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COMPARISON OF METHIMAZOLE, METHIMAZOLE AND SODIUM IPODATE, AND METHIMAZOLE AND SATURATED SOLUTION OF POTASSIUM IODIDE IN THE EARLY TREATMENT OF HYPERTHYROID GRAVES' DISEASE

E. ROTI, G. ROBUSCHI, E. GARDINI, M. MONTERMINI, M. SALVI, A. MANFREDI, A. GNUDI AND L. E. BRAVERMAN

Cattedra di Endocrinologia e Patologia Costituzionale, l'Clinica Chirurgica, Universita degli Studi di Parma, Parma, Italy; Divisione di Chirurgia, Ospedale S. Maria, USL N.6, Borgotaro, Italy; Division of Endocrinology and Metabolism, University of Massachusetts Medical School, Worcester, MA 01605, USA

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SUMMARY

We have evaluated three regimens for the rapid control (10 days' therapy) of thyrotoxicosis in hyperthyroid Graves' disease: methimazole (MMI, 40 mg/day), MMI and sodium ipodate (MMI+Na Ipodate, 1 g/day and MMI and saturated solution of potassium iodide (MMI+SSKI, 6 drops twice daily). When serum T4 and T3 concentrations were analysed as the percent change from pre-treatment values, the following results were observed. Serum T4 concentration decreased in the three treatment groups and the decrease was similar in the MMI and MMI+SSKI groups but significantly lower than in the MMI+Na ipodate group. The serum T3 concentration decreased to the normal range in all seven MMI+Na Ipodate treated patients by the fourth day of treatment and the per cent decrease in serum T3 from pre-treatment values was significantly greater than in the MMI and MMI+SSKI treated patients. The decrease in serum T3 was similar in the latter two groups. Heart rate decreased in all three groups, but the decrease was significantly more in the MMI+Na Ipodate-treated patients. The present findings suggest that the rapid control of hyperthyroid Graves' disease is similar in patients treated with MMI and MMI+SSKI and that the combination of MMI+Na Ipodate is more efficacious since the decrease in serum T3 concentrations and heart rate was significantly greater in the MMI+Na ipodate-treated patients.

Stable iodine in combination with anti-thyroid drugs is generally recommended when a rapid return to normal of serum thyroid hormone concentrations is required, such as in the treatment of patients with thyroid storm and in those undergoing urgent thyroidec-

Correspondence: Dr L. Braverman, Division of Endocrinology and Metabolism, University of Massachusetts Medical School, Worcester, MA 01605, USA.

tomy (Braverman, 1983). Iodine induces a rapid decrease in serum total and free thyroxine (T4) and 3,3′,5-triiodothyronine (T3) concentrations by blocking their release from the thyroid (Wartofsky *et al.*, 1970; Roti *et al.*, 1985; Robuschi *et al.*, 1986). Iodine containing oral cholecystographic X-ray contrast agents, either alone or in combination with anti-thyroid drugs, have also been recommended in the treatment of hyperthyroidism (Brown *et al.*, 1978). The administration of these compounds to hyperthyroid patients induces a rapid decrease in serum total and free T3 (FT3) concentrations, a slight decrease in serum total and free T4 (FT4) concentrations, and a marked increase in serum total 3,3′,5′-triiodothyronine (reverse T3,rT3) concentrations (Roti *et al.*, 1985; Robuschi *et al.*, 1986). These changes are the result of their inhibition of outer ring 5′-deiodination of T4 and rT3 (Burgi *et al.*, 1976; Suzuki *et al.*, 1979, 1981; Beng *et al.*, 1980; Kleinmann *et al.*, 1980) and of the blocking effect of iodine generated from these agents on thyroid hormone release (Grayson, 1960; Wartofsky *et al.*, 1970).

In the present report, we have compared the short-term effects of methimazole (MMI), MMI and sodium ipodate (MMI + Na ipodate) and MMI and saturated solution of potassium iodide (MMI + SSKI) on serum thyroid hormone concentrations and the clinical response in patients with thyrotoxic Graves' disease. A comparative study of the effects of these three different treatment regimens on thyroid function has not previously been reported.

