Adherence and blood pressure control in patients with primary aldosteronism

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\section*{ABSTRACT}

**Purpose:** The aim of our study was to evaluate the adherence to mineralocorticoid receptor (MR) antagonists and other antihypertensive therapy and blood pressure control in conservatively treated patients with primary aldosteronism (PA).

**Materials and methods:** Conservatively treated subjects with previously confirmed PA (n=50, 64.5 ± 9 years of age, 24% women) were investigated via our outpatient hypertension clinic. All subjects underwent regular examinations in our clinic. In addition to basic laboratory and clinical parameters, 24 h ambulatory blood pressure monitoring (ABPM) (Spacelabs) was evaluated. Unplanned blood sampling for assessment of serum antihypertensive drug concentrations by the means of liquid chromatography–mass spectrometry was performed in all patients. In case of spironolactone, its active metabolite canrenone was also evaluated. Total non-compliance was then defined as the absence of all measured antihypertensive drugs. Partial non-compliance was calculated as the absence of serum levels of at least one, but not all antihypertensive drugs prescribed.

**Results:** Good blood pressure control was detected (mean 24 h systolic/diastolic BP 130 ± 12/77 ± 9 mmHg). The average number of antihypertensive drugs was 3.9 ± 1.5. All subjects were treated by MR antagonists. 44% of patients received spironolactone (average daily dose 45 ± 20 mg) and in the remaining 56% of subjects eplerenone was administered (average daily dose 80 ± 30 mg) due to spironolactone side effects. Assessment of antihypertensive drug concentrations revealed full adherence in 80% of all subjects, partial nonadherence was noted in the remaining 20% of subjects. MR antagonist levels were detected in almost all subjects (49 out of 50).

**Conclusions:** Good blood pressure control and adherence to therapy were detected in conservatively treated patients with PA. Eplerenone had to be used quite often as male subjects did not tolerate dose escalation due to spironolactone side effects.

\section*{Introduction}

Arterial hypertension is a common cardiovascular disease with high prevalence worldwide. Although the disease can be treated by a variety of antihypertensive drugs, less than 50% of patients is appropriately controlled and reaches target blood pressure values [1]. Nonadherence to therapy is one of the major factors contributing to poor blood pressure control [2]. Evaluation of adherence should thus become an integral part of the assessment of patients with apparently treatment-resistant hypertension [3]. In addition, adherence testing should also be done in subjects taking two antihypertensive drugs with a less than 10 mmHg decrease in systolic blood pressure after addition of the second antihypertensive medication [4].

Initial period of pharmacotherapy with antihypertensive drugs might be critical for adherence to
medication. Newly diagnosed hypertensive patients have >40% likelihood of interruption of therapy after 3 months. In a study with 13,303 hypertensive patients on monotherapy, 42.6% withdrew from the drug therapy within 3 months [5]. Younger age might be an important factor for nonadherence with antihypertensive treatment as well. Nonadherence to therapy in NHANES register was 12 times more frequent in hypertensive subjects below 30 years of age compared to middle aged or older population (above 50 years of age). Male gender was also a risk factor for nonadherence in this study (OR 1.31) [6]. Diuretic therapy may possess further risk factors as we have found in our collaborative study with our allied UK centre [7].

The risk of nonadherence to therapy is substantially higher in subjects taking a higher number of antihypertensive drugs and thus patients with severe/resistant hypertension frequently revealed poor adherence [8,9]. We have investigated the adherence to antihypertension pharmacotherapy in a previous study conducted in our centre. Partial or total nonadherence was found in 47% of all patients with resistant hypertension [10]. However, few data are available, concerning the adherence to therapy and blood pressure control in specific forms of hypertension, especially in primary aldosteronism (PA) [11,12]. Since PA is a common form of secondary hypertension [13,14], we have focussed on this disease.

We thus aimed to evaluate the adherence to antihypertensive therapy with special focus on MR antagonists in conservatively treated patients with PA. As spironolactone has a short half-life and may become even undetectable during one dosing interval, its metabolite canrenone was evaluated as it has considerably steadier levels and may serve as a better indicator for spironolactone adherence [15]. Furthermore, the focus of our study was blood pressure control and the type of antihypertensive drugs in our subjects.

