METABOLIC STUDIES IN A PATIENT WITH A PHAEOCHROMOCYTOMA ASSOCIATED WITH HYPOKALAEMIA AND HYPERALDOSTERONISM

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(Received 20 April 1972)

SUMMARY

A case of phaeochromocytoma with hypokalaemia, hyperaldosteronism, normal cortisol production and normal urinary corticosteroid excretion is described. Both α-adrenergic blockade and combined α and β blockade resulted in marked antidiuresis with urinary sodium and potassium retention and a rise in plasma volume. Combined α and β blockade led to some reduction in the high aldosterone production rate. The hypokalaemia was corrected by α-adrenergic blockade. After operative removal of the tumour the aldosterone production rate was normal.

The marked reduction in urinary sodium excretion in response to α-adrenergic blockade, if reproducible in other cases of phaeochromocytoma, might be a useful test for the presence of a phaeochromocytoma.

INTRODUCTION

In patients with a phaeochromocytoma the plasma volume and red cell mass may be abnormal (Brunjes, Johns & Crane, 1960; Sjoerdsma, Engelman, Waldman, Cooperman & Hammond, 1966) and α-adrenergic blockade results in antidiuresis (Corcoran, Dustan & Page, 1956) and expansion of plasma volume (Ross, Prichard, Kaufman, Robertson & Harries, 1967). Urinary and plasma electrolyte changes in response to combined α- and β-adrenergic blockade in patients with phaeochromocytoma do not appear to have been reported.

Interrelationships of adrenal medullary and cortical activity in phaeochromocytoma have been described in a number of reports (Cope, Labbe, Raker & Bland, 1952; Williams, Crockett, Butler & Crispell, 1960; Walters, Wyatt & Kelleher, 1962; Liddle, Island, Ney, Nicholson & Shimizu, 1963). Aldosterone excretion has rarely been estimated in such patients but when reported has usually been normal (Ross, 1959; Ramsey & Langlands, 1962). One report of excess aldosterone excretion was in a patient who also had excess corticosteroid production (Bourgoignie, Dupont & Noiret, 1964).

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In this paper we describe studies in a patient with a phaeochromocytoma who appears to be unique in having excess aldosterone production with normal cortisol production. The effects of adrenergic blockade on plasma and urinary electrolytes, on renal function and on the production of aldosterone are reported.

CASE REPORT

The patient, a 60-year-old housewife, presented in November 1966 complaining of tiredness, nervousness and intermittent attacks of sweating and diarrhoea for some years. Excessive thirst, polyuria and nocturia had been present for some months. Always thin with a maximum weight of 47 kg, she had lost much weight in 1962 and thereafter had remained at about 37 kg.

She was a thin nervous woman, perspiring profusely and with marked tremor of the hands. There was mild generalized brown skin pigmentation, not more marked in skin folds and not present in the mouth. There were no café-au-lait patches. The left lobe of the thyroid was moderately enlarged. The pulse rate was around 100/min with frequent extrasystoles. There was moderate cardiomegaly, a very forceful apex beat, a precordial systolic murmur of medium intensity but no evidence of heart failure. The blood pressure, supine, varied between 130/80 and 210/140 mm Hg: on standing it often fell to 80/40 mm Hg. There was no papilloedema.

A smooth mass was palpable in the left hypochondrium: there was no bruit over it. The liver was impalpable. Clinical examination was otherwise normal.

The haemoglobin was 8 g/100 ml., the haematocrit 32%, white cell count 19000/ mm³ with 89% polymorphonuclear leucocytes and E.S.R. 37 mm/h. The red cells on the film appeared hypochromic. The serum iron was 31 µg/100 ml., total iron-binding capacity 515 µg/100 ml and serum B₁₂ 275 pg/ml. The urine showed a trace of protein and variable glycosuria. The electrocardiogram showed left ventricular hypertrophy and strain and multiple ventricular ectopic beats. On the chest X-ray the lung fields were clear but the heart was enlarged.

