BRIEF REPORT

Thyrotropin Suppression by Metformin

Robert A. Vigersky, Amy Filmore-Nassar, and Allan R. Glass

Endocrinology Service, Walter Reed Army Medical Center, Washington, DC 20307

Drug-drug interactions are common but often are discovered only long after initial drug release. Metformin has been available in the United States for almost a decade and elsewhere for many more years, but as of yet there are no reports that the drug modifies thyroid hormone economy.

Objective: The objective of the study was to describe the clinical and biochemical findings of four patients with chronic hypothyroidism, previously euthyroid on fixed doses of L-T4, for several years, in whom the metformin was initiated.

Design: This was a retrospective review.

Setting: The study was conducted at a tertiary care military hospital providing care to active-duty soldiers, sailors, and marines, retirees of the armed forces, and their eligible dependents.

Participants: Four patients with chronic hypothyroidism who were placed on metformin participated in the study.

Results: Initiation of treatment with metformin (three for diabetes mellitus and one for nonalcoholic steatohepatitis) caused suppression of TSH to subnormal levels without clinical symptoms of hyperthyroidism in any patients. There was no change in free T₄ or free T₃ in patient 1.

Conclusions: No other potential causes of TSH suppression, including medication changes or interference in the TSH assay, could be identified. The mechanism of the fall in serum TSH in these four patients is unclear at this time. Should these findings be confirmed in larger prospective studies, metformin’s ability to suppress TSH without causing clinical or chemical hyperthyroidism might render this drug a useful adjunct to the treatment of patients with thyroid cancer. (J Clin Endocrinol Metab 91: 225–227, 2006)
6 wk. To confirm this presumed relationship between metformin administration and serum TSH suppression, the drug was readministered, with the patient’s informed consent, from October 2002 until October 2003 in the same dose as before. Once again, serum TSH suppression was noted, and after discontinuation of metformin and substitution of rosiglitazone (4 mg twice daily), serum TSH rose back into the normal range. During both periods of metformin administration, there were no changes in fT4 or fT3 levels, and there was no weight loss or symptoms consistent with hyperthyroidism. The suppression and recovery of serum TSH was not associated with changes in medications other than metformin. Medication compliance was verified by the patient and confirmed by reviewing refill frequency in the integrated military electronic record.

Patient 2 is a 67-yr-old Caucasian woman who had type 2 diabetes mellitus for 12 yr complicated by mild nephropathy. Treatment of diabetes with neutral protamine Hagedorn (NPH) (NovoNordisk, Princeton, NJ) and regular insulin taken twice daily resulted in moderate glycemic control (A1C 7.8%). Primary hypothyroidism due to Hashimoto’s thyroiditis had been treated with l-T4 224 mg daily, a dose that was stable for 5 yr. Other medical problems include breast cancer stage II, hypertension, hyperlipidemia, and osteoarthritis. Her other medications were aspirin, calcium, verapamil, hydrochlorothiazide, gabapentin, lisinopril, and furosemide. After diagnosis of type 2 diabetes mellitus in 1998, treatment with insulin was initiated, resulting in moderate control (A1C 7.6%). Addition of metformin XR (500 mg daily) in February 2003, did not improve glycemic control (A1C 8.5% after 3 months) but was associated with a fall in serum TSH from 1.91 to 0.39 μIU/ml over 3 months. Five and 14 wk after discontinuation of metformin, serum TSH increased to 0.54 and 1.17 μIU/ml, respectively. The patient’s weight did not change while on metformin.

Table 2. TSH responses of patients 1–4 to the administration of metformin

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age (yr)/gender</th>
<th>Underlying disease</th>
<th>Dose of l-T4 (mg)</th>
<th>Duration of DM (yr)</th>
<th>Metformin (mg/d)</th>
<th>Baseline fT4 (pmol/liter)</th>
<th>Post-Met fT4 (pmol/liter)</th>
<th>Baseline TSH (μIU/ml)</th>
<th>Post-Met TSH (μIU/ml)</th>
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<tbody>
<tr>
<td>1</td>
<td>58/M</td>
<td>Graves’ disease treated with I-131</td>
<td>150</td>
<td>N/A</td>
<td>1500</td>
<td>15.3–23.9</td>
<td>13.4</td>
<td>1.19–1.90</td>
<td>0.11</td>
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<td></td>
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<td>(n = 5)</td>
<td>(n = 5)</td>
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<tr>
<td>2</td>
<td>67/F</td>
<td>Hashimoto’s</td>
<td>150</td>
<td>1500</td>
<td>1500</td>
<td>15.3–23.9</td>
<td>13.4</td>
<td>1.19–1.90</td>
<td>0.11</td>
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<tr>
<td>3</td>
<td>66/M</td>
<td>Thyroidectomy for MNG</td>
<td>125</td>
<td>5</td>
<td>1000</td>
<td>N.D.</td>
<td>1.65a</td>
<td>1.3</td>
<td>0.36</td>
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<tr>
<td>4</td>
<td>75/F</td>
<td>Thyroidectomy for PTC</td>
<td>175</td>
<td>5</td>
<td>500</td>
<td>N.D.</td>
<td>35.6</td>
<td>1.91</td>
<td>0.39</td>
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<td>(n = 5)</td>
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</tr>
</tbody>
</table>

M, Male; F, female; DM, diabetes mellitus; MNG, multinodular goiter; PTC, papillary thyroid carcinoma; Met, metformin; N.D., not done.

a Analog assay with normal range 1.01–1.79 ng/dl.

