Comparison of the action of amiloride and thiazide in the reduction of lithium-NDI in patients with affective disorders

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To compare the effect of amiloride on lithium-induced Nephrogenic Diabetes Insipidus with the effect of hydrochlorothiazide, measured as urine volume and maximal urine osmolality.

Ethical review	Approved WMO
Status	Pending
Health condition type	Manic and bipolar mood disorders and disturbances
Study type	Interventional

Summary

ID

NL-OMON29880

Source
ToetsingOnline

Brief title
Treatment lithium-NDI

Condition

- Manic and bipolar mood disorders and disturbances
- Renal disorders (excl nephropathies)

Synonym
Nephrogenic diabetes insipidus

Research involving
Human

Sponsors and support

Primary sponsor: Universitair Medisch Centrum Sint Radboud
Source(s) of monetary or material Support: Ministerie van OC&W

Intervention

Keyword: lithium, nephrogenic diabetic insipidus amiloride, thiazide

Outcome measures

Primary outcome

The primary study parameters are urine volume (in 24 hrs) and maximal urine osmolality (after dDAVP administration). Urine osmolality and urine volume will be analyzed by comparing before and after treatment values, to see if amiloride or thiazide on its own have a significant effect. The effect of amiloride and thiazide treatment will be compared to see which treatment has the best effect.

Secondary outcome

Seconcary study parameters are the effect of amiloride and thiazide on:

- blood levels of sodium, potassium, chloride, bicarbonate, lithium, creatinine, hemoglobin and osmolality

- urine levels of sodium, potassium, urea and creatinine, and osmolality

- AQP2 concentration in urine

- vital signs (bodyweight, blood pressure)

- side effects and subjective symptoms

- psychiatric outcome

Study description

Background summary

Lithium is the drug of choice for treating bipolar disorders. It is successful in reducing both manic and depressive symptoms in 70-80% of the patients. Lithium is also used to treat schizoaffective disorders and depression, and is thus an indispensable pharmaceutical component of current psychiatric therapy.

Unfortunately, lithium often causes the development of Nephrogenic Diabetes Insipidus (NDI), a disorder in which the kidney is unable to concentrate urine in response to vasopressin, leading to polyuria and polydipsia.
About 0.1% of humans in Western countries are on lithium therapy. Because lithium causes a decrease in urine concentrating ability in 50% of patients, and in 20% leads to NDI, lithium NDI is of high clinical relevance.
In lithium-induced NDI, thiazide diuretics have been used successfully in selected patients to reduce both polyuria and polydipsia and thiazide diuretics are at the moment used to reduce excessive urine output in patients receiving lithium. However, thiazide treatment may lead to hypokalemia, because thiazides cause an increased potassium excretion.
Amiloride is a potassium-sparing diuretic, not causing hypokalemia. Amiloride blocks sodium uptake through the epithelial sodium channel expressed in the apical membrane of renal connecting tubules and collecting ducts. This channel is probably a major pathway for lithium accumulation in the cell. By this action, amiloride could directly block lithium entry into the cell, and in this way prevent or cure NDI. In studies with a limited number of patients it was suggested that amiloride indeed counteracts lithium-NDI to a great extent. In view of amiloride*s potassium-sparing and less natriuretic (thus less toxicity risk) properties, it may be advantageous over thiazide. However, formal comparisons between the drugs are lacking and it is not common practice to treat lithium-NDI in patients in the Netherlands with amiloride.

Study objective

To compare the effect of amiloride on lithium-induced Nephrogenic Diabetes Insipidus with the effect of hydrochlorothiazide, measured as urine volume and maximal urine osmolality.

Study design

A double blind, randomized, parallel group, multi-center study. Amiloride will be compared with hydrochlorothiazide

Intervention

Patients will be treated with 2 x 5 mg/ day amiloride or 2 x 12.5 mg / day hydrochlorothiazide. After 4 weeks the dose will be increased to 2 x 10 mg/day for amiloride and 2 x 25 mg/day for hydrochlorothiazide, if no side effects are present and potassium levels and blood pressure are still normal. After 3 months, treatment with amiloride or hydrochlorothiazide will be ended. All patients will continue to use lithium during the study.

Study burden and risks

Patients will visit the hospital 7 times. At all these occasions, blood samples

(10 ml) wil be collected. At 4 times, a dDAVP test will be performed; dDAVP will be administered intranasally and urine will be collected for 6 hours. Besides this, patients are 4 times asked to collect 24 hrs urine.

Risks for the patient include side effects of the medication, or side effects caused by changes in the plasma-lithium concentration. To avoid these risks, patients are first treated with a lower dose of the medication, which will be increased after a month, if no side effects are present. Besides this, the lithium levels will be measured during the study, and the dose of lithium will be adjusted if necessary. Other parameters, like blood pressure and potassium concentration are also measured during the study.

The study will increase the knowledge about the best treatment for lithium-induced NDI, and will in the study population probably also result in a decrease of the polyuria.

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

-Stable patients treated with lithium for affective disorders
-Age above 18
-Lithium-NDI

Exclusion criteria

Hypercalceamia
Hypo/hyperthyroidism
Hypo/hyperkalemia
renal insufficiency, underlying renal diseases
diabetes mellitus
heart rhythm disorders
systolic blood pressure below 90 mmHg
treatment with either hydrochlorothiazide or amiloride in the preceding 3 months, or
treatment with other diuretics

Study design

Design

Study phase:	4
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Double blinded (masking used)
Control:	Active
Primary purpose:	Treatment

Recruitment

NL
Recruitment status: Pending
Start date (anticipated): 04-01-2006

Enrollment:	50
Type:	Anticipated

Medical products/devices used

Product type:	Medicine
Brand name:	Hydrochlorothiazide
Generic name:	hydrochlorothiazide
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	Midamor
Generic name:	Amiloride
Registration:	Yes - NL outside intended use

Ethics review

Approved WMO Date:	01-02-2007
Application type:	First submission
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)

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	EUCTR2006-001202-84-NL

Register	ID
CCMO	NL11335.091.06