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COMPARISON OF PROPRANOLOL AND METOPROLOL IN THE MANAGEMENT OF HYPERTHYROIDISM

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1 Propranolol and metoprolol were both effective in controlling the symptoms and signs of hyperthyroidism.

2 Propranolol caused a highly significant increase in serum reverse T_3 concentrations, with lesser changes in other serum thyroid hormone levels, whereas metoprolol did not have this effect.

3 Steady-state plasma propranolol and metoprolol levels showed marked inter-individual variation. Metoprolol concentrations showed relatively little intra-individual variability, and could be related to the clinical efficacy of the drug, whereas no such relationship was demonstrated for propranolol.

Introduction

The use of propranolol to control the clinical features of hyperthyroidism is well-established (Turner, Granville-Grossman & Smart, 1965). The selective β_1-adrenoceptor antagonist practolol has also been shown to be effective (Murchison, Bewsher, Chesters & Ferrier, 1976) but was withdrawn from use because of serious adverse effects (*Br. med. J.*, 1975). The selective β_1-adrenoceptor antagonist metoprolol has the possible advantage over practolol of having no partial agonist activity (Ablad, Borg, Carlsson, Ek, Johnsson, Malmfors & Regardh, 1975). The present report is a comparison of the clinical and metabolic responses to metoprolol and propranolol in 24 hyperthyroid patients.

Methods

Twenty-four hyperthyroid patients participated in the study, and hyperthyroidism was confirmed by elevated levels of serum thyroxine (T_4) and triiodothyronine (T_3) and raised thyroidal uptake of radio-iodine. Their ages ranged from 20 to 57 years (mean—43 years) and 19 were females. Patients with a history of obstructive airways disease, cardiac failure, heart block or renal failure were excluded. In addition to the drugs under trial, a non-barbiturate night sedative was permitted provided that this was continued unchanged throughout the trial.

In a double-blind cross-over study, each patient received consecutively 4 weeks' treatment with propranolol (40 mg) six-hourly and 4 weeks' treatment with metoprolol (50 mg) six-hourly, in random order. Each patient was assessed before treatment, and after 2, 4, 6 and 8 weeks of drug therapy. The informed consent of all patients was obtained, and the study was approved by the local ethical committee.

The following investigations were carried out: hyperthyroidism diagnostic index (Crooks, Murray & Wayne, 1959), Taylor manifest anxiety scale (Taylor, 1953), symptomatic enquiry for possible adverse reactions, tablet count, limited physical examination, ankle reflex tracing (Gilson, 1959) and finger tremor tracing (Marsden, Gimlette, McAllister, Owen & Miller, 1968). Objective assessments of eye signs (exophthalmos, lid retraction, lid lag) and of muscle power (difficulty in rising from a squatting position) were made according to an arbitrary scoring technique using 0, 1 and 2 for grading increasing severity, and ventilatory function was measured by Vitalograph. A fasting blood sample was obtained at each visit after 30 min rest (the morning drug dose having been taken 1 to 2 h earlier) for measurement of the following: thyroxine both by radioimmunoassay (RIA) (Seth, Rutherford & McKenzie, 1975), and by a competitive protein binding method (CPB) (Abreau, Vagenakis, Azizi, Portnay & Braverman, 1973); effective thyroxine ratio (Mincey, Thorson, Brown, Morrison & McIntosh, 1972); triiodothyronine (based on Lepetit kit); 3, 3′, 5′—triiodothyronine (reverse T_3, Biodata kit); triglyceride and free glycerol (Boehringer enzymatic analysis); serum cholesterol, calcium, phosphate, albumin, total protein, urea, sodium, potassium and liver function tests (measured by standard laboratory techniques); haemoglobin, total and differential white blood cell counts. In addition, during the periods of drug

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administration, plasma metoprolol (Degen & Riess, 1976) or propranolol concentrations (Shand, Nuckells & Oates, 1970) were measured as appropriate.

All patients completed the trial apart from one who developed atrial fibrillation and a right femoral artery embolus 5 days after entering the trial, having commenced propranolol therapy. For analysis of the results the remaining 23 patients were divided into two groups. The drug sequence in group 1 was propranolol followed by metoprolol, and in group 2 metoprolol followed by propranolol. The results were analysed using the Student's *t*-test for paired data, and the findings of statistical significance confirmed by multivariate analysis of variance, and the Friedman rank sum test.

