Practolol in Hyperthyroid Cardiac Failure*

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SUMMARY

Practolol (Eraldin†), a recently developed beta-adrenergic blocking agent, has been found useful in conjunction with digitalis and diuretics in 6 patients with thyrocardiac disease who had been refractory to therapy. In all cases cardiac failure improved dramatically, suggesting better myocardial efficiency and a return of digitalis responsiveness after practolol. This drug might be a useful therapeutic adjunct in thyrocardiac disease.

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Blockade of beta-adrenergic receptor sites produces dramatic improvement in many of the catecholamine-mediated features of hyperthyroidism, notably the pulse rate,[1] tremor,[2] nervousness, agitation[3] and sweating.[4] As a consequence, beta-adrenergic blockade with propranolol has been successfully used in a number of clinical situations in hyperthyroidism, namely with ^{131}I therapy,[5] preoperatively with Lugol's iodine,[6] and in thyroid crisis.[7] While some workers have claimed this drug to be effective in thyrocardiac disease,[8] its known depressive action on myocardial function[9] has been implicated in the precipitation of cardiac failure. Most clinicians, therefore, are hesitant in using propranolol in thyrocardiac patients, many of whom have an ischaemic element to their disease. Practolol is a new beta-adrenergic blocking agent with certain advantages over propranolol. Apart from a longer half-life,[10] necessitating only bi-daily administration, and cardio-selectivity leading to a lower incidence of bronchospasm, it produces less myocardial depression, probably due to its intrinsic sympathomimetic activity.[11] This article records our experience with this therapy in 6 patients with severe refractory congestive cardiac failure associated with hyperthyroidism.

CASE REPORTS

Case 1

The patient, a 60-year-old female, complained of swelling of the ankles and dyspnoea for one year, which did not respond to digitalis and diuretic therapy. Other features were 28 kg weight loss, and a decided preference for cold weather. Examination showed a diffuse thyroid enlargement with a continuous bruit, hyperactivity, tremor, lid-lag, warm sweaty palms, and a proximal myopathy. In addition, signs of cardiac failure were found, notably ankle oedema, a raised jugular venous pressure, hepatomegaly and atrial fibrillation. Protein-bound iodine concentration was 12 μg/100 ml and neck ^{131}I uptake 73% and 69% at 6 and 24 hours respectively. X-ray of the chest showed cardiomegaly with congestion of the lung fields.

The patient was diagnosed as having thyrotoxicosis and cardiac failure. Previous therapy (digoxin, Lasix and potassium) was continued and practolol was started with an initial dose of 50 mg. This was gradually increased over 2 days to 200 mg *b.d.* Within 4 days, dramatic improvement was evident. The pulse rate slowed from 150 to 110/minute with a decrease in jugular venous pressure, and improvement in her tremor, hyperkinesis, sweating and general well-being. A therapeutic dose of ^{131}I was subsequently given, followed later by neomercazole.

Case 2

The patient was a known diabetic woman of 60 years, maintained on oral hypoglycaemic agents for the past 10 years. Six months before admission, proximal muscle weakness developed and progressed markedly, followed a few months later by paroxysmal nocturnal dyspnoea, dyspnoea on effort and orthopnoea. The thyroid was enlarged. The eyes had a staring appearance with minimal proptosis. A fine tremor of the outstretched hands and a tachycardia of over 100/minute was noted. Blood pressure was 150/100 mmHg, with elevation of jugular venous pressure, hepatomegaly and ankle oedema. The fundi showed diabetic retinopathy. Marked proximal muscle weakness was present in both upper and lower limbs with absent knee and ankle jerks and impaired distal sensation.

Urine analysis showed albumin 3+ and glucose 3+. Myopathy in the deltoid, triceps and vastus medialis muscles was confirmed by electromyography. Her random blood glucose concentration was 260 mg/100 ml. The ECG showed left ventricular hypertrophy and sinus tachycardia of 120/minute. ^{131}I uptakes at 6 and 24 hours were 75% and 85% respectively. Creatine phosphokinase and nerve conduction time were normal.

The patient's diabetes was controlled on oral hypoglycaemic agents and diet. Her congestive cardiac failure responded only partially to digoxin and diuretics, leaving her with tachycardia, dyspnoea and oedema. Practolol 50 mg was then given, the dose being increased over 36 hours to 200 mg *b.d.* The patient's cardiac failure improved rapidly within 2 - 3 days. The pulse rate dropped to 80/minute, diuresis followed and dyspnoea lessened. No improvement in the myopathy was observed. ^{131}I therapy was given, followed 6 days later by the administration of neomercazole.

Case 3

A 50-year-old woman had had proven thyrotoxicosis at another hospital 4 years before the present admission, but had received no definitive therapy. Angina pectoris had subsequently developed, with severe dyspnoea and fluid retention. The patient had taken her medication irregularly and was admitted to hospital in severe congestive cardiac failure after stopping her treatment altogether.