Results and Discussion

All four hypothyroid patients described in this report had decreases in serum TSH to subnormal levels after the administration of metformin. We are unaware that this finding has been previously reported. By contrast, Oleandri et al. (2) found no differences in thyroid function tests among 28 patients with no known thyroid disease who were treated for obesity with short-acting metformin (500 mg twice daily), dexfenfluramine, or placebo for 3 months in a randomized, controlled trial; weight loss was similar in each group.

Generally, serum TSH levels in a patient on a stable dose in the dose of l-T4 (from 125 μg daily to 125 μg 6 d/wk or 107 μg daily average). A premetformin fT4 was not obtained. Serum fT4 fell during metformin treatment from 1.65 to 1.06 ng/dl (Table 2).

Patient 4 is a 75-yr-old woman treated with l-T4 175 μg daily for many years after hypothyroidism developed after a thyroidectomy for papillary thyroid cancer 50 yr previously. She also has hypertension and osteoarthritis. Her other medications were aspirin, calcium, verapamil, hydrochlorothiazide, gabapentin, lisinopril, and furosemide. After diagnosis of type 2 diabetes mellitus in 1998, treatment with insulin was initiated, resulting in moderate control (A1C 7.6%). Addition of metformin XR (500 mg daily) in February 2003, did not improve glycemic control (A1C 8.5% after 3 months) but was associated with a fall in serum TSH from 1.91 to 0.39 μIU/ml over 3 months. Five and 14 wk after discontinuation of metformin, serum TSH increased to 0.54 and 1.17 μIU/ml, respectively. The patient’s weight did not change while on metformin.

Metformin addition to normal serum

When metformin was added to normal serum whose baseline serum TSH was 1.20 μIU/ml, the serum TSH concentration varied from 1.06 to 1.20 μIU/ml.

Table 2. TSH responses of patients 1–4 to the administration of metformin
of l-T₄ change only when there is a change in absorption, alteration in the dose (or brand) or its bioavailability, a substantial change in weight, or variability in compliance. Reciprocal changes in T₄ levels are usually seen in these circumstances. In patient 1, however, marked changes in serum TSH to subnormal levels were observed without any reciprocal change in serum thyroid hormone levels. In the other three patients, a baseline fT4 was not available. However, TSH remained suppressed in patients 2 and 3 despite lower doses of l-T₄ and lower fT4 levels. These observations were not due to interference in the TSH assay because metformin did not change the TSH value when added to normal serum in concentrations up to 40 times higher than the therapeutic range.

There are several possible mechanisms for the metformin-induced TSH suppression in our patients, but these should be considered speculative at the present time. Metformin may have changed the affinity and/or number of thyroid hormone receptors, increased dopaminergic tone, or induced constituent activation of the TSH receptor. These hypotheses would require that metformin be able to cross the blood-brain barrier. Although metformin is a low-molecular-mass, water-soluble molecule (168 Da), its penetration of the blood-brain barrier has not been studied. The mechanism of action of metformin at a cellular level is not completely understood but is likely to be multifactorial (3–5). The mechanism of thyroid hormone action has been better defined and is quite complex (6). Whether metformin may affect any of the steps in thyroid hormone action that have been defined to date remains to be determined.

If metformin produced subtle increases in the absorption of l-T₄ from the gastrointestinal tract, then suppression of serum TSH might be predicted. However, we believe that this is unlikely because there was no increase in serum thyroid hormone levels in our most completely studied subject (patient 1). Furthermore, whereas metformin inhibits the absorption of vitamin B12 and folate (7, 8), it is not known to increase the absorption of nutrients or medications. We cannot exclude the possibility that the TSH suppression in our patients was the result of a subtle, sustained increase in T₄ absorption and consequent rise in free serum thyroid hormone levels that was too small to be detected. In our small retrospective case series, such factors as interassay variation, biological variability of T₄ absorption, or changes in the volume of distribution may have contributed to our findings.

Could our findings be explained by a metformin-induced change in the bioavailability of circulating thyroid hormones? In some circumstances the free fraction of circulating hormones may not be the same as the level of bioavailable hormones in the circulation, e.g. both the free testosterone and non-SHBG-bound testosterone are bioavailable and the combination of both best correlates with the clinical state of the patient (9, 10). It is of interest in this regard that hormone transport proteins, such as transthyretin, facilitate the passage of T₄ across the cellular barrier, specifically the blood-brain barrier in the choroid plexus (11, 12).

In summary, we report four patients in whom metformin appeared to suppress serum TSH to subnormal levels without resulting in biochemical or clinical hyperthyroidism. If our findings are verified and the effect of metformin is central and not peripheral, metformin could be used as an adjunct for the treatment of patients with thyroid cancer because it appears to suppress serum TSH without causing biochemical hyperthyroxinemia or clinical hyperthyroidism.

Acknowledgments

Received May 31, 2005. Accepted October 3, 2005. Address all correspondence and requests for reprints to: Robert A. Vigersky, M.D., Endocrinology Service, Walter Reed, Army Medical Center, Washington, DC 20307. E-mail: robert.vigersky@na.amedd.army.mil.

The opinions expressed in this paper reflect the personal views of the authors and not the official views of the United States Army or the Department of Defense.

References


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