The antihypertensive effect of spironolactone in oligo-anuric haemodialysis patients.

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1. to study the effect of spironolacton and triamterene on blood pressure in anuric hemodialysis patients.2. to study the effect of treatment on body weight, serum elektrolytes, 24-hours sodium excretion, plasma aldosterone and renin concentrations...

Ethical review	Approved WMO
Status	Recruiting
Health condition type	Renal disorders (excl nephropathies)
Study type	Interventional

Summary

ID

NL-OMON36327

Source
ToetsingOnline

Brief title
Spironolactone in dialysis patients.

Condition

- Renal disorders (excl nephropathies)
- Vascular hypertensive disorders

Synonym
high blood pressure, hypertension

Research involving
Human

Sponsors and support

Primary sponsor: Maasstadziekenhuis
Source(s) of monetary or material Support: Ministerie van OC&W

Intervention

Keyword: aldosterone, hemodialysis, hypertension, Spironolactone

Outcome measures

Primary outcome

The primary endpoint is the change in predialysis systolic blood pressure

during automatic blood pressure measurement after treatment with spironolactone

and triamterene.

Secondary outcome

Secondary endpoints are changes in 24-hours blood pressure, neurohormonal

profile, interdialysis weight gain, 24-hours sodium excretion, and serum

elektrolyte concentrations.

Study description

Background summary

The adrenocortical hormone aldosterone causes a rise in blood pressure through stimulation of renal water and salt reabsorption, via, among other mechanisms, the upregulation of the epithelial sodium channel (eNac) in the distal renal tubule. Inhibition of these effects with aldosterone-receptor-antagonists such as spironolactone has gained an important place in the treatment of hypertension. There is, however, growing evidence that aldosterone also acts outside the kidney. Aldosterone has been shown to increase blood pressure via other, extrarenal, mechanisms and the antihypertensive actions of spironolactone could in part be attributable to extrarenal effects.
In humans, however, it is hardly impossible to identify these effects separate from the diuretic actions. An exception is formed by patients with end-stage renal failure with no (relevant) remaining diuresis. These patients form an ideal model to study the extrarenal actions of antihypertensive drugs. A study in eight oligoanuric patients showed a significant decrease in blood pressure after a two weeks treatment with spironolactone. In this project the potential mechanisms behind this effect are further explored. Our hypothesis is that the decline in blood pressure is caused by affecting other neurohormonal systems, such as the sympathetic nervous system and the pituitary-adrenal-axis.

If the decrease in blood pressure is indeed mediated outside the kidney, an inhibitor of eNaC should have no effect on blood pressure in these patients. To test this assumption a treatment arm with triamterene, an eNaC inhibitor, is included in the protocol.

Study objective

1. to study the effect of spironolacton and triamterene on blood pressure in anuric hemodialysis patients.

2. to study the effect of treatment on body weight, serum elektrolytes, 24-hours sodium excretion, plasma aldosterone and renin concentrations

3. to identify potential mechanisms by studying changes in sympathetic tone, endothelin-1 concentrations, hypothamalic-pituitary-adrenal, and thyroid axis.

Study design

The design is a placebo-controlled cross-over study consisting of three treatment periods: spironolactone, triamterene, and placebo.

1. Phase 0: preparation
After inclusion a 3-week preparation phase starts. If patients are on an angiotensin-converting-enzyme (ACE) inhibitor, angiotensin-receptor blocker (ARB),or potassium-sparing diuretic these will be discontinued. In case of an unacceptable rise in blood pressure a calciumantagonist of alphablocker will be added to the antihypertensive regimen. After three weeks baseline parameters are measured, such as blood pressure, neuroendocrine profile, and serum elektrolytes.

2. Phase 1
Phase 1 consists of a double-blinded, placebo-controlled, randomized cross-over trial comparing treatment with spironolactone 50 mg (twice daily) with triamterene (50 mg twice daily), and placebo. Each treatment period has a duration of two weeks followed by a 2-week washout period. The last treatment period is not followed by a washout period. The treatment order is determined by randomisation.
On baseline, day 7, and day 14 the following parameters are determined:

-blood pressure by automatic blood pressure monitoring for 30 minutes.
-on day 14 collection of blood samples for assessment of renin and aldosterone concentations, adrenocorticotropic hormone (ACTH), plasma cortisol, noradrenalin, and endothelin-1. These samples are drawn after installation of the dialysis device followed by a 30-minute resting period in sitting position.
-on day 13 a 24-hours ambulatory blood pressure measurement (24-hrs ABPM) is performed.

-on day 14 24-hours sodium excretion is determined in a 24-hours urine sample. At every hemodialysis session during the study body weight, and serum elektrolyte concentrations are measured.

Intervention

All patients will be treated with spironolactone, triamterene and placebo for a 2-week period. During the whole study, all subjects will continue their own antihypertensive drugs as described earlier.

Study burden and risks

If the subjects are on ACE-inhibitor, angiotensin-receptor-blocker, or potassium-sparing diuretic therapy this will be discontinued at the start of the study. If this results in an unacceptable rise in blood pressure, a calciumantagonist of alphablocker will be added to the antihypertensive regimen. Blood pressure will be measured three times a week during haemodialysis which will guarantee an early detection of an unacceptable rise in blood pressure.

Important side effects of spironolactone are its anti-androgenic and progestagenic actions, such as gynaecomastia, erectile and menstrual disorders. These side effects are mainly relevant during longterm treatment and are considered to be of minor importance during shortterm treatment such as in this protocol.
Another serious side effect of spironolactone and triamterene is the occurence of hyperkalemia. Patients with renal failure are especially at risk for this. This is related to the impaired renal potassium excretion. However, in oligo-anuric patients the renal potassium excretion is largely absent. An additonal risk of hyperkalemia is therefore not te be expected. Several studies have indeed shown spironolactone in low doses can be used safely in hemodialysis patients.

Theoretically, treatment responses can be characterized by hypotension. Because the frequency of dialysis in this population (three times weekly) adverse events will be recognized in an early stage.

The burden for participants is considered acceptable. No relevant changes will be made to their dialysis schedule. Once weekly the dialysis session will be half an hour longer of duration because of an automatic blood pressure measurement and the collection of blood samples for hormone assays. Furthermore, a 24-hour ambulatory blood pressure measurement will be performed four times. This is a noninvasive procedure that is sometimes experienced as dreadful.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

-age 18 years and older
-on hemodialysis at least 3 months before inclusion
-daily diuresis less than 500 mL
-predialysis serum potassium < 6 mmol/L

Exclusion criteria

-myocardial infarction, stroke or transient ischaemic attack less than 6 months before inclusion
-angina pectoris
-heart failure

-hypotension (predialysis systolic blood pressure below 100 mmHg) or severe hypertension (predialysis SBP>180 mmHg and/or DBP>100 mmHg)
-pregnancy
-known allergy to study drugs
-any acute illness requiring treatment
-malignant disease
-expected non-adherence to treatment

Study design

Design

Study type:	Interventional
Intervention model:	Crossover
Allocation:	Randomized controlled trial
Masking:	Double blinded (masking used)
Control:	Placebo
Primary purpose:	Basic science

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	30-03-2011
Enrollment:	24
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	spironolactone
Generic name:	spironolactone
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	triamterene
Generic name:	triamterene
Registration:	Yes - NL intended use

Ethics review

Approved WMO Date:	23-03-2010
Application type:	First submission
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	30-03-2010
Application type:	First submission
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	19-04-2012
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	03-05-2012
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
EudraCT	EUCTR2009-018217-39-NL
CCMO	NL31034.101.10