Special investigations

Plasma bicarbonate (between 23 and 28 mequiv./l) and plasma sodium (between 131 and 144 mequiv./l) concentrations were normal but the plasma potassium level was consistently low (between 2-7 and 3-0 mequiv./l). The blood urea varied from 52 to 97 mg/100 ml and endogenous creatinine clearance from 16 to 26 ml/min.

Urinary vanillyl mandelic acid (VMA) excretion was 153 mg/day (normal range, up to 8-6 mg/day). Intravenous injection of 5 mg phentolamine produced a fall in systemic blood pressure from 190/90 to 110/60 mm Hg, followed by a rebound to 250/120 mm Hg. The B.M.R. was +38%, plasma protein-bound iodine 6 µg/100 ml, and ¹³¹I uptake by the thyroid at 4 h 15% (normal up to 20%). A glucose tolerance test after 50 g glucose orally gave half-hourly values for blood glucose, starting with a fasting level of 115 mg/100 ml, of 160, 177, 240, 262, 262, and 255 mg/100 ml. Faecal fat excretion over a 5-day period was 7 g/day.

The urinary 17-oxosteroids were 3·2 mg and 17-oxogenic steroids 7·0 mg/day. The cortisol production rate (by the method of Brooks, Dupre, Gogate, Mills & Prunty, 1963) was 23 mg/day (normal range 7–30 mg/day).
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A retroperitoneal pneumogram showed a large mass anterior to the left kidney: no separate left adrenal gland was seen. The right adrenal gland was not obviously abnormal.

Metabolic studies

The patient was maintained on a diet containing 10 mequiv. sodium/day with an additional 5 g sodium chloride as capsules given in divided doses. Twenty-four hour collections of urine were made from 10-00 h to 10-00 h and analysed for sodium and potassium using an Eppendorf flame photometer. Endogenous creatinine clearances were determined over 24-h periods, the creatinine being measured in an autoanlyser. Plasma volume was measured by means of $^{125}$I-labelled albumin. Aldosterone production rate was measured by the method of Brooks (1960). The effects of $\alpha$-adrenergic blockade and of combined $\alpha$- and $\beta$-adrenergic blockade on plasma and urinary electrolytes, aldosterone production rate and plasma volume and renal function were studied.

RESULTS

The results are shown in Figs 1 and 2 and in Table 1. On a low sodium diet (Fig. 1) the patient came into balance by the 3rd day but the sharp rise in blood urea and the fall in creatinine clearance suggest that a fall in G.F.R. played a significant part in this.

In the control period of this study and the subsequent one, there was an appreciable fluctuation in the urinary sodium excretion as is frequently seen in hypertensive patients. Since this patient sweated considerably, this no doubt contributed to the variation in urinary sodium excretion. The administration of phenoxybenzamine led to a precipitous fall in the urinary sodium excretion (Fig. 2) but this rose despite continuing administration of the drug. Similarly the urinary potassium fell for 4 days and then rose again. This potassium retention was associated with a rise in plasma potassium but no rise in blood urea or fall in creatinine clearance. This suggests that there was either a decrease in the delivery of sodium to the distal tubule where sodium and potassium are exchanged, or a fall in aldosterone production or both.

When phenoxybenzamine was given in much larger dosage together with propranolol, the urinary sodium fell sharply and remained at a low level so long as the drugs were continued (Fig. 2). The excretion of potassium also fell but the plasma level fluctuated around the level of 3·0 mequiv./l. With the combined $\alpha$- and $\beta$-adrenergic blockers there was a rise in blood urea which was probably due to the $\beta$ blocker because the rise began during the administration of propranolol alone. This resembles the findings during the treatment with a low sodium diet; again the creatinine clearance fell, reaching its lowest value of 12 ml/min.