MATERIALS AND METHODS

Twenty-two patients with hyperthyroid Graves' disease were studied after informed consent was obtained. The diagnosis of Graves' disease was established by clinical and laboratory evaluation. Patients were randomly assigned on admission to different treatment groups. The treatment regimens were unknown to the investigators during their hospitalization. Seven females aged 34·1 ± 7 years (mean ± SE) were treated with 10 mg MMI every 6 h (MMI). Seven females aged 42·1 ± 4·3 years were treated with 10 mg MMI every 6 h and 1 g Na ipodate administered in a single dose at 0800 h (MMI + Na Ipodate). Eight patients, seven females and one male, aged 45·6 ± 2·5 years, were treated with 10 mg MMI every 6 h and 6 drops SSKI every 12 h (MMI + SSKI). The three groups of patients were treated for 10 days. Patients were hospitalized during the study and no other medications were administered. Blood samples were obtained in the morning before the administration of the medications.

Blood samples were obtained before treatment and thereafter every other day during treatment. At the same time intervals, blood pressure (BP), heart rate (HR) and body weight (BW) were recorded. BP and HR were always measured between 0800 h and 0900 h with the patients lying in bed. BW was recorded in the morning.

Serum samples were kept frozen at −20°C until analysis. Serum T4 concentration was measured by radioimmunoassay (RIA) with materials obtained from Biodata (Milan, Italy). Serum T3 and rT3 concentrations were measured by RIA by methods previously described (Bandini *et al.*, 1975; Roti *et al.*, 1979). Serum TSH concentration was measured with materials kindly supplied by the National Pituitary Agency, NIDDK, Bethesda, MD.

All values are reported as the mean ± SE. One way ANOVA and Kruskal-Wallis test were employed to compare basal values in patients in the three treatment groups. Linear regression has been used to analyse the changes in serum hormone concentrations and the

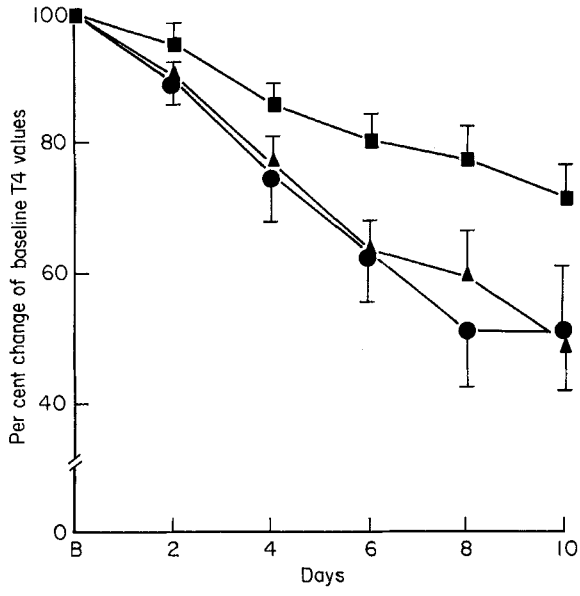

Fig. 1. The effects of MMI (●), MMI + Na ipodate (■) and MMI + SSKI (▲) administration on serum T4 concentration in patients with thyrotoxic Graves' disease. The per cent values of baseline of the three groups of patients are represented. The 100% values for the serum T4 concentrations in the three groups are: MMI, 235 ± 36 nmol/l; MMI + Na ipodate, 199 ± 23; MMI + SSKI, 212 ± 23. Patients treated with MMI + Na ipodate had higher T4 values than MMI and MMI + SSKI treated patients ($P < 0{\cdot}001$, two-way ANOVA). No difference was observed between MMI and MMI + SSKI-treated patients.

clinical results in each group. To compare the changes in serum hormone concentrations and the clinical parameters between the three groups, individual absolute values have been transformed to the percent of their respective basal values. Two way ANOVA has been employed to compare hormone and clinical parameters among the three groups of patients. Statistical calculations have been conducted with the aid of a CDC 7300 computer.

