ADDITION OF SPIRONOLACTONE IN PATIENTS WITH RESISTANT ARTERIAL HYPERTENSION (ASPIRANT) - STUDY PROTOCOL

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Background. There is currently limited data on which drug should be used to improve blood pressure control in patients with resistant hypertension. Recent observational trials reported spironolactone as having good effects. This study is designed to assess the effect of the addition of 25 mg of spironolactone on blood pressure (BP) in patients with resistant arterial hypertension.

Methods. Patients with office systolic BP >140 mmHg or diastolic BP >90 mmHg despite treatment with at least 3 antihypertensive drugs including a diuretic, are enrolled in this double-blind, placebo-controlled, multicentre trial. Patients are randomly assigned to receive spironolactone or a placebo at a ratio of 1:1 by the method of simple randomisation. Our primary endpoints are to show a statistically significant difference in the fall of mean day-time systolic and diastolic BP by ambulatory blood pressure monitoring (ABPM), between the spironolactone and placebo groups, after 8 weeks of treatment. Secondary outcomes are changes of serum potassium, sodium, creatinine, body weight, casual blood pressure in office, difference in the fall of mean night-time and 24-hour ABPM BP and treatment response depending on different baseline levels of aldosterone and aldosterone/PRA ratio. This study is registered with ClinicalTrials.gov, No. NCT00524615.

Discussion. If spironolactone proves effective, it might become the standard of treatment in patients with resistant arterial hypertension.

BACKGROUND

Resistant hypertension is usually defined as blood pressure (BP) exceeding 140/90 mmHg (or exceeding 130/80 mmHg in patients with diabetes mellitus or renal insufficiency, i.e. creatinine levels above 133 μ mol/l or proteinuria of more than 300 mg per 24 hours) despite regular use of full doses of an appropriate three-or-more-drug regimen that includes a diuretic¹.

Currently, there is a shortage of data on the prevalence of resistant hypertension. At least 10% of hypertensive patients are considered to be resistant to therapy^{2,3}. In large clinical trials^{4,5}, treatment led to target diastolic BP under 90 mmHg in as many as 90% of patients but systolic BP under 140 mmHg in only about 60% of patients. In the ALLHAT study² comprising more than 33,000 patients, 8% of the patients used 4 or more antihypertensive drugs at the end of the study and another 7% of the patients did not achieve the target BP. Thus, a total of 15% of cohort subjects could be classified as resistant hypertensive patients. In another study carried out at a specialized hypertension clinic, careful titration of doses administered to

hypertensive patients resulted in target BP under 140/90 mmHg in only 59% of patients⁶. Therefore, it seems that, depending on the degree of study population selection, the proportion of resistant hypertensive patients may range from 10% to 40%.

In patients with resistant hypertension, assessment of treatment adherence is recommended as the first step. To exclude the white coat syndrome, home BP monitoring or preferably Holter ambulatory BP monitoring (ABPM) is advocated. Next, excess alcohol and dietary salt intake should be ruled out, as well as drug interactions and the use of substrates leading to BP increase (most commonly non-steroidal anti-rheumatic agents, corticosteroids and oral contraceptives). As the next step, the secondary cause of hypertension should be uncovered. It is relatively frequent in resistant hypertension (at least 10% (ref. ⁷)) and should be treated if found.

If a secondary cause of hypertension is not found, treatment regimens containing combinations of 3, 4, 5 or, in some cases, even more antihypertensive agents are used since it is desirable to decrease BP to prevent cardiovascular events⁸. As yet, insufficient data supported by

evidence from clinical trials are available as to which anti-hypertensive agents are optimal as drugs of third, fourth or fifth choice. Recently, increasingly more attention has been paid to the use of spironolactone in patients with resistant hypertension.

Spironolactone is a pharmacologic aldosterone antagonist. Its mechanism of action is primarily competitive binding to receptors in the distal renal tubule, a site of reabsorption of sodium and secretion of potassium dependent on aldosterone. Thus, spironolactone leads to increased secretion of sodium and water together with retention of potassium. By this mechanism, it acts both as a diuretic and antihypertensive.

At present, spironolactone is especially used in more advanced forms of cardiac failure, significantly decreasing both morbidity and mortality⁹. Spironolactone also effectively decreases BP in patients with or without hyperaldosteronism^{10–18}. Small, uncontrolled studies have also shown its effectiveness in patients with resistant hypertension^{19–22}.

