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Experience with carbimazole in the treatment of the hyperthyroidism of Graves' disease in Nigerian patients

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Summary

To estimate the rate of remission and relapse in patients with thyrotoxic Graves' disease following therapy with thionamides, the course of 49 patients who were treated with carbimazole and followed for a mean (\pm S.D.) of 22.0 ± 17.8 months, was analysed. A remission rate of 61% was obtained. Remissions were more common in patients with small goiters and those with a short duration of illness. Relapse occurred most commonly within the first few months following the discontinuation of the drug. Thirty-two per cent of the patients left the clinic either before or soon after achieving euthyroidism. It is concluded that the thionamides are quite efficacious in the induction of remission in newly diagnosed Nigerian patients with toxic Graves' disease and probably should presently be the principal treatment modality for these patients, rather than subtotal thyroidectomy. Efforts should be made to reduce the frequent drop-out of our patients from the clinic during follow-up.

Résumé

Afin de déterminer le taux de rémission et de rechute chez les patients souffrant de la maladie thyrotoxique de Graves après une thérapie de thionamides, nous avons analysé le traitement de 49 patients qui ont été traités au carbimazole et suivi pour le moyen (\pm S.D.) de 22.0 ± 17.8 mois.

Un taux de rémission de 61% est obtenu. La rémission est plus fréquente chez des patients avec de petits goitres et qui ont eu une courte durée de

maladie. La rechute vient d'habitude dans les premiers mois de cessation des médicaments. Trente-deux pour cents (32%) des patients ont quitté la clinique avant ou juste après d'arriver à l'euthyroidisme.

En conclusion, les thionamides sont efficaces pour avoir la rémission chez de nouveaux patients Nigériens souffrant de la maladie toxique de Graves et pourrait constituer son traitement principal pour le moment au lieu de la thyroïdectomie subtotale. On doit essayer de réduire la fréquence des patients qui ne reviennent plus pour des examens médicaux.

Introduction

Modalities which are currently available for the treatment of patients with toxic Graves' disease fall into two general categories [1]. The first group includes the ablative procedures such as radioiodine — 131 therapy or subtotal thyroidectomy. The second involves the use of drugs to inhibit or block various steps in the synthesis, release or extrathyroidal metabolism of the thyroid hormones [2]. One class of the antithyroid drugs, the thionamides, additionally exerts immunosuppressive effects in patients with Graves' disease by inhibiting autoantibody production [3,4]. The choice of a specific therapeutic modality for a patient with Graves' disease generally depends on several factors which, among others, include the experience of the physician or surgeon, and the availability of appropriate resources. In most hospitals in Nigeria, including ours, the lack of facilities for radioiodine

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therapy limits the available options to only subtotal thyroidectomy and antithyroid drug therapy.

Current clinical practice in most of our local hospitals favours the use of the thionamides principally for the pre-operative preparation of patients for thyroidectomy despite the fact that several early reports suggest that these agents, probably as a result of their immunosuppressive effects, can induce a long or permanent remission in a substantial proportion of patients with toxic Graves' disease [5-7]. If comparable results can be obtained in our local population, these drugs would probably be preferable to thyroidectomy as the definitive therapy in the management of most of our patients with toxic Graves' disease at the present time since the number of experienced thyroid surgeons in our hospitals is limited and the reported incidence of post-operative complications is high, particularly in inexperienced hands [8,9].

The following report presents the results of a personal experience in the drug treatment of a group of patients with toxic Graves' disease seen in Enugu, Nigeria over a 10 year period. This analysis has been made in order to estimate the remission rate and define the problems encountered during the treatment of this disorder with thionamides in this environment.

Subjects and methods

All patients seen personally between October 1979 and October 1989 with newly diagnosed thyrotoxic Graves' disease and who received carbimazole for at least 4 months, were analysed. Any patient with a doubtful diagnosis was excluded. Toxic Graves' disease was diagnosed on the basis of the presence of a typical history and physical signs of hyperthyroidism in association with a diffuse goiter and elevated serum concentration of thyroxine (T4) and/or triiodothyronine (T3) determined by radioimmunoassay and adjusted for any thyroid hormone binding protein abnormality with a resin T3 uptake test. Most of the patients had dysthyroid ophthalmopathy and a few had dermopathy.