RESULTS

Basal serum iodothyronine concentrations, age, weight, pulse rate and BP were not significantly different between the three treatment groups (one-way ANOVA, Kruskal-Wallis test).

Serum T4 concentration

In the patients treated with MMI alone, basal serum T4 concentrations were 235 ± 36 nmol/l and they significantly declined during treatment. On days 8 and 10 of treatment, serum T4 concentrations were in the normal range.

In the patients treated with MMI + Na Ipodate, basal serum T4 concentrations were 199 ± 23 nmol/l and significantly declined during treatment and normal serum T4 concentrations were reached on days 8 and 10.

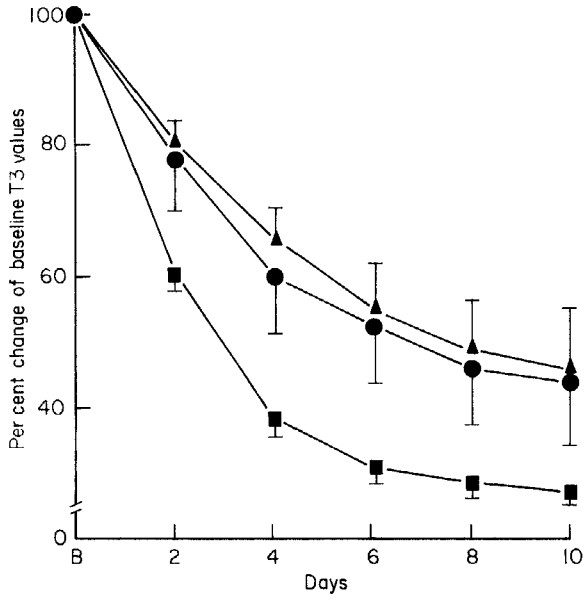

Fig. 2. The effects of MMI (●), MMI + Na ipodate (■), and MMI + SSKI (▲), administration on serum T3 concentration in patients with thyrotoxic Graves' disease. The per cent values of baseline of the three groups of patients are represented. The 100% values for the serum T3 concentrations in the three groups are: MMI, 8·7 ± 1·3 nmol/l; MMI + Na ipodate, 5·6 ± 0·8; MMI + SSKI, 5·8 ± 0·8. Patients treated with MMI + Na Ipodate had lower T3 values than MMI and MMI + SSKI treated patients ($P < 0·001$, two-way ANOVA). No difference was observed between MMI and MMI + SSKI-treated patients.

Basal serum T4 concentrations were 212 ± 23 nmol/l in the patients treated with MMI + SSKI. A significant decrease in the serum T4 concentration was observed during treatment and normal values were reached on days 8 and 10 of treatment.

When the changes in the serum T4 concentration were analysed as the percent change of baseline values, the serum T4 concentration in patients treated with MMI + Na Ipodate was significantly less ($P < 0·001$, two-way ANOVA) than values observed in patients treated with either MMI or MMI + SSKI. Furthermore, no significant difference in serum T4 concentrations was observed between patients treated with MMI alone as compared to those treated with MMI + SSKI.

Serum T3 concentration

In the patients treated with MMI alone, basal serum T3 concentrations were 8·7 ± 1·3 nmol/l. During treatment, a significant decrease in the serum T3 concentration was observed. However, serum T3 concentrations remained elevated during the 10-day treatment period in four of the seven patients.

In the patients treated with MMI + Na Ipodate, basal serum T3 concentrations were 5·6 ± 0·8 nmol/l and rapidly declined during treatment. From days 4–10, serum T3 concentrations were in the normal range in all seven patients.

