age, because she did not maintain regular respiratory efforts; clinical examination revealed a moderate goiter. Twin N°2 had clear evidence of airway obstruction and was also intubated at 2 min of age; her clinical examination revealed a large goiter. Both twins were given l-thyroxine (50 µg/day; 19 µg/Kg). One of twins was extubated on day 2; a thyroid ultrasound on day 5 showed a diffuse bilateral goiter with thyroid volume (TV) of 6.5 ml (normal: 0.3-1.7 ml). The other twin required external ventilation for a longer period and was extubated on day
her TV was 3 ml. Both twins remained well after these initial events with normal development. Concerning thyroid function, both twins had a raised serum TSH at birth (46 & 59 mU/L) with slightly decreased serum free T4 (8.1 & 8.5 pM/L) and very low serum TG values (paradoxical in a context of prolonged thyroidal stimulation). Therefore, the presumptive diagnosis was that of a thyroglobulin synthesis defect, and the diagnosis was confirmed by molecular genetic studies, showing in both twins the same pattern of compound heterozygocity with presence of two mutations.

The authors indicate that, retrospectively, they probably failed to gain maximal information from the MRI, in particular concerning potential airway obstruction associated with fetal goiter. Obstetric care providers felt that the potential risks of intra-amniotic thyroxine administration outweighed the benefits and the treatment was therefore not given. Perhaps now, with the knowledge that there was tracheal compression, neonatal hypothyroidism, and evolving polyhydramnios, they should have considered antenatal treatment at 34-35 weeks of gestation.

Fetal goiters can arise secondary to the transplacental passage of maternal thyroid autoantibodies (for instance, TSH-receptor blocking-type Abs) and also secondary to the effects of antithyroid drugs, given to treat maternal Graves’ disease. In the absence of maternal thyroid disease, fetal goiter is usually due to dyshormonogenesis.

Was there a case for performing cordocentesis or amniocentesis? Such procedures carry a small (but significant) risk but would have provided direct information on fetal thyroid function (serum TSH, free hormone levels, serum Tg levels). Given that the diagnosis of dyshormonogenesis had already been suspected clinically, the additional information would probably not have added much to help clinicians decide on the best therapy.

With regard to fetal goiter imaging, fetal ultrasonography (US) is the first line test. Its accuracy can be further improved by the use of high-resolution US, three-dimensional US, and color flow Doppler. There is not much reported experience with MRI in the assessment of fetal goiter, but in the present cases it failed to disclose the possibility of upper airway obstruction.

Finally with regard to therapy, the administration of intra-amniotic thyroxine (alone or combined with I-T3) has been reported in several publications (as early as 1991). In all reported cases, thyroxine treatment led to goiter shrinkage, reduction in amniotic fluid volume in cases of polyhydramnios, and normalization of fetal thyroid function. The risk and hazard of intra-amniotic instillation of large doses of thyroxine must be balanced against the risk of untreated fetal thyroid function and goiter development (not an easy balance for clinicians).

(Daniel Glinoer, M.D.; Ph.D.)
**SUMMARY**

**Background:** Cellular entry of thyroid hormones is mediated by plasma membrane transporters. The authors have identified rat monocarboxylate transporter (MCT8) as an active and specific thyroid hormone transporter.

**Human relevance:** The MCT8 gene is located on the X-chromosome. The physiological relevance of MCT8 has been demonstrated by the identification of hemizygous mutations in this gene in males who present extremely severe mental retardation and elevated serum T3 levels.

**Study and Results:** The authors have characterized human (h) MCT8 by analysis of iodothyronine uptake and metabolism in cell lines transiently transfected with hMCT8 cDNA alone or together with iodothyronine deiodinase D1, D2, or D3. MCT8 mRNA was detected by RT-PCR in a number of human cell lines as in COS1 cells but was low to undetectable in other cell lines, including JEG3 cells. MCT8 protein was not detected in nontransfected cell lines tested by immunoblotting using a polyclonal C-terminal hMCT8 antibody but was detectable in transfected cells. Transfection of COS1 and JEG3 cells with hMCT8 cDNA resulted in 2- to 3-fold increases in uptake of T3 and T4, but little or no increase in reverse-T3 (rT3) or 3, 3’-T2. The expression of MCT8 produced large increases in T4 metabolism when co-transfected with D2 or D3, T3 metabolism by D3, rT3 metabolism by D1 or D2, and 3, 3’-T2 metabolism by D3. Affinity labeling of hMCT8 protein was observed after incubation of intact transfected cells with N-bromoacétyl-radiolabelled-T3. Human MCT8 also facilitated the affinity labeling of co-transfected D1 by bromoacétyl-T3.