Results

The results of the clinical measurements are shown in Table 1 for patients who were treated with propranolol followed by metoprolol (group 1), and in Table 2 for patients treated with metoprolol followed by propranolol (group 2).

All patients showed progressive improvement in clinical symptoms and signs, as measured by the hyperthyroidism diagnostic index, throughout the 8 weeks of the trial, and the results were similar in the two treatment groups. Metoprolol led to a fall in resting pulse rate equal to that produced by propranolol. The systolic blood pressure was reduced by a similar extent by both drugs, while the diastolic blood pressure was unchanged. Lid lag was equally improved by both drugs, although the change was statistically significant only in group 1. Exophthalmos (present in only five patients) and lid retraction showed no change. There was no significant weight loss in either group during the study, although all patients had lost weight prior to entry to the trial. There was a consistent small reduction in anxiety as measured by the Taylor manifest anxiety scale, but this reached levels of statistical significance on only one occasion during propranolol therapy (Table 1). Tremor amplitude as measured by accelerometer was reduced in both groups during treatment with propranolol, but during metoprolol treatment the only significant reduction was at 8 weeks in group 1. Tremor frequency was unchanged. When assessed clinically, as part of the hyperthyroidism diagnostic index, both treatments significantly improved finger tremor. The improvement was greater on propranolol, but not significantly so. Both treatments also resulted in

Table 1 Effect of propranolol and metoprolol on clinical features in group 1 (mean ± s.e. mean).

		Propranolol		*Metoprolol*	
	Pretreatment	*2 weeks*	*4 weeks*	*6 weeks*	*8 weeks*
Hyperthyroidism diagnostic index	32 ± 2	15*** ± 2	11*** ± 2	9*** ± 2	10*** ± 2
Pulse (beats/min)	107 ± 3	82*** ± 4	82*** ± 3	80*** ± 4	79*** ± 3
Systolic blood pressure (mm Hg)	135 ± 4	123*** ± 4	116*** ± 3	117*** ± 5	118*** ± 2
Diastolic blood pressure (mm Hg)	69 ± 4	64 ± 3	65 ± 2	66 ± 3	68 ± 2
Lid lag score	0.91 ± 0.29	0.27* ± 0.20	0.27* ± 0.20	0.46 ± 0.25	0.27* ± 0.20
Taylor manifest anxiety scale	22.3 ± 2.6	19.4* ± 2.7	18.7 ± 3.2	18.5 ± 3.6	18.6 ± 3.7
Weight (kg)	53.0 ± 2.0	52.5 ± 1.9	52.7 ± 2.0	52.4 ± 1.9	52.3 ± 1.8
Tremor amplitude (mm)	9.7 ± 1.4	7.3* ± 1.3	7.8 ± 1.9	7.2 ± 1.3	6.4** ± 1.3
Ankle reflex time (ms)	215 ± 8	223 ± 10	217 ± 12	232 ± 12	218 ± 10
Muscle power score	0.73 ± 0.24	0.27* ± 0.14	0.09* ± 0.09	0.27* ± 0.14	0.27* ± 0.14
Forced vital capacity (l)	2.80 ± 0.18	2.88 ± 0.18	2.72 ± 0.18	2.80 ± 0.16	2.80 ± 0.14
FEV_1 (l)	2.49 ± 0.19	2.50 ± 0.16	2.45 ± 0.16	2.43 ± 0.17	2.51 ± 0.13

Significant difference from mean pretreatment value *$P<0.05$, **$P<0.01$, ***$P<0.001$.

significant reduction of the clinical observation of 'hot hands' and 'moist hands', and the effect was the same for the two drugs. The tendency to prolongation of the ankle reflex time during drug therapy did not reach levels of statistical significance. Both drugs significantly improved muscle power in group 1 and the degree of improvement was the same for both treatments. No changes occurred in the patients in group 2, who were less severely affected. No significant change in respiratory function tests occurred in group 1, but in group 2 there was a reduction in both vital capacity and forced expiratory volume (1 s) at 4 weeks on metoprolol therapy, and this reduction was maintained throughout the propranolol period.

The results of the serum biochemical measurements are shown in Table 3 for patients who were treated with propranolol followed by metoprolol (group 1) and in Table 4 for patients treated with metoprolol followed by propranolol (group 2).

