NOTE

Studies on the T_3 Suppression Test with Reference to the Thyroidal ^{123}I Uptake in Graves' Disease: Comparison of 24-Hour and 3-Hour Uptake

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Abstract

Eighty-three patients with Graves' disease had been treated with methylmercaptoimidazole (MMI). They were prescribed a maintenance dose of anti-thyroid drug (MMI, 5 mg/day) at the time of a T_3 suppression test. The 3-hour and 24-hour thyroidal ^{123}I uptake after T_3 administration (75 $\mu\text{g/day}$, 2 weeks) were measured (post T_3 uptake). In 38 patients whose post T_3 uptake was below 35% in post T_3 24-hour uptake, treatment was stopped. The T_3 suppression test was then repeated 1 and 3 months later. During a one-year follow up, 26 remained well, while 12 relapsed within 6 to 12 months.

We have observed a good correlation between 3-hour uptake and 24-hour uptake of ^{123}I after T_3 administration ($r=0.847$, $p<0.001$). In 38 patients who showed positive T_3 suppression, most patients with MMI withdrawal produced a marked overshoot of post T_3 3-hour and 24-hour uptake at one month. Retrospective analysis indicated that there was no significant difference in circulating thyroid hormone levels between remission and relapse groups.

The present study provides evidence that 3-hour uptake values are able to be substituted for 24-hour uptake values during a T_3 suppression test. In addition, overshoot of thyroidal uptake after antithyroid drug withdrawal was observed in 3-hour values, similar to 24-hour values.

T_3 suppression test has been widely used to predict the outcome of medical treatment with antithyroid drug for patients with Graves' disease (Cassidy and Vander Laan, 1960; Alexander *et al.*, 1966; Burke, 1967; Hales *et al.*, 1969; Alexander *et al.*,

1970; Cassidy, 1970; Yamamoto *et al.*, 1979). In normal subjects, TSH is suppressed by exogenous T_3 and the uptake of radioiodine remarkably decreased. In contrast, the uptake of radioiodine is not suppressed in patients with Graves' disease shortly after the initiation of therapy because of the thyroid abnormal stimulators. On the other hand, the uptake of radioiodine after T_3 administration becomes

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suppressed in the remission stage of Graves' disease, since the thyroid function is dependent on endogenous TSH but not on thyroid abnormal stimulators.

The protocol of the T₃ suppression test varies according to the laboratory. Previously, we have utilized the 24-hour uptake of ¹³¹I in patients receiving thionamide drugs (Kobayashi *et al.*, 1983; Kobayashi *et al.*, 1984), but recently the early uptake has been recommended because of its convenience during thionamide drug therapy (Nielsen *et al.*, 1973; Nagataki *et al.*, 1974; Yamamoto *et al.*, 1979; Yamamoto *et al.*, 1983; Yamada *et al.*, 1984).

Nagataki *et al.* reported a T₃ suppression test utilizing 20-min and 24-hour thyroidal ¹³¹I uptake in patients receiving thionamide drugs (Nagataki *et al.*, 1974). Their results suggested that there was little overlap between the suppressibility by the 20-min uptake and by the 24-hour uptake even in patients receiving thionamide drugs. However, a tracer dose of ¹³¹I was given intravenously in their studies. Many investigators have recently employed a tracer dose of ¹²³I given orally. On the other hand, we have reported an overshoot phenomenon of radioiodine uptake one month after the discontinuation of antithyroid drug, particularly methylmercaptoimidazole (MMI) (Kobayashi *et al.*, 1983), resulting in negative T₃ suppression in some patients. From the above observations, when we have performed a T₃ suppression test after MMI withdrawal, we must be careful in evaluating the results. The present study was undertaken to determine which values for post T₃ 3-hour uptake or 24-hour uptake were useful in predicting sustained remission or relapse in Graves' disease. In addition, we determined thyroid stimulators during the overshoot phenomenon from post T₃ 3-hour and 24-hour ¹²³I uptake following the withdrawal of MMI.

Materials and Methods

Eighty-three patients, 57 females and 26 males, had been treated with MMI for from 12 to 70 months. On the basis of the circulating thyroid hormone concentration, the initial dose of antithyroid drug had been gradually lowered to a maintenance dose (5 mg/day) for several months prior to the administration of T₃. All of the patients were regarded as in a euthyroid state at the time of the first T₃ suppression test, since their serum free T₃ (FT₃) and free T₄ (FT₄) concentrations were within the normal range and their serum TSH values were within the normal range.