**Conclusions:** The present findings indicate that hMCT8 mediates plasma membrane transport of iodothyronines, thus increasing their intracellular availability for further metabolic events.

**COMMENT**

The biological activity of thyroid hormone is determined by the intracellular concentration of T3 which, among other factors, depends on circulating T3 concentrations and its prohormone precursor (T4). T4 only becomes an active hormone after entering the cells and transformation into T3, under the catalytic action of deiodinases (D1 & D2). During the last three decades, studies have demonstrated the importance of transporters for thyroid hormone to be taken up by target cells. Such transporters have only been recently identified at the molecular level, including several members of the Na-independent organic anion-transporting polypeptide family (OATPs). MCT8 is a member of the
monocarboxylate transporter family and has been characterized to be an active iodothyronine transporter, whereas it does not transport the aromatic amino-acids or the typical monocarboxylate ligands (such as lactate and pyruvate).

In man, a novel syndrome of severe X-linked mental retardation with elevated serum \( T_3 \) levels has been described in 2004 and is associated with mutations in the monocarboxylate transporter gene (MCT8). The severity of the phenotype is best explained by the recent demonstration that MCT8 is localized in different tissues such as the brain, where it is expressed in specific thyroid hormone-sensitive neuronal populations. Thus, mutations of MCT8 in the developing brain would deprive neurons of essential local presence of \( T_3 \) and hence result in psychomotor retardation.

In the present study, the authors aimed at characterizing human MCT8 as a thyroid hormone transporter. They transfected cell lines without hMCT8 expression with its cDNA and showed that the transfected cells had higher \( T_4 \) and \( T_3 \) transport rates. Furthermore, the metabolism of all iodothyronines was markedly stimulated in cells with iodothyronine deiodinase activities if these cells were also transfected with hMCT8. Most remarkable are the results showing that transfection of cells with hMCT8 in addition to that of the deiodinases facilitated the intracellular metabolism of the different iodothyronines. This represents the most direct evidence that hMCT8 increased the intracellular availability of these substrates for deiodination.

(Daniel Glinoer, M.D.; Ph.D.)
Topic: POSTPARTUM THYROIDITIS

Title: Prevalence of postpartum thyroid dysfunction: a quantitative review.

Authors: Nicholson WK, Robinson KA, Smallridge RC, Ladenson PW, & Powe NR (Baltimore & Jacksonville, USA)

Reference: Thyroid 16: 573-582, 2006

SUMMARY

Background: Estimates of the prevalence of postpartum thyroid dysfunction (PPTD) vary widely because of variations in study design, populations, and duration of screening.

Objectives: The objective of the authors was to estimate the prevalence of PPTD among general and high-risk women, across geographical regions and in women with antithyroid peroxidase antibodies (TPO-Ab).

Study: The authors conducted a systematic review and pooled analysis of the literature published between 1975 and 2004, simultaneously accounting for sample size, study quality, percentage follow-up, and duration of screening. Data sources were MEDLINE and the bibliography of candidate studies. Two reviewers independently extracted data. Of 587 studies identified, 21 articles, comprising 8081 subjects, met the study criteria.

Main Results: The pooled prevalence of PPTD, defined as an abnormal TSH level, was 8.1% for the general population (95% CI: 6.6%-10.0%). The risk ratios for the development of PPTD among women with TPO-Ab, compared to women without thyroid autoimmunity features, ranged between 4 and 97, with a pooled risk ratio of 5.7. Global prevalence varied from 4.4% in Asia to 5.7% in the USA. Prevalence among women with type 1 diabetes was 19.6%. PPTD occurs in 1 of 12 women in the general population worldwide, 1 of 17 women in the USA and is 5.7 times more likely to occur in TPO-Ab positive women.

Conclusion: The high prevalence may warrant routine screening for TPO-Ab, but the benefits, cost, and risks related to subsequent therapy must be weighed.