Materials and methods

Study population

Conservatively treated subjects with previously confirmed PA (n - 50, 64.5 ± 9 years of age, 24% women) were investigated via an outpatient hypertension clinic. All subjects were regularly followed-up in our hypertension clinic. We prospectively included all subjects with previously confirmed PA who were scheduled for a regular check-up during a 3-month period during which our study took place. Only two patients refused to participate due to Covid-19 infection. All subjects provided written informed consent to participation in our study during their visit. Ethical approval has been obtained for this study from the Ethics Committee of the General University Hospital, Prague, chairman Zbyněk Sklenář, under number 227/21 S-IV.

All subjects underwent prior thorough investigation for potential secondary hypertension during hospitalisation in our clinic due to severity of hypertension and/or hypokalaemia. The screening/diagnosis of PA was based on repeatedly elevated serum aldosterone concentrations (above 20 ng/dl), low direct plasma renin (below 3 pg/ml) and repeatedly high aldosterone-to-renin ratio (ARR) above 5.7 (ARR expressed in ng/dl per pg/ml) [16]. The diagnosis of PA was confirmed in all patients by the confirmatory test with saline infusion in agreement with the current guidelines/position paper [16,17]. The cut-off value of 7 ng/dl for plasma aldosterone after 4 h of 2 l saline infusion was used. PA patients were treated by conservative approach because of bilateral aldosterone overproduction based on adrenal venous sampling or due to refusal of surgery.

**Blood pressure measurement**

Detailed medical history and physical examination were performed during the patients’ visits. Conventional office blood pressure was measured by validated oscillometric tonometer Omron M6 (Omron Healthcare, Kyoto, Japan) in agreement with current guidelines of European Society of Hypertension [1]. Three blood pressure measurements were taken and the average of second and third values was calculated. Twenty-four-hour ambulatory blood pressure monitoring (ABPM) was performed using oscillometric Spacelabs 90217 device (Spacelabs Healthcare, Issaquah, WA).

**Laboratory analysis**

Laboratory parameters (plasma potassium, creatinine) were analysed using commercial automated procedures.

During the visit, we performed unanticipated blood sampling (10 ml of venous blood with subsequent transport to the Department of Toxicology) to measure serum antihypertensive drug concentrations in PA patients (with their informed consent). The time interval between ABPM and measurement of serum drug concentrations did not exceed 3 d. The timing of sampling was at least 3 h after the drug intake.
Measurement of amlodipine, verapamil, nitr LDipine, lecanidipine, betaxolol, bisoprolol, metoprolol, doxazosin, losartan, telmisartan, candesartan, hydrochlorothiazide, indapamide, chlorthalidone, perindoprilat, ramiprilat, rilmenidine, moxonidine, eplerenone and spironolactone along with its metabolite canrenone was performed. The drug concentration analysis was performed in the Toxicology Laboratory of the Institute of Forensic Medicine and Toxicology by means of liquid chromatography–tandem mass spectrometry (LC–MS/MS) [18,19]. The chromatographic separation was performed on a 1200 RRLC (Agilent, Waldbronn, Germany), consisting of a degasser, binary pump, autosampler and column compartment with controlled temperature. The mass spectrometry analysis was performed using a 3200 Q-trap triple quadrupole/linear ion trap mass spectrometer with a TurboIonSpray source (MDS Sciex, Ontario, Canada). LC–MS/MS with electrospray ionisation method was used for the simultaneous determination of spironolactone and its active metabolite canrenone in human serum [20]. LC–MS/MS with electrospray ionisation method was used for the determination of eplerenone in human serum [21].

The drug was considered positive when the concentration was at least at the lowest detectable level. Total non-compliance was defined as the absence of all measured antihypertensive drugs. Partial non-compliance was calculated as the absence of serum levels of at least one, but not all antihypertensive drugs apparently taken [10].

**Statistical analysis**

The data analysis was performed using software R version 4.1.2 [22].

An exploratory data analysis was performed for all parameters. Continuous parameters were tested using the Shapiro–Wilk test. If the test was not significant ($p > .05$), the parameters were considered normally distributed and are reported as mean and standard deviation. Non-normally distributed continuous parameters are presented as median with 25th and 75th percentile. Categorical parameters are reported as counts and frequencies. The effect of categorical variables on canrenone levels were assessed using the Mann–Whitney U test. GraphPad Prism version 8.2.1 software (GraphPad Inc., La Jolla, CA) for evaluation of all relationships and $p$ levels $<.05$ were considered as statistically significant. For statistical analysis of MR antagonist levels differences between sexes chi-square test was used.