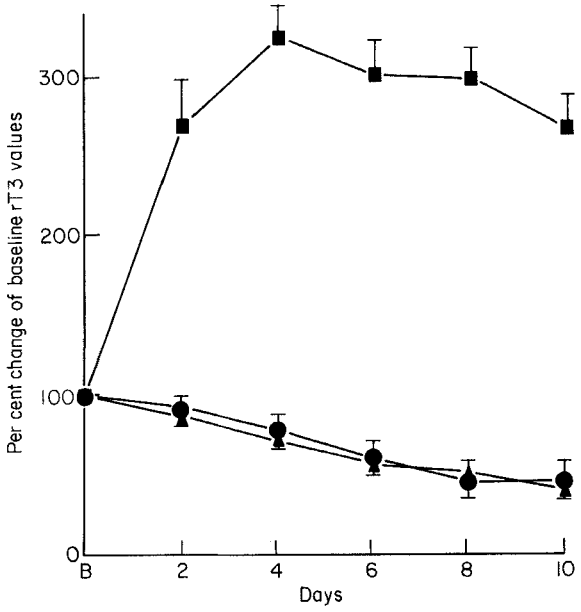

Fig. 3. The effects of MMI (●), MMI + Na ipodate (■) and MMI + SSKI (▲) administration on serum rT3 concentration in patients with thyrotoxic Graves' disease. The per cent values of baseline of the three groups of patients are represented. The 100% values for the serum rT3 concentrations in the three groups are: MMI, 1·5 ± 0·3 nmol/l; MMI + Na Ipodate, 1·0 ± 0·2; MMI + SSKI, 1·2 ± 0·2. Patients treated with MMI + Na Ipodate had higher values than those treated with MMI and MMI + SSKI ($P < 0·001$, two-way ANOVA). No difference was observed between MMI and MMI + SSKI-treated patients.

Basal serum T3 concentrations were 5·8 ± 0·8 nmol/l in the patients treated with MMI + SSKI. A significant decrease in the serum T3 concentration was observed during the treatment period and normal T3 values were reached on days 8 and 10 in six of the eight patients.

When the changes in the serum T3 concentration were analysed as the percent of baseline values, the serum T3 concentration in patients treated with MMI + Na ipodate were significantly lower than values observed in patients treated with MMI alone or in those treated with MMI + SSKI ($P < 0·001$, two-way ANOVA). No significant difference was observed between the patients treated with MMI alone as compared to those treated with MMI + SSKI.

Serum rT3 concentrations

In the patients treated with MMI alone, basal serum rT3 concentrations were 1·5 ± 0·3 nmol/l and they significantly declined during treatment.

Basal serum rT3 concentrations averaged 1·0 ± 0·2 nmol/l in the patients treated with MMI + SSKI and significantly declined during therapy.

In contrast, serum rT3 concentrations progressively increased during treatment in the patients treated with MMI + Na ipodate. Basal serum rT3 concentrations were 1·2 ± 0·2

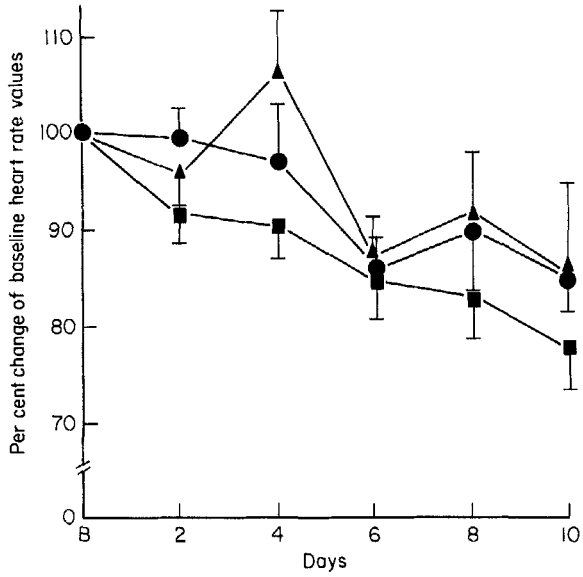

Fig. 4. The effects of MMI (●), MMI + Na ipodate (■), and MMI + SSKI (▲), on heart rate in patients with thyrotoxic Graves' disease. The per cent values of baseline of the three groups of patients are represented. The 100% values for the heart rate in the three groups are: MMI, 112 ± 9 beats/min; MMI + Na ipodate, 101 ± 7; MMI + SSKI, 94 ± 9. Patients treated with MMI + Na Ipodate had lower heart rate values than MMI and MMI + SSKI ($P < 0{\cdot}03$, $P < 0{\cdot}01$ respectively, two-way ANOVA). No difference was observed between MMI and MMI + SSKI-treated patients.

