EFFECT OF LITHIUM AND ORAL THYROTROPHIN-RELEASING HORMONE (TRH) ON SERUM THYROTROPHIN (TSH) AND RADIOIODINE UPTAKE IN PATIENTS WITH WELL DIFFERENTIATED THYROID CARCINOMA

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ABSTRACT

Oral thyrotrophin-releasing hormone (TRH) and lithium were given to patients on follow-up for well-differentiated thyroid carcinoma to see their effect on serum thyrotrophin level (TSH) and radioiodine (I-131) uptake (RAIU). The study was randomised and doubled-blinded and consisted of a total of 19 patients in 3 groups. Group 1 received placebo and TRH, group 2 received lithium and placebo, and group 3 received lithium and TRH. Serum TSH and RAIU at 24 hours were measured before, and after treatment, with TRH, lithium, and/or placebo. In group 1, mean (±SEM) TSH increased from 48.9 (±15.2) mU/l to 148.2 (±48.0) mU/l ($p<0.05$); in group 2, the change of 24.9 (±15.9) mU/l to 31.7 (±14.1) mU/l in TSH was not statistically significant; and in group 3, TSH increased from 108.1 (±13.8) mU/l to 187.0 (±39.1) mU/l ($p<0.05$). However, despite the significant change in TSH, there was no significant increase in I-131 uptake in any group: 7.70% to 10.43%, 7.15% to 7.43% and 2.49% to 2.61%, in groups 1, 2 and 3 respectively ($p>0.05$). We conclude that while oral TRH will increase endogenous serum TSH significantly, there is no significant increase in I-131 uptake. Lithium was not an useful adjunct in increasing serum TSH or I-131 uptake in these patients.

Keywords: *follicular carcinoma, I-131 uptake, papillary carcinoma, serum thyrotrophin (TSH), lithium*

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INTRODUCTION

Well-differentiated thyroid carcinoma accounts for at least 80% of all thyroid malignancies. By virtue of their differentiation, these tumours retain significant functioning endocrine properties that are similar to normal thyroid tissue. They are thus able to concentrate and organify small but significant amounts of iodine and this important property is used in the detection and treatment of the primary tumour and also detection of tumour recurrence in the follow-up of these patients after treatment.

Radioiodine (I-131) uptake therefore is a valuable adjunct in the detection of recurrence and metastases in well-differentiated thyroid carcinoma. This radionuclide is trapped and organified like inorganic iodine, and its β-emitting properties make this isotope useful in the eradication of residual thyroid tissue and in the treatment of local recurrence and/or distant metastases. Radioiodine (I-131) also emits gamma rays that can be used for scintigraphy and thus enables the detection of residual tissue, local and distant disease.

However, the detection of I-131 uptake in thyroid remnant, tumour residues and distant metastases can be difficult if the quantity of tissue is small. Several ways have been used to try to increase the I-131 uptake. These include a low iodine diet (such as reduced intake of seafood, flour products, medication containing iodine, etc)[1], thiazide diuretics[2], mannitol[3], and intravenous thyrotrophin releasing hormone (TRH)[4]. It has been shown that TRH not only increased the serum thyroid stimulating hormone (TSH) concentration, but also increase its bioactivity[5,6]. On the other hand, lithium inhibits the secretion and release of free iodine from the thyroid gland and hence increases retention of the amount of radioiodine taken up by the thyroid tissue[7,8]. Both these properties may well increase the uptake of radioiodine by the remnant thyroid tissue or residual thyroid tumour.

In this study, we investigated the effect of either oral TRH or lithium alone, or both in combination, on the serum level of circulating TSH and on I-131 uptake in patients with well-differentiated thyroid carcinoma.

PATIENTS AND METHODS

Twenty-one consecutive patients who had prior total thyroidectomy for carcinoma of the thyroid were entered in the study between May to October 1989. They had a mean (±SE) duration of 2.95 (±1.21) years post-thyroidectomy. All the patients were taken off thyroxine for five weeks prior to receiving I-131 treatment.