COMMENT

Postpartum thyroiditis (PPT) was originally described 25 years ago, in a seminal article published by Nobu Amino in the NEJM. Since then, a large number of studies have extended our knowledge on the prevalence, the pathogeny, the clinical consequences and diseases (such as psychiatric manifestations) associated with this syndrome. Today, we live with the notions that PPT occurs in approximately 50% of women who have positive thyroid antibodies, that women with diabetes have a significantly higher risk, and that PPT has a strong tendency to reappear (after a subsequent pregnancy) in women who presented a first episode of PPT (after a previous pregnancy). Clinical manifestations are often mild or absent. Typically, a series of thyroid dysfunction patterns can be observed, from early transient...
thyrotoxicosis only, to thyrotoxicosis followed by hypothyroidism with spontaneous recovery later on, to transient hypothyroidism only, and finally to hypothyroidism that becomes permanent (in 10-15% of cases). Even though often mild clinically, PPT is also associated to more severe presentations of either hyper- or hypothyroidism, although the hypothyroid form is more common. The main question is how to diagnose PPT and how to predict who is at risk of having PPT?

In the present analytical review, the first striking finding was the large number of articles identified in the literature (almost 600), although only a minority of studies (< 5%) fulfilled the criteria for analysis. The study confirmed the wide geographical variability of the prevalence of PPT and underscored some reasons explaining the variability: sample size, quality of study, percentage of follow-up, duration of screening. I would also tend to include the methods used for screening (such as measurement of TPO-Ab alone or with TG-Ab) and the timing of serum TSH screening since an abnormal TSH was the criteria used for the diagnosis. In PPT, we are dealing with a syndrome linked to the thyroid repercussions of a rebound in thyroid antibody production, after the immunosuppressive effect of pregnancy has faded away. Thus, abnormalities in serum TSH may be extremely brief and the timing of TSH measurements (say, every month during a 6-month period versus only once at 6 months postpartum) may lead to completely different results. The second important findings (not new but highly confirmatory) were the prevalence of PPT close to 10% in the general population, its 6-fold increase in women with positive TPO-Ab, and its 2-3-fold increase in women with type 1 diabetes. Finally, the authors advocated (albeit cautiously) the utility of systematic screening for PPT but omitted to present valuable algorithmic approaches for such screening to reach maximal efficacy.

(Daniel Glinoer, M.D.; Ph.D.)

See Figure below

**FIG. 1.** Prevalence of postpartum thyroid dysfunction in the general population from 15 studies and pooled estimate weighted by sample size. Prevalence estimates and 95% confidence interval from 15 studies conducted in the general population. Sample size and the total number of women with postpartum thyroid dysfunction are also shown. The pooled estimate represents a weighted prevalence and 95% confidence interval based on the sample size and inverse variance of each individual study.
Topic: SIMULATION OF THYROID HORMONE REPLACEMENT

Title: Levothyroxine bioequivalence and hormone replacement studies via feedback control simulations.

Authors: Eisenberg M, Samuels M, DiStefano JJ III (Los Angeles CA, USA)

Reference: Thyroid 16: 1279- 1292, 2006

SUMMARY

Background: FDA guidance for testing bioequivalence of levothyroxine (L-T4) preparations has been challenged by several groups, based on multiple issues. The efficacy of single versus combined hormone therapy is also receiving additional scrutiny.

Study: The authors developed a new nonlinear feedback system simulation model of whole-body regulation mechanisms involving dynamics of T3, T4, TSH, plasma protein binding, extravascular regulatory enzyme systems, and the hypothalamic-pituitary-thyroid axis, all quantified from human data. To address bioequivalence, the authors explored how to best account for varying and unmeasured endogenous T4 following dosing with exogenous L-T4 in euthyroid volunteers in pharmacokinetic (PK) studies, by simulating various dosing scenarios and developing a new and simple correction method. They computed and assessed dosing error effects and baseline corrections using simulator-predicted endogenous T4 level variations, and compared these with approximate corrections computed directly from PK data.

Results: Simulated replacement after thyroidectomy required 141 µg L-T4 only to normalize T3 tissue levels and 162 µg L-T4 to normalize plasma T3 levels. A combined dose of approximately 103 µg L-T4 plus approximately 6 µg T3 (i.e. a ratio of 18:1) was needed to normalize both plasma T3 and T4 and average T3 tissue levels. However, simulated average tissue T3 levels were normalized with standard L-T4-only therapy, and plasma T3 levels were still within the normal range.

