Abstract. Two groups of patients with newly diagnosed thyrotoxicosis were treated with propylthiouracil (PTU) 400 mg every 6 h for 4 days followed by methimazol (MMI) 40 mg every 6 h for 4 days or by MMI for 4 days followed by PTU for 4 days. The shift from MMI to PTU induced a considerable decrease in serum T3 while shift from PTU to MMI led to an increase in serum T3. Serum T4 decreased gradually during the whole treatment period. The opposite variations in serum T3 were accompanied by similar opposite variations in basal metabolic rate (BMR) (P < 0.001). Hence the rapid variations in serum T3 which can be induced by PTU in thyrotoxic patients, are followed by rapid alterations in the thyrotoxic state as evaluated by BMR.

The two medications most commonly employed for basic medical treatment of thyrotoxicosis are methimazol (MMI) and propylthiouracil (PTU). Both interfere with the formation of iodothyronines in thyroglobulin and thereby decrease thyroid hormone secretion (Green 1978a). PTU has an additional effect on thyroid hormone formation which is not shared by MMI, i.e. an inhibitory effect on the enzyme(s) which deiodinate T4 to the more metabolically active T3 in the thyroid (Green 1978b; Laurberg 1978, 1979) and in some of the peripheral organs where this process takes place (Chopra 1977; Hufner et al. 1977; Kaplan & Utiger 1978; Visser et al. 1975).

This effect leads to a more rapid decrease in serum T3 when PTU is employed for the treatment of thyrotoxicosis than during MMI administration (Abuid & Larsen 1974; Laurberg & Weeke 1978). To achieve the maximum effect of PTU on serum T3 it is necessary to use doses higher than those most often employed during the initial treatment of thyrotoxicosis (Laurberg & Weeke 1981).

The aim of the present study was to evaluate if these PTU-induced variations in serum T3 have any importance for the peripheral thyroid hormone effects in thyrotoxicosis. As measures of peripheral thyroid hormone effects we used some commonly employed indices, the basal metabolic rate (BMR), the duration of the achilles tendon reflex (ATR), the resting pulse rate, and serum cholesterol.

Patients and Methods

Six men and 6 women with newly diagnosed Graves' disease were randomized for the study. Their mean age was 38 years, range 27–57 years. The diagnosis was based on a typical clinical picture, a thyroid isotope scan, and measurements of serum T4 and T3. Mean pre-treatment serum T4 was 236 nmol/l, range 129–351 nmol/l (normal range 77–148) and mean pre-treatment serum T3 was 7.10 nmol/l, range 4.95–12.05 nmol/l (normal range 1.25–2.46). Except for Graves' disease all patients were healthy and none received medication.
They were admitted to the clinical department at least 3 days before the beginning of the study, and a pre-study run of BMR and ATR measurements were performed in all patients several days before the study. Informed consent was obtained and the study was approved by the ethical committee of the County of Aarhus. No side effects of the treatment was observed.

Since the rate of improvement in both biochemical and clinical measures varies considerably during the initial treatment of thyrotoxic patients a cross-over design was used. This design improved sensitivity by allowing within-patient comparisons.

Half of the patients (3 men and 3 women) received 6-PTU (DAK, Copenhagen, Denmark) 400 mg at 6 h intervals for 4 days followed by MMI (GEA, Copenhagen, Denmark) 40 mg at 6 h intervals for 4 days. The remaining patients received MMI followed by PTU in an otherwise identical scheme. BMR, ATR measurements and blood samples for measurements of serum T₄, T₃ and cholesterol were obtained at days 0, 4 and 8. The treatment was started after the testing at day 0, and shift in medication was performed after testing at day 4.

BMR was measured by a conventional technique with determination of oxygen consumption in the resting patient after an overnight fast, and expressed as percentage of standard normal values for persons of the same age, sex and surface area using the Harris-Benedict standards (Diem & Lentner 1970). Each value was the mean of three 10 min measurements. For ATR measurements the patients were placed in a supine position with the knee bended about 90° and the foot fastened to a pedal. The pedal was connected to a strain gauge system capable of measuring the mechanical reflex momentum. The reflex was elicited by means of an electro-mechanical hammer applying standardized taps to the achilles tendon (Pedersen & Klemar 1974). The measured time interval was from the stimulus until half-relaxation. Each value was the mean of 10 measurements. T₄ and T₃ were measured by radioimmunoassays (Weeke & Ørskov 1975; 1978). Resting pulse rate was mean of three 1 min measurements. Cholesterol was measured by the Chod-pap kit from Boehringer Mannheim, W. Germany. All measurements were carried out in ignorance of the treatment being given.

Statistical analyses were performed using the t-test for unpaired and paired comparisons.