Although the effective thyroxine ratio and serum thyroxine measured by the CPB method were unchanged, there was a small but significant increase in the thyroxine level, as measured by radioimmunoassay, during propranolol therapy in both groups. There was also a tendency to reduction in the tri-iodothyronine level during propranolol therapy and although this did not reach levels of statistical significance, the tri-iodothyronine/thyroxine ratio was significantly reduced. The reverse T_3 concentration rose significantly during treatment with propranolol in both groups. There were no significant changes in thyroid hormone concentrations during metoprolol therapy.

The calcium level, which was elevated in only two patients, was unchanged, but the inorganic phosphate concentration rose progressively during the 8 weeks period of drug therapy. The alkaline phosphatase, initially elevated in six patients, showed a progressive increase during the 8 week period in all subjects. Bilirubin, aspartate aminotransferase, γ-glutamyl transpeptidase, creatinine phosphokinase, cholesterol, triglyceride, free glycerol, urea, sodium, potassium and protein concentrations were unchanged. The haemoglobin and white cell count were also unchanged throughout the study.

No major adverse drug reactions were noted during the study. Two patients complained of headaches, new or worsening, only when taking metoprolol compared with three patients when on propranolol, while three patients had headaches during both periods of drug treatment. Slight temporary nausea occurred only once with each drug. Six patients complained of minor sleep disturbance

Table 2 Effect of propranolol and metoprolol on clinical features in group 2 (mean ± s.e. mean).

		Metoprolol		*Propranolol*	
	Pretreatment	*2 weeks*	*4 weeks*	*6 weeks*	*8 weeks*
Hyperthyroidism diagnostic index	28 ± 2	17*** ± 3	12*** ± 3	7***† ± 3	5***† ± 3
Pulse (beats/min)	107 ± 4	82*** ± 4	78*** ± 3	83*** ± 3	81*** ± 4
Systolic blood pressure (mm Hg)	143 ± 6	131* ± 6	128*** ± 6	131* ± 7	131* ± 7
Diastolic blood pressure (mm Hg)	78 ± 5	77 ± 5	71 ± 5	76 ± 7	77 ± 6
Lid lag score	0.67 ± 0.26	0.42 ± 0.23	0.42 ± 0.23	0.17 ± 0.17	0.33 ± 0.23
Taylor manifest anxiety scale	20.2 ± 2.7	18.1 ± 2.8	18.2 ± 3.3	17.8 ± 3.4	17.1 ± 3.5
Weight (kg)	60.3 ± 2.3	60.0 ± 2.3	60.1 ± 2.4	60.5 ± 2.5	60.1 ± 2.5
Tremor amplitude (mm)	9.8 ± 1.0	9.7 ± 1.2	9.7 ± 1.2	7.0*†† ± 0.8	7.2* ± 0.8
Ankle reflex time (ms)	214 ± 7	228 ± 12	213 ± 8	220 ± 10	215 ± 10
Muscle power score	0.50 ± 0.23	0.50 ± 0.23	0.50 ± 0.23	0.50 ± 0.23	0.42 ± 0.19
Forced vital capacity (l)	3.00 ± 0.20	2.89 ± 0.21	2.86* ± 0.23	2.94 ± 0.23	2.93 ± 0.22
FEV_1 (l)	2.46 ± 0.11	2.37 ± 0.14	2.25** ± 0.14	2.28* ± 0.15	2.32* ± 0.12

Significant difference from mean pretreatment value $*P<0.05$, $**P<0.01$, $***P<0.001$.
Significant difference from mean value at 4 weeks $†P<0.05$, $††P<0.01$.