The patients were randomised into three groups. Group 1 was given placebo 3 times/day for seven days, and on day 8, oral TRH (40 mg, Roche, Switzerland) was given. Group 2 was given lithium carbonate 200 mg (Camcolit, Norgine, UK) 3 times/day for seven days and placebo on day 8. Group 3 was given lithium 3 times/day for seven days and TRH (40mg) on day 8. The study was double-blinded and the code was broken after completion of the entire study. Ablative treatment of the patients with I-131 was not dependent on the results of the study. Each patient gave informed consent.

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Serum was obtained for TSH and T4 measurements on 0 hour of day one (as baseline) and 0 hour and 4 hour on day 8. Radioiodine uptake was measured at 24 hours post tracer dose before (day 0) and again at the end of the study (day 9). Statistical analysis was performed in two ways. The student's t-test for paired samples was used within each group to see the effect on TSH level and I-131 uptake before and after the treatment with TRH and lithium. The three groups were compared using analysis of variance on the general linear model in the Statistical Analysis Systems (SAS-institute, USA). The Mann-Whitney test was used to assess the statistical significance of any difference between the three groups.

RESULTS

A total of 21 consecutive patients were included in the study. At entry, group 1 had seven patients, group 2 had six patients and group 3 had eight patients. Two patients dropped out of the study, one each from groups 1 and 3. The mean ages were 46, 63, 36 years for groups 1, 2 and 3, respectively. Although the groups were not of similar age as a result of the double-blinded randomisation, age is not known to affect thyroid uptake of I-131[9].

The histological type was similar in the three groups: Groups 1 and 2 both had four patients with papillary carcinoma and two patients with follicular carcinoma in each group; and Group 3 had four patients with papillary carcinoma and three patients with follicular carcinoma.

In group 1, there was no significant increase in serum TSH in the seventh day after placebo; the mean TSH (±standard error of mean) was 36.6 (±13.2) mU/l before and 48.9 (±15.2) mU/l after placebo ($p > 0.05$). However, the blood sample taken 4 hours after oral TRH on day 8 revealed a significant increase in the TSH level from 48.9 (±15.2) mU/l on 0 hour of day 8 to 148.2 (±48) mU/l on 4 hour of day 8 ($p < 0.05$).

In group 2 after seven days of oral lithium, there was no significant increase in the TSH level at the end of the seventh day; TSH was 21.5 (±18.4) mU/l on day 1 and was 24.9 (±15.9) mU/l on 0 hour of day 8 ($p > 0.05$); 4 hours after placebo on day 8, the TSH was 31.7 (±14.1) mU/l.

In group 3, where the patients received both oral TRH and lithium, the lithium given from days 1 to 7 did not change the TSH significantly, it was 88.4 (±18.8) mU/l before and 108.1 (±13.8) mU/l after ($p > 0.05$). However, the addition of oral TRH did increase the TSH level significantly from 108.1 (±13.8) mU/l to 187.0 (±39.1) mU/l ($p < 0.05$).

As shown in Fig 1, when the change in TSH in group 3 was compared with group 1, which did not receive lithium but received only oral TRH, there was no significant difference between the two groups. Both groups 1 and 3 were significantly different from group 2 in the change in TSH level. Hence, TRH causes a significant change in TSH but lithium does not.

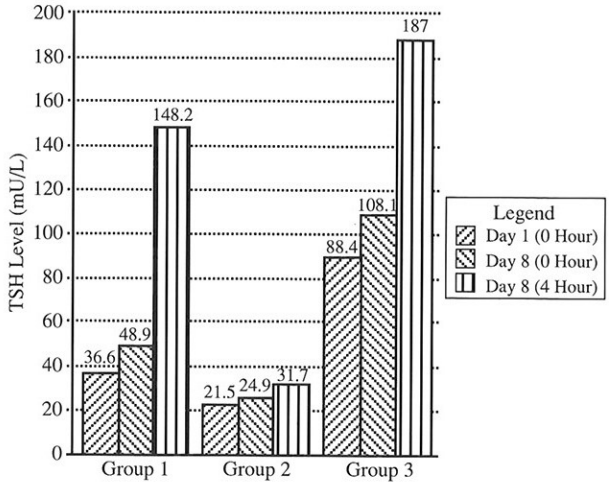
Unfortunately, although the serum TSH increased significantly in groups 1 and 3, all three groups did not show any significant increase in the I-131 uptake. Radioiodine uptake before and after were 7.70% and 10.43%, 7.15% and 7.43%, and 2.49% and 2.61% in groups 1, 2, and 3 respectively ($p > 0.05$ in all three groups).