The first T₃ suppression test was performed on patients receiving the maintenance dose of antithyroid drug. Each patient was given by 25 µg T₃ three times a day for 2 weeks with the continuous administration of MMI. On the 13th day of T₃ administration, a tracer dose of 925 kBq (25 µCi) ¹²³I was given orally and 3-hour thyroidal ¹²³I uptake (post T₃ uptake) was measured 3 hours later. On the 14th day, 24-hour uptake was measured 2 hours after the last administration of T₃. The positive T₃ suppression by 24-hour uptake was defined as lower than 35% (Werner and Spooner, 1955; Kobayashi *et al.*, 1983). When the T₃ suppression test was positive, treatment was then stopped and the T₃ suppression test was repeated at one and 3 months later. During the one year follow-up period after withdrawal of the antithyroid drug, relapse was regarded as a recurrence of clinical signs with increased FT₃ and FT₄. Serum FT₃, FT₄, TSH levels and TSH binding inhibitor immunoglobulins (TBII) before exogenous T₃ administration were measured. Circulating thyroid hormone concentrations and TSH were measured by radioimmunoassay (RIA). TBII were determined by radioreceptorassay using Smith's kit. The normal range of serum FT₃, FT₄, TSH and TBII were 2.6–5.4 pg/ml, 0.8–2.0 ng/dl, less than 5 µU/ml and less than 10%, respectively. Statistical evaluation was made by Student's *t*-test. AP value less than 0.05 was considered statistically significant.

Results

1. Comparison of 24-hour and 3-hour thyroidal radioiodine uptake in the first T₃ suppression test

In 83 patients receiving a maintenance dose of MMI, we have observed a good correlation between 3-hour uptake and 24-hour uptake of ¹²³I ($r=0.847$, $p<0.001$). For the correlation expression ($Y=0.62X+5.57$), we showed clearly that 35% 24-hour uptake was equivalent to about 27% 3-hour uptake.

2. Retrospective analysis of thyroid ¹²³I uptake after T₃ administration in patients with sustained remission and further relapse after stopping anti-thyroid drug

Thirty-eight patients had post T₃ 24-hour uptake below 35% in the first T₃ suppression test at the end of treatment with antithyroid drug. Results of the T₃ suppression test during the administration of a maintenance dose of MMI in these patients with positive suppression are summarized in Table 1. Follow-up studies were performed for one year. Relapse became

Fig. 1. The relation between 24-hour and 3-hour thyroid uptake in patients in the first T₃ suppression test.

There is a good correlation between 3-hour uptake and 24-hour uptake of ¹²³I ($r=0.847$, $P<0.001$). For the relation expression ($Y=0.62X+5.57$), 35% in the 24-hour uptake was equivalent to about 27% in 3-hour uptake. The shaded area represents the normal range.

Table 1. The post T₃ uptake in patients with positive suppression during antithyroid drug therapy at the time of the first T₃ suppression test

	Group	No. of patients	Age (years)	Post T ₃ uptake (24-hour, %)	Post T ₃ uptake (3-hour, %)
A	Remission	26	45.2±3.4	15.5±1.9	12.2±1.0
B	Relapse	12	41.4±5.1	12.3±2.4	9.7±0.7

All patients studied had been treated with MMI (5 mg/day) at the time of the study. 38 showed positive suppression (post T₃ uptake < 35%). Data are shown in relation to sustained remission and relapse during one-year follow up after treatment was stopped. Relapse became evident in 12 patients after withdrawal of antithyroid drug. Values given are the mean ± SEM. There was no significant difference between the remission group and the relapse group in the post T₃ 24-hour uptake and 3-hour uptake.

evident in 12 of 38 patients after withdrawal of the antithyroid drug while 26 remained in remission. There was no significant difference between remission and relapse groups in the post T₃ 24-hour uptake and 3-hour uptake.

3. Changes in thyroidal ¹²³I uptake after withdrawal of MMI

MMI was withdrawn in 38 patients who

showed signs of positive T₃ suppression. The T₃ suppression test was repeated at one month and 3 months later. For 24-hour uptake, the highest value for post T₃ uptake was obtained at one month after the discontinuation of therapy in both groups, indicating a rebound phenomenon in the thyroid uptake. One month after the withdrawal of MMI, 12 of 26 patients (46.2%) in the further sustained remission group

Fig. 2. Changes in post T₃ 24-hour uptake in the remission group and the relapse group following antithyroid drug withdrawal

Fig. 3. Changes in post T₃ 3-hour uptake in the remission group and the relapse group following antithyroid drug withdrawal

had more than 35% post T₃ 24-hour uptake.

A similar result was obtained with 3-hour ¹²³I uptake. The overshoot phenomenon of thyroidal uptake was observed at one month after the withdrawal of the antithyroid drug. One month after the

withdrawal of MMI, 7 of 26 patients (26.9%) in the remission group had more than 27% post T₃ 3-hour uptake.

