Medical treatment as an alternative to adrenalectomy in patients with aldosterone-producing adenomas

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Abstract

Primary aldosteronism (PA) and, in particular, its two commonest subtypes (i.e. idiopathic hyperaldosteronism (IHA) and aldosterone-producing adenoma (APA)) have been recognized as the most common cause of secondary hypertension. While ‘conservative’ medical treatment with aldosterone receptor antagonists is the therapeutic approach of choice in controlling blood pressure in patients with PA due to IHA, the more invasive (laparoscopic) adrenalectomy seems to be the most suitable therapy for patients with APA. In this review, we focus on the medical approach for the management of APA in cases where surgical excision of the adrenal is not possible.

Introduction

Primary aldosteronism (PA) represents the most common form of secondary hypertension (Schirpenbach & Reincke 2007) that is increasingly being diagnosed and may account for 5–13% of unselected hypertensive patients (Gordon et al. 1993, Fardella et al. 2000, Nishikawa & Omura 2000). In 1954, Conn (1955) described the case of a 34-year-old woman with hypertension, severe hypokalaemia, mild hypernatraemia and alkalosis. Laboratory investigation showed that mineralocorticoid activity per day in this patient was 22-fold greater compared with normotensive controls. The surgical removal of a 4 cm unilateral adrenal tumour resulted in total reversal of the clinical and metabolic abnormalities. This new clinical entity, named PA, was the first demonstration of the relationship between aldosterone-producing adenomas (APA) and hypertension.

In the late 1960s, bilateral adrenal hyperplasia was shown to represent another form of PA and since then it is often referred to as idiopathic hyperaldosteronism (IHA; Davis et al. 1967). APA (35% of cases) and IHA (60% of cases) are the most common subtypes of PA; however, five more subtypes exist (Young 2007). Primary or unilateral adrenal hyperplasia (2% of cases) and pure aldosterone-producing adrenocortical carcinoma (<1% of cases) are two more infrequent forms. Familial hyperaldosteronism (FH) type I (glucocorticoid-remediable aldosteronism; McMahon & Dluhy 2004), FH type II (familial APA, IHA or both; So et al. 2005) and ectopic aldosterone-secreting tumours are even more rare forms (Abdelhamid et al. 1996).

Experimental studies showed that excess aldosterone has detrimental effects on the heart, brain and kidneys independent of blood pressure (BP) level (Rocha & Stier 2001). In turn, either mineralocorticoid antagonists or adrenalectomy markedly reduced myocardial injury and prevented cerebral haemorrhage and renal vascular disease (Rocha & Stier 2001).

Clinical studies also suggested that excessive secretion of aldosterone has adverse effects on the cardiovascular system. It was shown that left ventricular mass is greater in patients with PA than in age- and sex-matched patients with essential hypertension, pheochromocytoma or Cushing’s syndrome.
Furthermore, aldosterone excess appears to independently increase the risk for cardiac fibrosis (Brilla & Weber 1992). The increased prevalence of left ventricular hypertrophy and cardiac fibrosis potentially account for the increased risk for arrhythmic disorders in states of excess aldosterone (Ramires et al. 2000). Re-entry mechanisms also appear to play a role, particularly in the pathogenesis of atrial fibrillation in these patients (Benjamin et al. 1994, Ramires et al. 2000, Yee et al. 2001). Patients with PA have a higher urinary albumin excretion rate and a prevalence of metabolic syndrome than patients with essential hypertension (Fallo et al. 2006, Giacchetti et al. 2007). More importantly, patients with either APA or IHA appear to have higher cardiovascular morbidity than age-, sex- and systolic and diastolic BP-matched patients with essential hypertension (Milliez et al. 2005). Cardiovascular outcome is comparable in patients with PA treated with either adrenalectomy or aldosterone antagonists. BP-lowering per se is the most important mechanism responsible for the beneficial effects of both the treatments and remains fundamental for the prevention of major cardiovascular events in patients with PA (Catena et al. 2008).

**Management of APA**

These adverse effects of aldosterone excess stress the importance of establishing the diagnosis of PA and its underlying cause. It is generally accepted that adrenalectomy is the treatment of choice for APA, whereas lifelong administration of aldosterone antagonists is the most suitable therapy for patients with IHA. Laparoscopic adrenalectomy is the preferred surgical approach since it is associated with a shorter hospitalization time, faster recovery from surgery and lower long-term morbidity compared with the conventional open approach (Rossi et al. 2002, Assalia & Gagner 2004). The latter is nowadays indicated only for adrenal tumours larger than 5 cm, where a carcinoma is suspected (Sirén et al. 1998, Shen et al. 1999).