In a recently published retrospective subanalysis of the ASCOT-BPLA study²³, spironolactone added to a combination of three hypertensive agents resulted in a significant decrease in BP by 21.9/9.5 mmHg over an average treatment length of 1.3 years in a total of 1,411 patients. The authors concluded that a prospective, randomized, double-blind study is needed to confirm the effectiveness of aldosterone blockade in patients with resistant hypertension. To our knowledge, such study has not been carried out as yet. Therefore, we designed a prospective randomized trial to evaluate the effect of adding 25 mg of spironolactone in patients with resistant arterial hypertension.

METHODS

Study design

ASPIRANT is an investigator-led, prospective, multicentre, randomised, double-blind, placebo-controlled, parallel-group trial. The study will compare the effect of the intervention (spironolactone administered at a dose of 25 mg once daily) to control (placebo administered once daily) on decrease in blood pressure in patients with resistant arterial hypertension.

Ethics committee approval and registration of the clinical trial

The study will be carried out in different secondary and tertiary care hospitals in accordance with the protocol, Good Clinical Practice and legislature of the Czech Republic. The University Hospital Olomouc Ethics Committee approved the ASPIRANT clinical trial on 14 May 2007 and the protocol was subsequently approved by the local ethics committees at all other participating centers.

Prior to patient recruitment, the study was insured in accordance with the legislation by the Gerling insurance company. The liability of the sponsor and investigators are also insured.

The study is registered in the international registry of clinical trials ClinicalTrials.gov as NCT00524615 and the EudraCT No. of the trial is 2007-003558-27.

Inclusion criteria

Patients over 18 years of age with resistant hypertension will be included in the study.

Resistant hypertension is defined as casual blood pressure during clinical examination of more than 140/90 mmHg (a mean of the 2nd and 3rd measurements during a single examination, at least 3 min apart) despite the use of full doses of an appropriate three-or-more-drug regimen that includes a diuretic (thiazide, chlortalidone, indapamide, metipamide, furosemide, amiloride or their combinations).

In diabetic patients or those with renal insufficiency (creatinine levels above 133 $\mu\text{mol/l}$) or proteinuria of more than 300 mg per 24 h, resistant hypertension is defined as blood pressure during clinical examination (a mean of the 2nd and 3rd measurements during a single examination) of more than 130/80 mmHg despite the use of full doses of an appropriate three-or-more-drug regimen that includes a diuretic.

The patients will sign informed consent prior to their enrollment in the study. In women capable of becoming pregnant, a pregnancy test will be carried out during the initial examination.

A total of 160 subjects are expected to be enrolled in the study.

Exclusion criteria

Excluded will be patients with BP values in the range of severe hypertension (systolic BP >180 mmHg and/or diastolic BP >110 mmHg) requiring immediate adjustments to therapy, patients with renal insufficiency (acute or chronic) with creatinine levels above 180 $\mu\text{mol/l}$ or a MDRD glomerular filtration rate of less than 40 ml/min, hyperkalemia over 5.4 mmol/l, hyponatremia below 130 mmol/l, porphyria, hypersensitivity to ingredients of Verospiron (Richter Gedeon, Hungary), women who are lactating, pregnant or of childbearing age and not using contraceptives, and patients already using any of the aldosterone antagonists (spironolactone, eplerenone, canrenone).

Randomization and treatment during the clinical study

At baseline, the patients will be divided into arms by simple randomization in the individual centers in a ratio of 1:1. In addition to the current medication, the patients will take capsules containing 25 mg of spironolactone or placebo once daily, in the morning. The drug will be taken for 8 weeks. Throughout the study, the drug for each patient will be prepared in a special bottle labeled with a code. During the study, the drug/placebo codes will be kept in a sealed envelope to be opened after the study is completed. Throughout the study, the patients will continue taking medication initiated prior to the study without any changes.

Calculation of the population sample size

Since the study compares mean values of continuous variables of two populations, it is necessary to estimate the population standard deviation of the variable (s) and the size of the difference in values to be detected (d). The sizes of the two arms is expressed by the formula

$$n = 1 + 2C (s/d)^2 \text{ Snedecor and Cochran 1989}$$

where C is a constant; for $\alpha = 0.05$ and $1-\beta = 0.80$, the value is 7.85. To detect the difference in systolic BP of at least 10 mmHg and in diastolic BP of at least 5 mmHg, with the standard deviation values being 18.0 mmHg and 10.7 mmHg for systolic and diastolic BP²³, populations of 102 and 146 patients would be needed to detect decreases in systolic and diastolic BP. When accepting the higher number and adding an extra 10% of patients, the resulting sample size is 160 patients.

The statistical analysis will involve all participants who complete the study. Standard methods of statistical analysis will be used to analyse the data, with a $p < 0.05$ being considered statistically significant.