**Results**

Basic characteristics of studied subjects are summarised in Table 1. Patients were relatively old with mildly elevated BMI. Hypokalaemia was not observed and mild renal dysfunction was detected. Data on office and 24 h blood pressure indicate good hypertension control in the majority of our subjects.

Most of our patients (80%) showed very good adherence with all administered drugs detected. Partial adherence was found in the remaining 20% of our subjects, thus we did not detect any case of a completely nonadherent patient.

Table 2 summarises the analysis of antihypertensive treatment and adherence to different drug classes. As expected, all patients were treated with MR blockers, i.e. spironolactone or eplerenone. Eplerenone was given more frequently due to the side effects of spironolactone in men. Almost all subjects treated with MR antagonists were adherent to this therapy. Majority of patients received calcium channel blockers and low doses of diuretics. Due to coexistence with other diseases and/or severity of hypertension other classes of drugs were given to some patients (alpha-blockers, beta-blockers, ACE-inhibitors, AT1-blockers Table 2 summarises the analysis of antihypertensive treatment and adherence to different antihypertensive drug classes. As expected, all patients were treated with MR blockers, i.e. spironolactone or eplerenone. Eplerenone was given more frequently due to the side effects of spironolactone in men. Almost all subjects treated with MR antagonists were adherent to this therapy. Majority of patients received calcium channel blockers and low doses of diuretics. Due to coexistence with other diseases and/or severity of hypertension other classes of drugs were given to some patients (alpha-blockers, beta-blockers, ACE-inhibitors, AT1-blockers

**Table 2. Analysis of antihypertensive treatment and adherence to different antihypertensive drug classes.**

| Frequency of prescribed drugs | Compliance (calculated only from analysed medication) |
|------------------------------|-------------------------------------------------------|
| (n = 50)                     |                                                       |
| No. | % | Positive no. | Analysed no. | %  |
|--------------------------------|--------------------------------------|
| Spironolactone | 22 | 44 | 21 | 22 | 95 |
| Eplerenone | 28 | 56 | 28 | 28 | 100 |
| ACE-inhibitors | 14 | 28 | 11 | 12 | 92 |
| AT1-blockers | 9 | 18 | 8 | 8 | 100 |
| $\beta$-blockers | 22 | 44 | 15 | 18 | 83 |
| Calcium channel blockers | 36 | 72 | 36 | 36 | 100 |
| Diuretics | 33 | 66 | 28 | 30 | 93 |
| $\alpha$-blockers | 22 | 44 | 16 | 19 | 84 |
| Centrally acting sympatholytics | 5 | 10 | 4 | 4 | 100 |

BMI: body mass index; eGFR: estimated glomerular filtration rate; SBP: systolic blood pressure; DBP: diastolic blood pressure.
Table 3. Average dosage and plasma drug concentrations of MR antagonists.

|               | Average daily dose (mg/d) | Plasma concentration (ng/ml) | Metabolite plasma concentration (ng/ml) |
|---------------|---------------------------|------------------------------|----------------------------------------|
| Spironolactone| 46 ± 21                   | 10 ± 15                      | 52 ± 38                                |
| Eplerenone    | 80 ± 31                   | 987 ± 496                    | –                                       |

and centrally acting sympatholytics). Adherence to all antihypertensive classes was good.

Table 3 shows average dose of spironolactone and eplerenone in our patients with PA as well as their plasma concentrations and spironolactone metabolite (canrenone) levels.

Discussion

The main finding of our study is a very good adherence to antihypertensive therapy including MR antagonists and subsequently very good blood pressure control in conservatively treated patients with PA. This observation might be rather surprising in the view of frequent nonadherence in patients with severe and/or difficult-to-treat hypertension [8–10]. Very low nonadherence was, however, also described in a recent multicentre study at Norway university hospitals [23]. A large study involving almost 50,000 participants in Japan also revealed very good adherence (92%) to antihypertensive therapy [24]. Our results are in agreement with a retrospective study from a hypertension clinic showing higher prevalence of PA in adherent patients with treatment-resistant hypertension compared to nonadherent [11].