Conclusion: Current standard L-T4-only treatment is supported for routine replacement needs.

COMMENT

The group of Jo DiStefano is well known for their remarkable, elegant (and often complicated, as it is the case herein) metabolic and pharmacokinetic studies of thyroid hormones. There has been much speculation lately concerning the bioequivalence of thyroid hormone preparations (a problem that not yet exists in our country, but may well appear soon with the generics). Also, several recent articles have dealt with the well-being effects of small changes in thyroxine dosage in hypothyroid patients, as well as with the additional benefit of adding small doses of L-T3 to standard L-T4 therapy. In brief, these studies have shown that minor modifications of the L-T4 dosage did not affect well-being (Walsh, JCEM 2006) and that addition of L-T3 was not warranted in the vast majority of patients (Grozinsky-Glasberg, JCEM 2006).

In the present study, 33 volunteers received an oral dose of 400, 450 and 600 µg of L-T4 and were submitted to sophisticated pharmacokinetic studies, assuming a mean 88% absorption rate. The most important
result of these simulation studies was that a replacement dose of 162 µg of L-T₄ after thyroidectomy was needed (and sufficient) to return plasma T₃ levels to prethyroidectomy values and 141 µg was needed to normalize tissue T₃ levels for full replacement. The 'ideal' physiological dose regimen would be a ratio of 10:1 between L-T₄ and L-T₃. In the present study, a ratio of 18.1 was evidenced, and average simulated tissue T₃ level was normalized with standard L-T₄-alone therapy. These results are concordant with clinical observations indicating that patients receiving levothyroxine have serum T₃ levels within the normal range. This may be interpreted as supporting current standard replacement therapy with L-T₄ alone. (Daniel Glinoer, M.D.; Ph.D.)

See Figure below

![Graph]

**FIG. 4.** The three mean $TSH_p(t)$ data sets, from plasma samples collected over 96 hours following 400-, 450-, and 600-µg oral L-T₄ doses in pharmacokinetic (PK) studies by Blakesley et al. (5). These were used as inputs for closed-loop parameter estimation, with all data fitted simultaneously, as described in the text and Figure 6. Resulting parameter estimates are given in Table 1.
**SUMMARY**

**Objective**: The present study determined the cost effectiveness of treating thyrotoxicosis using thionamide therapy, radioiodine or surgery in the United Kingdom.

**Design**: One hundred thirty-five patients diagnosed with thyrotoxicosis (62% Graves’ disease, 7% nodular disease, 5% thyroiditis, and 27% unknown etiology) referred over a period of twelve months were offered a fully informed choice of treatment modality. Thirteen patients with transient thyrotoxicosis were subsequently excluded from the analysis. Seventy-four patients (61%) received an 18-month course of thionamide therapy, 43 received radioiodine therapy (35%), and 5 had a thyroidectomy (4%) within the first year of diagnosis as their primary treatment. A successful outcome (“cure”) was defined as euthyroidism 12 months after thionamide therapy or euthyroidism or hypothyroidism on thyroxine replacement at 24 months following radioiodine or thyroidectomy. Costs were calculated for outpatient attendances, laboratory tests, and initial and subsequent treatment.

**Main outcome**: In the thionamide group, 73% were “cured” at 30 months after initiating treatment compared to 95% in the radioiodine group and 100% treated by thyroidectomy at 24 months. Cost per “cure” was calculated to be 3.763 £ (5.645 €) per patient who received thionamides, 1.375 £ (2.063 €) per patient given radioiodine and 6.551 £ (9.826 €) per patient who underwent thyroidectomy.

**Conclusion**: The most cost-effective primary treatment modality for thyrotoxicosis is radioiodine.

**COMMENT**

In these times of heavy budgetary constraints, it is important to consider the cost-benefit ratios of the treatments we use, especially in the field of hyperthyroidism where three effective therapeutic options exist: antithyroid drugs (ATD), radioiodine (RI-131), and surgery (Tx). The present study aimed at comparing costs in what can be considered a homogeneous group of patients with hyperthyroidism, followed in a teaching hospital in London. All patients (except for a few with recurrences of thyrotoxicosis) had a first episode of thyroid disease. For the patients with ATD therapy, a low dose titration regimen was used (CMI or PTU) for 18 months. For the patients with RI-131 therapy, a single dose of 400-600 MBq was used, followed by ATD treatment during one month. For the patients submitted to Tx, all were rendered euthyroid prior to surgery by a short course of treatment with ATD.

