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Prazosin’s Effect in High Renin Hypertension Complicating Pheochromocytoma

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Summary: During three consecutive days of prazosin treatment in a patient with pheochromocytoma, urinary catecholamine metabolite levels were correlated with plasma renin activity. Suppression of renin plasma activity resulted in sustained hemodynamic and clinical improvement, while no remarkable changes were observed in urinary catecholamine metabolite levels. This suggests that prazosin may interrupt the vicious cycle of worsening hypertension provoked by further activation of the renin-angiotensin system mediated by excessive circulating catecholamines.

Key words: hypertension, pheochromocytoma, prazosin, renin

Introduction

The extent to which increased plasma renin activity contributes to the elevation of blood pressure in patients with pheochromocytoma is unknown. Hypertension generally has been ascribed to the excessive circulating catecholamines released from the tumor. However, in view of the lack of correlation between arterial pressure and circulating levels of catecholamines and the potential effect of angiotensin II in maintaining the high blood pressure, it would be logical to assume that certain therapeutic efforts to reduce blood pressure may be hampered by continuous activation of the renin-angiotensin system.

Prazosin, a selective alpha-1 antagonist, either alone or in combination with beta blockers, has proved to be an effective therapeutic option in the management armamentarium of hypertensive patients with pheochromocytoma. It has already been suggested, but not proved, that prazosin may decrease renin production by reducing venous tone and expanding intravascular volume. We describe a patient with high renin hypertension due to a catecholamine-secreting tumor. Blockade of alpha-1 post-synaptic receptors resulted in a significant hemodynamic and clinical improvement. While levels of catecholamine metabolites were unchanged, a gradual decline in plasma renin concentration was observed. Controlled blood pressure was achieved once plasma renin activity fell to normal.

Case Report

A 51-year-old woman was admitted to the hospital because of syncope and nonspecific electrocardiographic repolarization alterations. She had been transferred to our intensive coronary care unit because of cardiac muscle enzymes elevation compatible with acute myocardial infarction. The patient had a 14-year history of labile hypertension, treated occasionally with Visken. During the preceding two years she had experienced transient episodes of cluster headaches associated with palpitations. On admission, physical examination elicited no abnormal findings. While being examined she complained of headache, sweating, and breathlessness. Paroxysmal increases of arterial pressure were subsequently recorded. During repeated attacks of hypertensive crisis, blood pressure rose steeply to maximal level of 340/190 mmHg with pulse rate of 130 beats/min, followed immediately by bradycardia and escape nodal rhythm. The possibility of pheochromocytoma was promptly raised and subsequent urinary metanephrines and vanillylmandelic acid determinations...
supported this diagnosis. Chest x-ray showed no abnormalities. ECG revealed sinus tachycardia, prominent P waves, and ST-T-segment changes. Gradual incremental oral prazosin therapy was instituted followed by an impressive hemodynamic stabilization and clinical improvement. No remarkable changes in vanillylmandelic acid and metanephrine levels were observed over the following three consecutive 24-h period urine collections (Table 1).

High plasma renin activity (measured by radioimmunoassay) was found in two consecutive measurements prior to any therapeutic intervention. Retrospectively, the gradual hemodynamic stabilization was well correlated with the pattern of decreased plasma renin activity, repeatedly measured at the same time on each of the next consecutive 3 days with the patient at rest and in the supine position, under regular daily dietary sodium and fluids. Computed tomography, intravenous pyelography, and ultrasound assessment localized an isolated solid mass displacing the right kidney laterally and forward. Imaging procedure by 131I-labelled metaiodobenzylguanidine uptake showed identical localization of a single mass corresponding to the right adrenal gland.

Blood pressure and heart rate were remarkably constant throughout the two-week period of preoperative treatment with prazosin. The patient underwent right radical adrenalectomy and a single well-circumscribed encapsulated spherical mass 8 cm in diameter was removed and confirmed histologically as a pheochromocytoma. During surgery, two self-terminating hypertensive episodes occurred, with accompanying tachycardia and ventricular premature beats. Following removal of the tumor, blood pressure remained in the range of 130–140/100–110 mmHg.

Electrocardiographic and echocardiographic abnormalities gradually disappeared. Determinations of plasma renin activity and catecholamine metabolite measurements were carried out once more (Table 1). The patient was discharged without any medical treatment after one week of uneventful postoperative recovery.