Goals and purpose of the study

The primary end-points of the ASPIRANT study are to find a statistically significant difference between the fall in mean day-time systolic and mean day-time diastolic blood pressure measured by ABPM (ambulatory blood

pressure monitoring) at baseline and after 8 weeks in groups treated with spironolactone and placebo.

The secondary end-points are to compare changes in potassium, sodium and creatinine levels, body weight, night-time BP and 24 h BP by ABPM and casual BP in the office (a mean of the 2nd and 3rd measurements during a single session) between groups treated with spironolactone and placebo, and to assess the treatment response in relation to the baseline aldosterone level and aldosterone/PRA ratio.

Course of the study

The study chart is shown in (Fig. 1).

I. During the first week after enrollment in the study, the following *initial examination* will be carried out:

- 1) pulse rate and casual BP measurements in the office (a mean of the 2nd and 3rd measurements on a seated patient with the arm raised to the level of the heart and supported, during a single examination, measurements at least 3 min apart)
- 2) ABPM (24 h ambulatory blood pressure monitoring) using a monitor validated to the standards of the British Hypertension Society (BHS) or Association for the Advancement of Medical Instrumentation (AAMI)(ref.^{24,25}), with the validation being published in a peer-reviewed medical journal.
The mean daytime blood pressure will be calculated from values measured between 9 a.m. and 9 p.m., the mean night blood pressure from values measured between 1 a.m. and 6 a.m.²⁶. The mean 24 h BP will be calculated as the mean of all the measured values.
- 3) Serum urea, creatinine, sodium, potassium, chloride and glucose levels will be measured. The patient's height and weight will be recorded. To assess the potential contribution of secondary hypertension, serum plasma renin activity (PRA) and aldosterone, TSH, morning cortisol level assays and 24 h urine collection for microalbuminuria, proteinuria and cortisol excretion will be carried out. To rule out a pheochromocytoma, plasma free metanephrine tests or 24 h urinary fractionated metanephrine measurement will be performed.

II. Any antihypertensive or concomitant therapy will be recorded at both the beginning and end of the study, as well as any changes in therapy in the course of the study.

III. Based on the randomization results, 25 mg of spironolactone 1x daily or placebo 1x daily will be added to the patients' current therapy during the first week of the study.

IV. Patients with baseline creatinine levels of more than 133 $\mu\text{mol/l}$, patients over 75 years of age, those taking amiloride prior to their enrollment in the study and all diabetics (at a higher risk of hyperkalemia or progression of renal insufficiency) will undergo two follow-up examinations in the course of the study - 2 and 4 weeks after initiation of the drug. The other patients will undergo only one follow-up examination 4 weeks after the initiation of the drug.

Fig. 1. Flow chart of the study.

The follow-up examination will include: pulse rate and BP measurements (to rule out hypotension; a mean of the 2nd and 3rd measurements during a single examination, at least 3 min apart), measurements of sodium, potassium, chloride, urea and creatinine levels. The patients will be specifically asked about the presence of adverse effects of spironolactone such as pain, increased breast tenderness or erectile dysfunction.

In cases of potassium levels rising to more than 6.0 mmol/l at any time during the study, development of symptomatic hypotension below 100/60 mmHg, creatinine levels increasing by more than 25% compared with the baseline and exceeding the upper reference limit of 104 μ mol/l or the patient's intolerance to the drug (due to adverse or any other effects), the patient's participation in the study and administration of the drug will be discontinued. The patient has the right to discontinue his/her participation in the study at any time based on his/her own decision.

V. Eight weeks after initiation of the drug, *final examination* of the patients will be carried out, including:

- 1) ABPM under conditions identical to those in part I
- 2) casual BP measurements in the office (a mean of the 2nd and 3rd measurements during a single examination, at least 3 min apart)
- 3) serum urea, creatinine, sodium and potassium levels, PRA and aldosterone assays, 24 h microalbuminuria
- 4) records of potential side effects of the therapy and changes in medication in the course of the study

VI. The data will be entered into a MS Excel database and statistically processed.

Description of the "discontinuation rules" and "discontinuation criteria" for individual subjects and the entire study

The patient has the right to discontinue his/her participation in the study at any time based on his/her own decision. The patient will immediately inform his/her doctor about such a decision.

Additionally, the patient's participation in the study will be discontinued in cases of potassium levels rising to more than 6.0 mmol/l at any time during the study, development of symptomatic hypotension below 100/60 mmHg or creatinine levels increasing by more than 25% compared with baseline and exceeding the upper reference limit of 104 μ mol/l, or in case of patient intolerance to the drug (due to adverse or any other effects).

