ADRENERGIC BLOCKADE AND THYROTOXICOSIS

By

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ABSTRACT

Guanethidine was used to induce adrenergic blockade in a patient with exophthalmic goitre. When a postural fall of blood pressure was attained with a large dose of guanethidine, the abnormal tremor was abolished, the sleeping pulse rate fell and the basal metabolic rate fell to +20% of normal. The addition of methyl thiouracil caused a return of the sleeping pulse rate, basal metabolic rate, body weight and plasma cholesterol to normal levels. Guanethidine alone or in combination with methyl thiouracil did not affect the exophthalmos. Reasons are advanced for suggesting that thyroid hormone acts independently of the increased peripheral sensitivity to the catecholamines in producing many of the signs of thyrotoxicosis. A simple method of recording the tremor in thyrotoxicosis is described.

It has been suggested for some years that the clinical features of thyrotoxicosis may be accounted for by an increased peripheral sensitivity to adrenaline and nor-adrenaline. A depression of peripheral sympathetic activity may therefore be expected to relieve the features of hyperthyroidism and it has been shown that the hyperkinetic circulatory state of experimental hyperthyroidism in dogs may be corrected by epidural blockade (Brewster et al. 1956), and in man some of the features of thyrotoxicosis may be alleviated by reserpine (Canary et al. 1957). Guanethidine has a similar peripheral action to reserpine in reducing the tissue stores of nor-adrenaline in organs with sympathetic innervation, but it also blocks the release of nor-adrenaline at sympathetic post-ganglionic nerve endings. Unlike reserpine, guanethidine does not pass the blood-brain barrier, and has no effect on the brain (Burn 1961). This makes

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it a more useful agent in assessing the contribution of the increased sensitivity to catecholamines in the clinical picture of thyrotoxicosis. In man, guanethidine has reduced the tachycardia and the elevated basal metabolic rate of tri-iodothyronine induced hyperthyroidism (Gaffney et al. 1961), and it would therefore be of interest to extend these observations to the treatment of a patient with exophthalmic goitre.

CASE REPORT

A 31 year old female patient suffered an emotional shock, and following this became increasingly nervous and irritable. Two months before admission she first noticed a swelling of the neck and some prominence of the eyes. During this period she lost weight, although her appetite increased, and she became increasingly tired and breathless.

Examination showed marked signs of thyrotoxicosis. The hands were moist and warm and there was a fine finger tremor. The heart rate was 120 per minute at rest and the blood pressure 140/65 mm mercury. She had marked lid retraction and a variable lid lag. Bilateral exophthalmos was present (19 mm in both eyes measured by exophthalmometer) and there was moderate conjunctival oedema. The thyroid gland was diffusely enlarged and there was a loud bruit and systolic thrill over it. The protein bound iodine was 13 µg/100 ml, plasma cholesterol 160 mg/100 ml, and four hour radio-active iodine uptake 72 %.

Observations during treatment

The patient was allowed a period of one week to settle down in the ward. Following this, serial observations of the sleeping pulse rate, erect and supine blood pressure, basal metabolic rate, weight, plasma cholesterol and protein bound iodine were made during a further control period of one week and during treatment with guanethidine, later combined with thiouracil. Guanethidine was commenced in a dosage of 10 mg daily and this was slowly increased until a postural fall of blood pressure was attained with 80 mg daily. A further single increment to 90 mg was made 9 days later and was maintained for 5 days before treatment with methyl thiouracil was started. During treatment with methyl thiouracil 600 mg per day, the dosage of guanethidine was gradually reduced to maintain the postural fall of blood pressure as constant as possible.

RESULTS

Sleeping pulse rate (Fig. 1). – During the period of treatment with guanethidine before a postural fall of blood pressure was attained, there was a slight slowing of the heart rate below the control readings. When a postural fall of pressure was attained there was an abrupt fall in the rate by about 10 beats per minute. A further increase in the dose of guanethidine did not affect the pulse rate. The addition of methyl thiouracil, however, slowed the rate again to about 65 per minute.
The effect of guanethidine and methyl thiouracil on the sleeping pulse rate and erect and supine blood pressure in a patient with thyrotoxicosis.

The effect of guanethidine, postural fall of blood pressure, and methyl thiouracil on the basal metabolic rate and body weight in a patient with thyrotoxicosis.

**Basal metabolic rate** (Fig. 2). – When a postural fall of blood pressure was achieved, guanethidine reduced the basal metabolic rate to +21 % of normal.
A further fall to normal levels occurred when methyl thiouracil was given.

