New Insights into the Medical Management of Primary Aldosteronism

Principal Discussant
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Case Presentation
A 30-year-old woman was admitted to the hospital because of hypertension and hypokalemia. She had had a normal blood pressure measurement 5 years prior to admission and had been in good health until approximately 1 year before admission when a severe frontal headache and cramping in her hands and feet developed. She was seen in an emergency room and was noted to be hypertensive with a blood pressure of 170/110 mm Hg. She was treated with methyldopa (Aldomet), and a blood sample analysis yielded the following values: serum sodium, 142 mEq/L; serum potassium, 2.2 mEq/L; CO₂ level, 35 mEq/L; blood urea nitrogen, 13 mg/dl; and glucose, 91 mg/dl. Electrocardiogram (ECG) was normal except for the presence of U waves. An intravenous pyelogram was normal.

While on the methyldopa regimen, the patient's headaches resolved; however, 9 months before admission, the patient discontinued all medications and her headaches returned. Three months before admission she again was seen in an emergency room with headaches and cramping in her hands. Her blood pressure was 170/110 mm Hg, and her serum potassium level was 2.6 mEq/L. Her methyldopa prescription was renewed, and she was given hydrochlorothiazide, potassium, and butalbital (Fiorinal). The hydrochlorothiazide was discontinued after 10 days.

She was referred to this hospital for evaluation of her hypertension. The patient had noted nocturia for approximately 4 to 5 years. There was no history of constipation, diarrhea, weight loss, nausea, or vomiting. She had not been taking birth control pills and had normal menstrual cycles. She had never been pregnant. She had had a renal stone 4 years previously that had been passed spontaneously. Her medications included methyldopa (Aldomet), 250 mg twice a day, potassium chloride, three tablets twice a day, and butalbital (Fiorinal). The patient smoked and drank occasionally.

Family history was significant in that a younger sister was hypertensive and obese, and had an "ovarian tumor." Three brothers had died; one in Vietnam, one of polio, and one as an infant. Her mother, who had died in an automobile accident, had had diabetes mellitus and thyroid surgery for an unknown thyroid condition.

On examination, she weighed 139 pounds. The blood pressure was 160/98 mm Hg. The pulse was 76/min and regular. She was afebrile. The pupils were round, regular, and reactive to light and accommodation. The thyroid was normal to palpation. Funduscopic examination was normal. The chest was clear to percussion and auscultation. The heart examination revealed regular rhythm without murmurs. No breast masses were noted, although there was a nodule just lateral to the lower outer border of her right breast. It was smooth, firm, about 1.5 cm in size, and nontender. The abdomen was soft and without bruits, masses, or organomegaly. Bowel sounds were normal. Dorsalis pedis pulses were 1+ and equal bilaterally. There was no peripheral edema. Results of a neurological examination were normal.

On admission, complete blood count and electrolyte values were within normal limits with a potassium level of 3.5 mEq/L. Urinalysis results and ECG were normal. All medications were stopped, and the patient was placed on a 10-mEq sodium, 100-mEq potassium,
These diagnoses must be differentiated because of the relative ease of surgical care of adrenal adenoma. In this patient the severity of the hypokalemia (< 2.5 mEq/L on presentation), the drop in plasma aldosterone level in response to upright posture, and the lack of angiotensin II stimulation of aldosterone suggest that an aldosterone-producing adenoma was the cause of the primary aldosteronism. This diagnosis was ultimately confirmed by a CT scan, which revealed the presence of an adenoma on the right adrenal gland.