Examination revealed a thin female, severely dyspnoeic, with basal crepitations, oedema and atrial fibrillation. The pulse rate was approximately 120/minute and the blood pressure 150/100 mmHg. Tremor, lid-lag and enlargement of the thyroid gland were found. Urine analysis showed a heavy proteinuria. Haemoglobin concentration was 9·5 g/100 ml and

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blood urea 200 mg/100 ml on repeated occasions. Creatinine clearance varied between 1·5 - 2 ml/minute. Chest X-ray showed cardiomegaly with congested lung fields. Thyroid function studies showed that ^{131}I uptakes at 6 and 24 hours were 24% and 46% respectively, and protein-bound iodine was 8·0 µg/100 ml. 'Charcoat' resin test was, however, in the hyperthyroid range.

The patient was treated cautiously with digitalis and intravenous diuretics with deterioration in the cardiac status. Because of the past history of thyrotoxicosis and the confirmatory clinical signs, treatment with practolol and neomercazole was started, despite equivocal function studies. Practolol 50 mg was given as a single dose and increased gradually to 200 mg *b.d.* Within 2 days her extreme dyspnoea had markedly improved, and the neck veins had become less distended. The pulse rate (though still fibrillating) had decreased to 100/minute and sweating was less. Her renal function remained unchanged, however, and in spite of a maintained response of her cardiac and thyroid status, she died in terminal renal failure 2 months later.

Case 4

In February 1969 a 68-year-old woman was investigated for atrial fibrillation and congestive cardiac failure. No cause was established and the patient was treated with digoxin, diuretics and potassium with good initial improvement. However, a few months later, cardiac failure recurred in spite of continued therapy. Careful interrogation at this stage revealed a loss of weight over the previous 2 years. A nodular enlarged thyroid was found on examination.

She was admitted to hospital distressed and dyspnoeic with evidence of loss of weight and muscle bulk. Cardiomegaly was evident with aortic systolic and diastolic murmurs and an apical soft systolic murmur. Atrial fibrillation 140 - 150/minute, basal crepitations, hepatomegaly and ankle oedema were also found. Generalized weakness of both upper and lower proximal muscle groups was elicited. Cardiomegaly and congested lung fields were evident on chest X-ray. An ECG showed a ventricular rate of 140/minute, atrial fibrillation and probably an old anterior infarct. A patchy myopathy was suggested by electromyography. Thyroid function tests showed ^{131}I uptakes of 48% and 76% at 6 and 24 hours and protein-bound iodine of 10·2 µg/100 ml.

Digitalis and diuretics were maintained in spite of previous refractoriness, and in view of the thyrotoxicosis, 50 mg practolol was given. As no adverse effects were observed, the dose was increased 12 hours later to 100 mg *b.d.* Improvement was dramatic over 3 days with diminution of pulmonary congestion, dyspnoea and pulse rate (from 140 to between 90 and 100/minute). A therapeutic dose of ^{131}I was administered followed 14 days later by neomercazole.

Case 5

A 42-year-old female was first seen in 1967 when thyrotoxicosis was diagnosed and treatment with neomercazole and propranolol commenced. In spite of a good response, she failed to return for long-term continuation of therapy. Two months before admission, a 'flu-like' illness occurred, associated with vomiting and an upper respiratory tract infection. On the day of admission in August 1970, the patient developed a left-sided hemiplegia. Definite symptoms of thyrotoxicosis were not evident. The patient was distressed and extremely dyspnoeic with thyroid enlargement, a coarse tremor of the outstretched hands and gross proptosis. Her pulse was 140/minute and fibrillating. Cardiomegaly, a gallop rhythm, pulmonary congestion and oedema were marked. Chest X-ray confirmed pulmonary oedema and cardiomegaly with an enlarged pulmonary conus. The ECG showed a ventricular rate of 140/minute with atrial fibrillation and ventricular ectopic beats. Thyroid function tests showed that ^{131}I uptakes at 6 and 24 hours were 72% and 66% respectively, with 'charcoat' resin test in the hyperthyroid range. Pulmonary function tests were normal.

The patient was immediately started on digoxin, diuretics and anticoagulants, the provisional diagnosis being an embolus following atrial fibrillation. In view of the past history and obvious physical signs of thyrotoxicosis, practolol was added to the therapy shortly thereafter. A test dose of 50 mg was given, followed 12 hours later by 50 mg *b.d.* for 1 day and then 100 mg *b.d.*, on which the patient was maintained. The response to this regimen was rapid. Ventricular rate slowed to 100/minute after the initial 50 mg dose of practolol. Two days after the start of therapy pulmonary congestion had improved both clinically and radiologically. Her general condition was also markedly improved at this stage. Two weeks after admission a therapeutic dose of ^{131}I was given followed 5 days later by the commencement of neomercazole.