Nevertheless, there are obvious queries and criticism relating to this study:
1) Is one population (UK) comparable to another (Belgium)?
2) The study was retrospective and it is difficult to truly believe that the patients effectively made the choice of their therapy. When I try to do this in my practice, most patients (after listening carefully to my long and precise explanations) usually conclude “you are the doctor and therefore I will accept the choice you consider to be the best for me”.

3) Costs of treatments and others costs (scintigraphy, consultations, lab tests, etc.) may be quite different from one country to another and, therefore, results of this study in the UK cannot (and should not) be extrapolated to other countries without seriously pondering the implications.

4) Therapeutic options were not randomised and the authors admit that some treatment choices may have been dependent on the clinical presentation or by personal preference among the five endocrinologists who participated into the study.

5) Etiology of hyperthyroidism was not homogeneous, and was unknown for 27% of the patients.

6) Therapy groups were quite different in size, with two thirds of them receiving ATD treatment, one third RI-131 administration, and finally only 5 patients submitted to Tx.

Finally and despite the limitations alluded to above, this retrospective study has shown that RI-131 and Tx had a better overall rate of success (95-100%) than ATD administration (73%), a well known fact whose advantage is limited, however, by the advantage of giving the patient a chance to be cured without radical therapy. Based on cost and success rates, the authors conclude by favouring RI-131 administration for the treatment of hyperthyroidism.

(Daniel Glinoer, M.D.; Ph.D.)

See Table below

<table>
<thead>
<tr>
<th></th>
<th>N</th>
<th>Cure rate</th>
<th>Cost/patient</th>
<th>Cost/cure</th>
</tr>
</thead>
<tbody>
<tr>
<td>ATD</td>
<td>74</td>
<td>73%</td>
<td>3.279 €</td>
<td>5.644 €</td>
</tr>
<tr>
<td>Tx</td>
<td>5</td>
<td>100%</td>
<td>9.826 €</td>
<td>9.826 €</td>
</tr>
<tr>
<td>RI-131</td>
<td>43</td>
<td>95%</td>
<td>1.919 €</td>
<td>2.063 €</td>
</tr>
</tbody>
</table>

(table reconstructed from Table 2)
**Topic:** TREATMENT OF TYPE 2 DIABETES & OPHTHALMOPATHY

**Title:** Treatment with a thiazolidinedione increases eye protrusion in a subgroup of patients with type 2 diabetes.

**Authors:** Dorkhan M, Lantz M, Frid A, Groop L, Hallengren B (Lund & Malmö, Sweden)

**Reference:** Clinical Endocrinology 63: 35-39, 2006

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**SUMMARY**

**Context:** Activation of peroxisome proliferators-activated receptor gamma (PPRγ) with synthetic ligands such as thiazolidinediones (TZD) has been demonstrated to improve glucose tolerance and decrease insulin resistance in patients with type 2 diabetes. It has been demonstrated that TZD can increase the amount of adipose tissue by activating the PPRγ receptor in predominantly subcutaneous preadipocytes. Recently, a type 2 diabetic patient, with stable & inactive Graves’ ophthalmopathy (GO), experienced worsening of GO after treatment with pioglitazone.

**Objective:** This open-label prospective study addresses the question of whether treatment with a glitazone could change eye protrusion in type 2 diabetic patients.

**Setting:** The degree of eye protrusion was measured before and 26 weeks after treatment with pioglitazone, using Krahn’s exophthalmometer.

**Patients:** Thirty-six Caucasian patients with poorly controlled type 2 diabetic patients were included in a study where pioglitazone was added to current therapy with sulphonylurea and metformin. The study was open-labelled and prospective with 26 weeks of follow-up. The pioglitazone dose was increased to 45mg/d (n = 12) after 16 weeks if HbA1c was > 6.5 %.