The aldosterone production rate was initially determined while the patient was on a sodium intake of 95 mequiv./day and it was extremely high at 685 $\mu$g/day (normal range 70–200 $\mu$g/day on an intake of 100 mequiv. sodium/day). At this time the plasma volume was 2·2 litres and the calculated blood volume 3·1 litres (Table 1). After 13 days of combined $\alpha$- and $\beta$-adrenergic blockade the aldosterone production rate though still high had fallen to 475 $\mu$g/day, while the plasma volume had risen.
to 3.1 litres. After the removal of the tumour the production rate of aldosterone was normal at 77 μg/day. At this time the plasma volume was 2.1 litres and the calculated blood volume 3.5 litres.

![Graphs showing creatinine clearance, blood urea, urinary K, and urinary Na](image)

Fig. 1. Effect of reduction of sodium intake on urinary electrolytes and renal function in a patient with phaeochromocytoma, hypokalaemia and hyperaldosteronism.

**Preoperative care and postoperative progress**

Before operation the patient was treated with phenoxybenzamine orally, initially at a dose of 10 mg four times daily and rising to 20 mg four times a day. Propranolol was added in a dose of 20 mg four times daily and raised to 40 mg four times a day. On these drugs she became normotensive (130/80 mm Hg) with no postural fall in her blood pressure. After 12 days on these drugs, she was transfused with the packed...
cells of five bottles of blood, and after a few days a further transfusion of packed red cells from three bottles of blood was made.

At operation a large, apparently benign tumour weighing 480 g was resected. There was only a minor disturbance of the pulse and blood pressure and E.C.G. showed only a few ectopic beats during the handling of the tumour. No fall in blood

**Fig. 2.** Effect of adrenergic blockade (phenoxybenzamine and propranolol) on plasma and urinary electrolytes and renal function in a patient with phaeochromocytoma, hypokalaemia and hyperaldosteronism.
pressure occurred after removal of the tumour and no infusion of pressor amines was given.

The tumour had the histological appearance of a phaeochromocytoma with extensive ganglioneuromatous differentiation. It was composed mainly of cords and clumps of pale polygonal cells with granular cytoplasm, separated by a richly vascular stroma; interspersed were groups of abnormal nerve ganglia cells surrounded by spindle-shaped cells often arranged in palisades. No adrenal cortex was identified.

Postoperative progress was uneventful and 7 weeks after the operation the patient’s blood pressure was 160/80 mm Hg, urinary VMA was 5-1 mg/day, plasma potassium was 3-9 mequiv./l, haemoglobin was 15-2 g/100 ml and the haematocrit 45%. She was feeling very much better than before the operation, had gained 5-5 kg in weight but had developed mild bilateral ankle oedema.

Table 1. Changes in aldosterone production rate and blood volume in response to adrenergic blockade and after removal of phaeochromocytoma

<table>
<thead>
<tr>
<th></th>
<th>Plasma volume (l)</th>
<th>Blood volume* (l)</th>
<th>Aldosterone production (µg/day)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Before operation</td>
<td>2.2</td>
<td>3.1</td>
<td>685</td>
</tr>
<tr>
<td>α blockade†</td>
<td>2.4</td>
<td>3.3</td>
<td>—</td>
</tr>
<tr>
<td>α and β blockade‡</td>
<td>3.1</td>
<td>4.1</td>
<td>475</td>
</tr>
<tr>
<td>After operation</td>
<td>2.1</td>
<td>3.5</td>
<td>77</td>
</tr>
</tbody>
</table>

* Calculated.
† Phenoxybenzamine, 20 mg/day, for 8 days.
‡ Phenoxybenzamine, 40–80 mg/day, and propranolol, 40–160 mg/day, for 13 days.

DISCUSSION

The diagnosis of phaeochromocytoma was suggested by the finding of a fluctuating level of hypertension in association with episodes of postural hypotension, and was confirmed by the extremely high urinary VMA excretion and by the response of the systemic blood pressure to intravenous phentolamine. Nervousness, sweating, weight loss, tachycardia, a high B.M.R. and a diabetic glucose tolerance test were suggestive of high adrenaline secretion. 131I studies and measurement of plasma P.B.I. excluded thyrotoxicosis.