### Discussion

The patient with pheochromocytoma is prone to develop hyperreninemia. Increased sympathetic activity, volume depletion, vascular compression, and associated renal artery stenosis may all account for increased plasma renin activity and for the elevated blood pressure seen in these patients. Under these circumstances, regulation of blood pressure and hormonal interrelationship activity are more complicated than traditional views suggest. Inability to show a consistent correlation between arterial pressure and catecholamine activity may conceivably be related to complex interactions of circulating catecholamines with co-secreted vasoactive factors, such as angiotensin II. The vasoconstrictive effect of catecholamines is amplified by renin release mediated by renal sympathetic nerves which are important modulators of renin secretion.

The extent to which renin-angiotensin system contributes to elevation of blood pressure seen in patients with pheochromocytoma is controversial. Bravo et al. utilizing a central nervous system acting antihypertensive agent (clonidine) concluded that much of the hypertension associated with these tumors is due to increased adrenergic activity rather than related to plasma renin activity. However, in view of the few cases of hypertension coincident with pheochromocytoma effectively treated by captopril and saralasin, we may assume that certain patients with elevated renin levels may derive benefit from angiotensin converting enzyme inhibitors.

Prazosin may be highly effective and life-saving management in patients with pheochromocytoma. Hypotensive effect is accompanied by unremarkable change in heart rate or plasma norepinephrine concentration, thus providing significant clinical priority over non-selective alpha-adrenergic antagonists. While plasma renin activity has been seen to increase during prazosin treatment in patients with heart failure, a correlation was found between attenuation of blood pressure and decreased plasma renin activity in our patient.

### Table 1: Daily relationship between plasma renin activity, urinary catecholamine metabolites, and prazosin therapy

<table>
<thead>
<tr>
<th></th>
<th>PRA ng/ml/h</th>
<th>CR in urine mg/day</th>
<th>VMA in urine µg/mg</th>
<th>MN in urine µg/day</th>
<th>Prazosin mg/day</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline level</td>
<td>5.22</td>
<td>1170</td>
<td>47</td>
<td>12,000</td>
<td>—</td>
</tr>
<tr>
<td>First day</td>
<td>2.66</td>
<td>980</td>
<td>51</td>
<td>20,800</td>
<td>5</td>
</tr>
<tr>
<td>Second day</td>
<td>1.07</td>
<td>1924</td>
<td>45</td>
<td>24,000</td>
<td>8</td>
</tr>
<tr>
<td>Third day</td>
<td>0.85</td>
<td>2190</td>
<td>48</td>
<td>8,180</td>
<td>6</td>
</tr>
<tr>
<td>After operation</td>
<td>0.70</td>
<td>1820</td>
<td>&lt;10</td>
<td>580</td>
<td>—</td>
</tr>
<tr>
<td>Laboratory normal range</td>
<td>0.6–2.2</td>
<td>16–22 mg/kg/day</td>
<td>10–20</td>
<td>&lt;800</td>
<td>—</td>
</tr>
</tbody>
</table>

**Abbreviations:** CR = creatinine; MN = metanephrines; PRA = plasma renin activity; VMA = vanillylmandelic acid.
In contrast to beta-adrenergic-blocking agents which have direct control over renin release, there is no known direct interference by prazosin to account for the laboratory results obtained in this patient. However, prazosin’s known "adverse effect" of fluid retention\(^7\) might prove unexpectedly beneficial in volume-depleted high renin hypertensive patients, counteracting the contribution of the renin-angiotensin system to the raised blood pressure caused by volume-depleted state and, on the other hand, opposing sympathetic renal vasoconstrictive activity of circulating catecholamines which lead to further increased renin secretion. Lowering systemic peripheral resistance mediated by postsynaptic alpha blockade and decreased angiotensin activity may explain both the enhanced diuresis and creatinine elimination observed, which probably reflects improved renal perfusion and cardiac performance.

In conclusion, prazosin has proved effective in reducing blood pressure in pheochromocytoma probably mediated by alpha-adrenergic blockade and indirect suppression of plasma renin activity. We believe that prazosin offers sufficiently sustained benefit to justify its therapeutic application in high renin hypertension associated with pheochromocytoma.

References