Effect of sodium ipodate and iodide on free T_4 and free T_3 concentrations in patients with Graves' disease

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ABSTRACT. Graves' hyperthyroid patients were treated daily for 10 days with 1 g sodium ipodate, a cholecystographic agent which exerts a blocking effect on the peripheral conversion of T_4 to T_3, or with 12 drops of saturated solution of potassium iodide (SSKI). Serum concentrations of free T_4 (FT_4) and free T_3 (FT_3) were measured before, during and 5 and 10 days after the administration of each drug. Sodium ipodate treatment induced a rapid decrement of serum FT_4 concentrations which declined from 48.9 ± 6.6 pg/ml to 26.0 ± 2.7 pg/ml. In these patients serum FT_3 concentrations declined from 12.4 ± 2.0 pg/ml to 2.5 ±0.4 pg/ml. Ten days after sodium ipodate withdrawal, serum FT_4 and FT_3 concentrations returned to baseline values. In patients treated with SSKI serum FT_4 concentrations declined from 51.1 ± 8.8 pg/ml to 11.3 ± 1.4 pg/ml and FT_3 from 15.7 ± 2 pg/ml to 2.6 ± 0.3 pg/ml. Moreover, after therapy interruption serum free thyroid hormone concentrations returned to baseline values in these patients. Serum FT_4 pattern during the study was not different between the two groups of subjects whereas serum FT_3 concentrations were significantly lower in patients treated with sodium ipodate. These findings indicate that SSKI and sodium ipodate are effective in inducing a rapid decrement of serum free thyroid hormone concentrations. Therefore the employment of these drugs may be useful in the treatment of patients with thyroid storm and those undergoing thyroidectomy.

INTRODUCTION

The administration of oral cholecystographic agents has been reported to be useful in the treatment of hyperthyroid patients (1). The therapeutical employment of these substances induces a significant decrement of biologically active iodothyronine concentrations with amelioration of clinical symptoms and signs of thyrotoxicosis (2-4). Stable iodine administration to hyperthyroid patients, as well, is accompanied by a rapid decrement of serum total thyroxine (TT_4) and total triiodothyronine (TT_3) concentrations (5). This last therapeutic approach has been recommended in association with antithyroid drugs only in certain conditions, principally in patients with thyroid storm (6).

Recently, we have compared the effect of the administration of these two drugs on serum TT_4 and TT_3 concentrations of patients with active Graves' disease (7). Since free thyroid hormone concentration measurement is a more reliable indication of the activity of thyroid hormone at cellular level (8), we believed interesting to measure serum free T_4 (FT_4) and free T_3 (FT_3) concentrations in those patients that we had previously studied.

MATERIALS AND METHODS

Twenty patients with active Graves' disease were studied. The diagnosis of Graves' disease was established by clinical and laboratory evaluation. Fourteen patients, twelve females and two males, with a mean age of 41.6 ± 5.1 years were treated with 1 g sodium ipodate orally (Biloptin, Schering, AG Berlin, 616 mg iodine), each day. Six patients, five females and one male, with a mean age of 34.5 ± 5.8 years were treated with 12 drops of saturated solution of potassium iodide orally (SSKI 456 mg iodine), each day. The difference in the number of patients in the two groups was due to the poor compliance of SSKI treated patients which did not continue the study protocol. Both drugs were administered as a single dose at 08:00 for 10 days. All patients were hospitalized during the study and no other medication was administered.

Blood specimens were obtained prior to treatment (baseline), at 6 and 12 hours after the administration of the first dose of each drug, and each day thereafter until the 10th day of treatment. Five and ten days after

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the interruption of the treatment, blood samples were also obtained. Serum samples were kept frozen at —20 C until hormone analysis.