Further examinations of discontinued subjects will be planned based on the reason for discontinuation and clinical status of the patients. If the proportion of discontinued subjects in the entire study exceeds 10% of the total study sample, i.e. 16 subjects, these may be replaced by other patients.

Patient recruitment will be discontinued if a preliminary analysis in the course of the study shows a significant difference in the primary goals between the arms. Patients already enrolled in the study with incomplete

follow-up will complete the entire study in accordance with the protocol.

Registration of the consumption of the drug/placebo

After having completed the study, the patients will return the remaining drug/placebo. The remaining capsules will be counted to calculate the difference between the number of days spent in the study and the number of capsules consumed.

Data in the study subject records

All data to be monitored according to the protocol will be recorded. These include: patient identification number, place of employment, age, sex, drug code; initial data – pulse rate, weight, height, baseline measurements of casual and ABPM systolic and diastolic BP, Na, K, Cl, urea, creatinine, Gly, PRA, aldosterone, aldosterone/PRA ratio, metanephrine, normetanephrine, TSH, plasma cortisol, 24 h urinary free cortisol, microalbuminuria and proteinuria; data on antihypertensive and other medication on entering the study; data from check-up examinations after 2 weeks (if carried out in accordance with the protocol) and after 4 weeks – casual BP, Na, K, Cl, urea, creatinine, adverse effects; the final data after 8 weeks – pulse rate, weight, casual and ABPM systolic and diastolic BP, Na, K, Cl, urea, creatinine, PRA, aldosterone, aldosterone/PRA ratio, microalbuminuria, changes in medication during the study.

Assessing the effectiveness

Drug efficacy will be assessed as differences between mean day-time systolic and diastolic BP measured by ABPM (see above) at the beginning and end of the study. Additionally, mean night-time and 24 h systolic and diastolic BP by ABPM and casual BP (measured repeatedly during visits to the office) will be repeatedly assessed.

Assessing the safety

Safety will be assessed as incidence of adverse effects of the drug (both clinical and laboratory) noticed in the course of the study. Clinical adverse effects include in particular, symptomatic hypotension of less than 100/60 mmHg, hormonal disorder symptoms in males (gynecomastia, erectile dysfunction), virilization in females (hirsutism, voice deepening, menstrual changes, mastodynia), skin allergies, fatigue, sleepiness, gastrointestinal problems such as cramps, diarrhea or dyspepsia, confusion and drug fever. Laboratory adverse effects are especially hyponatremia (below 130 mmol/l), hyperkalemia (over 6.0 mmol/l) or impaired renal function (creatinine levels increased by more than 25% compared with baseline values and exceeding the upper reference limit of 104 μ mol/l).

During each check-up, the attending physician will inquire about any symptoms and investigate signs of the above-mentioned potential side effects.

All drug side effects as well as intercurrent diseases will be immediately reported by phone to the study coordinator, recorded in writing and sent to the study coordinator.

In the case of development of adverse drug effects, the subjects will be observed either as inpatients or outpatients based on the severity and character of the side effects. The form and length of observation will be decided upon by the attending physician.

Data handling and record storage

All information will be confidential in accordance with relevant laws and/or directives. Medical records and information acquired during the clinical study may be studied, directly, by physicians carrying out the study or relevant health personnel, local health authorities, auditors, ethics committees or sponsor representatives. No personal data of any study participant will be published.

The patients will sign informed consent to collection, transfer, processing and archiving of personal data including those on health status, relevant to the clinical study, as well as informed consent to storage of blood samples for later analyses: These samples will be stored for a maximum of 1 year after completion of the study.

DISCUSSION

We report the protocol for a randomized, controlled trial that aims to determine the effect of spironolactone on blood pressure lowering in patients with resistant arterial hypertension.

The reason why we initiated this trial is the lack of evidence-based treatment for the significant number of 100,000,000 people with resistant arterial hypertension worldwide (based on the global prevalence of hypertension totalling about one billion people and the prevalence of drug resistant hypertension being about 10–15%). Hypertension leads to a significant morbidity and mortality and optimal treatment of this condition is being intensively looked for. Spironolactone is a cheap drug and widely available in developing countries as well. Its use in the treatment of resistant hypertension could help to improve the blood pressure (BP) control and thus prevent significant numbers of possible cardiovascular events in the future.

To our knowledge, no randomised trial has been performed to this date to assess the antihypertensive effects of low dose spironolactone in patients with true drug resistant hypertension. Therefore, we designed this prospective randomized trial to evaluate the effect of adding 25 mg of spironolactone in patients with resistant arterial hypertension. If spironolactone proves effective, it might become the standard of treatment of these patients.

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