MEDICAL MEMORANDA

Excess Deoxycorticosterone Secretion from Adrenocortical Carcinoma

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A patient with hypertension, oedema, and hypokalaemia due to excessive secretion of deoxycorticosterone (DOC) is described. Her symptoms were cured by removal of an adrenal cortical carcinoma but recurred four years later when a metastasis was found in bone. The high plasma levels of DOC were suppressed by dexamethasone, suggesting that production of this steroid by the tumour cells was ACTH-dependent.

Case History

A 64-year-old woman presented with a history of tiredness and weakness for three years and weight gain (12.7 kg), ankle swelling, and increase in dyspnoea for two years. She had also noticed giddiness and unsteadiness when walking.

On admission to Guy's Hospital in October 1968 her blood pressure was found to be 220/130 mm Hg and there was evidence of mild congestive cardiac failure. Plasma electrolytes were sodium 141 mEq, potassium 2.2 mEq, and bicarbonate 36 mEq/l. and her blood urea was 28 mg/100 ml. Potassium supplements by mouth (160 mEq/day for eight days) failed to raise the plasma potassium above 2.5 mEq/l. but spironolactone 100 mg daily led to an increase to 4 mEq/l. and the return of the blood pressure to normal. The urinary excretion of potassium during the period of hypokalaemia was 120 mEq/24 hr. Her haemoglobin was 16 g/100 ml, E.S.R. 8 mm/hr (Westergren), and W.B.C. 8,200/mm³. Plasma 11-hydroxycorticosteroid concentration estimated by fluorimetry (Mattingly, 1962) was 16.7 µg/100 ml at 09.30 hours and 13.6 µg at 00.30 hours.

The urinary excretion of vanillylmandelic acid was 2.4 mg/24 hr (normal <5 mg/24 hr). An intravenous urogram showed depression of the right kidney by a suprarenal mass. At operation (Mr. F. N. Glover) on 21 October the right adrenal gland (263 g) was removed and found to contain a mass 94 by 77 by 58 mm. The cut face of the mass was chiefly dark red but was also part cream and part pale yellow. Histologically it was a pleomorphic adrenal cortical carcinoma made up mostly of cells resembling the zona reticularis, though a few were akin to those of zona fasciculata. After operation her plasma potassium remained above 4 mEq/l. and her blood pressure fell to 150/80 mm Hg without medication.

She was readmitted in November 1972. Two months earlier she had experienced severe pain in the right buttock radiating to the

anterior and lateral borders of the right thigh. Both ankles were swollen (the right one more than the left) and she had recently put on weight. She had also noticed increased growth of facial hair, which required daily shaving. Examination again showed congestive cardiac failure and hypertension (blood pressure 220/130 mm Hg) and she was tender over the right side of the pelvis. Clinically she showed neither the physical signs nor the tissue changes of Cushing's syndrome. The plasma electrolytes again showed a pattern of hypokalaemic alkalosis (sodium 138 mEq, potassium 2.2 mEq, and bicarbonate 34 mEq/l.). A radiograph of the right hip showed expansion and severe rarefaction of the greater trochanter by a central osteolytic lesion, which on biopsy proved to be histologically similar to the parent adrenal carcinoma. Extensive investigation, including chest radiography, intravenous urography, aortography, and a complete radiological skeletal survey, failed to identify further metastases or recurrence of the primary growth.

Amiloride 10 mg daily from 16 December resulted in a fall in blood pressure to 130/85 mm Hg and a rise in plasma potassium to 3.7 mEq/l. Radiotherapy (3,600 rads) was administered to the metastatic site from 20 December to 17 January, during which time the plasma DOC and corticosterone were first estimated. The plasma corticosteroid levels (see table) were measured by the technique of gas-liquid chromatography with electron-capture detection, and 11-hydroxycorticosteroids by the competitive protein-binding technique of Murphy (1967) while the patient was taking amiloride. The striking abnormality was a marked rise in plasma DOC concentration with normal levels of aldosterone. Urinary 17-oxosteroids were 15 mg/24 hr (normal 3.3-14.7 mg/24 hr) and 17-oxogenic steroids 34 mg/24 hr (normal 5-16 mg/24 hr).

Though she was subsequently discharged from hospital without symptoms, by April 1973 the plasma DOC had risen to a higher level than had previously been recorded. In mid-February treatment with dexamethasone 8 mg daily by mouth for three days had been followed by a temporary fall in plasma DOC to the lower part of the normal range (see table and chart).