Urinary 17-oxo-steroid and 17-oxogenic steroid excretion and cortisol production rate were normal, while aldosterone production was markedly increased. There have been a number of cases reports on phaeochromocytoma with raised corticosteroid output, in association with bilateral adrenal cortical hyperplasia (Liddle et al. 1963) or adrenal adenoma (Cope et al. 1952), or where a single tumour, a phaeochromocytoma (Williams et al. 1960), adrenal carcinoma (Walters et al. 1962), or a mixed corticomedullary adenoma (Mathison & Waterhouse, 1969) appeared to lead to increased secretion of both catecholamines and corticosteroids. In the few cases of phaeochromocytoma for which aldosterone data are available, values have been normal (Ross, 1959; Ramsey & Langlands, 1962; Liddle et al. 1963) except in one case in which increased aldosterone secretion was associated with increased corticosteroid production leading to Cushing’s syndrome (Bourgoignie et al. 1964). In the case of adrenal carcinoma mentioned earlier with features of a phaeochromocytoma,
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aldosterone excretion was increased. Kogut & Donnell (1961) reported a case of Cushing's syndrome associated with a renal ganglioneuroma; aldosterone excretion was raised. We believe that our patient is unique in the association of phaeochromocytoma with hyperaldosteronism in the absence of increased corticosteroid production.

The pathogenesis of the hyperaldosteronism in this patient is uncertain. Catecholamine infusions in normal subjects have not induced consistent changes in aldosterone excretion or secretion (Ames, Borkowski, Sicinski & Laragh, 1965). The reduction in aldosterone production during combined α- and β-adrenergic blockade may have been related to the observed sodium retention and rise in plasma volume. Another possibility is that adrenergic blockade led to reduction in plasma renin and hence in aldosterone production. Ganong (1972) has summarized evidence that the sympathetic nervous system increases renin secretion by way of a β-adrenergic receptor mechanism, and that the increase in plasma renin induced by increasing plasma catecholamine levels may be potentiated by α-adrenergic blockade and is abolished by β-adrenergic blockade. Plasma renin has been found to be increased in some cases of phaeochromocytoma (Werning, Zeigler, Baumann, Endres, Gysling, Weidman & Seigenthaler, 1970).

Unfortunately in the present case no determination was made of the aldosterone production rate with α-adrenergic blockade alone. After removal of the tumour there was no evidence of aldosterone deficiency and subsequently the production rate was normal. This contrasts with the situation usually seen after removal of an aldosterone-secreting tumour. Although the red cell mass was not directly determined, calculation indicates that it was markedly reduced, and so the total blood volume would also be low and this should tend to stimulate aldosterone production.

In rare cases of phaeochromocytoma associated with bilateral adrenal cortical hyperplasia it seems likely that the tumour is producing a corticotrophin-like material (Liddle et al. 1963). This might lead to a temporary increase in aldosterone production but would also lead to increased corticosteroid production.

The possibility that the tumour itself secreted aldosterone cannot be entirely excluded as no incubation or extraction procedures were carried out.

A further theoretical possibility is that the tumour may have been producing some substance other than adrenaline or noradrenaline, which stimulated aldosterone production.

Plasma volume and total blood volume were low in our patient and plasma volume rose during α-adrenergic blockade, and during combined α and β blockade. Patients with hypertension have an increased tendency to excrete sodium and their plasma volume covers a much wider range than normal, some being above normal and some being below (Jones, Clapham, Barraclough & Mills, 1964). This patient may represent one extreme of the range found in hypertensive patients. Blood volume has been found to be low in some but not all cases of phaeochromocytoma (Brunjes et al. 1960; Sjoerdsma et al. 1966). Infusion of adrenaline (Kaltreider, Meneely & Allen, 1942) or of noradrenaline (Finnerty, Buckholz & Guillaudeau, 1958) lead to reduction in plasma volume. The plasma volume rises during α-adrenergic blockade both in phaeochromocytoma (Ross et al. 1967) and in normal subjects (Weil & Chidsey, 1968).
β-Adrenergic blockade alone, using propranolol, led to sustained severe hypertension. Presumably removal of the β vasodilator effects of adrenaline led to an increase in peripheral vascular resistance which more than offset any possible reduction in the strength of cardiac contraction. The use of β-blocking drugs alone in known or suspected cases of phaeochromocytoma appears dangerous.

