Goserelin-induced transient thyrotoxicosis in a hypothyroid woman on L-thyroxine replacement

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ABSTRACT

An increase in free thyroxine (fT4) and a decrease in thyroid-stimulating hormone (TSH) was observed in a hypothyroid woman on levothyroxine treatment after implantation of goserelin, a gonadotropin-releasing hormone (GnRH) analogue. In the literature no data are available that describe a drug interaction between GnRH analogues and thyroid hormone replacement. Our hypothesis to explain this observation is that goserelin decreased serum thyroxine-binding-globulin (TBG), resulting in an increase in fT4 and thereby a decrease in serum TSH.

KEYWORDS

GnRH analogue, hypothyroidism, sex hormones, thyroid function

INTRODUCTION

Sometimes patients ask their doctors questions about drug interactions, which are hard to answer because the literature contains insufficient data on the particular topic. In our case, the question was if there was a known drug interaction between thyroxine and goserelin, a gonadotropin-releasing hormone (GnRH) analogue. Nothing could be found in the literature on such an interaction. Subcutaneous implantation of goserelin will suppress luteinising hormone (LH) and follicle-stimulating hormone (FSH) via sustained delivery of GnRH, resulting in a decrease in oestrogens and chemical castration. The question from our patient, who was on levothyroxine replacement because of primary hypothyroidism, led us to hypothesise that in her case goserelin administration could indeed have an adverse interaction with thyroxine treatment. For, the fall in serum oestrogens will decrease the serum concentration of thyroxine-binding globulin (TBG), the major transport protein for thyroid hormones in serum. Consequently less thyroid hormone is needed for TBG binding. If the thyroid gland is unable to decrease its thyroxine secretion (as in our patient), continuation of the exogenous dose of thyroxine might result in an increase of serum free thyroxine (fT4). This case report tests our hypothesis that this indeed might happen.
We hypothesised that an elevated fT4 might occur after total T4 decreased significantly in both groups within four and two weeks, respectively. In the control group fT4 levels remained unchanged and TSH decreased slightly. In the hypothyroid group on levothyroxine replacement fT4 levels increased and TSH decreased within two weeks. These biochemical changes were associated with complaints of tachycardia, hyperhydrosis and insomnia. Thyroid hormone doses had to be reduced by between 25 and 50% to maintain euthyroidism. After discontinuation of the androgens, the TSH levels increased and fT4 levels decreased when patients continued on the same thyroxine dose. TBG levels returned to normal after eight to ten weeks after therapy was discontinued.

The opposite study was done several years later. Thirty-six postmenopausal women were given oral oestrogens. In both groups TBG and total T4 became significantly elevated after 12 weeks but in the healthy group TSH and fT4 did not change. In the hypothyroid women on thyroid replacement fT4 and TSH were significantly decreased and elevated, respectively, at 12 weeks; one woman had symptoms of hypothyroidism and needed an increase in levothyroxine replacement dose. This effect persisted during the whole study period. No data were shown after discontinuation of oestrogens.

The difference in fT4 and TSH between the control groups and the women on thyroxine is explained by the notion that subjects on levothyroxine replacement are not able to adjust their serum fT4 concentration via changes in the TSH secretion. For example, administration of androgens will decrease TBG, in all likelihood due to a decrease of glycosylation of TBG and thereby an increase in the clearance of TBG. According to the law of mass action, the reduction in TBG will increase the free fraction of circulating thyroxine (fT4), followed by a decrease in TSH secretion. Under physiological conditions the lower TSH secretion will reduce thyroxine secretion by the thyroid gland, and the equilibrium between bound and fT4 in the circulation is restored under normalisation of serum fT4. In hypothyroid patients on a fixed dose of exogenous thyroxine the adaptation to changes in serum TBG via the negative feedback of thyroid hormones on the pituitary is failing. Upon administration of androgens to women the decrease in TBG concentration as reported by Arafah is between 9 to 13 mg/l (167 to 241 nmol/l). The TBG level in our patient decreased by only 40 nmol/l upon suppression of endogenous oestrogens. Thus the decrease in our patient was modest and may explain the limited increase in fT4 and minimal decrease in TSH. The effect of sex hormone therapy on thyroid function depends on the route of administration. Transdermal oestrogens or testosterone therapy do not raise serum TBG and therefore do not alter the fT4 level, because transdermal sex hormones do not have a hepatic first-pass effect in contrast to oral sex hormones. Thus the transdermal route is preferable in women receiving thyroid-hormone replacement.

TBG and T4 are also influenced by tamoxifen, droloxifene and by intramuscular testosterone (table 1). No data of alterations in fT4 due to tamoxifen or intramuscular
testosterone are known in patients with hypothyroidism. But it can be assumed that fT4 levels would change in substituted hypothyroidism. The clinical relevance of these changes is minor in many but not all patients as shown by Arafah.1,2 The symptoms in our patient after goserelin implantation are, in our opinion, non-thyroid-related side effects. First TSH was not completely suppressed and second, T3 remained unchanged.

| Table 1. The effect of exogenous oestrogens and androgens on thyroid function tests |
|---------------------------------|---|---|---|---|
| Oral oestrogens                | ↑ | ↑ | = | = |
| Transdermal oestrogens         | = | = | = | = |
| Tamoxifen, droloxifene         | ↑ | ↑ | No data | No data |
| Oral androgens                 | ↓ | ↓ | = | = |
| Intramuscular testosterone     | ↓ | ↓ | = | = |
| Transdermal testosterone       | = | = | No data | No data |
| Goserelin                      | ↓ | ↓ | ↑ (Hypo on T4) | ↓ (Hypo on T4) |

TBG = thyroxine-binding globulin; T4 = thyroxine; TSH = thyroid-stimulating hormone.

CONCLUSION

Our advice is to check thyroid function regularly in patients on thyroid hormone substitution therapy who are being treated with sex hormones.

REFERENCES

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