The differentiation of adenoma from hyperplasia cannot be made on clinical presentation alone, although the hypertension and hypokalemia tend to be worse in adenoma. The regulators of aldosterone production in adenoma and hyperplasia will be discussed later in more detail. In general, hyperplastic adrenal glands are more sensitive to changes in circulating angiotensin II levels, so that these patients respond to upright posture or angiotensin II infusion with a rise in plasma aldosterone levels. Adenomas, on the other hand, are more sensitive to changes in adrenocorticotrophic hormone (ACTH) concentration, so they demonstrate a fall in plasma aldosterone levels when a supine sample taken at 0800 is compared with a sample obtained at 1200 after 4 hours of upright posture. This "anomalous" fall corresponds to the diurnal fall in ACTH levels. Unfortunately, these types of maneuvers are only about 60% accurate in differentiating adenoma from hyperplasia. Because of its relative ease, the CT scan is the method of choice to differentiate adenoma from hyperplasia. Since tumors less than 5 mm in diameter may not be visualized, patients may also require bilateral simultaneous adrenal vein sampling for plasma aldosterone/cortisol ratio determination. A comparatively higher ratio on one side would confirm the diagnosis of an adenoma on that side.

Surgical removal of the right adrenal gland would be the treatment of choice for this patient; however, she refused the operation, but accepted medical management. Patients with idiopathic hyperplasia, which occurs in 30 to 50% of patients with primary aldosteronism, require medical management, as they respond poorly to bilateral adrenalectomy. Since primary aldosteronism commonly appears in the 40- to 65-year-old age group, numerous patients with adenoma will have other disorders that increase the surgical risk and they will also require medical management.

The following discussion highlights new aspects in the regulation of aldosterone production, abnormalities of various modulators in adenoma and hyperplasia, and potential new medical therapy for primary aldosteronism.

Potassium, angiotensin II, and ACTH are the classic regulators of adrenal aldosterone production. In the

**Table 1: Angiotensin II Infusion**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Time (min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sodium (mEq/L)</td>
<td>0-10</td>
</tr>
<tr>
<td>Potassium (mEq/L)</td>
<td>0-45</td>
</tr>
<tr>
<td>Cortisol (mg/dL)</td>
<td>0-45</td>
</tr>
<tr>
<td>Aldosterone (ng/dL)</td>
<td>0-122</td>
</tr>
<tr>
<td>PRA (ng/ml/hr)</td>
<td>0-&lt;0.1</td>
</tr>
<tr>
<td>ANG II (pg/ml)</td>
<td>0-28</td>
</tr>
</tbody>
</table>

**Table 2: Intravenous Saline Infusion**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Time (hr)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sodium (mEq/L)</td>
<td>0-139</td>
</tr>
<tr>
<td>Potassium (mEq/L)</td>
<td>0-3.7</td>
</tr>
<tr>
<td>PRA (ng/ml/hr)</td>
<td>0-0.1</td>
</tr>
<tr>
<td>Aldosterone (ng/dL)</td>
<td>0-52</td>
</tr>
<tr>
<td>Cortisol (mg/dL)</td>
<td>0-11</td>
</tr>
</tbody>
</table>

PRA = plasma renin activity; ANG II = angiotensin II.
past decade, however, several new factors that modulate aldosterone secretion have been recognized and are included in the following list:

Stimulators
Angiotensin II
Potassium
Pituitary factors
Aldosterone stimulating factor (ASF)
Proopiomelanocorticotropin (POMC) derivatives
ACTH
β-Lipotropin (β-LPH)
β-Melanocyte-stimulating hormone (β-MSH)
N-terminal sequences of POMC, i.e., γ-MSH
Serotonin
Inhibitors
Dopamine
Atrial natriuretic factor (ANF)

The role of these substances in normal physiological control of aldosterone secretion is currently under investigation. Some of these factors have been strongly implicated as contributors to the pathogenesis of primary aldosteronism due to idiopathic hyperplasia. These exciting investigations potentially pave the way for the development of new forms of medical therapy for primary aldosteronism. Aldosterone antagonists presently constitute the medical treatment of choice for nonsurgical candidates with primary adrenal hypersecretion of aldosterone. Spironolactone competes for the aldosterone receptor and reduces aldosterone synthesis; however, it also blocks testosterone biosynthesis and peripheral androgen action. About 60 to 80% of men ingesting spironolactone complain of decreased libido, and 50% experience breast tenderness and enlargement. Other aldosterone antagonists include triamterene, which inhibits distal tubule sodium reabsorption independent of aldosterone, and amiloride, which blocks transport of sodium in the distal tubule. However, spironolactone appears to be more effective in controlling blood pressure and potassium in patients with aldosterone-producing adenoma than these other agents. In patients with idiopathic hyperplasia, aldosterone antagonists control potassium but often do not normalize blood pressure. Thus, new alternatives for the medical management of primary aldosteronism would represent clinically important contributions to the treatment of this disorder.

