Effects of different regimes of metyrapone on steroid production by a patient with a corticotrophin secreting bronchogenic carcinoma

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THE SECRETION of hormones or closely related substances by tumours arising from tissues other than the endocrine glands has been widely reported and was reviewed recently by Bower & Gordan (1965) and Anderson (1966). The commonest example is the production of adrenocorticotrophic hormone (ACTH) by some oat-cell carcinomas of the bronchus (Brown, 1928; Christy, 1961; O'Riordan *et al.*, 1966; and others). The prognosis in this condition is even worse than with non-hormone producing oat-cell carcinomas, as high plasma levels of corticosteroids have been claimed to increase tumour growth and spread (Green & Whiteley, 1952; Wolf *et al.*, 1960; Sherlock & Hartmann, 1962).

Many attempts have been made to treat the associated adrenocortical hyperfunction but with little success. Metyrapone (SU-4885, 1,2-bis (3 pyridyl)-2 methyl-1 propanone, 'metopirone'. Ciba) inhibits the enzyme 11- β -hydroxylase, which is essential for the final step in the synthesis of 11-hydroxycorticosteroids (11-OHCS), of which the most important in man is cortisol (Friedman, Marshall-Jones & Ross, 1966; Meador *et al.*, 1962; Mattingly *et al.*, 1964). There have been few studies of the value of this drug in treating patients with corticotrophin-secreting tumours (Mattingly *et al.*, 1964; Hugh-Jones, 1964; O'Riordan *et al.*, 1966). O'Riordan *et al.* (1966) treated two patients with ACTH-secreting tumours, one with a bronchogenic carcinoma who showed very little improvement and one with an anaplastic carcinoma of the thyroid gland who responded well for several months. The dose of metyrapone used was 0.75 g at intervals of 6 hr.

Treatment with metyrapone in doses at intervals of 6 hr has usually proved unsatisfactory. There is evidence, however, that more adequate

suppression of plasma 11-OHCS can be obtained by administering the drug at intervals of 2 hr. J. G. Sprunt (personal communication, 1967) has shown that the 11- β -hydroxylase-inhibiting activity of metyrapone has a half-life of 26 min. Buus, Binder & Petersen (1962) previously demonstrated that in normal people, metyrapone when given 4-hourly produces poor suppression of plasma 11-OHCS, but complete inhibition if given every 2 hr.

The purpose of this communication is to describe the effects of different dosage regimes of metyrapone (the total amount administered per 24 hr remaining constant) in a patient presenting with severe adrenocortical hyperfunction associated with an oat-cell carcinoma of the bronchus secreting ACTH.

Case report

The patient was a 63-year-old housewife with known mild rheumatic heart disease involving the aortic and mitral valves. She presented with a history of an unproductive cough and dyspnoea on exertion for the previous 8 weeks. In the final week she developed rapidly increasing generalized oedema and marked lassitude. Her face then suddenly became swollen, suggesting obstruction of the superior vena cava, and this led to her admission as an emergency.

Her general appearance with slight hirsutism of the upper lip and vitiligo of the chest and arms was clearly in keeping with a diagnosis of Cushing's syndrome. She was extremely weak, being unable to sit up in bed unsupported. There was generalized oedema. Stridor was audible on deep inspiration. There was non-pulsatile distension of the left internal jugular vein. Blood pressure 160/90 mmHg. The heart was moderately enlarged but no change was found in the signs

of rheumatic heart disease noted previously. The liver edge was just palpable.