**Weight** (Fig. 2). – Guanethidine did not appear to affect the weight. Weight gain occurred when methyl thiouracil was given.

**Plasma cholesterol** (Fig. 3). – Guanethidine did not affect the plasma cholesterol, but the addition of methyl thiouracil caused an increase.

**Protein bound iodine** (Fig. 3). – There was no significant change in the protein bound iodine during treatment with guanethidine, but when methyl thiouracil was given there was a fall to hypothyroid levels.

**Eye signs.** – There was no apparent change in lid retraction and lid lag during treatment with guanethidine, and there was only slight improvement with methyl thiouracil. The exophthalmos was re-measured during the period of treatment with 90 mg guanethidine daily and again on the last day of treatment with thiouracil. There was no change.

**Finger tremor** (Fig. 4). – The fine lateral tremor of the right index finger was recorded on a piezo-electric crystal pulse wave recorder. Before treatment there was a rapid tall excursion at approximately 1/10 s intervals. Treatment with guanethidine reduced this to a tremor comparable with that of a normal control. There was no further change on methyl thiouracil.

**Thyroid gland.** – No change in size of the gland was apparent on simple palpation, but it was thought that the bruit and thrill over the gland became less intense.

**Side effects.** – The patient felt faint on rising the first day that she had a
The lateral finger tremor of a normal control and of a patient with thyrotoxicosis before and after treatment with guanethidine. The two examples illustrated of the thyrotoxic patient were taken on the day before treatment with guanethidine and again when receiving 80 mg daily. The tracings were taken on a piezo-electric crystal pulse wave pick-up and recorded at 50 mm/s on a standardized Sanborn «Polyviso» recorder.

postural fall of blood pressure. This did not recur on subsequent days, and there were no other notable side effects.

Following this period of observation the patient was prepared for thyroidectomy with potassium iodide.

**DISCUSSION**

Guanethidine produced a subjective improvement of the symptoms in a patient with thyrotoxicosis, but its effect on the observed clinical features was variable. It appeared to abolish the abnormal tremor, modify the tachycardia and elevated basal metabolic rate, but had no significant effect, during the period of observation, on the eye signs, the plasma cholesterol or the body weight. A similar reduction of the basal metabolic rate to +20% of normal has been observed both during the treatment of thyrotoxicosis with reserpine (Canary et al. 1957), and the treatment of experimental hyperthyroidism with guanethidine (Gaffney et al. 1961). An improvement in lid retraction has been reported with reserpine (Canary et al. 1957), and it is disappointing that similar results were not obtained with guanethidine in this patient. Adrenergic blockade is probably responsible for the effect of guanethidine in thyrotoxicosis, as there was no accompanying fall in the protein bound iodine, and the results of treatment were not apparent until sufficient guanethidine had been given to produce a postural fall of blood pressure. Further, a slight increase
in the dose of guanethidine above this level did not appear to be more effective.

The hypothesis of an increased peripheral sensitivity to the catecholamines occurring in thyrotoxicosis is supported by the large dose of guanethidine required to produce adrenergic blockade and a postural fall of blood pressure in this patient before treatment with thiouracil. On thiouracil, the fall in output of thyroxine was accompanied by a reduction in the amount of guanethidine required to produce a postural fall of blood pressure. This, presumably, resulted from the decreasing peripheral sensitivity to nor-adrenaline.

The addition of methyl thiouracil to guanethidine produced a fall of the protein bound iodine and this was accompanied by a fall of the sleeping pulse rate and basal metabolic rate to normal levels, an increase in the plasma cholesterol and a gain in weight. These results suggest that the increased sensitivity of the hyperthyroid subject to the catecholamines is only a single manifestation of thyrotoxicosis although it may be responsible for the characteristic tremor, and partly responsible for the rapid pulse and elevated metabolic rate. Thyroid hormone itself probably acts independently in producing many of the important features of the disease, such as the weight loss and the low plasma cholesterol as well as contributing directly to the tachycardia and elevated metabolic rate.

In clinical practice, there may be a useful place for guanethidine in the treatment of thyrotoxicosis. Methyl thiouracil usually takes about ten days to three weeks to control the clinical features of the disease (Dunlop & Macgregor 1961), but in this patient it was effective in a shorter period, when used in combination with guanethidine. This combination may therefore be an advantage in the treatment of severe thyrotoxicosis, when rapidity of control is desirable. It may also be of some value in combination with potassium iodide in the pre-operative preparation of a thyrotoxic patient with a large vascular goitre, as it probably does not have the same goitrogenic properties as thiouracil. In both these examples the effective dose of guanethidine is likely to be fairly large.

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REFERENCES


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