Thyrotoxicosis was treated with 20-60 mg of carbimazole per day in divided doses. A short course of propranolol was also used in the early phase of therapy in some cases. Treatment was given until euthyroidism was achieved clinically and biochemically after which the drug was continued at a lower dose for approximately three additional

months. The patients were subsequently seen in the clinic at monthly intervals for the first few months and later at longer intervals while looking out for the recurrence of symptoms and signs of thyrotoxicosis. A relapse was considered to have occurred when obvious clinical hyperthyroidism, accompanied by supranormal concentrations of serum T3 and T4, was observed after previous drug-induced euthyroidism.

The patients' medical records were reviewed for the documentation of the following: age at presentation, sex, duration of symptoms before presentation, estimated size of the gland at presentation, duration of therapy before euthyroidism was achieved, and the duration of follow-up till relapse. A gland was classified as small or only slightly enlarged if it was estimated by palpation to be 45-50 gm or less. Otherwise it was said to be large.

Statistical comparison between groups was made by the student's t-test and results are given as the mean \pm standard deviation (S.D.).

Results

Forty-nine patients (36 females and 13 males) with thyrotoxic Graves' disease met the criteria for inclusion in the study. Their mean age (\pm S.D.) was 31.0 ± 11.4 years (range: 15-55 years). All had elevated serum T3 and/or T4 concentration. They had been symptomatic for 1 month to 2 years before presentation. In 28 (57%) of them, the thyroid gland was estimated by palpation to be small or only slightly enlarged (45-50 gm or less). Infiltrative ophthalmopathy was observed in 34 patients.

Nine patients (5 females and 4 males) never achieved euthyroidism despite therapy with carbimazole for 4-38 months. Poor drug compliance was suspected to be responsible for the lack of control in 5 of them although each also had a large goitre. Two of these five patients required subtotal thyroidectomy after 9 and 13 months of unsuccessful drug therapy; both of them became hypothyroid post-operatively. Two other patients were lost to follow-up after 8 and 13 months while the fifth patient still comes to the clinic at irregular intervals more than 3 years after the initiation of therapy with carbimazole. Information on four additional patients was limited because each stopped coming to the clinic after only a few visits.

Forty patients (31 females and 9 males) became euthyroid within 4-13 months of starting carbi-

mazole. Euthyroidism was achieved in significantly more of those with symptoms for 6 months or less ($p < 0.01$), and in those with small or only minimally enlarged glands ($p < 0.01$).

Of the patients that become euthyroid, 7 were lost to follow-up 3-32 months after carbimazole was discontinued; three of them within the first 6 months. Three other patients elected to have a subtotal thyroidectomy soon after achieving euthyroidism. A mild but sustained hypocalcemia occurred in one of them. All three patients also subsequently stopped attending either the medical or surgical clinic. Thirty-five (29 females and 6 males) of the adequately treated patients were seen regularly in the clinic for 6 or more months after carbimazole was discontinued. Four of them (2 females and 2 males) relapsed, three within the first 6 months and the other at 15 months. Other than that single patient, all who were euthyroid for 6 months have remained so for a follow-up period of 6 months to over 7 years (mean \pm S.D. = 22.0 ± 17.8 months). Five patients have been euthyroid for 6-9 months, 12 for 10-15 months, 9 for 16-36 months and 4 patients for 40-88 months. Because of the small number of patients who have relapsed, it was not possible to evaluate the impact of sex, size of gland, presence of ophthalmopathy or duration of symptoms on the rate of relapse.

The rate of remission for the entire population was 61%. No adverse drug reaction which required changing to an alternate form of therapy occurred in any patient. However, minor drug eruptions developed in two patients. Also two other patients became hypothyroid while on carbimazole but this resolved when the drug was discontinued. No patient in remission has so far become hypothyroid during follow-up.

Discussion

The present study permits an estimation of the rate of remission induced by carbimazole in our patients with thyrotoxic Graves' disease. Although the study population is small and the duration of follow-up limited, the results are probably applicable to a larger population of Nigerian patients with this disorder.

The achievement of high remission rates in patients with Graves' disease after thionamide therapy has previously been reported from several parts of the world [5-7]. More recent reports from North America and Europe however suggest a

decline in the rate of remission induced by these drugs [10,11], a finding that has been attributed to an increase in the level of iodine consumption in these areas [12]. The present report, the first on this subject from Nigeria, documents a relatively high remission rate of 61% in our patients after a mean follow-up period of 22.0 ± 17.8 months. Although remission rates will vary with the duration of follow-up, the fact that only one patient in the present study who remained euthyroid for 6 months after the discontinuation of carbimazole subsequently relapsed during a follow-up period of up to 7 years in some, suggests that the observed short-term remission rate offers a reasonable estimate of the long-term value. A longer period of follow-up of a larger group of patients would, however, still be necessary for a more accurate estimate of the true remission rate for our patients with Graves' disease who are treated with carbimazole.