Hypokalaemia is not a usual feature of phaeochromocytoma though it has been noted in cases associated with high corticosteroid production. Cortisol production was normal in our patient, but aldosterone production was high and presumably played a part in the development of the hypokalaemia. The very high catecholamine output of the tumour may also have influenced the plasma potassium level. Short-term infusion of adrenaline has been shown to induce hypokalaemia (Jacobson, Hammarsten & Heller, 1951), an effect which may be blocked by propranolol (Massara, Tripodina & Rotunno, 1970), while noradrenaline may cause a rise in plasma potassium (Ross, 1961).

In our patient there was reduction in urinary sodium and potassium output during α blockade, a rise in plasma potassium and no great change in G.F.R. This suggests that α-adrenergic blockade led to either reduced distal tubular sodium load and hence to conservation of potassium despite hyperaldosteronism, or a fall in aldosterone production, or both. With combined α and β blockade there was again a reduction in urinary sodium and potassium excretion, and a modest reduction in the high aldosterone production rate, but hypokalaemia persisted. However, there was some diarrhoea at this time and faecal potassium loss may have increased.

Experimental studies of the effects of catecholamines on urinary composition have shown considerable variation in response depending on the nature of the catecholamine, dose levels, route and duration of administration, and sodium status of the subject. Thus short-term infusion of adrenaline (Smythe, Nickel & Bradley, 1952) or of noradrenaline (Nickel, Smythe, Papper & Bradley, 1954) in the dog led to reduction in urinary sodium and potassium output. With more long-term infusion in man, Laragh (1962), Tuttle (1962) and Ames et al. (1965) showed that noradrenaline induced a small natriuresis and that this effect was more marked in sodium-depleted subjects. Green & Sim (1961) demonstrated that both adrenaline and noradrenaline could induce natriuresis in rats, and that pretreatment with phenoxybenzamine greatly reduced the diuretic effect. Pearson & Williams (1968) showed in dogs that noradrenaline administered into the left renal artery had a direct sodium-retaining effect on the kidney, and that the natriuresis induced by systemic administration of noradrenaline seemed to depend upon increased systemic arterial blood pressure and a concentration with minimal direct renal actions. They also showed that isoprenaline, having a β-adrenergic action, induced natriuresis by a direct renal action, though administration of isoprenaline into a peripheral vein produced sodium retention.

In our patient the situation was made more complicated by the fact that presumably both noradrenaline and adrenaline were circulating in excess. In view of the antidiuresis induced by adrenergic blockade it seems reasonable to assume that the overall effect of the excess circulating catecholamines had been natriuretic and diuretic. Antidiuresis, with sodium and potassium retention, occurred during combined α- and β-adrenergic blockade as well as during α blockade alone. Thus the
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effects must have been at least in part due to blockade of \( \alpha \)-adrenergic activity. It is not possible to say for certain whether uncovering of unopposed \( \beta \) activity may also have played a part, for the antidiuresis observed during combined blockade may have been due to the effect of more complete \( \alpha \) blockade obscuring any diuretic or anti-diuretic activity associated with \( \beta \) blockade. However, there was little change in urinary sodium or potassium output when propranolol alone was administered for 2 days. Corcoran et al. (1956) have reported antidiuresis after \( \alpha \) blockade in phaeochromocytoma and have described its possible use as a test in phaeochromocytoma (Leiser & Corcoran, 1956). The urinary electrolyte effects during adrenergic blockade in phaeochromocytoma do not appear to have been reported before, and do not occur during administration of \( \alpha \)-adrenergic blocking drugs to patients with essential hypertension (Craig, G. M., unpublished observations).

REFERENCES