Majority of our patients with PA presented with moderate to severe hypertension with subsequent necessity of combination therapy including MR antagonists. One of the potential important factors markedly contributing to adherence of our PA patients is a long-term follow up. Patients with confirmed PA were regularly examined in our outpatient clinic in 6-month intervals and the average duration of follow-up was 7.6 years (1–21 years). Certainly, we cannot exclude potential preselection bias, but this notion seems unlikely since we investigated all but two conservatively treated patients with PA scheduled for a regular visit to our outpatient clinic during the 3-month interval of our study (the two patients refused examination due to Covid-19 infection). The patients were informed about medication adherence testing only at the time of the visit before blood sampling and not ahead. Patients with PA could have higher motivation to adhere to antihypertensive therapy in a specialised setting with the same physician during longer periods of follow-up.

Another factor potentially increasing the adherence was the notion of the importance of specific therapy of PA by MR antagonist therapy. This perception is further supported by our data showing 95% adherence for spironolactone and 100% adherence for eplerenone. Adherence positivity was considered when the drug concentration was at least at the lowest detectable level. Patients with irregular MR antagonist intake may have been missed. Nevertheless, all patients but one had higher levels of canrenone than spironolactone, which is expectable after prolonged spironolactone use as canrenone has a longer half-life than the parent drug [25]. This proves that at least patients taking spironolactone did not pretend adherence by taking single drug dose shortly before the outpatient visit. Certainly, drug levels might be inconclusive in cases of partial adherence [26], which can at least partially be eliminated by further pharmacological analysis [27]. Nevertheless, this concept is not widely used and currently used biochemical methods of adherence testing without further analysis are unable to exclude this type of pretended adherence.

Relatively higher age of our patients may also contribute to better adherence since younger hypertensive subjects usually reveal poorer adherence [6]. However, the age factor probably did not modify the results since we have several relatively younger patients (below 50 years of age) with shorter duration of follow-up who also showed good adherence and good blood pressure control. In addition, it might be difficult to recruit younger patients with PA since newly detected PA cases below 40 years of age are not common. The median age of PA patients at the time of diagnosis is around 50 years [17]. The average age of patients with PA in the German registry is 61 ± 13 years [28].

Our study indicated very good blood pressure control in conservatively treated patients with PA which is also related to excellent adherence. These data correspond with previous data showing effective blood pressure reduction and correction of hypokalaemia in patients with PA [29,30]. Average dose of spironolactone in our study was 46 ± 21 mg/d and thus a marked proportion of PA patients were treated with low dose spironolactone in agreement with previous observation [30]. Prescription of eplerenone to our patients was common, mainly in males. Due to shorter half-life and inferior antihypertensive efficacy in comparison with spironolactone [31], we had to administer eplerenone twice a day and in higher doses.
(average dose was 80 ± 31 mg). In contrast with other studies, we were unable to manage hypertension in our patients with MR antagonist monotherapy [30]. Combination antihypertensive therapy was necessary in all patients. One of the potential explanations could be relatively higher age of our patients and/or presence of comorbidities like obesity, diabetes mellitus and/or renal dysfunction. Calcium-channel blockers and thiazide/thiazide-like diuretics were mainly used in combination with MR antagonists which is in accordance with other data [32]. Other antihypertensive classes were also used (RAS blockers, beta-blockers, alpha-blockers and centrally acting agents) depending on blood pressure values and/or individual clinical profile of our patients (for example presence of coronary artery disease, prostatic hyperplasia).

Our study certainly has some limitations. We included on a consecutive basis a relatively low number of patients, which might correspond to their poor willingness for thorough investigation during the Covid pandemic. Older age of patients with PA might also not give an accurate picture of medication adherence in PA in the general population. The serum drug concentrations were not analysed with regard to the thorough pharmacokinetics of the drugs which may bring more accuracy in the analysis and distinguish more properly between true compliance and so-called white coat compliance when patients use the medication shortly before the visit [27]. Nevertheless, at least for spironolactone this is not likely, as all but one patient had a higher level of canrenone than the parent drug which shows that the metabolite had accumulated in the body for several days before the sample draw. The absence of control group may also limit the interpretation, although appropriate control group of patients with severe hypertension can be difficult to obtain. All patients were followed-up and investigated in one centre, which may also limit to some extent the generalisability of the results.

Conclusions
Good blood pressure control and adherence were detected in conservatively treated patients with PA. Combination therapy involving MR antagonists had to be used in practically all patients. Eplerenone had to be used quite often as male subjects did not tolerate dose escalation due to spironolactone side effects.

Disclosure statement
The authors report there are no competing interests to declare.

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