Laparoscopic adrenalectomy results in normalization of serum potassium and plasma aldosterone concentration as well as plasma renin activity. However, hypertension persists in some patients post-operatively. Several studies showed that BP decreases in the majority of patients but antihypertensive agents are required in a significant proportion of cases in order to achieve a normal BP. Reported rates of BP control vary between 33 and 85% (Table 1), but the definition of normal BP was not uniform in these studies, ranging from DBP < 100 mmHg to DBP < 114 mmHg. Table 1 displays the number of patients, cured, BP cut-off, length of follow-up, size of tumours and incidence of complications in the studies reviewed.

**Table 1** Characteristics of patients and outcome data in the studies reviewed

<table>
<thead>
<tr>
<th>Study</th>
<th>Number of patients (n)</th>
<th>Cured (%)</th>
<th>BP cut-off (mmHg)</th>
<th>Length of follow-up (months, range or mean ± S.D.)</th>
<th>Size of tumours (cm; range)</th>
<th>Incidence of complications (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Favia et al. 1992</td>
<td>52</td>
<td>71</td>
<td>DBP &lt; 100</td>
<td>77 (13–189)</td>
<td>NM</td>
<td>1.9</td>
</tr>
<tr>
<td>Obara et al. 1992</td>
<td>63</td>
<td>62</td>
<td>160/95</td>
<td>49.2 (12–114)</td>
<td>NM</td>
<td>1.9</td>
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<tr>
<td>Simon et al. 1993</td>
<td>10</td>
<td>54</td>
<td>160/95</td>
<td>26.4 (6–66)</td>
<td>1.0–3.0</td>
<td>1.9</td>
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<td>Blumenfeld et al. 1994</td>
<td>43</td>
<td>35</td>
<td>140/90</td>
<td>0.5–180</td>
<td>NM</td>
<td>1.9</td>
</tr>
<tr>
<td>Weigel et al. 1994</td>
<td>35</td>
<td>59</td>
<td>140/90</td>
<td>36</td>
<td>1.48</td>
<td>1.9</td>
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<tr>
<td>Mantero et al. 1995</td>
<td>34</td>
<td>61</td>
<td>NM</td>
<td>106 (12–280)</td>
<td>NM</td>
<td>1.9</td>
</tr>
<tr>
<td>Celen et al. 1996</td>
<td>42</td>
<td>60</td>
<td>160/95</td>
<td>51 (1–132)</td>
<td>1.5 (0.8–4.5)</td>
<td>13</td>
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<td>Lo et al. 1996</td>
<td>44</td>
<td>77</td>
<td>160/95</td>
<td>69 (6–252)</td>
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<td>1.9</td>
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<tr>
<td>Proye et al. 1998</td>
<td>100</td>
<td>56</td>
<td>160/95</td>
<td>76 (9–154)</td>
<td>1.5 (0.8–3.2)</td>
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<tr>
<td>Sapienza et al. 1999</td>
<td>18</td>
<td>46</td>
<td>NM</td>
<td>63 (8)</td>
<td>2.6 (0.8*)</td>
<td>0</td>
</tr>
<tr>
<td>Shen et al. 1999</td>
<td>79</td>
<td>85</td>
<td>DBP &lt; 100</td>
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<td>26</td>
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<td>Sawka et al. 2001</td>
<td>93</td>
<td>33</td>
<td>140/90</td>
<td>29 (0.1–77.9)</td>
<td>NM</td>
<td>5.0</td>
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<td>Fukudome et al. 2002</td>
<td>46</td>
<td>72</td>
<td>140/90</td>
<td>292.8</td>
<td>1.47 (0.8*)</td>
<td>6.6</td>
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<td>Rossi et al. 2002</td>
<td>30</td>
<td>67</td>
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<td>63 (26.1)</td>
<td>2.0 (1.12)</td>
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<td>33</td>
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<td>NM</td>
<td>5 (1–96)</td>
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<tr>
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<td>Goh et al. 2004</td>
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<td>NM</td>
<td>21 (1–60)</td>
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<td>86 (48)</td>
<td>2.1 (0.9)</td>
<td>8.0</td>
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<td>Pang et al. 2007</td>
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<td>140/90</td>
<td>59</td>
<td>1.7 (1.5–2.0)</td>
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<td>Gockel et al. 2007</td>
<td>40</td>
<td>37</td>
<td>NM</td>
<td>45 (7–114)</td>
<td>1.8 (0.7–6.0)</td>
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DBP, diastolic blood pressure; NM, not mentioned; ± S.D.; *, S.E.M.