Regulation of Aldosterone Secretion
Potassium and angiotensin II have long been recognized as physiological regulators of aldosterone secretion. Potassium directly enhances aldosterone secretion from isolated zona glomerulosa cells. Short-term potassium loading or increases in dietary potassium increase aldosterone secretion, while potassium depletion decreases it. During alterations in posture, circulating volume, or dietary sodium intake, plasma aldosterone responses parallel those of plasma renin, which suggests that the renin-angiotensin system is a dominant factor controlling aldosterone secretion under these conditions. Angiotensin II stimulates aldosterone production in the intact animal or in isolated adrenal cells, and angiotensin II receptors on the adrenal cell membrane have been characterized extensively. Angiotensin II binding to its receptors correlates well with aldosterone secretion. Although ACTH enhances aldosterone secretion in vivo or in vitro, long-term stimulation in humans results in prolonged cortisol production but diminishing aldosterone secretion. This response has suggested that ACTH has a less important role than potassium or angiotensin II in controlling aldosterone secretion in normal humans.

Many of the previous studies suggested that the effects of potassium, angiotensin II, and ACTH on aldosterone were relatively independent of each other, although one regulator could modify the response of another. Recently, however, Pratt and colleagues demonstrated that inhibition of angiotensin II production eliminated the aldosterone response to potassium and ACTH infusion in the dog and that treatment of rats with converting enzyme inhibition eliminated the stimulatory effect of potassium on rat perfused adrenal slices. These results suggest that angiotensin II may be necessary to increase the sensitivity of the adrenal glomerulosa’s response to increases in ambient potassium levels.

Confusion has arisen from these results because 1) potassium is an excellent stimulator of aldosterone production in vitro and in media in which no angiotensin II has been added, and 2) studies in anephric humans have demonstrated a potassium-induced rise in plasma aldosterone levels. These observations may not be inconsistent, since the presence of an adrenal renin-angiotensin system has been increasingly recognized. Renin exists in animal and human zona glomerulosa. Low salt diet and high potassium diet increase rat adrenal renin content. Thus, local formation of angiotensin II could serve as a “fine-tuning” mechanism to regulate aldosterone production.

Recent investigations delving further into the intracellular mechanisms by which these regulators control aldosterone secretion suggest their actions are interdependent. Mounting data indicate that calcium is a final common pathway for the expression of the effects of potassium and angiotensin II and may even mediate events after production of cyclic adenosine 3',5'-monophosphate (cAMP) in the action of ACTH. Hence, it would not be surprising that a strong interrelationship exists between these secretagogues through calcium-mediated mechanisms to ultimately control aldosterone production.

Angiotensin II has emerged as a model hormone whose effects are mediated by calcium. Following the binding of angiotensin II to its membrane receptor, alterations in calcium fluxes have been demonstrated in nearly every tissue studied that contains angiotensin II receptors, including adrenal glomerulosa, vascular smooth muscle, and liver. The effects of angiotensin II on these tissues are inhibited if extracellular calcium is eliminated. In the zona glomerulosa, the calcium channel blocker verapamil and the calcium flux blocker lanthanum decrease basal steroidogenesis and steroidogenesis stimulated by angiotensin II, potassium, and ACTH. Other calcium antagonists, such as nifedipine and the dihydropyridine antagonists, also...
have been shown to inhibit potassium- and angiotensin II-induced aldosterone secretion. Angiotensin II increases cytosolic free calcium concentration. According to the model of Rasmussen and co-workers, angiotensin II increases calcium efflux and influx through the cell membrane. Influx is enhanced because of the opening of receptor-operated calcium channels. Angiotensin II binding of its receptor initiates two key pathways. The first increases levels of inositol triphosphate, which stimulates release of calcium from the endoplasmic reticulum into the cytosol. The increase in cytosolic free calcium concentration activates calmodulin, which in turn activates a number of kinases to induce a rapid, but short increase in aldosterone production. Activated calmodulin also enhances calcium efflux from the cell, so that cytosolic free calcium levels do not continue to rise.