Results

The variations in serum T₄ and T₃ in the two groups of patients are depicted in Fig. 1. The cross-over design of the study gave very different patterns in serum T₃ alterations. In the group receiving MMI/PTU T₃ alterations during the periods 0–4 and 4–8 days were not significantly different, while they were highly significantly different in the group receiving PTU/MMI (P < 0.001). Fig. 2 shows the variations in BMR which varied in parallel with serum T₃. In the MMI/PTU group BMR variations were similar during the 0–4 and 4–8 days periods while they were highly significantly different in the PTU/MMI group (P < 0.001). When comparing the two groups of patients the values for BMR alterations 0–4 day/4–8 day, were also significantly different (P < 0.05). The alterations in resting pulse rate are also shown in Fig. 2. The tendency was the same as observed in BMR, however, the scatter between different patients was greater and the differences not statistically significant. Serum cholesterol increased gradually in both groups (0, 4 and 8 days values in the PTU/MMI group 139 ± 16, 146 ± 15 and 155 ± 16; MMI/PTU group 138 ± 2, 144 ± 5 and 163 ± 8 mg/dl). The difference between the groups was also in the direction of a greater peripheral effect in the group shifted to PTU, than in the group shifted to MMI. However, the difference was not statistically significant. Alterations in ATR (Fig. 2) developed more slowly than in the other variables measured and there was no significant difference between groups.

![Fig. 1.](image-url)

Serum T₄ and T₃ in 6 patients with newly diagnosed thyrotoxicosis treated with PTU 400 mg every 6 h for 4 days followed by MMI 40 mg every 6 h for 4 days, and 6 patients treated with MMI followed by PTU. In each patient the measured values were expressed in per cent of the first value. T₄ 100% ~ 236 ± 29 nmol/l in the PTU/MMI group and 237 ± 25 nmol/l in the MMI/PTU group. Corresponding values for T₃: 7.16 ± 0.88 and 7.04 ± 1.04 nmol/l, mean ± se.
Discussion

As expected shift between high doses of MMI and PTU in thyrotoxic patients was followed by considerable variations in serum T₃ while serum T₄ was nearly unaffected. To obtain the most sensitive measure of the influence of PTU on peripheral thyroid hormone effects we compared the effect of PTU withdrawal in one group of patients with the effect of PTU administration in another group.

The assessment of possible correlations between variations in serum T₃ and peripheral thyroid hormone effects in thyrotoxic patients is hampered in several ways. Some of the commonly employed measures of peripheral thyroid hormone action vary considerably during alterations in the hypothalamic range but only slightly during variations in hyperthyroid patients. Such a pattern is found in serum cholesterol, heart rate and ATR (Bantle et al. 1980). In the present study serum cholesterol and resting pulse rate varied corresponding to serum T₃ but the differences were not statistically significant. Another problem is the time lag in peripheral effects of alterations in T₃ availability. This time lag was found to be especially long for ATR alterations, and this measure was not suitable for evaluation of the effects of alterations in serum T₃ of only 4 days duration.

BMR is a more complex measure of peripheral thyroid hormone effects, reflecting variations in many processes in different tissues. In groups of hyperthyroid patients it correlates reasonably to the elevation in serum T₃ (Johansen et al. 1978) possibly due to amplified responses of some enzymes to increases in T₃ (Oppenheimer et al. 1978). In hyperthyroid patients BMR tends to be measured gradually lower during the initial period of repeated testing. Such an effect may be partly responsible for the BMR decrease observed in the present study during the initial treatment period, even if a pre-run of BMR measurements had been performed. However, it could not be responsible for the highly significant difference observed in patients shifted from MMI to PTU compared to patients shifted from PTU to MMI.

The dose of PTU (400 mg every 6 h) was chosen from our previous study where we measured the dynamics of serum T₃ and rT₃ after 200 and 800 mg doses of PTU to hyperthyroid patients. After 200 mg PTU the decline in serum T₃ ceased after approximately 4 h, while serum T₃ was still steadily declining during the period 6 to 9 h after ingestion of a single dose of 800 mg PTU (Lauberg & Weeke 1981). Possibly a most effective scheme would be to start therapy with 800 mg PTU and continue with 400 mg every 6 h. The dose of MMI (40 mg every 6 h) was chosen to be very large to ascertain a nearly complete blockage of thyroid hormone synthesis. Hence it is very unlikely that the PTU effect observed was due to more effective blockage of thyroid hormone synthesis during PTU than during MMI treatment.

The principle in the investigation was that thyroid hormone synthesis should be nearly completely inhibited during the whole period of investigation, and only the additional effect of inhibition of thyroidal and peripheral T₄ deiodination by PTU investigated. Since the effect of PTU on T₄ deiodination is rather short-lived (Lauberg & Weeke 1981) treatment periods of 4 days without
wash-out periods should be sufficient. It was also felt that if the PTU-induced variations in serum T₃ did not lead to any difference in the hyperthyroid state within 4 days it would be of little clinical interest.

In conclusion the investigation demonstrates that the rapid variations in serum T₃ obtainable by PTU treatment of thyrotoxicosis are accompanied by rapid alterations in peripheral thyroid hormone effects as measured by BMR. The basic mechanisms for the development of thyrotoxic crisis are unknown. However, the results of the present study support that PTU should be preferred for MMI as the 'thyroid blocking drug' in the combination of medications administered when rapid amelioration of the thyrotoxic state is important.

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References


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