**Results:** Thirteen patients (group A) exhibited a > 2 mm increase of proptosis and 23 patients (group B) exhibited a < 2 mm increase of proptosis. Patients in group A versus group B had the same BMI, HbA1C and mean dose of pioglitazone, but lower levels of adiponectin at the start (4.9 ± 2.1 vs 7.1± 2.5 µg/ml) and at the end of the study (10.2 ± 4 vs 14.9 ± 5 µg/ml). Patients with thyroid disturbances were more frequent in group A (5 vs 1). In a logistic regression analysis, thyroid disturbance, low adiponectin levels and pioglitazone dose predicted a significant change in eye protrusion.

**Conclusion:** A subgroup of patients with type 2 diabetes, treated with pioglitazone, responded with increased eye protrusion. This subgroup had decreased plasma concentration of adiponectin and more frequent thyroid disturbances, and was treated with higher dose of pioglitazone. The relationship between insulin resistance, thyroid disturbance and thiazolidinedione-induced eye protrusion should be studied further.

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**COMMENT**

In present study of type 2 diabetic patients who received pioglitazone for 6 months (in addition to sulphonylurea and metformin), the authors observed an overall small but significant increase in the degree of eye protrusion. No imaging (with MRI or CT-scan) was performed to measure more accurately the degree of eye protrusion and examine possible changes in extra-ocular muscles or orbital adipose tissue. No other
clinical sign of ophthalmopathy was observed in these patients. Obesity and type 2 diabetes are associated with low plasma levels of adiponectin and hypo-adiponectinemia is closely related to the degree of insulin resistance and hyperinsulinemia. An hypothesis to explain present results might be that environmental factors, such as TZD combined with a pre-existing susceptibility (insulin resistance), may result in remodelling of orbital tissue and lead ultimately to increased eye protrusion in patients with type 2 diabetes. This observation needs confirmation but it seems prudent not to treat patients with Graves’ disease with a thiazolidinedione.

(Chantal Daumerie, M.D.; Ph.D.)

See Table below

Patients’ characteristics before & 6 months after treatment with pioglitazone in 2 subgroups according to changes in eye protrusion

<table>
<thead>
<tr>
<th>Changes in eye protrusion</th>
<th>Increase ≥ 2 mm:</th>
<th>Increase &lt; 2 mm:</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Group A</td>
<td>Group B</td>
<td></td>
</tr>
<tr>
<td>n (%)</td>
<td>13 (36%)</td>
<td>23 (64%)</td>
<td></td>
</tr>
<tr>
<td>Age (years)</td>
<td>59 ± 8</td>
<td>60 ± 8</td>
<td>0.7</td>
</tr>
<tr>
<td>Gender: female/male (%)</td>
<td>4/9 (44%)</td>
<td>9/14 (64%)</td>
<td></td>
</tr>
<tr>
<td>Proposis at start, right eye</td>
<td>17.3 ± 3 (12-23)</td>
<td>17.5 ± 2.5 (13-23)</td>
<td></td>
</tr>
<tr>
<td>Proposis at start, left eye</td>
<td>17.4 ± 2.9 (13-24)</td>
<td>17.6 ± 2.5 (13-22)</td>
<td></td>
</tr>
<tr>
<td>Proposis at study end, right eye</td>
<td>19.5 ± 3.1 (14-25)</td>
<td>17.7 ± 2.3 (24-22)</td>
<td></td>
</tr>
<tr>
<td>Proposis at study end, left eye</td>
<td>18.9 ± 2.8 (14-24)</td>
<td>17.6 ± 2.5 (13-22)</td>
<td></td>
</tr>
<tr>
<td>BMI at start</td>
<td>30.4 ± 5</td>
<td>31 ± 3.7</td>
<td>0.7</td>
</tr>
<tr>
<td>BMI after 6 months</td>
<td>31.6 ± 5.3</td>
<td>32.3 ± 3.7</td>
<td>0.5</td>
</tr>
<tr>
<td>Current or previous smokers (%)</td>
<td>10 (77%)</td>
<td>13 (56%)</td>
<td>0.3</td>
</tr>
<tr>
<td>Thyroid disturbance</td>
<td>5 (38%)</td>
<td>1 (4%)</td>
<td>0.02</td>
</tr>
<tr>
<td>HbA1c percentage at start</td>
<td>7.4 ± 0.5</td>
<td>7.6 ± 0.8</td>
<td>0.7</td>
</tr>
<tr>
<td>HbA1c percentage after 6 months</td>
<td>6.2 ± 0.7</td>
<td>6.4 ± 1.1</td>
<td>0.9</td>
</tr>
<tr>
<td>Pioglitazone dose, high/low † (%)</td>
<td>5/13 (38%)</td>
<td>7/23 (30%)</td>
<td>0.001</td>
</tr>
<tr>
<td>Adiponectin at start (µg/ml)</td>
<td>4.9 ± 2.1</td>
<td>7.1 ± 2.5</td>
<td>0.017</td>
</tr>
<tr>
<td>Adiponectin at study end (µg/ml)</td>
<td>10.2 ± 4</td>
<td>14.9 ± 5</td>
<td>0.007</td>
</tr>
</tbody>
</table>