The second pathway initiates increases in diacylglycerol levels, which activates calcium-dependent protein kinase C. This process induces a slow, more sustained rise in aldosterone production. The calcium ionophore A23187 can activate the first pathway by increasing cytosolic free calcium. The phorbol ester 12-O-tetradecanoylphorbol-13-acetate (TPA) activates the second pathway without increasing cytosolic calcium. When added together, A23187 and TPA induce a rise in aldosterone production mimicking that seen with angiotensin II with respect to both time and amplitude. Thus, the rise in cytosolic free calcium is responsible for the initial response of the glomerulosa cell to angiotensin II, while the diacylglycerol pathway is responsible for the sustained response. Current evidence suggests that these two pathways act synergistically to mediate the cellular response to angiotensin II in vascular smooth muscle as well as adrenal glomerulosa.

Potassium also increases cytosolic free calcium levels. It induces a rapid depolarization of the glomerulosa cell, which represents the opening of voltage-dependent calcium channels. The increase in cytosolic calcium concentration stimulates calmodulin-dependent kinases to increase aldosterone production. Dantrene, which blocks endoplasmic reticulum release of calcium into the cytosol, does not block the effect of potassium but does block that of angiotensin II. Hence, the rise in cytosolic free calcium concentration seen with potassium is due mainly to influx into the cell and is not dependent on endoplasmic reticulum release. Potassium does not increase diacylglycerol levels, but it does increase cell content of cAMP. The cAMP pathway appears to be responsible for the sustained response of the zona glomerulosa cell to potassium. When A23187 is combined with forskolin, which stimulates cAMP production, a rise in aldosterone concentration is induced, which mimics the response seen with potassium alone. 9

Further evidence suggests that the cAMP pathway may be calcium-dependent. Removal of extracellular calcium or addition of lanthanum inhibits cAMP-stimulated aldosterone secretion from zona glomerulosa cells. An inhibitor of intracellular calcium mobilization, TMB 8, also inhibits the effects of cAMP. Thus, an increase in cytosolic free calcium concentration is necessary to mediate the stimulatory effects of angiotensin II, potassium, and cAMP on aldosterone production.

Pituitary factors other than ACTH have long been implicated as contributors to the regulation of aldosterone secretion. Subjects with hypopituitarism have no increase in aldosterone secretory rate in response to ACTH infusion as compared with that in normal or cortisol-suppressed subjects. Hypophysectomy in the rat abolishes the aldosterone response to sodium depletion. Adrenocorticotrophic hormone is synthesized as a larger precursor molecule, proopiomelanocorticotrophin (POMC), which is enzymatically cleaved to β-lipotrophin (β-LPH) as well as an intermediate that is further cleaved to ACTH. Cleavage products of β-LPH are β-melanocyte-stimulating hormone (β-MSH) and β-endorphin. Exciting studies by Matsuoka et al. have demonstrated that β-LPH and β-MSH stimulate aldosterone production in rat adrenal capsular cells without increasing corticosterone production. Stimulation appeared to be independent of ACTH, angiotensin II, and cAMP. In this study, β-endorphin did not stimulate aldosterone production, however, infusions of β-endorphin into humans and hypophysectomized nephrectomized dogs increased plasma aldosterone levels. The N-terminal segment of POMC containing α-MSH has also been shown to stimulate aldosterone production in human aldosteronoma cells in culture. 20, 21

