Treatment of an adrenal cortical carcinoma with a combination of o,p'-DDD and aminoglutethimide

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Summary
A patient with Cushing's syndrome due to an adrenocortical carcinoma is described. Treatment of residual disease and functional metastases was attempted with o,p'-DDD and later aminoglutethimide. Aminoglutethimide in a daily dose of 1 g appeared to have little effect additional to o,p'-DDD. It is important to maintain replacement therapy with cortico-steroids throughout the use of these drugs.

Introduction
The prognosis of inoperable adrenal carcinoma has altered since the introduction of 1,1-dichloro-2-(o-chlorophenyl)-2-(p-chlorophenyl)-ethane-o,p'-DDD—which has been demonstrated to have a cytotoxic action on the adrenal cortex (Vilar and Tullner, 1959). Its use has been limited by the high incidence of toxic effects on the gastrointestinal tract and central nervous system (Hutter and Kayhoe, 1966; Bergenstal et al., 1960). Aminoglutethimide has no cytotoxic activity but reduces output of active steroids by inhibiting the enzymatic production of the precursor pregnenolone (Cash et al., 1967). It might therefore be expected that the actions of o,p'-DDD and aminoglutethimide would be complementary but their combined use appears to have been reported previously in only a single case of metastatic adrenal carcinoma (Bochner et al., 1969).

A second case is now described.

Clinical course
A 44-year-old man presented with a history of severe persistent backache of sudden onset 1 month previously. He had gained 20 lb in weight in the previous 6 months.

He was typically Cushingoid in appearance. There was localized tenderness over the lower thoracic vertebrae. His blood pressure was 200/120 mmHg. The diagnosis of Cushing's syndrome was established and the probability of an autonomous adrenal cause indicated by measurements of plasma and urinary steroids (Table 1), using standard methods. Radiologically moderate osteoporosis was observed, with several healed rib fractures and compression fractures of several vertebrae. Intravenous pyelography showed depression of the left kidney, and left renal arteriography demonstrated an enlarged left adrenal with several abnormal vessels surrounding it. At operation (Mr J. E. Newsam), an adrenal carcinoma invading the left renal pedicle was found. Left adrenalectomy and nephrectomy were performed with removal of some but not all of the involved paraaortic lymph nodes. The diagnosis was confirmed histologically.

<table>
<thead>
<tr>
<th>Plasma 11-hydroxycorticosteroids (11-OHCS)</th>
<th>Dexamethasone dose</th>
</tr>
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<tbody>
<tr>
<td>at 2300 hr</td>
<td>0 2 mg/24 hr</td>
</tr>
<tr>
<td>45 µg/100 ml</td>
<td>8 mg/24 hr</td>
</tr>
<tr>
<td>at 0800 hr</td>
<td></td>
</tr>
<tr>
<td>32 µg/100 ml</td>
<td></td>
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<tr>
<td>30 minutes after tetracosactrin</td>
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<tr>
<td>39 µg/100 ml</td>
<td></td>
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<tr>
<td>250 µg i.v.</td>
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<tr>
<td>Cortisol production rate (CPR)</td>
<td>182 mg/24 hr</td>
</tr>
<tr>
<td>Urinary steroid response to dexamethasone:</td>
<td></td>
</tr>
<tr>
<td>17-hydroxycorticosteroids (17-OHCS) mg/24 hr</td>
<td>99 91 104</td>
</tr>
<tr>
<td>17-oxosteroids (17-OS) mg/24 hr</td>
<td>124 80 95</td>
</tr>
<tr>
<td>11-hydroxycorticosteroids (11-OHCS) mg/24 hr</td>
<td>3.9 2.9 4.0</td>
</tr>
</tbody>
</table>

At the time of operation treatment was started with betamethasone 2 mg/24 hr and this was continued thereafter. Serial measurements were made of plasma 11-OHCS, urinary 11-OHCS, 17-OHCS, 17-OS, and CPR. The results are shown in Fig. 1, with the exception of the urinary 11-OHCS, which closely paralleled urinary 17-OHCS excretion.