Serum FT_4 and FT_3 concentrations were measured with Amerlex Free T_4 and Free T_3 kits (Amersham International plc. Amersham, UK). Each sample was measured in duplicate, in the same assay and in random order. Normal values for FT_4 and FT_3 are 6.6-19 pg/ml and 2.8-6.6 pg/ml, respectively. The intraassay coefficient of variation was 3.1% for FT_4 and 4.2% for FT_3.

Statistical analysis was conducted with one way analysis of variance (ANOVA) to compare hormone variation in each group of patients. For each treatment group, the Duncan's multiple range test (9) was employed to compare hormone concentrations during and after treatment with respect to baseline values. Comparison of hormone values during the treatment period (days 1 to 10) between the two groups of patients was carried out by two ways analysis of variance (two ways ANOVA).

RESULTS

Serum FT_4 concentration (Fig. 1).

Basal serum FT_4 concentration in the group of patients treated with sodium ipodate was 48.9 ± 6.6 pg/ml. During the treatment period a significant decrement of serum FT_4 concentrations was observed ($p < 0.001$; ANOVA test). The lowest FT_4 value was observed at the 9th day of the treatment ($p < 0.01$ *vs* baseline; Duncan's test). Ten days after the interruption of sodium ipodate administration (day 20 of the study) serum FT_4 concentration returned to values approximately equal to the baseline ones. During the treatment period and after drug withdrawal serum FT_4 concentrations were constantly above the normal range.

In the group of patients treated with SSKI, basal serum FT_4 concentration was 51.1 ± 8.8 pg/ml. A significant decrement of serum FT_4 values was observed ($p < 0.001$; ANOVA test) during treatment. The lowest value was observed at the 10th day of treatment: 11.3 ± 1.4 pg/ml ($p < 0.005$ *vs* baseline; Duncan's test). Ten days after the interruption of SSKI administration FT_4 concentrations returned to values similar to the baseline ones. From day 7 to day 10 of the study serum FT_4 concentrations were in the normal range.

When comparing serum FT_4 concentrations in the two groups of patients, no significant difference was observed ($p > 0.05$, two ways ANOVA).

Serum FT_3 concentration (Fig. 2)

In the group of patients treated with sodium ipodate, serum FT_3 concentration was 12.4 ± 2.0 pg/ml. During treatment a striking decrement of serum FT_3 concentration was observed ($p < 0.001$; ANOVA test). As for serum FT_4, the lowest FT_3 value was measured at the 10th day of treatment ($p < 0.001$ vs baseline; Duncan's test). From the 2nd day of the treatment period to the 5th day after sodium ipodate withdrawal, serum FT_3 concentration was in the normal range. At the 10th day after interruption of treatment, serum FT_3 concentration returned to baseline value.

In the group of patients treated with SSKI, the basal serum FT_3 concentration was 15.7 ± 2 pg/ml. During the treatment period, a significant decrement of serum FT_3 values was oberved ($p < 0.001$; ANOVA test). Five days after the interruption of SSKI administration, FT_3 value returned to baseline ($p > 0.05$; Duncan's test). In the patients treated with SSKI FT_3 concentrations were in the normal range only from day 5 to day 10 of the treatment period. When comparing the two groups of patients, serum FT_3 concentration was significantly