Another substance found in human anterior pituitary gland, urine, and plasma is a 26,000 molecular weight glycoprotein that stimulates aldosterone secretion and increases blood pressure when given to rats. This aldosterone-stimulating factor (ASF) is biochemically different from ACTH, β-LPH, or angiotensin II, and its effect is not mediated by cAMP but is dependent on potassium. 22, 23 In rabbit isolated adrenal cells, ASF is less potent than ACTH or angiotensin II in stimulating aldosterone production 24 However, ASF potentiates the aldosterone response to angiotensin II during sodium depletion, which suggests that it may be the pituitary factor that contributes to regulation of aldosterone production during sodium deficiency.

Dopamine, a sympathetic neurotransmitter, and ANF, a newly described hypotensive peptide, constitute the known inhibitors of aldosterone secretion. Metoclopramide, a specific inhibitor of dopamine, enhances the effect of angiotensin II infusion on plasma aldosterone in normal humans without changing other factors known to regulate aldosterone secretion. Adrenal dopamine receptors have been characterized and appear to differ from pituitary receptors responsive to bromocriptine. The main physiological effect of dopamine inhibition is exerted during alterations in dietary sodium intake. Circulating dopamine levels increase during a high sodium diet. Sodium loading diminishes the aldosterone response to infusions of angiotensin II; metoclopramide increases the responses during sodium loading to levels seen with angiotensin II infusion during sodium depletion. Dopamine itself inhibits angiotensin II–induced aldosterone secretion
during sodium depletion but not during sodium loading in humans. In fact, the responses to angiotensin II plus dopamine during sodium depletion are similar to those seen with angiotensin II alone during sodium loading. Taken together, these results suggest that dopaminergic mechanisms modulate aldosterone production during changes in sodium balance.

Atrial natriuretic factor (ANF) represents a family of peptides found in mammalian atria (about fivefold less in humans than in rats) that induces an increase in urinary volume and sodium excretion, relaxes precontracted smooth muscle, and inhibits adrenal aldosterone secretion. These peptides appear to be released into the circulation, which renders them capable of exerting physiological effects at target tissues. In suspensions of bovine adrenal glomerulosa cells, ANF inhibits basal aldosterone production and blunts the stimulatory effect of angiotensin II, potassium, ACTH and dibutyl cAMP. Since ANF also blunts angiotensin II vascular smooth muscle contraction, the possibility exists that ANF interferes with the mechanism of angiotensin II action. However, studies by Goodfriend et al. indicate that ANF does not inhibit angiotensin II binding to its receptors, angiotensin II stimulation of phospholipid turnover, or surprisingly, angiotensin II-induced alterations in calcium fluxes. Although ANF does inhibit an early step in aldosterone biosynthesis preceding cholesterol side chain cleavage, the mechanism of this inhibition of steroidogenesis needs further investigation.

**Alteration of Regulatory Factors in Primary Aldosteronism**

Aldosterone-producing adenoma and idiopathic hyperplasia of the zona glomerulosa are the major causes of primary aldosteronism. The adenoma can be surgically removed, which results in cure or improvement of hypertension and hypokalemia in 80% of patients. Hyperplasia requires medical management. Thus, differentiation of the two etiological processes is important. Recognition of new factors that regulate aldosterone production has led to new concepts regarding the pathophysiology and differentiation of adenoma and hyperplasia.

Early studies suggested that aldosterone production in patients with idiopathic hyperplasia was sensitive to changes in angiotensin II levels, while in patients with adenoma, aldosterone production was more sensitive to ACTH. This finding led to the postural test to differentiate adenoma from hyperplasia. With assumption of upright posture from 0800 to 1200, small changes in circulating angiotensin II levels result in a rise in plasma aldosterone concentration in patients with hyperplasia. In contrast, patients with adenoma experience a decrease in plasma aldosterone concentration that parallels the decrease in ACTH and cortisol levels. Subsequent studies revealed that testing for the anomalous postural decrease in aldosterone in patients with adenoma was only about 60% accurate, probably because of the marked variability in the postural rise in renin and angiotensin II levels in these patients. Infusions of angiotensin II, angiotensin III, and ACTH were still only partially successful in differentiating adenoma from hyperplasia.

