

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.

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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

(Tanabe *et al.* 1997). 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

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

Study	Number of patients (n)	Cured (%)	BP cut-off (mmHg)	Length of follow-up (months, range or mean \pm s.d.)	Size of tumours (cm; range)	Incidence of complications (%)
Favia <i>et al.</i> 1992	52	71	DBP < 100	77 (13–189)	NM	1.9
Obara <i>et al.</i> 1992	63	62	160/95	49.2 (12–114)	NM	NM
Simon <i>et al.</i> 1993	10	54	160/95	26.4 (6–66)	1.0–3.0	NM
Blumenfeld <i>et al.</i> 1994	43	35	140/90	0.5–180	NM	NM
Weigel <i>et al.</i> 1994	35	59	140/90	36	1.48	NM
Mantero <i>et al.</i> 1995	34	61	NM	NM (12–240)	NM	NM
Celen <i>et al.</i> 1996	42	60	160/95	106 (12–280)	NM	NM
Lo <i>et al.</i> 1996	44	77	160/95	51 (1–132)	1.5 (0.8–4.5)	13
Proye <i>et al.</i> 1998	100	56	160/95	69 (6–252)	NM	NM
Sirén <i>et al.</i> 1998	27	41	NM	76 (9–154)	1.5 (0.8–3.2)	0
Sapienza <i>et al.</i> 1999	18	46	NM	63 (8)	2.6 (0.8 [#])	0
Shen <i>et al.</i> 1999	79	85	DBP < 100	4–72	NM	5.0
Brunt <i>et al.</i> 2001	26	31	DBP < 100	27.9 (2–72)	1.9 (1.2 [#])	20.0
Sawka <i>et al.</i> 2001	93	33	140/90	29 (0.1–77.9)	NM	NM
Fukudome <i>et al.</i> 2002	46	72	140/90	292.8	1.47 (0.8 [*])	NM
Rossi <i>et al.</i> 2002	30	67	140/90	63 (26.1)	2.0 (1.12 [#])	6.6
Harris <i>et al.</i> 2003	33	62	NM	5 (1–96)	NM	9.0
Meria <i>et al.</i> 2003	212	58	NM	44 (6–84)	1.76	10.0
Stowasser <i>et al.</i> 2003	14	50	140/90	10.5 (3–21)	NM	NM
Goh <i>et al.</i> 2004	42	50	NM	21 (1–60)	1.75 (0.6)	NM
Meyer <i>et al.</i> 2005	24	33	140/90	86 (48)	2.1 (0.9 [#])	NM
Pang <i>et al.</i> 2007	62	34	140/90	59	1.7 (1.5–2.0)	8.0
Gockel <i>et al.</i> 2007	40	37	NM	45 (7–114)	1.8 (0.7–6.0)	2.5

DBP, diastolic blood pressure; NM, not mentioned; [#], s.d.; ^{*}, s.e.m.

between 140/90 and 160/100 mmHg (Favia *et al.* 1992, Obara *et al.* 1992, Simon *et al.* 1993, Blumenfeld *et al.* 1994, Weigel *et al.* 1994, Celen *et al.* 1996, Lo *et al.* 1996, Proye *et al.* 1998, Sirén *et al.* 1998, Sapienza & Cavallaro 1999, Shen *et al.* 1999, Brunt *et al.* 2001, Sawka *et al.* 2001, Fukudome *et al.* 2002, Rossi *et al.* 2002, Harris *et al.* 2003, Meria *et al.* 2003, Stowasser *et al.* 2003, Goh *et al.* 2004, Meyer *et al.* 2005, Gockel *et al.* 2007, Pang *et al.* 2007). Table 2 summarizes the criteria used to establish the diagnosis of primary APA in the studies reviewed. Adrenal venous sampling, which is the reference test to differentiate unilateral from bilateral disease in patients with PA, was used in the majority of the studies (Young *et al.* 2004, Tamura *et al.* 2008). Predictors of persistent hypertension after adrenalectomy include older age, family history with more than one first-degree relative with hypertension, use of more than two antihypertensive drugs preoperatively, duration of hypertension of more than 5 years, concomitant essential hypertension, large gland size at operation, increased serum creatinine levels and coexistence of other forms of secondary hypertension (Favia *et al.* 1992, Sawka *et al.* 2001, Fukudome *et al.* 2002, Harris *et al.* 2003, Karagiannis *et al.* 2005, Lumachi *et al.* 2005, Meyer *et al.* 2005, Gockel *et al.* 2007, Pang *et al.* 2007). On the other hand, a preoperative

reduction in mean BP of 15 mmHg or more after 10 days of spironolactone therapy, 100 mg/d, suggests a strong likelihood of post-operative cure of hypertension (Saruta *et al.* 1987).

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

Study	ARR	Saline infusion test	Postural test	Preoperative response to spironolactone	CT scan	MRI	Adrenal venous sampling	¹³¹ I-6-β-iodocholesterol scintigraphy
Favia <i>et al.</i> 1992	+	+	+	–	+	–	+	+
Obara <i>et al.</i> 1992	+	–	+	–	+	–	+	+
Simon <i>et al.</i> 1993	+	+	+	–	+	–	–	–
Blumenfeld <i>et al.</i> 1994	+	–	+	–	+	–	+	–
Weigel <i>et al.</i> 1994	+	–	–	–	+	–	+	–
Mantero <i>et al.</i> 1995	+	–	+	–	+	–	+	+
Celen <i>et al.</i> 1996	+	–	+	+	+	–	+	+
Lo <i>et al.</i> 1996	+	–	+	–	+	–	+	–
Proye <i>et al.</i> 1998	+	–	–	+	+	+	+	+
Sirén <i>et al.</i> 1998	+	–	+	–	+	+	–	+
Sapienza <i>et al.</i> 1999	+	+	+	–	+	+	+	+
Shen <i>et al.</i> 1999	+	–	+	–	+	–	+	+
Brunt <i>et al.</i> 2001	+	–	–	–	+	–	+	–
Sawka <i>et al.</i> 2001	+	–	–	–	+	+	+	–
Fukudome <i>et al.</i> 2002	+	–	–	–	–	–	–	–
Rossi <i>et al.</i> 2002	+	–	–	–	+	–	–	–
Harris <i>et al.</i> 2003	+	–	+	+	+	+	+	+
Meria <i>et al.</i> 2003	+	–	–	–	+	–	+	–
Stowasser <i>et al.</i> 2003	+	–	+	–	+	–	+	–
Goh <i>et al.</i> 2004	+	–	+	–	+	–	+	–
Meyer <i>et al.</i> 2005	+	+	+	–	+	+	–	–
Pang <i>et al.</i> 2007	+	–	–	–	–	–	–	–
Gockel <i>et al.</i> 2007	+	–	–	–	+	+	–	–

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 painful 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 $\sim 50\%$ 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, Carpené *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 11 β -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 & Pasięka 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.

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