DISCUSSION

In the treatment of well-differentiated thyroid cancer, a near total thyroidectomy is first done, and if patients are to be treated with I-131, they are allowed to become hypothyroid in order to increase TSH secretion by the pituitary gland that will stimulate the remnant thyroid tumour to take up the I-131 more readily.

This practice has several disadvantages as it requires L-thyroxine replacement to be withheld for a period of about four to five weeks, during which time the patients are subject to the effect of hypothyroidism. This is made worse by the fact that during this period of time, the tumours are under the continued influence of TSH stimulation, and therefore, there is at least a theoretical possibility of tumour growth stimulation. Moreover, many patients in our department are foreigners from neighbouring countries and if they are not adequately hypothyroid it increases their inconvenience, time and financial burden to either stay longer or go back and return at a later date. It would be useful if we could increase the endogenous serum TSH, and therefore the I-131 uptake over a shorter period of time.

Fig 1 – Changes in serum TSH in the three treatment groups



The results of our present study showed that endogenous serum TSH could be significantly elevated with TRH, but I-131 uptake was not elevated. Our study was carefully double-blinded and the code was broken only on completion of the entire study. When the codes were opened, group 3 had a significantly higher baseline TSH compared to the other 2 groups. However, the RAIU, which was the final (clinically useful) end-point of the study, was comparable in the three groups, and serum TSH did rise significantly with oral TRH in group 3 in a similar manner as in group 1. We therefore think that our results remain valid in demonstrating that, while serum TSH was significantly raised by TRH, the I-131 uptake did not change significantly in any of the three study groups.

Earlier studies by Pons[8] and others[10] had shown an increase in radiation dose to the tumour site with lithium by means of retaining the I-131 at the site of tumour tissue although the therapeutic: toxic ratio was not affected by lithium.

Our results do not show much of a lithium effect. The lithium effect may be more important in the presence of significant or larger remnants than was present in our study patients.

Our study shows for the first time, that TRH is effective in increasing the serum TSH significantly even when given orally. This is much simpler than the intravenous TRH that was used by other groups[4] to increase RAIU in these patients. Unfortunately, despite the significant increase in TSH, our results did not translate into a significant increase in I-131 uptake, with or without the addition of lithium. This lack of a clinically and therapeutically useful difference may be because of the small numbers in our study, or to the absence of sufficiently large secondary deposits. It is certainly theoretically possible that in certain situations, where significant time has elapsed after thyroidectomy, and significant recurrence at the thyroid remnant or in secondary deposits had occurred, that the use of TRH orally,

with or without lithium, might prove to be clinically useful. Therefore, our negative results should not prevent further studies in these situations.

However, our negative results do concur with an earlier study[4] which used intravenous TRH on patients with thyroid carcinoma and also found no significant change in I-131 uptake, even though there was an increase in the TSH level when the patients were given intravenous TRH.

CONCLUSION

In conclusion, this study describes an attempted new approach to the problem of increasing radioiodine uptake in well-differentiated thyroid cancer, using oral TRH and/or oral lithium as a means to increase the I-131 uptake. Our results showed no significant increase in the I-131 uptake by either oral TRH alone, or in combination with lithium, although oral TRH significantly increased the serum TSH. Further studies are required to look for effective means of increasing I-131 uptake significantly in patients with thyroid cancer after thyroidectomy.

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