There was an immediate postoperative reduction in plasma and urinary steroid levels and the CPR fell to within the high normal range, at 28 mg/24 hr, but as the patient was still receiving betamethasone 2 mg/24 hr, a dose normally sufficient to suppress the adrenals, it was clear that hyperfunction was
Case reports

Fig. 1. Plasma and urinary steroid measurements with variations in drug therapy. Lower graph: broken line, 17-OHCS; solid line, 17-OS mg/24 hr. Upper graph: plasma 11-OHCS, 9 a.m.

still present. A 4-week course of radiotherapy was given to the left renal area, but during this period a mass developed in the left supraclavicular fossa. This rapidly enlarged until treatment with o,p'-DDD was introduced. With doses of this drug increasing to 9 g daily, steroid excretion was markedly reduced within 2 weeks, but, owing to the development of intolerable side effects, namely nausea, vomiting and diarrhoea, the dose had to be reduced to 3 g daily. Despite an increase in steroid excretion the drug was withdrawn at the patient's request. The swelling in the neck began to enlarge further, accompanied by a progressive rise in steroid excretion. Reintroduction of the drug at a dose which could be tolerated had little effect on steroid levels, but the patient was able to return to light work for 10 months.

Aminogluthethimide was introduced in a dose of 250 mg q.i.d. 15 months after operation, in an attempt to suppress cortisol production which had increased to 120 mg/24 hr. Four subsequent attempts to measure the CPR were technically unsatisfactory, and no clinical or biochemical improvement was observed.

After 6 months' combined treatment with o,p'-DDD and aminogluthethimide there was a rapid deterioration in his condition with further enlargement of the supraclavicular mass. Diplopia had developed with nystagmus and slight cerebellar ataxia. In view of the high plasma 11-OHCS measurements it was considered that treatment with betamethasone was probably superfluous and might be contributing to the progression of his bone disease, so this was withdrawn. Ten days later, after a single treatment with radiotherapy to the left supraclavicular mass, he collapsed suddenly and died.

At post mortem (Dr J. M. Drennan) metastatic carcinoma was identified only at the site of the left adrenal, in the mediastinum and lungs, and in the left supraclavicular area. Histologically the metastases were of uniform appearance, with predominant coagulative necrosis interspersed with clumps of nuclear debris, granules of calcification and islets of degenerating tumour cells. The right adrenal was atrophic. The thyroid gland was normal.

Discussion

This patient's prognosis was poor from the time he was first seen because he had high urinary steroid levels and because metastases were evident (Hutter and Kayhoe, 1966a; Thorn and Lauler, 1972). That he survived for 2 years after the discovery of functional metastases and was able to work for part of this time might be attributed to the use of o,p'-DDD and aminogluthethimide. His failure to respond to radiotherapy is in accordance with published experience (Hutter and Kayhoe, 1966b; Thorn and Lauler, 1972).

O,p'-DDD was poorly tolerated in this patient although the symptoms of gastro-intestinal and
central nervous system dysfunction did not differ from those usually encountered (Hutter and Kayhoe, 1966b). The maximum reduction in steroid levels was achieved with a daily dose of 9 g supporting the suggestion that 10 g daily is the optimum dose (Cope, 1972; Geyer, 1967). Although steroid excretion was not suppressed, the growth rate of the metastasis in the supraclavicular fossa appeared to have been retarded, and the cytotoxic activity of o,p'-DDD was demonstrated histologically at autopsy.

Aminoglutethimide in the conventional dose of 1 g daily was well tolerated and at autopsy the thyroid gland was normal, in contrast to the occasional finding of goitre (Rallison, Kumagai and Tyler, 1967). After the introduction of aminoglutethimide, steroid excretion did not fall rapidly (Philbert et al., 1966), apart from the slight predictable decline in urinary 17-OHCS excretion (Fishman et al., 1967; Schteingart and Conn, 1967). It is possible, however, that there was a rapid decline in steroid production after the withdrawal of betamethasone.

This experience suggests that replacement therapy with corticosteroids should be maintained throughout treatment with aminoglutethimide for adrenal carcinoma. A similar recommendation has also been made for patients receiving o,p'-DDD (Helson, Wollner and Murphy, 1971), although it has also been suggested that the combination of steroid replacement therapy with o,p'-DDD may not be necessary (Temple et al., 1969).

Experience with this patient confirmed that although o,p'-DDD had an effective cytolytic action on adrenocortical tissue, steroid production was only slightly reduced. Aminoglutethimide, in contrast to o,p'-DDD, was tolerated well, but had little effect on steroid excretion. It is possible that earlier introduction of aminoglutethimide might have had more effect. The early introduction of the combination of o,p'-DDD and aminoglutethimide should be considered for the treatment of patients with inoperable or metastatic adrenal carcinoma, when corticosteroid production is increased.

Acknowledgments
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References


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