Case 6

Eighteen months after a thyroidectomy performed for thyrotoxicosis in 1930, a 77-year-old woman developed pretibial myxoedema and aggravation of exophthalmos which had been present before the operation. Thyroid sicca 4 gr. daily was started, and continued until 1964 when the patient was admitted to hospital in left ventricular failure, thought to be on an ischaemic basis because of associated angina pectoris. She responded well to digitalis and diuretic treatment. Thyroid sicca was changed to thyroxine 0·1 mg *t.d.s.* This therapy was maintained until her present admission. In 1969, she developed asthma and thereafter was seen on numerous occasions in congestive cardiac failure exacerbated by respiratory infections.

In September 1970 she was admitted to hospital with increasing dyspnoea, frequent palpitations, and a 'constant pressure on the chest' which she distinguished from her long-standing angina pectoris. For the previous 14 months her dose of thyroxine had been 0·2 mg/day. Otherwise she had been on digitalis and diuretics as previously.

The patient was plethoric, dyspnoeic and sweating with warm hands. Pretibial myxoedema and endocrine exophthalmos were marked. No thyroid remnant was palpable in the neck. The pulse rate was 120/minute at rest and the blood pressure was 180/100 mmHg/minute. A triple rhythm was audible at the cardiac apex. Bilateral basal crepitations and a tender hepatomegaly confirmed her cardiac failure. The ECG showed a sinus rhythm with atrial premature systoles and non-specific left ventricular changes. Blood urea and electrolytes were normal. Lasix, digoxin, Aminophyllin and thyroxine were continued, but improvement on the regimen and bed rest was limited. Dyspnoea, sweating and palpitations persisted and the diagnosis of 'thyrotoxicosis artefacta' was entertained. Thyroid ^{131}I uptakes (on thyroxine therapy) were 2% and 7% at 6 and 24 hours respectively, and serum cholesterol was 233 mg/100 ml.

Thyroxine was stopped and 50 mg practolol was given, and increased 12 hours later to 100 mg *b.d.*, on which dose she was maintained. Within 24 hours, marked improvement was noted. The pulse rate decreased to 88/minute, dyspnoea eased and the lung bases cleared. The patient commented 'that it was as if the load had been lifted off my chest'. Practolol was continued for 3 weeks. One month after stopping the thyroxine, thyroid function studies were repeated and ^{131}I uptakes were 3·7% and 1·5% at 6 and 24 hours respectively, and serum thyroxine 1·3 µg/100 ml (normal 5 - 13 µg/100 ml). Accordingly she was restarted on thyroxine 0·1 mg daily.

DISCUSSION

Six patients with hyperthyroidism (in 1 instance thyroxine-induced) and severe cardiac failure, refractory in 5 cases to standard digitalis and diuretic therapy, were additionally treated with the new beta-adrenergic blocking agent practolol, starting with a single trial dose of 50 mg. In all patients there was considerable improvement in the symptoms and

signs of cardiac failure within 2 - 4 days of starting the drug. Many of the hyperthyroid manifestations—tremor, pulse rate, sweating—and general well-being improved. We cannot exclude a concomitant effect of bed rest, but the previous total refractoriness to standard treatment of all but one of the patients even while in hospital, and their rapid and dramatic improvement after the addition of practolol (a response which paralleled improvement of hyperthyroid features), suggests a direct and specific beneficial effect of this drug.

Beta-adrenergic blockade using propranolol is now established as an important adjunct in the therapy of hyperthyroidism.[5,6] Apart from the lack of cardioselectivity and hence a tendency to bronchospasm[12] the main contra-indication to the use of this drug has been the presence of cardiac failure because of its known depressant effect on myocardial function.[9] There have been reports in which propranolol has been successfully used in thyrocardiac disease[8] but because of the mixed nature of the cardiac disorder (many patients have severe ischaemic heart disease), most authorities tend to avoid the use of this agent in these specialized circumstances.

Practolol, by contrast, has less myocardial depressant effect, largely because of its intrinsic sympathomimetic activity.[11] It has been postulated that this might be a contra-indication to its use in thyrotoxicosis because of the long-held view that enhanced sensitivity to catecholamines is a feature of this condition.[13] On the other hand Levey *et al.*[14] have reported no increased sensitivity of cardiac adenylcyclase to catecholamines in the hyperthyroid animal, suggesting that at least in respect of the cardiac manifestations of thyroid disease, practolol might not be contra-indicated. Indeed, our own experience with oral practolol in other cases of thyrotoxicosis suggests a satisfactory improvement in well-being, sweating, nervousness and pulse rate.

The precise mechanism of the beneficial effect of practolol should be considered. Weiner *et al.*[15] have shown that beta-adrenergic blockade improves the positive chronotropic and inotropic effects of thyroid hormone and presumably reduces the increased myocardial oxygen requirements of thyrotoxicosis with improvement in myocardial efficiency. This, in turn, could lead to increased digitalis responsiveness, as has been described by Waldstein *et al.*,[16] with guanethidine.

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