It is apparent that laparoscopic adrenalectomy alone is not sufficient to achieve BP control in a significant proportion of patients. In addition, surgery is not without risks (Mantero et al. 1995, Ghose et al. 1999). Therefore, long-term medical therapy might represent an attractive alternative approach for the treatment of PA. The efficacy of spironolactone in the long-term management of PA was demonstrated more than 25 years ago (Brown et al. 1972, Biglieri & Schambelan 1973, Ferriss et al. 1978). Indeed, spironolactone controlled BP in patients with PA due to APA, while there was no evidence of escape of BP from control in any patient for up to 8 years of treatment (Brown et al. 1972, Ferriss et al. 1978). Moreover, a successful BP control for up to 11 years has been reported in five patients with APA (Biglieri & Schambelan 1973).

Another study included 24 patients with APA, who chose medical management instead of adrenalectomy (Ghose et al. 1999). After a follow-up time of 5–17 years, systolic and diastolic BP were at goal (<140 and <90 mmHg respectively) in 75 and 83% of patients respectively. At the last follow-up visit, 4 patients were

Table 2 Criteria used to establish the diagnosis of primary aldosterone-producing adenoma (APA) in the studies reviewed

<table>
<thead>
<tr>
<th>Study</th>
<th>ARR</th>
<th>Saline infusion test</th>
<th>Postural test</th>
<th>Preoperative response to spironolactone</th>
<th>CT scan</th>
<th>MRI</th>
<th>Adrenal venous sampling</th>
<th>131I-6-β-iodocholesterol scintigraphy</th>
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ARR, plasma aldosterone/plasma renin activity ratio; CT, computed tomography, MRI, magnetic resonance imaging.
receiving monotherapy with a potassium-sparing diuretic, 13 were receiving a potassium-sparing diuretic and 1 more antihypertensive drug, 6 were receiving 3 antihypertensive drugs and 1 was receiving 4 antihypertensive drugs. Serum potassium levels were normal (>3.5 mEq/l) in all patients. During follow-up, no patient experienced a cardiovascular event and none developed heart failure. Only five patients had a noticeable increase in the size of the adrenal adenoma and no malignant transformation was reported.

Based on the PA pathophysiology, there are several therapeutic options for the medical management of these patients (Lim et al. 2001). Both spironolactone and eplerenone, which directly antagonize the actions of aldosterone at the receptor level, are the most appropriate choice. Spironolactone has been widely and successfully used for treating PA, either as monotherapy or in combination with other antihypertensive drugs (Young 2007). However, many investigators used unnecessarily high doses of spironolactone (400–800 mg/d) to treat PA. The usual dose for long-term therapy is 12.5–25 mg/d; the dose is titrated to achieve serum potassium levels in the high-normal range. The theoretical risk of breast carcinoma, due to the effects of spironolactone on oestrogen/progesterone receptors, has not been confirmed in clinical practice (Jeunemaitre et al. 1987). The commonest side effects of spironolactone therapy are pain relief gynaecomastia in men, breast engorgement or tenderness, muscle cramps, decreased libido, erectile dysfunction and menstrual disturbances (Young 2007).

Potassium canrenoate, a slightly different aldosterone antagonist, is an effective antihypertensive drug in patients with PA (Mantero et al. 1995). This agent is a water-soluble derivative of spironolactone, sharing the same active metabolite canrenone, but probably has a different pattern of metabolism that avoids the formation of intermediate products with anti-androgenic effects (Armanini et al. 1985, Dupont 1985). However, experience with this drug is limited, mainly because it is not available in USA and only a parenteral formulation is available in the UK.

Eplerenone differs from spironolactone by virtue of its higher selectivity for the aldosterone receptor (Garthwaite & McMahon 2004). Eplerenone has 0.1 and <1% of spironolactone’s binding affinity for the androgen and oestrogen/progesterone receptor respectively (de Gasparo et al. 1987). This results in a significant reduction of its progestational and anti-androgenic actions compared with spironolactone (de Gasparo et al. 1987). Interestingly, eplerenone may relieve spironolactone-induced painful gynaecomastia (Karagiannis et al. 2007). The Food and Drug Administration approved eplerenone for the treatment of uncomplicated essential hypertension in 2002 but it has not yet been approved for PA. We showed for the first time that eplerenone (50–200 mg/d) controls BP in patients with PA due to IHA as effectively as spironolactone (50–400 mg/d; Karagiannis et al. 2008). Two patients in the spironolactone group presented bilateral painful gynaecomastia, which completely resolved after switching to eplerenone. The risk of severe hyperkalaemia was relatively low in both groups. Therefore, eplerenone might be a safe and effective alternative in patients with PA, who are treated with spironolactone and present sex hormone-related adverse effects.