Table 3 Effect of propranolol and metoprolol on serum biochemical values in group 1 (mean ± s.e. mean)

	Pretreatment	*Propranolol* 2 weeks	*Propranolol* 4 weeks	*Metoprolol* 6 weeks	*Metoprolol* 8 weeks
Thyroxine (T_4 RIA) (nmol/l)	264 ± 13	294** ± 16	296** ± 14	244††† ± 13	249†† ± 15
Tri-iodothyronine (T_3) (nmol/l)	8.65 ± 0.54	8.51 ± 0.70	8.15 ± 0.61	8.86 ± 0.75	8.32 ± 0.60
T_3/T_4 ratio × 100	3.28 ± 0.13	2.90* ± 0.20	2.73** ± 0.12	3.61† ± 0.20	3.39† ± 0.22
Serum thyroxine (CPB) (nmol/l)	254 ± 26	243 ± 18	240 ± 20	225 ± 17	232 ± 18
Effective thyroxine ratio	1.44 ± 0.07	1.44 ± 0.07	1.49 ± 0.09	1.43 ± 0.09	1.38 ± 0.07
Reverse T_3 (nmol/l)	1.60 ± 0.16	2.31*** ± 0.17	2.24** ± 0.16	1.61††† ± 0.17	1.56†† ± 0.16
Calcium (mmol/l)	2.52 ± 0.04	2.58 ± 0.04	2.55 ± 0.05	2.56 ± 0.04	2.55 ± 0.03
Phosphate (mmol/l)	1.21 ± 0.07	1.35 ± 0.08	1.36* ± 0.07	1.38** ± 0.08	1.42** ± 0.06
Alkaline phosphatase (u/l)	79.8 ± 7.4	87.3* ± 8.5	91.7* ± 8.7	89.7 ± 6.9	92.6* ± 8.2
Drug concentration (ng/ml)	—	82 ± 13	85 ± 13	114 ± 23	148 ± 35

Significant difference from mean pretreatment value *$P<0.05$, **$P<0.01$, ***$P<0.001$.
Significant difference from mean value at 4 weeks †$P<0.05$, ††$P<0.01$, †††$P<0.001$.

Table 4 Effects of propranolol and metoprolol on serum biochemical values in group 2 (mean ± s.e. mean)

	Pretreatment	*Metoprolol* 2 weeks	*Metoprolol* 4 weeks	*Propranolol* 6 weeks	*Propranolol* 8 weeks
Thyroxine (T_4 RIA) (nmol/l)	284 ± 19	268 ± 15	281 ± 12	321*† ± 15	300 ± 15
Tri-iodothyronine (T_3) (nmol/l)	7.19 ± 0.49	7.21 ± 0.51	7.78 ± 0.77	6.60 ± 0.39	6.73 ± 0.67
T_3/T_4 ratio × 100	2.60 ± 0.17	2.72 ± 0.18	2.80 ± 0.30	2.09*† ± 0.14	2.24† ± 0.22
Serum thyroxine (CPB) (nmol/l)	279 ± 24	252 ± 18	291 ± 11	275 ± 12	274 ± 23
Effective thyroxine ratio	1.42 ± 0.08	1.40 ± 0.08	1.41 ± 0.08	1.48 ± 0.08	1.39 ± 0.09
Reverse T_3 (nmol/l)	1.60 ± 0.19	1.61 ± 0.15	1.67 ± 0.17	2.21**††† ± 0.23	2.30**††† ± 0.27
Calcium (mmol/l)	2.59 ± 0.02	2.57 ± 0.02	2.58 ± 0.03	2.60 ± 0.02	2.60 ± 0.03
Phosphate (mmol/l)	1.10 ± 0.11	1.33* ± 0.04	1.34* ± 0.05	1.39** ± 0.05	1.36* ± 0.05
Alkaline phosphatase (u/l)	109.0 ± 15.0	126.8 ± 13.9	130.2 ± 14.6	134.7* ± 15.2	137.9* ± 16.5
Drug concentration (ng/ml)	—	124 ± 22	119 ± 35	133 ± 34	110 ± 18

Significant difference from mean pretreatment value *$P<0.05$, **$P<0.01$.
Significant difference from mean value at 4 weeks †$P<0.05$, †††$P<0.001$.

while taking propranolol compared to only one taking metoprolol, but mild depression affected one patient during the first week of metoprolol therapy. Three patients admitted to single attacks of slight wheezing during exercise or upper respiratory tract infections while taking propranolol, but no patient had bronchospasm on examination at clinic visits. One patient complained of irritation of the eyes prior to entry to the study and this symptom remained unchanged during the study.