Investigations: Chest X-ray: a large mass at the left hilum. Plasma sodium 140 mEq/l, potassium 2.4 mEq/l, chloride 98 mEq/l, CO_2 combining power 27.5 mEq/l, urea 26 mg/100 ml. Glucose tolerance test: fasting plasma glucose 122 mg/100 ml; after 50 g glucose by mouth; (plasma glucose levels at 30 min intervals), 169, 196, 200, 200 and 160 mg/100 ml. Plasma 11-OHCS. Plasma fluorescence $\equiv 40 \mu\text{g}$ of 11-OHCS/100 ml at 11 p.m. and $42 \mu\text{g}$ /100 ml at 9 a.m. (normal range 7–27 μg /100 ml, Mattingly, 1962). Urinary 17-oxosteroids: 11.1 mg/24 hr (normal range 5–15 mg/24 hr, Norymberski, Stubbs & West, 1953). Urinary 17-OHCS: 50 mg/24 hr (normal range 5–15 mg/24 hr, Appleby *et al.*, 1955). Plasma ACTH level 2.28 mUnits/100 ml (upper limit of normal 1 mUnits/100 ml plasma. Index of precision for the assay=0.17. Vernikos-Danellis, Anderson & Trigg, 1966). Exchangeable body potassium=25.4 mEq/kg (predicted normal=35 mEq/kg, Aikawa, Hassell & Eisenberg, 1952). Total body potassium=75 g (predicted normal=94.5 g, Oberhausen & Onstead, 1965). Bronchoscopy showed narrowing of the main carina with nodular tissue protruding from the inferior margin of the left upper lobe bronchus. Biopsy from left upper lobe bronchus: biopsy showed columnar bronchial epithelium; submucosa was infiltrated by an oat-cell carcinoma.

Treatment and progress

Treatment at first with oral potassium supplements in the form of a mixture of potassium bicarbonate and potassium chloride, providing a total dose of 63 mEq K/day, had no effect on the level of her serum potassium.

Three weeks later she received a course of palliative radiotherapy which reduced the size of the primary tumour dramatically; the distension of the left jugular vein disappeared.

Despite the shrinkage of the tumour the features of Cushing's syndrome increased and the hypokalaemia persisted. It was therefore decided to treat the patient with metyrapone. She was given the drug by mouth 4.0 g/24 hr, initially in a dose of 1.0 g at intervals of 6 hr for one period of 24 hr. Immediately thereafter the dose regime was changed to 500 mg at 6.00 a.m., 250 mg at 8.00 a.m., 500 mg at 10.00 a.m. and 12 noon, 250 mg at 2.00 p.m., 500 mg at 4.00 p.m., 250 mg at 6.00 p.m., 500 mg at 8.00 and 10.00 p.m. and 250 mg at 2 a.m. Plasma 11-OHCS were estimated (Mattingly, 1962) at intervals throughout these two periods of treatment with mety-

rapone (Fig. 1). Comparison of the mean levels of 11-OHCS showed no significant difference, though it did appear that the fluctuations in plasma 11-OHCS were less with the 2-hourly regime. For this reason it was decided to continue long-term treatment with this regime modifying it slightly in that the 2 a.m. dose was

FIG. 1. Effects of plasma 11-OHCS of two dosage regimes of oral metyrapone given over two 24-hr periods. ●, response to metyrapone 6-hourly (mean 37.3 μg /100 ml); ○, response to metyrapone 2-hourly (mean 34.6 μg /100 ml).

omitted but the total dose of 4.0 g/24 hr was maintained by increasing the 8.00 a.m. dose to 500 mg. Soon after this the serum potassium rose to within the normal range but a few days later total body potassium measured by whole body counting of 40K and exchangeable potassium determined by 42K studies remained low (see above). The plasma 11-OHCS fell slightly and the urinary 17-OHCS rose (Fig. 2). Clinically she improved slightly in that her generalized weakness became less marked and after 6 weeks she was able to return home. Five weeks later, however, she had become virtually bedridden and required readmission to hospital. Facial hirsutism had increased considerably; skin pigmentation and vitiligo by this time were much more severe than previously. She was severely wasted, but did not at any time become hypertensive the highest recorded BP being 170/100. Also she did not become alkalotic, as judged by the highest plasma CO_2 combining power of 72.5 mEq/l and a persistently normal plasma chloride (range 95–106 mEq/l). In view of the striking deterioration in her clinical condition metyrapone treatment was withdrawn. Following this, she deteriorated even more rapidly, becoming almost immobile and drowsy. Estimation of her plasma 11-OHCS levels, 10 days after discontinuing metyrapone, showed that these had risen to 96 μg /100 ml. Her fasting blood sugar rose to

416 mg/100 ml and the plasma CO_2 combining power fell to 18 mEq/l. Urinalysis showed continuous glycosuria of more than 2.0% and ketonuria. She died 12 days after metyrapone therapy was stopped.