Although useful in differentiating primary aldosteronism from essential hypertension, converting enzyme inhibition also did not differentiate adenoma from hyperplasia. Saralasin, a partial angiotensin II agonist, does show promise in separating these two entities. Brown et al. demonstrated a significant increase in plasma aldosterone concentration following administration of saralasin to eight patients with hyperplasia, while no significant rises occurred in six patients with adenoma.

Analogous to Cushing's disease, pituitary factors are likely candidates to induce hyperplasia of the zona glomerulosa. Franco-Saenz et al. recently reported a patient with bilateral adrenal hyperplasia with documented primary aldosteronism associated with basophilic hyperplasia of the anterior and intermediate lobes of the pituitary gland. Immunohistochemistry demonstrated the presence of ACTH-like peptides in the basophilic cells, which suggests that hyperplasia of the pituitary was related to adrenal hyperplasia in this patient. In other studies, circulating levels of pituitary factors have been found to be elevated in patients with hyperplasia but not with adenoma. Plasma β-endorphin levels were elevated in 10 patients with hyperplasia but normal in four patients with adenoma. Plasma ASF concentration was elevated in seven patients with idiopathic hyperplasia but was normal in four postoperative patients who had had adenal adenomas removed. Urinary levels of ASF also were elevated in these patients and were not suppressed by administration of dexamethasone, 2 mg/day for 2 days.

More recently, Griffing et al. reported that patients with idiopathic hyperaldosteronism have significantly higher levels of plasma immunoreactive α-MSH than patients with aldosterone-producing adenomas. They suggested that this difference may be due to an abnormality of the pars intermedia, where POMC-derived products may be under positive serotonergic control and negative dopaminergic control and are unresponsive to glucocorticoid feedback inhibition. Further evidence to support the pathogenetic role of pituitary factors in idiopathic hyperplasia lies in the report that the serotonergic antagonist cyproheptadine acutely decreased aldosterone production in six patients with hyperaldosteronism due to hyperplasia but not in eight patients with adenoma. A postulated mechanism for the development of hyperplasia is that hyperactivity of certain serotonergic neurons stimulates pituitary production of ASF and some of the POMC derivatives. Increased levels of ACTH and the development of Cushing's disease would not necessarily occur because of different processing of ASF and POMC by different areas of the pituitary. Increased circulating levels of ASF would lead to hyperplasia of the zona glomerulosa and increased sensitivity of aldosterone production to angiotensin II. Thus, "idiopathic" aldosteronism due to adrenal hyperplasia may not be idiopathic.
Medical Management of Primary Aldosteronism

Based on the preceding discussion, the following variety of new medical treatments for primary aldosteronism might be considered:

**Current therapies**
- Aldosterone antagonists: spironolactone, triamterene, amiloride
- Calcium channel blockers (inhibit final common pathway)
- Pituitary factor inhibitors: antiserotonergic agents in idiopathic hyperplasia
- Steroid biosynthesis inhibitors

**Potential therapies**
- Dopamine agonists
- ANF
- ASF inhibitors
- Opioid antagonists

Inhibition of pituitary factors, in particular ASF, would be of prime consideration for patients with idiopathic hyperplasia. However, development of inhibitors to ASF will likely depend on its complete purification and structural analysis. Because of the stimulatory effects of POMC derivatives on aldosterone production, opioid antagonists could also be considered. Cyproheptadine acutely decreases aldosterone in patients with hyperplasia; however, effects on blood pressure and potassium and long-term effects on aldosterone production have not been reported. Whether other agents that alter neurotransmitter function will be helpful remains to be determined. Since humans have maximal tonic dopaminergic inhibition of the zona glomerulosa it is doubtful that dopamine agonists will be useful in further decreasing aldosterone production in primary aldosteronism.