The mean plasma levels of propranolol and metoprolol between 1 and 2 h after the morning dose are shown in Table 3 and 4. There was a wide range of drug levels, varying from 26 to 467 ng/ml for propranolol and from 21 to 446 ng/ml for metoprolol. While there was little relationship between the propranolol levels at 2 weeks and 4 weeks in individual patients (correlation coefficient $r = 0.28$), the metoprolol levels at 2 and 4 weeks were closely correlated ($r = 0.91$, $P < 0.001$). There was no significant correlation between propranolol and metoprolol levels in individual patients ($r = 0.35$). Neither with propranolol nor metoprolol was the drug concentration related to the initial severity of the hyperthyroidism, as judged by the pre-treatment serum thyroid hormone levels or the hyperthyroidism diagnostic index score. Patients with low plasma metoprolol concentrations (<75 ng/ml) had more persistent hyperthyroid features as judged by a 4 week hyperthyroidism diagnostic index score of 16.3 ± 2.3 (mean $\pm$ s.e. mean) than those with high metoprolol levels (>150 ng/ml), who had a score of 7.7 ± 2.1 ($P < 0.02$), while those with intermediate levels had an intermediate score (9.2 ± 3.8). There was no relationship between plasma propranolol levels and clinical response to treatment.

All patients took their medication regularly, as judged by the tablet count. At completion of the trial, all the patients were asked whether they had a preference for the tablets used in the first month or the second month of therapy. Twelve patients expressed a preference for propranolol (a strong preference in three cases), five had a preference for metoprolol (a strong preference in one case), and six considered both drugs to be equally effective. These differences were not statistically significant.

Discussion

The results show that metoprolol appears to be as effective as propranolol in controlling the clinical manifestations of hyperthyroidism as judged by the hyperthyroidism diagnostic index. Metoprolol lowered the pulse rate and systolic blood pressure to an extent equal to that of propranolol. In our previous study (Murchison *et al.*, 1976) another β_1-selective adrenoceptor antagonist practolol was less effective in this respect, presumably owing to its partial agonist activity (Turner & Hill, 1968), whereas in a recent trial atenolol, another β_1-selective adrenoceptor antagonist, was as effective as propranolol in control of the heart rate in hyperthyroidism (McDevitt & Nelson, 1978). Metoprolol appeared to be rather less effective than propranolol in controlling finger tremor, and this is in favour of the suggestion that finger tremor may be mediated by β_2-adrenoceptors (Larsson & Svedmyr, 1977). However, there is evidence (Young, Growdon & Shahani, 1975) to suggest that in essential tremor the efficacy of chronic oral propranolol is mediated, not via its peripheral β-adrenergic receptor blocking action, but by an alternative effect, possibly in the central nervous system. Such an effect might be of therapeutic importance also in thyrotoxic tremor. Our findings (maximal improvement with propranolol, rather less with metoprolol, and no significant change in the case of practolol) are consistent with this suggestion, since the improvement in tremor with each of these three drugs parallels their ability to penetrate the central nervous system. In this study we showed only a minor effect of β-adrenoceptor blockade on relief of subjective symptoms of anxiety as measured by the Taylor manifest anxiety scale, whereas in our previous study (Murchison *et al.*, 1976) there was a progressive reduction in anxiety throughout the 8-week study period, and practolol was as effective as propranolol in this respect. The latter finding is in keeping with an action on peripheral adrenoceptors rather than a central effect. This study showed no difference in effectiveness of the two drugs on eye signs, but since only 6 patients in each group had eye signs of hyperthyroidism, the numbers were too small for an effective comparison. An improvement in the myopathy of hyperthyroidism treated with propranolol has been shown previously (Pimstone, Marine & Pimstone, 1968), but this appears to be the first report of improvement produced by an alternative β-adrenoceptor blocking agent. As in our previous study (Murchison *et al.*, 1976), both drugs led to cessation of the weight loss noted before entry to the trial. It is of interest that a rapid improvement in nitrogen retention has been demonstrated in hyperthyroid patients treated with propranolol (Georges, Santangelo, Mackin & Canary, 1975).