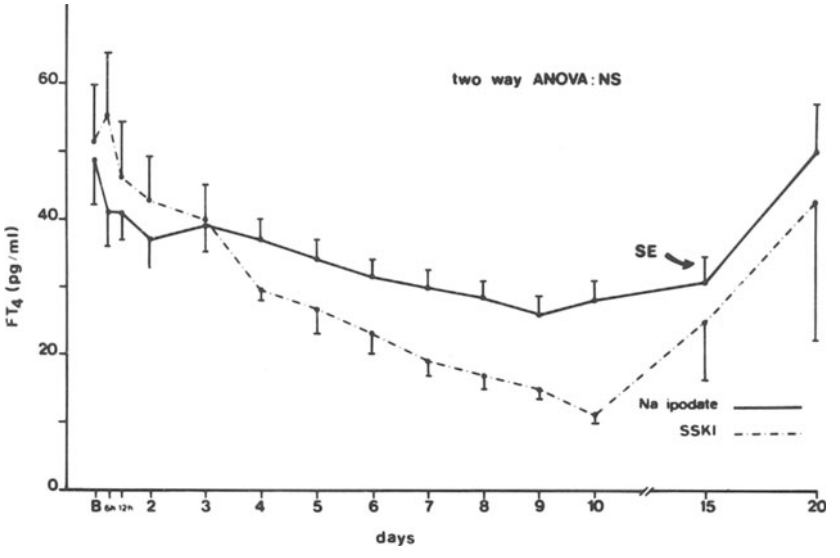

Fig. 1 - *Effect of sodium ipodate (●——●) SSKI (●- - -●) administration on serum FT_4 concentration in patients with thyrotoxic Graves' disease. Bars represent SE. No significant difference was observed between the two treatments (two ways ANOVA). B = baseline value.*

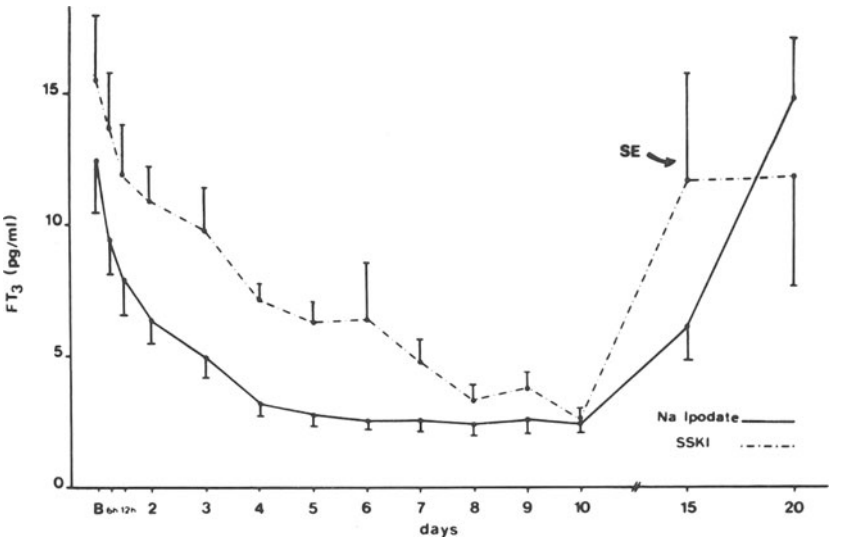

Fig. 2 - Effect of sodium ipodate (●——●) and SSKI (●- - -●) administration on serum FT_3 concentration in patients with thyrotoxic Graves' disease. Bars represent SE. A significant difference was observed between treatments ($p < 0.001$; two ways ANOVA). B = baseline value.

lower in the group of subjects treated with sodium ipodate ($p < 0.001$; two ways ANOVA).

DISCUSSION

Administration of iodide (6, 10) and of oral cholecystographic agents (1) has been indicated as a possible adjuvant in the treatment of some hyperthyroid conditions. However they are not generally recommended as the sole therapy in hyperthyroid patients (6, 11). The action of these drugs on thyroid function is in part different. Iodide administration induces a rapid block of T_4 and T_3 release from the hyperfunctioning gland (12) restoring, after a ten-day treatment course (7) normal serum TT_4 and TT_3 concentrations. However, the effect of iodide administration on thyroid function is not permanent and a rebound of serum TT_4 and TT_3 concentrations is usually observed either during treatment or after withdrawal of iodine preparations (5, 7).