Since calcium is the final common pathway for aldosterone production, calcium channel blockers represent obvious candidates for the treatment of primary aldosteronism. In addition, calcium antagonists inhibit smooth muscle contraction, thereby reducing vascular resistance. This is the major mechanism by which calcium channel blockers decrease blood pressure. Nadler et al. demonstrated that nifedipine acutely decreased blood pressure and plasma aldosterone levels in five patients with adenoma and five patients with hyperplasia. After 4 weeks of nifedipine (20 mg sublingually t.i.d.), four patients with hyperplasia and two with adenoma had decreases in plasma aldosterone levels and normalization of blood pressure and serum potassium levels (Table 3). Addition of spironolactone with nifedipine led to supranormal elevations of serum potassium levels, which suggests that combinations of antialdosterone agents should be used with caution.

Other inhibitors of aldosterone production include ANF and those inhibiting steroid biosynthesis. The physiological effects of ANF are currently under extensive investigation.

In this patient, spironolactone or nifedipine would be the medical treatment of choice before she became pregnant, since she refused the operation. Because of the antiandrogenic properties of spironolactone, its use during pregnancy with its potential risk of feminizing a male fetus would be contraindicated, particularly during the first trimester when most of the development of the fetal genitalia occurs. Little is known about the use of nifedipine during pregnancy except that two-thirds to twice the maximum recommended dose resulted in small placentas and underdeveloped chorionic villi in monkeys. There is also little reported experience with triamterene or amiloride in pregnancy.

Hypertension in the pregnant patient with primary aldosteronism probably should be managed with the antihypertensives commonly used in pregnancy (i.e., a-methyldopa and hydralazine). Potassium supplementation should be administered as much as tolerated to correct the hypokalemia. Since patients with primary aldosteronism lose magnesium in their urine, serum magnesium levels also should be monitored closely and the magnesium supplemented as necessary.

**Acknowledgment**

We thank Dr. Gail K. Adler for the preparation and presentation of this clinical case.

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**TABLE 3**

*Effect of Long-term Nifedipine Therapy on Morning Supine Plasma Aldosterone, Potassium, and Blood Pressure Levels in Six Subjects with Primary Aldosteronism*

<table>
<thead>
<tr>
<th>Patient classification</th>
<th>Plasma aldosterone (ng/dl)</th>
<th>Plasma potassium (mEq/L)</th>
<th>Blood pressure (mm Hg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>IHA</td>
<td>58</td>
<td>3 1</td>
<td>170/110</td>
</tr>
<tr>
<td>IHA</td>
<td>29</td>
<td>3 0</td>
<td>144/92</td>
</tr>
<tr>
<td>IHA</td>
<td>28</td>
<td>3 3</td>
<td>136/92</td>
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<td>33</td>
<td>3 2</td>
<td>185/108</td>
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<tr>
<td>APA</td>
<td>75</td>
<td>2 6</td>
<td>188/112</td>
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<tr>
<td>APA</td>
<td>54</td>
<td>3 0</td>
<td>150/96</td>
</tr>
</tbody>
</table>

Mean ± SEM

<table>
<thead>
<tr>
<th>Plasma aldosterone</th>
<th>46±8</th>
<th>20±3*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Plasma potassium</td>
<td>3 0±0.1</td>
<td>3 7±0.1*</td>
</tr>
<tr>
<td>Blood pressure</td>
<td>162±9/102±4</td>
<td>134±58/85±25</td>
</tr>
</tbody>
</table>

*IHA = idiopathic hyperplasia; APA = aldosterone-producing adenoma
*p < 0.02  **p < 0.01, compared with baseline value.  #p < 0.01, compared with systolic baseline value.  $p < 0.001, compared with diastolic baseline value.

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References


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