Changes in serum thyroid hormone levels were observed in both groups during propranolol therapy, namely a highly significant rise in reverse T_3 and thyroxine with a tendency to reduction in triiodothyronine. That propranolol reduces serum triiodothyronine with a concomitant rise in reverse T_3 has now been amply confirmed (Verhoeven, Visser, Docter, Henneman & Schalekamp, 1977; Kallner, Ljunggren & Tryselius, 1978; Saunders, Hall, Crowther & Sönksen, 1978; Tevaarwerk, Malik &

Boyd, 1978), although its effects on thyroxine have been less consistent. Some workers have reported an increase in serum thyroxine during propranolol therapy (Williams & Jacob, 1970; Harrower, Fyffe, Horn & Strong, 1977; Kristensen & Weeke, 1977), whereas Ljunggren & Persson (1975) found a decrease, and others have shown no significant change (Lotti, Delitala, Devilla, Alagna & Masala, 1977; Theilade, Mansen, Skovsted, Faber, Kirkegaard, Friis & Siersback-Nielsen, 1977; Verhoeven *et al.*, 1977; Kallner *er al.*, 1978; Saunders *et al.*, 1978; Tevaarwerk *et al.*, 1978). In our previous study (Murchison *et al.*, 1976) we showed a small increase in serum thyroxine as measured by a competitive protein binding technique, while in the present study thyroxine as measured by the same technique was unchanged during propranolol therapy, while a significant rise occurred in thyroxine as measured by radioammunoassay. The conflicting reports on the effect of propranolol on serum thyroxine are therefore not readily explicable by differences in laboratory methodology, but may be due in part to the marked fluctuations in thyroxine levels noted in hyperthyroid subjects, and in part to differing effects of duration of propranolol therapy (Kallner *et al.*, 1978). Metoprolol treatment did not influence thyroid hormone levels and in this respect it resembles practolol (Murchison *et al.*, 1976). The effects of β-adrenoceptor antagonists other than propranolol on serum thyroxine, tri-iodothyronine and reverse T_3 have not previously been systematically studied. Our findings are relevant to hypotheses regarding the possible mode of action of β-adrenoceptor antagonists in hyperthyroidism. It has been suggested that much of the beneficial effect of propranolol in hyperthyroidism is due to the diversion of thyroxine metabolism to form the metabolically inactive reverse T_3 instead of the highly active triiodothyronine (Kallner *et al.*, 1978; Tevaarwerk *et al.*, 1978). While current knowledge does not permit definite conclusions, our findings would throw doubt on this hypothesis since we have shown that practolol and metoprolol, while having no influence on the peripheral metabolism of thyroid hormones, are therapeutically effective in the symptomatic treatment of hyperthyroidism. As in our previous study, β-adrenoceptor antagonists did not appear to influence serum calcium levels. The rise in serum alkaline phosphatase confirms the findings of our previous study, and may reflect early healing of hyperthyroid osteodystrophy. The alkaline phosphatase appears to be mainly of bone origin since the remaining liver function tests were unchanged. The rise in inorganic phosphate is of interest. A recent study of the non-selective β-adrenoceptor antagonist, timolol, showed a rapid rise in serum inorganic phosphate in healthy individuals, and this was thought to be due to an alteration in renal excretion of phosphate (Lindsay, Ramsay, Hettiarrachchi, Davies & Beastall, 1978).

There was little difference in frequency of adverse reactions to either drug. The changes in ventilatory function tests, although small, were rather surprisingly greater during metoprolol than propranolol therapy. Metoprolol as a rule causes less bronchoconstriction than propranolol, but may produce a clinically significant fall in forced expiratory volume in some asthmatic subjects (Skinner, Gaddie, Palmer & Kerridge, 1976), and patients with known obstructive airways disease were excluded from this study. Although measurement of drug concentrations in single blood samples must be of limited value, the levels obtained between one and two hours after an oral dose are likely to represent near-peak drug levels. The marked variation in plasma propranolol levels during chronic oral administration has been noted previously (Shand, 1974; Feely, Forrest, Gunn, Hamilton, Stevenson & Crooks, 1977). It is of interest that plasma metoprolol levels showed much less fluctuation in individuals between 2 and 4 weeks therapy, and that the metoprolol levels showed some relationship to the clinical efficacy of the drug. We have been unable to demonstrate any such relationship in the case of propranolol, possibly due in part to the complicating factor of active circulating metabolites of propranolol which were not accurately measured by the technique used in this study. The fact that serum levels of metoprolol and propranolol did not appear to be influenced by the severity of the pretreatment hyperthyroid state is in keeping with the observation (Bell, Russell, Nelson, Kelly & McDevitt, 1977) that thyroid dysfunction had little influence on the elimination of propranolol.

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