Values are means ± SD if not stated otherwise.

*The degree of proptosis by exophthalmometric reading shown in mean ± SD (range) mm.
†High dose = 45 mg/day, low dose = 30 mg/day.
**Topic:** SECOND PRIMARY TUMORS IN PATIENTS WITH DTC

**Title:** The incidence of second primary tumors in thyroid cancer patients is increased, but not related to treatment of thyroid cancer.

**Authors:** Verkooijen RB, Smit JW, Romijn JA, Stokkel MP (Leiden, The Netherlands)

**Reference:** European Journal of Endocrinology 155: 801-806, 2006

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**SUMMARY**

**Objective:** The aim of the present study was to assess the prevalence of second primary tumors in patients treated for thyroid cancer. Furthermore, the authors wanted to assess the standardized risk rates for all second primary tumors, but especially for breast cancer, as data in the literature have indicated an excessive risk in differentiated thyroid cancer (DTC) patients for this tumor.

**Material & Methods:** Consecutive patients (n=282) were included, who had received ablation treatment with I-131 at the Leiden Medical Center (between January 1985 & December 1999). The mean period of follow-up was 10.6 ± 4.1 years.

**Results:** Thirty-five of the 282 patients (12.4%) had a second primary tumor (SPT), either preceding or following the diagnosis of thyroid cancer. Five other patients had three primary tumors, including DTC. As a result, 40 additional tumors were found in this group, revealing an overall prevalence of 14.2%. Twenty tumors (7.1%) preceded the thyroid cancer with a mean interval of 5.7 years (range: 0.5-22.0 years), whereas 20 tumors (7.1%) occurred after this tumor with a mean interval of 6.7 years (range: 1.0-15.0 years). In 13 female patients, breast cancer was found as SPT. The standardized incidence rate (SIR) for all cancers after the diagnosis of DTC in this study population was not increased (SIR: 1.13; C.I.: 0.68-1.69). There was, however, an increased SIR for all cancers either following or preceding DTC (SIR: 2.26; C.I.: 1.60-3.03), and this increased SIR was mainly caused by breast cancer (SIR: 3.95; C.I.: 2.06-6.45).

**Conclusion:** Patients with DTC have an overall increased standardized incidence rate for second primary tumors, but not for second primary tumors following I-131 therapy. These findings suggest a common etiologic and/or genetic mechanism to explain the increased risk of having more than one tumor, instead of a causal relation.

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**COMMENT**

Differentiated thyroid cancer (DTC) accounts for approximately 0.5-1.5% of all malignancies. Some studies have found a relationship between I-131 administration and the occurrence of secondary cancers (bone, soft tissue, colorectal, salivary glands, etc.). Other studies have reported an increased incidence of breast and kidney cancers among women treated for DTC, although the increased incidence was unrelated to exposure to I-131.

Present results indicate that I-131 therapy is not associated with an increased incidence of malignancies following treatment of DTC. Present results also indicate that there is an increased incidence of second primary tumors (especially breast cancer) in patients with DTC. The
authors speculate that genetic predisposition and probably environmental factors seem to be a better explanation for the double occurrence, as at least half of the breast tumors appeared before treatment of DTC with I-131. Even though the mean follow-up period was relatively long (over ten years), one obvious limitation of the study was the relatively small number of patients included in the database.