4. Comparison of various thyroid parameters

For the both the remission group and

Table 2. Changes in serum FT₃, FT₄, TSH and TBII before and after withdrawal of the antithyroid drug

Group	Parameter	Months after antithyroid drug withdrawal		
		0	1	3
A Remission	FT ₃ (pg/ml)	3.62±0.13	3.85±0.14	4.01±0.16
	FT ₄ (ng/dl)	1.30±0.06	1.42±0.06	1.46±0.06
	TSH (μU/ml)	3.49±0.56	1.66±0.21**	1.28±0.22**
	TBII (%)	2.85±0.56	2.39±0.50	4.17±0.73
B Relapse	FT ₃ (pg/ml)	3.90±0.13	4.13±0.28	4.52±0.31
	FT ₄ (ng/dl)	1.20±0.10	1.21±0.11	1.39±0.08
	TSH (μU/ml)	4.28±0.63	2.15±0.49*	1.28±0.37*
	TBII (%)	7.04±1.24	4.96±1.26#	7.20±1.19#

Serum concentrations of FT₃, FT₄, TSH and TBII before exogenous T₃ administration are shown. Values given are the mean±SEM.

* P<0.05, ** P<0.01 vs. the values at the first suppression test (Time 0).

P<0.05 vs. remission group.

the relapse group, thyroid parameters in each period during and after treatment with a maintenance dose of antithyroid drug are shown in Table 2. No significant difference between the thyroid hormone concentrations in the relapse and remission groups was found after withdrawal of antithyroid drug. Serum TSH in both groups was significantly lower at one month and 3 months after withdrawal of MMI. On the other hand, TBII were significantly higher in the relapse group than in the remission group, although the values were within the normal range in both groups.

Discussion

The thyroid suppression test has been carried out by the various methods: the preparation of thyroid hormones, the daily dose and the duration of the administration of hormone, the kind of radiosotope utilized as uptake (^{123}I , ^{131}I , $^{99\text{m}}\text{Tc}$), the method of administration (oral, intravenous) and the measurement of time (Cassidy, 1965; Martino *et al.*, 1976; Tamai *et al.*, 1980; Lee *et al.*, 1980) seemed to be different. Until now, we have been carrying out 24-hour thyroidal uptake by the original method of Werner *et al.* (Werner and Spooner, 1955). Three-hour uptake in the present study significantly correlated with 24-hour uptake, and it seems that 24-hour uptake can be replaced by 3-hour uptake. We are now using a comparison of the post T_3 3-hour uptake with the post T_3 24-hour uptake in predicting relapse following discontinuation of antithyroid drug.

T_3 suppression test was defined as positive when 24-hour uptake was below 35%, while it was equivalent to 27% in 3-hour uptake in our study. Furthermore, other investigators considered the T_3 suppression test result to be positive when 24-hour uptake was below 20% (Burke, 1967). In this case, approximately 17% in 3-hour

uptake seemed to be equivalent to 20% in 24-hour uptake. Previously we have reported that the rebound phenomenon takes place in the radioiodine post T_3 uptake after withdrawal of antithyroid drug (Kobayashi *et al.*, 1983; Kobayashi *et al.*, 1984). In this study, we found a similar rise in 3-hour uptake. From the above observations, when 3-hour uptake in a T_3 suppression test is introduced, it is possible to judge positive below 27% or 17% in iodine uptake and to discontinue the administration of the antithyroid drug. Therefore, we must set up new criteria, when we perform a T_3 suppression test after withdrawal of the antithyroid drug. On the other hand, we proved that there was not always a relapse of hyperthyroidism, even if a transitional iodine uptake rise occurred after withdrawal of the antithyroid drug.

Our data are in accordance with the findings of Lowry *et al.*, (Lowry *et al.*, 1971), who measured the 20-min uptake of ^{123}I . Medeiros-Neto *et al.* suggested that iodine deficiency may play a role in the rebound phenomenon of the post T_3 uptake without the effect of goitrogen (Medeiros-Neto *et al.*, 1975). Furthermore, Studer and Greer reported that the degree of thyroidal ^{131}I uptake in the rat after goitrogen withdrawal depended to a great extent on the amount of inorganic iodine available (Studer and Greer, 1971). They suggested that the rebound phase of thyroid characteristics following goitrogen withdrawal may be related to the excess of the preferential synthesis and secretion of T_3 through TSH stimulation in the thyroid and the reduced concentration of iodine in the thyroglobulin. In the present study, since serum FT_3 and TSH levels before exogenous T_3 administration after the discontinuation of MMI therapy were within the normal range (Table 2), it is possible that factors other than iodine deficiency influence this phenomenon. Previous studies revealed that thyroid stimulators might be

implicated in the rebound of Graves' disease (Lowry *et al.*, 1971). However, it is possible that thyroid stimulating immunoglobulins may not be related to the overshoot of thyroidal ¹²³I uptake, since our data resulted in normal range of TBII after MMI withdrawal, although TBII did not always indicate thyroid stimulators. Further studies are needed to clarify the role of thyroid stimulating antibodies in the rebound phenomenon of post T₃ uptake following withdrawal.

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