nmol/l and increased to the highest values of 3·4 ± 0·5 nmol/l on day 4. On day 10, serum rT3 concentration remained elevated at 2·7 ± 0·3 nmol/l.

In the patients treated with MMI + Na ipodate, when values were expressed as per cent of basal values, serum rT3 concentrations were significantly higher than in those treated with MMI or MMI + SSKI ($P < 0{\cdot}001$, two-way ANOVA). No difference was observed between the patients treated with MMI and MMI + SSKI.

Serum TSH concentrations

Serum TSH concentrations were below the limit of detectability of the assay (0·6 mU/l) in all subjects throughout the study.

Blood pressure

Pre-treatment systolic blood pressure (BP) readings were 141 ± 10 mmHg, 140 ± 10 and 143 ± 6 and pre-treatment diastolic BP readings were 69 ± 7, 79 ± 5, and 82 ± 3 in the MMI, MMI + Na Ipodate and MMI + SSKI treated groups, respectively. No significant changes in systolic or diastolic readings occurred during the 10 days of therapy.

Heart rate

Basal heart rate (HR) was 122 ± 9/min in the patients treated with MMI. During treatment, a significant decrease was observed, reaching a nadir of 103 ± 8/min on days 8 and 10.

In the patients treated with MMI + Na ipodate, basal HR was 101 ± 7/min and a highly significant decrement was observed during treatment, reaching a nadir of 77 ± 4/min on day 10.

In the patients treated with MMI + SSKI, basal HR was 94 ± 9/min. HR significantly declined during treatment, reaching a nadir of 79 ± 3 beat/min on day 10.

When HR was calculated as a percent of the basal value, patients treated with MMI + Na ipodate had significantly lower values than the patients treated with either MMI alone ($P < 0{\cdot}03$, two-way ANOVA) or MMI + SSKI ($P < 0{\cdot}01$, two-way ANOVA). No significant difference in HR was observed between patients treated with MMI alone and MMI + SSKI.

Body weight

Basal body weight (BW) was 47·9 ± 5·5 kg, 61·1 ± 7·3 kg and 61·4 ± 4·4 kg in the MMI, MMI + NA Ipodate and MMI + SSKI treated groups, respectively. No significant changes in BW occurred in any group during the 10 days of treatment.

DISCUSSION

In previous studies (Roti *et al.*, 1985; Robuschi *et al.*, 1986) we have observed that iodine administration to hyperthyroid patients decreased serum total and free thyroid hormone concentrations into the normal range within 5 to 7 days. A rapid restoration of serum T4 and T3 concentrations to normal in patients with thyrotoxic Graves' has been observed by Feek and co-workers during the administration of SSKI and propranolol for 10–14 days (Feek *et al.*, 1980). In contrast, Emerson and co-workers observed that iodine, as sole therapy of thyrotoxic Graves' disease, decreased serum thyroid hormone concentrations but normal values were rarely achieved (Emerson, *et al.*, 1975). These authors also observed that serum thyroid hormone concentrations began to rise in most of the patients during more prolonged iodine administration. After the cessation of short-term iodine therapy, serum thyroid hormone concentrations rapidly return to pre-treatment values (Roti *et al.*, 1985; Robuschi *et al.*, 1986). These observations suggest that iodine treatment, if employed as sole therapy for thyrotoxic Graves' disease, should only be carried out for a short period of time.