Comment

This patient presented on two occasions with the clinical and biochemical features of excessive mineralocorticoid activity. Only during the second admission, four years after removal of the primary tumour, were detailed corticosteroid measurements made; they showed a raised level of DOC (20 times normal), which was presumably secreted by the femoral metastasis (and perhaps in part by subclinical metastases elsewhere). Plasma levels of aldosterone, corticosterone, and 18-hydroxy-DOC, the other main mineralocorticoids, were normal. By comparison with the first level recorded 10 days after beginning radiotherapy, the concentration of DOC in the plasma fell by 57% after this course of treatment but later rose to a level of 50 times normal. Plasma DOC concentration was not influenced by injection of tetracosactrin (Synacthen). Unexpectedly dexamethasone 8 mg daily for three days was followed by a fall in plasma DOC concentration to the lower part of the normal range. At the same time the plasma aldosterone concentration rose transiently to a level above normal. The blood pressure remained unchanged during this test.

It has been assumed that the production of corticosteroids by adrenocortical tumours is autonomous. Dexamethasone given to normal subjects reduces corticosteroid secretion (Liddle, 1960) and DOC secretion (Schambelan and Biglieri, 1972; Wilson, 1973) by inhibiting the release of ACTH from the pituitary. The fall in plasma DOC induced by dexamethasone in our patient suggests that DOC secretion was dependent on the prevailing level of ACTH, previously shown to be normal (see table). Another interpretation of these results is that dexamethasone facilitated conversion of DOC to corticosterone and aldosterone within the tumour cells, which may have been

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Plasma Corticosteroid and N-Immunoreactive ACTH Levels During Second Admission

	DOC (ng/100 ml)	Cortisol (μ g/100 ml)	Deoxycortisol (ng/100 ml)	Corticosterone (ng/100 ml)	Aldosterone (ng/100 ml)	18-Hydroxy-DOC (ng/100 ml)	ACTH (pg/ml)
Method of:	Wilson and Fraser (1971)	Mason and Fraser (1974)				Mason and Fraser (1973)	Landon and Greenwood (1968)†
Normal range:	4.1-17.2	2.5-10	40-400	80-800	4-18	20-160	<10-80
30/12/72	256			283			
25/1/73	244	6.7	266	257	12.8	83	
7/2/73 (09:00 hours)	133	7.8 (12.5)*		210	6.8		48
		Tetracosactrin 0.25 mg Intramuscularly					
7/2/73 (09:30 hours)	113	10.9 (18.0)*		471	8.2		
16/2/73	110	(11.0)*			6.2		
		Dexamethasone 8 mg by mouth Daily for Three Days					
19/2/73	5.4	(8.5)*			30.5		
9/4/73	535	3.8	208	352	11.2	71	

*Figures in parentheses refer to measurements made using a competitive protein-binding technique (Murphy, 1967).

†As modified by Ratcliffe *et al.* (1972).

Plasma DOC level, December 1972 to April 1973. Note moderate fall after irradiation of femoral metastasis and striking fall to normal range after dexamethasone.

relatively deficient in the necessary enzyme 11 β -hydroxylase (West *et al.*, 1964). To our knowledge, however, there is no evidence that dexamethasone has such an intra-adrenal action. The failure of tetracosactrin to increase the plasma DOC concentration was perhaps due to the fact that stimulation of the neoplastic cells by the patient's ACTH was already maximal.

Biglieri *et al.* (1968) described two patients with Cushing's syndrome due to adrenal cortical carcinoma in whom the secretory rate of DOC was increased; they also described two men with feminizing adrenal carcinomata whose DOC was increased with reduction of aldosterone, and a woman with an androgenic adrenal tumour, by implication a carcinoma, in whom secretory rates of both DOC and aldosterone were increased. The effect of dexamethasone was not reported.

Fraser *et al.* (1968) described a woman with an adrenal carcinoma secreting excess corticosterone which was not suppressed by dexamethasone, but DOC was not measured. In three hypertensive patients with isolated DOC excess studied by Brown *et al.* (1972) no change in blood pressure was observed during dexamethasone therapy and there was no alteration in plasma DOC concentrations in the one patient so studied.

Treatment with dexamethasone is unlikely to be practicable in patients with adrenocortical tumours even when their secretory activity could be suppressed by its action. Unless prescribed in small dosage, the probability of adverse side effects would preclude long-term use. In the present case it was shown that hypertension and hypokalaemia resulting from an excess of DOC could be successfully reversed by treatment with either of the potassium-conserving diuretics, spironolactone or amiloride.

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