Recently, a large multi-national study was published of second primary cancers in patients with thyroid cancer (Sandeep et al; JCEM 91:1819-181825, 2006). It was conducted in 13 population-based cancer registries and included 39,000 patients with primary thyroid cancer. In that study, 2,821 second primary tumors (SPT) were observed, yielding an overall standardized incidence rate (SIR) of 1.31. Increased incidence rates were found for cancers of the oral cavity (SIR: 1.43), small intestine (SIR: 2.11), bone (SIR: 3.62), soft tissue sarcoma (SIR: 3.63), kidney (SIR: 2.33), endocrine glands (SIR: 6.75), lymphoma (SIR: 1.68), and leukemias (SIR: 2.26). Surprisingly, the SIR for breast cancer was 1.31, i.e. much lower than in present study. Conversely, the study of Sandeep et al also showed that the risk of thyroid cancer as a second primary tumor was also increased in patients who primarily had other cancers (lung, larynx, oesophagus, salivary glands).

The conclusion is that clinicians should maintain a high index of suspicion during follow-up, both for SPT following treatment for thyroid cancer and for cancer of the thyroid as SPT.

(Daniel Glinoer, M.D.; Ph.D.)

See Table below

<table>
<thead>
<tr>
<th>Tumors preceding DTC</th>
<th>n</th>
<th>Mean cumulative I-131 activity (MBq)</th>
<th>Mean interval (years) (range)</th>
<th>Tumors following DTC</th>
<th>n</th>
<th>Mean cumulative I-131 activity (MBq)</th>
<th>Mean interval (years) (range)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Melanoma</td>
<td>2</td>
<td>22 400</td>
<td>13 (4–22)</td>
<td>Melanoma</td>
<td>1</td>
<td>1850</td>
<td>1</td>
</tr>
<tr>
<td>Breast</td>
<td>8</td>
<td>4900</td>
<td>4.3 (2–10)</td>
<td>Breast</td>
<td>5</td>
<td>9000</td>
<td>6.6 (2–11)</td>
</tr>
<tr>
<td>Colon</td>
<td>2</td>
<td>9100</td>
<td>3.3 (0.5–6)</td>
<td>Cervix uteri</td>
<td>2</td>
<td>5050</td>
<td>4 (1–7)</td>
</tr>
<tr>
<td>Lung</td>
<td>2</td>
<td>8400</td>
<td>2.3 (0.5–4)</td>
<td>Ovary</td>
<td>2</td>
<td>2400</td>
<td>8.5 (2–15)</td>
</tr>
<tr>
<td>Adrenal</td>
<td>1</td>
<td>8900</td>
<td>15</td>
<td>Endometrium</td>
<td>1</td>
<td>16 512</td>
<td>7</td>
</tr>
<tr>
<td>Salivary gland</td>
<td>1</td>
<td>2800</td>
<td>17</td>
<td>Pancreas</td>
<td>1</td>
<td>2800</td>
<td>7 (3–11)</td>
</tr>
<tr>
<td>Grawitz tumor</td>
<td>1</td>
<td>7400</td>
<td>7</td>
<td>Bladder</td>
<td>1</td>
<td>2800</td>
<td>3</td>
</tr>
<tr>
<td>Stomach</td>
<td>1</td>
<td>24 735</td>
<td>2</td>
<td>Lung</td>
<td>1</td>
<td>2800</td>
<td>14</td>
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<tr>
<td>Prostate</td>
<td>1</td>
<td>26 740</td>
<td>2</td>
<td>Prostate</td>
<td>1</td>
<td>9400</td>
<td>1</td>
</tr>
<tr>
<td>Lymphoma</td>
<td>1</td>
<td>15 725</td>
<td>0.5</td>
<td>Hepatocellular</td>
<td>1</td>
<td>15 400</td>
<td>2</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Grawitz</td>
<td>1</td>
<td>21 100</td>
<td>14</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Leukemia</td>
<td>1</td>
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<td></td>
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<td></td>
<td></td>
<td>Lymphoma</td>
<td>1</td>
<td>2800</td>
<td>12</td>
</tr>
<tr>
<td>Overall</td>
<td>20</td>
<td>5.7 (0.5–22)</td>
<td></td>
<td>Overall</td>
<td>20</td>
<td>6.7 (1–15)</td>
<td></td>
</tr>
</tbody>
</table>

SPT, second primary tumor.