CLINICAL RESPONSE TO LONG-TERM PROPRANOLOL THERAPY IN HYPERTHYROIDISM*

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Propranolol has been shown to be effective in hyperthyroidism in a variety of situations. These include thyrotoxic crises,[1,2] preparation for subtotal thyroidectomy,[3] the control of residual thyrotoxic symptoms after radioactive iodine therapy[4] and in some cases of thyrotoxic myopathy.[5]

Standard antithyroid drugs are not without serious side-effects, and their prolonged use in hyperthyroidism may be complicated by the frequent need to adjust dosage to the changing clinical status of the patient. They also interfere with ^{131}I tests of thyroid function during treatment. Propranolol, by contrast, causes few unpredictable side-effects if patients are appropriately selected, does not appear to induce hypothyroidism, and allows thyroid function to be tested during therapy.[4] The present study was therefore undertaken to assess the effectiveness of this drug given as sole long-term treatment in hyperthyroidism.

PATIENTS AND METHODS

The trial group consisted of 27 patients (23 females and 4 males) attending the Thyroid Clinic, Groote Schuur Hospital, who were considered suitable candidates for long-term medical therapy and in whom there were no obvious contraindications to the use of propranolol, such as bronchospasm or overt cardiac failure. All were hyperthyroid by standard clinical and laboratory criteria. Their ages ranged from 21 to 63 years.

Propranolol (Inderal, ICI) was instituted as the sole therapeutic agent after assessment according to Wayne's therapy index;[6] each patient had an initial score of 20 or more. The starting dose of propranolol was generally 40 mg. orally *t.d.s.* Patients were reassessed at monthly (or more frequent) intervals, and if clinical response was judged to be partial but inadequate the dose was increased (to a maximum of 120 mg. *q.i.d.*). Those who responded poorly were given Neo-Mercazole after final clinical assessment for the trial.

After an average period of observation of 5 months (range 1 - 8 months), each subject was again carefully assessed clinically and a final therapy index score was assigned. Where possible, repeat radioactive iodine (^{131}I) neck uptakes were also performed. On the basis of these 2 criteria, patients were then divided into 4 groups: those with an adequate clinical response (final therapy index score <5) and normal ^{131}I studies (6- and 24-hour neck uptakes less than 40 and 50% respectively); those with an adequate response but elevated ^{131}I uptakes; those with a partial clinical response (final therapy index between 5 and 10)—all these had elevated ^{131}I uptakes; and those with a poor clinical response (therapy index score >10).

RESULTS

Groups of Responders

As indicated in Table I, 47% of the series were considered to have had an adequate clinical response when finally reassessed. In all cases marked subjective and objective clinical improvement was seen within the first few weeks after commencement of therapy, and the dose of propranolol required was comparatively small. Indeed, just under half of these patients seemed to have become euthyroid again as indicated by normal repeat ^{131}I neck uptakes. They could be differentiated from the patients who remained with elevated repeat uptakes, however, by their greater gain in weight.

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TABLE I. CLINICAL AND INVESTIGATIVE DATA ON 27 PATIENTS GIVEN LONG-TERM PROPRANOLOL IN HYPERTHYROIDISM

Group responses	No. of patients	% total	Propranolol dose (mg.)*	Weight change (lb.)*	^{131}I neck uptakes (%)* Initial 6 hr/24 hr	^{131}I neck uptakes (%)* Repeat 6 hr/24 hr
Adequate—normal repeat uptakes	6	22	40 *t.d.s.*	+12	78/77	39/45
Adequate—elevated repeat uptakes	7	25	40 *q.i.d.*	+4	79/73	68/68
Partial	9	34	80 *q.i.d.*	+1	79/77	68/74
Poor	5	19	80 *q.i.d.*	+1	75/75	—

*Mean values.

A further 34% of patients showed some degree of clinical improvement but were left with at least one important thyrotoxic symptom—usually persistent loss of weight. Features that generally improved in this group were nervousness, palpitation, excess sweating and tremor. The average propranolol dose ultimately employed here was double that used in the first two groups. Repeat ^{131}I uptakes were all elevated.

Finally, a comparatively small number (19%) responded poorly to the drug. They persisted with numerous thyrotoxic features. At least 2 patients in this group admitted to taking their medication irregularly.

Initial ^{131}I studies were similar in all 4 groups of responders.

Side-Effects

Three patients developed side-effects severe enough to warrant premature cessation of therapy. In one, congestive cardiac failure supervened some weeks after propranolol was started; another developed erythema multiforme after several months; and the third patient had severe bronchospasm after 5 months on large doses.