Oral colecystographic agents, when administered to hyperthyroid patients, induce a striking decrement of serum TT_3 concentrations and a mild decrement of serum TT_4 values (2-4, 7). The effect of oral cholecystographic agents on serum T_3 concentration is mainly the result of the inhibition of 5' deiodinase which converts T_4 to T_3 in the peripheral tissues (13-15), and of T_4 uptake from circulation into hepatic cells (16). These effects of oral cholecystographic drugs on serum thyroid function are related to their chemical structure. In fact other X-rays contrast media, such as diatrizoate salts, do not have relevant effect on serum thyroid hormone concentrations in euthyroid subjects (17, 18). However it is likely that oral cholecystographic agents have a partial blocking effect on the release of thyroid hormones from the gland since iodine is released from the drug by its deiodinating metabolism in body tissues. This interpretation is supported by the observation that oral cholecystographic agent administration results in a marked reduction of the thyroid radioiodine uptake (19).

In a previous report (7) we have studied the effect of sodium ipodate or SSKI administration on serum TT_4 and TT_3 concentrations in Graves' hyperthyroid patients. It was observed that the administration of sodium ipodate or SSKI resulted in a significant decrement of TT_4 and TT_3. However some differences were observed. The decrement of serum TT_4 concentrations was greater in the group of patients treated with SSKI whereas the decrement of serum TT_3 concentration was higher and more rapid in the group of patients treated with sodium ipodate. Free thyroid hormone concentrations in subjects treated with SSKI or ipodate have been occasionally measured. In normal subjects it has been observed that the administration of cholecystographic agents resulted in a marked increase of serum FT_4 concentrations (20, 21) with a concomitant decrement of FT_3 values (21). In few hyperthyroid patients it has been reported that ipodate treatment induces a decrement of TT_4 without any or minor changes of percent free fraction resulting in a decrement of serum FT_4 concentrations (4). In hyperthyroid patients Sharp et al. (22) have observed that the addition of sodium ipodate to propranolol and propylthiouracil treatment induces a more rapid decrement of free T_3 index (FT_3I) but not of free T_4 index (FT_4I).

In the present investigation, by means of a direct radioimmunoassay of free thyroid hormone concentrations, we have evaluated the effect of sodium ipodate or iodine administration on serum FT_4 and FT_3 concentrations.

In the group of patients treated with sodium ipodate, serum FT_3 concentration showed a striking and rapid decrement returning to normal range values at the

second day of treatment and remaining normal until 5 days off therapy. In the same patients, serum FT_4 concentrations significantly decreased from baseline, however their values were above the normal range through the treatment period and thereafter. SSKI treatment markedly reduced FT_4 concentrations which returned to normal range after seven days of treatment. In this group of patients serum FT_3 concentrations, as well, showed a significant decrement, however it was lower than that observed in patients treated with sodium ipodate. Furthermore, serum FT_3 concentrations returned to the normal range only on the 5th day of treatment. These results are similar to those previously reported for TT_4 and TT_3 (7) and account for the observation that sodium ipodate treatment induces an amelioration of the clinical symptoms and signs of hyperthyroidism (3, 4). In fact the biological effects of thyroid hormones are mainly mediated by their free amounts (8).

Although these findings indicate that sodium ipodate and SSKI administration induces a rapid decrement of free thyroid hormone concentration, they do not allow us to recommend the employment of these drugs as the sole treatment of hyperthyroid patients. In fact, after interruption of both drugs, serum FT_4 and FT_3 concentrations returned to values similar to those measured before treatment. If sodium ipodate and SSKI were administered in association with antithyroid drugs, free thyroid hormone concentrations would probably stay in the normal range also after the interruption of sodium ipodate and SSKI treatment. However, it has been pointed out that large amount of iodide might reduce the remission rate of Graves' hyperthyroidism (23).

The employment of sodium ipodate and SSKI may be beneficial in the treatment of patients with thyroid storm and those undergoing thyroidectomy. In fact we have recently observed (Roti et al., unpublished observations) that patients treated with sodium ipodate and SSKI in combination with methimazole have a more rapid decrement of serum FT_3 concentrations and heart rate than those treated with methimazole alone.

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