The administration of oral cholecystographic agents to hyperthyroid patients induces a marked decrease in serum T3 concentrations, a slight decrease in serum T4 concentrations, and a striking increase in serum rT3 concentrations (Wu *et al.*, 1978a,b, 1982; Sharp *et al.*, 1981; Shen *et al.*, 1985). Concomitant with the decrease in the serum T3 concentration, an amelioration of the clinical signs and symptoms of thyrotoxicosis has been observed (Wu *et al.*, 1978a; 1982). This marked decrease in the serum T3 concentration following the administration of X-ray contrast media is predominantly due to the inhibition of 5′-deiodinase, decreasing the peripheral conversion of T4 to T3 (Chopra *et al.*, 1978; Kaplan & Utiger, 1978; Silva *et al.*, 1978). Furthermore, these drugs reduce the flux of T4 from plasma to liver (Felicetta *et al.*, 1980). However, since these contrast agents probably have some contamination with iodide and iodide is released during their peripheral metabolism, the increase in serum iodide has an additional effect in reducing serum thyroid hormone concentrations by blocking the release of the active iodothyronines from the thyroid (Wartofsky *et al.*, 1970).

Various combinations of drugs have also been proposed to rapidly restore serum thyroid hormone concentrations to normal and to ameliorate the clinical manifestations of thyrotoxic Graves' disease. Thus, iodine, in combination with propranolol (Feek *et al.*, 1980) or anti-thyroid drugs (Abuid & Larsen, 1974; Croxson *et al.*, 1977) and oral cholecystographic agents administered with propylthiouracil and propranolol (Sharp *et al.*, 1981) or dexamethasone (Arteaga *et al.*, 1983), have been used successfully to treat patients with thyrotoxic Graves' disease.

In the present study, we have compared the effects of three therapeutic regimens in order to determine which was most effective in rapidly decreasing serum thyroid hormone concentrations in patients with thyrotoxic Graves' disease. Patients treated with MMI and MMI + SSKI had lower serum T4 values than those treated with MMI + Na ipodate. In contrast, the serum T3 values were far lower in patients treated with MMI + Na Ipodate than in those treated with MMI or MMI + SSKI. Furthermore, no significant difference in the pattern of the decrease in serum T3 was observed between patients treated with MMI and MMI + SSKI, although the serum T3 concentrations decreased to normal values more frequently in the latter patients. Serum rT3 values markedly increased in patients treated with MMI + Na ipodate and decreased in the patients in the other two treatment groups.

In the patients treated with MMI + Na ipodate, the more marked decrease in serum T3 was accompanied by a lower HR than that observed in patients treated with MMI and MMI + SSKI. This finding is in agreement with a previous study reporting a more rapid reduction in the pulse rate in hyperthyroid patients treated with Na ipodate than in those treated with propylthiouracil alone (Wu *et al.*, 1982). It was indeed surprising that the combination of MMI + SSKI, which is generally recommended to induce a more rapid improvement in thyroid function, was not more effective than MMI alone in restoring serum thyroid hormone concentrations to normal and in decreasing heart rate. Therefore, it seems reasonable to recommend the administration of MMI and sodium ipodate when a rapid return to normal of thyroid function and the associated improvement in heart rate and cardiac symptoms are required. The administration of a beta-blocker would certainly lower heart rate in thyrotoxic patients, irrespective of the other treatments, and should be used in thyrotoxic patients unless asthma or severe congestive heart failure are present. However, it should be pointed out that patients given cholecystographic dyes for X-ray studies 1 year earlier had 15 times more iodine in their adipose tissue than normal subjects (Costa *et al.*, 1978). In spite of the reported increase in the recurrence rate of hyperthyroidism when iodine intake is increased (Wartofsky, 1973), and a rebound increase in serum T4 and T3 concentrations above pre-treatment values following the withdrawal of sodium Ipodate after 10 days of therapy (Roti *et al.*, 1985), the present findings and those of others suggest the efficacy of sodium Ipodate alone and in combination with anti-thyroid drugs in both the short and long-term treatment (Shen *et al.*, 1985) of patients with thyrotoxic Graves' disease.

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