Evanescent attacks of mild bronchospasm occurred in two other subjects.

Effect of Propranolol on Specific Thyrotoxic Features

Myopathy occurred as a prominent clinical feature in 4 patients; 3 of them showed marked clinical improvement while on the drug, with a rapid return of normal muscle power. Details of these and other cases of myopathy have been previously reported.[5]

Amenorrhoea was a clinical feature in 7 women, and 4 noticed a return of normal menstruation within a month or two of starting therapy.

Improvement of these features occurred in patients who, at the end of the trial period, still had elevated ^{131}I uptakes, suggesting a true effect of propranolol, and not a coincident improvement due to spontaneous remission.

Lid lag and retraction, observed in the majority of subjects in the series, appeared to be completely unaffected by the drug.

DISCUSSION

Propranolol was capable of adequately controlling 47% of cases when used as the sole therapeutic agent in the long-term management of hyperthyroidism of all grades of severity. A proportion of those who responded well seemed to have gone into remission when subsequently retested with ^{131}I, although the over-all percentage that did so is less than reported after 6 months of carbimazole therapy.[7] Whether the remission was spontaneous or induced by propranolol is not yet clear and is being currently evaluated. Of particular interest were the 7 patients in this group who still showed elevated ^{131}I neck uptakes at the end; for their failure to gain as much weight as the patients who had become euthyroid suggests a degree of persisting 'hypermetabolism'. Our preliminary data on the effect of propranolol on basal metabolism[8] tends to confirm this.

Initial ^{131}I neck uptakes were unhelpful in predicting which patients were likely to respond satisfactorily to propranolol, but some indication was provided by the observation that those who did well could be controlled from the beginning on the starting dose. Where this had to be increased during the period of follow-up, eventual clinical response was usually incomplete.

Significant side-effects occurred in 3 patients; withdrawal of the drug and substitution of alternate therapy led to their resolution in each case. Thus there is little objective confirmation for the assertion that long-continued use of propranolol is fraught with risk in thyrotoxicosis,[9] provided proper care is taken.

It seems unlikely that all the beneficial effects observed with propranolol in this study can be attributed solely to adrenergic-β-receptor blockade. While propranolol-induced improvement in cardiovascular manifestations, tremor and anxiety in thyrotoxicosis is generally regarded as being largely the result of such sympathetic inhibition,[1,2,10] the improvement of myopathy and return of menstruation noted in some of our patients are not easily explicable on these grounds. That the response was not coincident with spontaneous remission, but reflected a true effect of propranolol, is suggested by the persistence of elevated ^{131}I uptakes in the majority of these patients. However, the precise mechanism awaits clarification.

With regard to the practical role of propranolol in the long-term medical management of hyperthyroidism, certain tentative conclusions can be drawn from this study. Although obviously inferior to the standard antithyroid drugs for routine therapy, it could be profitably employed in relatively low dosage (say 40 mg. *q.i.d.*) for the first few weeks of treatment in suitable subjects. Where a good response—including some increase in weight—is rapidly observed, it would seem rational to persevere with the drug. In cases where response, as judged by a standard therapy index, is incomplete, the addition of a thyroid-blocking agent (e.g. Neo-Mercazole) in *low* dosage may prove successful, lessening the risks of induced hypothyroidism and further thyroid enlargement. We are at present assessing the effects of this therapeutic approach. Facilities for regular patient-supervision and follow-up are a prerequisite for any such regimen.

SUMMARY

Twenty-seven patients with hyperthyroidism were treated solely with propranolol, an adrenergic-β-receptor blocking agent, for an average period of 5 months. They were then reassessed according to Wayne's therapy index and 47% of the series were considered to have responded adequately. Just under half of these had normal radioactive iodine (^{131}I) neck uptakes when retested. A further 34% showed some clinical improvement but were left with at least one major thyrotoxic manifestation—usually failure to gain weight. The remaining subjects were poorly controlled on therapy.

Patients who did well could be controlled from the outset by relatively small doses of propranolol. Side-effects requiring premature cessation of therapy occurred in 3 cases; these subsided when alternative therapy was given. The beneficial effects on myopathy and menstruation noted in some patients suggested that the drug's effectiveness in thyrotoxicosis might not be entirely due to sympathetic blockade. A practical role for the use of propranolol in the long-term management of hyperthyroidism is cautiously defined.

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