This study also found, as others have reported [7,13], that remissions occurred more readily in those patients with either small or slightly enlarged glands, or a recent onset of illness. Factors that are responsible for these observations are presently unknown.

A significant and disturbing finding in the present study is the fact that 16 (32.6%) of the patients were lost from the clinic during follow-up. Six of them left without achieving euthyroidism while the rest defaulted after becoming euthyroid. Although emotional instability and increased irritability, which may contribute to this observation, are well-known clinical features of toxic Graves' disease, it is doubtful that the high drop-out rate found here is peculiar to our patients with this disorder. Rather, it is more likely that the phenomenon is common among our patients with a variety of chronic medical illnesses who require long-term care. The low level of education of a substantial proportion of our patients, the seemingly impersonal attention they receive because of the large number of patients attending the clinics, the high cost of drugs, and the expectation by the patients for a rapid cure, are probably partly responsible. A study of these and other psychosocial factors, which may contribute to this high rate of default would be of immense benefit in establishing an effective strategy for the care of our patients who need treatment for prolonged periods.

The high remission rate and the absence of any serious adverse drug effect suggest that thionamides

would be quite efficacious in the long-term management of a large number of our patients with toxic Graves' disease. Its major disadvantage appears to be the need for prolonged therapy and close attention as against the fast action and prompt relief which appear to be expected by many patients. If a method can be found to keep more patients in the treatment program for longer periods, thionamides would probably be superior to subtotal thyroidectomy since the associated morbidity including hypothyroidism, hypoparathyroidism and recurrent laryngeal nerve palsy, resulting from operation by other than a very competent thyroid surgeon, is often unacceptable [8,9]. Although the present study was not designed to compare medical and surgical approaches to treatment, it is striking that post-operative complications developed in a substantial proportion of the few patients who underwent subtotal thyroidectomy in the present series. In fact, two studies [14,15] have reported that subtotal thyroidectomy is the most common cause of primary hypothyroidism among Nigerians. Further studies are obviously necessary to establish the place and problems of subtotal thyroidectomy in the care of our patients with toxic Graves' disease.

Several factors appear to be important in determining the incidence of remission and relapse in patients with toxic Graves' disease who have received thionamides. The type of patients treated is probably one. For example, it has been suggested that if only patients with mild symptoms, small goitres and having hyperthyroidism for the first time are treated, the incidence of prolonged remission will be high [13]. The results of the present study are partly in support of such a view. Secondly, the iodine intake of the patient population apparently has an important influence on the rate of remission induced by thionamides [10-12]. Although a low remission rate has been reported from an iodine deficient area after a short course of antithyroid drug [16], Wartofsky [10] and others [12], have suggested an increased dietary iodine content as the explanation for the decline in the rate of remission reported by North American and European workers. The mechanisms behind this effect of high iodine intake is unclear. Data on iodine consumption in Nigerians have not been published but it is very likely that dietary iodine is much lower in most parts of Nigeria than the level reported for North Americans. Whether this factor contributes to the high remission rate observed in this study is not known. Also, the HLA status of the

patient and the serum level of thyrotropin-receptor antibody at the time of drug withdrawal appear to be important factors in determining remission or relapse after antithyroid therapy [17]. These factors were not evaluated in this group of patients. Also, it has been reported by some [18], but not confirmed by others [19], that the duration of thionamide therapy affects the rate and duration of remission. The protocol used in the treatment of these patients does not permit an analysis of this factor in the present study. Finally, the administration of thyroxine during carbimazole treatment of patients with toxic Graves' disease has recently been reported by Hashizume and colleagues [20] to decrease the frequency of recurrence of hyperthyroidism from 34.7% to 1.7% among Japanese patients. It would be of interest to find out whether comparably impressive results can be obtained in our patients treated with the same protocol.

In conclusion, it would appear, from the data presented here, that carbimazole deserves a serious consideration as the principal modality for the definitive treatment of most of our patients with thyrotoxic Graves' disease at the present time. The drug should probably be used with the aim of inducing a remission rather than solely as an agent for the pre-operative preparation of patients for subtotal thyroidectomy. Many would be expected to achieve a fairly long remission while adverse drug reactions would be infrequent. Additionally, the results suggest the need to evolve a strategy to minimise the high drop-out rate found in this study. Educating our patients with diffuse toxic goitre about the need for a regular and prolonged follow up [21] would probably be an important first step.

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