FIG. 2. Results of prolonged treatment with metyrapone (4.0 g/24 hr) on serum potassium, plasma 11-OHCS and urinary 17-OHCS.

Necropsy. The left lung showed thickening by tumour around the main bronchus. There were massive nodular metastases in the liver and vertebral column and bilateral adrenal cortical hyperplasia, the glands weighing 13 and 16 g respectively. No tumour tissue was found in the adrenals. The pituitary gland appeared normal.

Discussion

This patient showed several unusual and striking features. In previously reported cases of this type (Bagshawe, 1960) a hypokalaemic alkalosis was always noted and was thought to be a useful means of distinguishing simple bilateral adrenal hyperplasia from that associated with a corticotrophin-producing malignant tumour. Bagshawe (1960) reported eighteen cases of nonadrenal malignant tumours associated with Cushing's syndrome. All had potassium levels below 3 mEq/l and total CO_2 levels between 31 and 52 mEq/l. Alkalosis was not demonstrated in our patient and is not, therefore, an invariable finding in

patients with ACTH-secreting tumours. It is possible that the patient may have been catabolizing so much body tissue that she was producing large quantities of acid metabolites which would serve to neutralize the alkalosis usually produced by corticosteroids.

Most authors, including Borstein, Nolan & Bernanke (1961) and O'Riordan *et al.* (1966), state that the typical features of Cushing's syndrome occur rarely in the presence of an ACTH-secreting carcinoma, and then only in patients whose tumours grow slowly with relatively moderate production of ACTH. The prognosis is also said to be better in these patients (Bower & Gordan, 1965). Many of the classical features of Cushing's syndrome, notably facial swelling, hirsutism and pigmentation, developed extremely quickly in this patient. These were associated with rapidly growing metastases which presumably were responsible for the high plasma level of ACTH found and the high levels of plasma 11-OHCS. Clinical deterioration was also very rapid.

An attempt was made to suppress the secretion of cortisol by using metyrapone 2-hourly, the total daily dose being 4.0 g. During this treatment the patient, after an initial slight improvement, continued to deteriorate clinically. On the other hand, the hypokalaemia seemed less severe, allowing adequate replacement by oral therapy. The diabetic state also remained mild. After withdrawal of metyrapone, however, extremely rapid deterioration both clinical and biochemical occurred. The treatment therefore appeared to slow the progress of the disease and to modify the biochemical abnormality thus perhaps contributing to the general wellbeing of the patient. The rise in urinary 17-OHCS after starting treatment with metyrapone was probably due to increased ACTH production by the tumour. A rise in 17-OHCS in response to metyrapone is uncommon in such patients because the existing level of ACTH is often so high that adrenal responsiveness to additional ACTH is minimal (Meador *et al.*, 1962). The subsequent fall of the urinary 17-OHCS while still on metyrapone is difficult to explain, but similar observations were made by Mattingly *et al.* (1964) on two patients given metyrapone for several days. One of these patients was extremely ill and oliguric, and the findings were thought to be due to an alteration in the renal handling of conjugated steroids. The other patient was not oliguric and Mattingly *et al.* (1964) suggested that metyrapone was possibly blocking other enzymes besides 11- β -hydroxylase.

In the patient described here, the tumour was growing very rapidly and generalized carcinoma-

tosis soon became apparent. In selected patients, therefore, and particularly in the slowly growing ACTH producing tumours, which have been previously described (O'Riordan *et al.*, 1966), metyrapone may be of value in reducing the distressing effects of hyperadrenocorticism. With a rapidly growing tumour metyrapone is probably ineffective and another approach with, for example, aminogluthetimide (Elipten, Ciba) would now be more appropriate.

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Granulosa-cell tumour of the ovary causing sexual precocity in a girl aged 3½ years

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ACCORDING to Eberlein *et al.* (1960) isosexual precocity in girls may be arbitrarily defined as the appearance of feminine secondary sexual characteristics before the age of 7 years or menstrual bleeding before the age of 8. The majority of such cases are 'idiopathic' or 'constitutional'; there is a true precocious puberty,

gonadotrophins being present and ovulation occurring, and there is no reversal of the early pubertal development.

A rare cause of sexual precocity is the presence of functioning ovarian tumours which are usually granulosa-cell or theca-cell tumours. In these cases gonadotrophins are not usually