It must be noted that patients with IHA are in general less responsive to monotherapy with mineralocorticoid receptor antagonists than those with APA. In patients with IHA, hypervolaemia is a major reason for resistance to drug therapy with aldosterone antagonists (Young 2007). In these cases, the addition of thiazide diuretics at low doses (e.g. 12.5–25 mg hydrochlorothiazide daily) can control BP. However, in several patients with IHA, other classes of antihypertensive drugs may need to be added in order to achieve BP control.

In patients with PA, the antihypertensive efficacy of epithelial sodium channel blockers, such as amiloride and triamterene, is suboptimal. Spironolactone is effective as monotherapy in ~50% of patients with PA (Mantero et al. 1995, Lim et al. 1999), whereas 75% of patients on amiloride need additional antihypertensive drugs to achieve BP control (Griffing et al. 1982). Triamterene (50 mg) in combination with hydrochlorothiazide (25 mg) decreased BP in eight patients with PA, but plasma renin activity increased only in two patients, indicating that excess aldosterone activity persisted in most patients (Ganguly & Weinberger 1981).

Calcium channel blockers (CCBs) may reduce aldosterone secretion and BP in patients with PA by blocking the influx of calcium into the adrenal glomerulosa cells. Several CCBs have been tested in PA with variable effects on BP and plasma aldosterone levels and small effects on plasma renin activity (Stimpel et al. 1988, Carpenê et al. 1989, Veglio et al. 1990, Brown & Hopper 1999).

Angiotensin-converting enzyme inhibitors (ACEIs) have moderate BP-lowering efficacy in patients with PA (Mantero et al. 1981, Griffing & Melby 1985). This could be related to the suppressed plasma renin activity and angiotensin II levels. ACEIs may be more effective in patients with IHA, since the latter have increased adrenal sensitivity to angiotensin II (Wisgerhof et al. 1978). Angiotensin receptor blockers may also have a
role in controlling BP in patients with PA when combined with other drugs (Stokes et al. 2001).

Deoxycorticosterone is converted to aldosterone by three successive reactions comprising 11β-hydroxylation, 18-hydroxylation and 18-oxidation (Curnow et al. 1991). Aldosterone synthase is the key enzyme in this pathway (Curnow et al. 1991) and is overexpressed in patients with PA (Mulatero et al. 2004). Aldosterone synthase inhibitors are under investigation and could be a new therapeutic option for hypertension and congestive heart failure (Ménard et al. 2006). Their effects may differ from those of mineralocorticoid receptor antagonists, by inhibiting extra-adrenal synthesis of aldosterone, which may occur at between 100 and 1000 times lower levels in the heart and the vessels than in the adrenal glands (Takeda et al. 1997, Silvestre et al. 1998), although this is still debated (Ahmad et al. 2004, Fiebeler et al. 2005). The identification of the gene for aldosterone synthase (CYP11B2) could potentially lead to the development of gene therapy for PA (Brand et al. 1998, Taymans et al. 1998, Raizada et al. 2000).

Lifelong medical treatment has some shortcomings, including compliance and some degree of morbidity. Treatment-related side effects may cause physical discomfort and may also negatively affect quality of life. These limitations should be taken into account when long-term medical management is being considered, particularly for a disease that can potentially be cured by surgery. Treatment costs should also be considered. Surgical intervention for APA appears to be significantly more cost-effective than lifelong medical treatment (Sywak & Pasieka 2002). Eplerenone may be as effective as spironolactone in treating PA, with the potential for fewer side effects, but is approximately six to seven times more expensive than spironolactone (Craft 2004).

Conclusions
In appropriately selected patients with APA, laparoscopic adrenalectomy is a safe and effective treatment. Lifelong medical treatment of APA should be considered as an alternative to adrenalectomy in elderly patients, in those unwilling to undergo surgery or in patients with comorbid conditions that preclude surgery. The mineralocorticoid receptor antagonists, spironolactone or eplerenone, are the drugs of choice to treat PA due to APA. Sex hormone-related side effects of spironolactone could affect compliance with treatment. Eplerenone appears to have better safety profile compared with spironolactone, but this should be weighed against its higher cost and the scarcity of data on its long-term effects in patients with PA. However, BP is not well controlled with monotherapy with either spironolactone or eplerenone in a significant proportion of patients with PA. Therefore, additional antihypertensive drugs are frequently required to achieve optimal BP control.

Declaration of interest
This review was written independently; no company or institution supported it financially. Some of the authors have attended conferences, given lectures and participated in advisory boards or trials sponsored by various pharmaceutical companies.

Funding
This research did not receive any specific grant from any funding agency in the public, commercial or not-for-profit sector.

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