Evaluation of urinary concentrating defects in lithium treated patients with a dDAVP test

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Primary Objective: to explore the prevalence of urinary concentration defects (NDI) in a Dutch population of lithium treated patients.Secondary Objectives: to determine the relation of the dDAVP test results with complaints (micturition history) and…

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

Summary

ID

NL-OMON37665

Source
ToetsingOnline

Brief title
Nephrogenic diabetes insipidus (NDI) in lithium treated patients

Condition

- Renal disorders (excl nephropathies)

Synonym
lithium-induced nephrogenic diabetes insipidus; excessive urine production due to an impaired concentrating ability of the kidneys as a result of the use of lithium

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: dDAVP, desmopressin, lithium, nephrogenic diabetes insipidus

Outcome measures

Primary outcome

Maximal urinary osmolality after intranasal administration of dDAVP.

Secondary outcome

Relation of the dDAVP test results with complaints (micturition history) and clinical parameters (duration of lithium therapy, plasma lithium concentration, baseline plasma creatinine, sodium and potassium concentration and baseline urinary osmolality).

Study description

Background summary

Lithium is a common therapeutic agent used to treat patients with various mood disorders. In Western countries about 0.1% of humans are being treated with lithium. However, its use has been associated with several forms of renal injury. The most common presentation of lithium-induced nephrotoxicity is nephrogenic diabetes insipidus (NDI), characterized by resistance to vasopressin, polyuria, and polydipsia. Slightly impaired renal concentrating ability is found in about 50% of patients. Initially, the decreased urinary concentrating ability is largely reversible after cessation of lithium. However, continued treatment ultimately results in polyuria due to nephrogenic diabetes insipidus (NDI) in about 20% of patients. Nephrogenic diabetes insipidus induced by lithium may even persist despite the cessation of treatment, indicating irreversible renal damage. This functional lesion is associated with chronic focal interstitial fibrosis predominantly in the medullary region of the kidney which may be progressive, leading to end-stage renal failure.

Lithium-induced nephrogenic diabetes insipidus results from accumulation of lithium in the collecting tubular cells after entry into these cells through the epithelial sodium channels (ENaC) in the luminal membrane. Lithium blocks vasopressin-induced reabsorption by inhibiting adenylate cyclase activity, and

hence cyclic adenosine monophosphate production, and also by decreasing the apical membrane expression of aquaporin 2, the collecting tubule water channel.

Besides polyuria due to nephrogenic diabetes insipidus, however, both central diabetes insipidus (CDI) and primary polydipsia have also been described in patients treated with lithium. Therefore, a dDAVP test should be performed to establish the correct diagnosis.

Lithium induced defects in urinary concentration can frequently be ameliorated by treatment with diuretics (thiazide, amiloride). In addition, early treatment with amiloride is thought to prevent the development of renal insufficiency. However, most patients with lithium induced nephrogenic diabetes insidipus only present with complaints in an advanced stage of the disease. The exact prevalence of urinary concentration defects in lithium treated patients is unknown. Early recognition of an impaired urinary concentration may be helpful in selecting lithium treated patients at risk of severe nephrogenic diabetes insipidus and allow increased surveillance and an earlier start of treatment.
In the current study we aim to explore the prevalence of urinary concentration defects and nephrogenic diabetes insipidus in a Dutch population of lithium treated patients.

Study objective

Primary Objective: to explore the prevalence of urinary concentration defects (NDI) in a Dutch population of lithium treated patients.

Secondary Objectives: to determine the relation of the dDAVP test results with complaints (micturition history) and clinical parameters (duration of lithium therapy, plasma lithium concentration, baseline plasma creatinine, sodium and potassium concentration and baseline urinary osmolality) of lithium treated patients.

Study design

This is a cross-sectional study with an estimated duration of one year.

Patients will be recruited from the populations of the participating hospitals. Patients willing to participate will be fully informed about the nature of the study. After having obtained written informed consent, an initial screening will be performed in order to assess the eligibility of these patients.

This screening includes evaluation of the exclusion criteria:
general contra-indications for participation in a trial:
o inability to give informed consent
o pregnancy
o unstable psychiatric condition

alternative causes of (nephrogenic) diabetes insipidus:
o hypo/hyperkalemia (plasma potassium < 3.0 or > 5.5 mmol/l)
o severe hypercalcemia (albumin-corrected plasma calcium > 2.80 mmol/l)
o hyperglycemia (plasma glucose > 10.0 mmol/l)
o history of amyloidosis, Sjögren*s syndrome or Sickle cell anemia
o previous treatment with ifosfamide
o established primary polydipsia or central diabetes insipidus

contra-indications for dDAVP administration:
o inability to comply with water restriction
o renal insufficiency (GFR < 45 ml/min/1.73 m2)
o hyponatremia (plasma sodium < 130 mmol/l)

other:
o concomitant treatment with desmopressin or democlocycline

Eligible patient will be evaluated during an additional visit (approximately 6 hours) at the outpatient clinic. At baseline, subjective symptoms (micturition history) and vital signs (body height and weight, blood pressure and heart rate) will be recorded. In addition, baseline blood levels of creatinine, sodium, potassium, calcium, osmolality and lithium and baseline urine levels of osmolality and glucose will be determined. Water intake will be restricted to 500 ml over the next 6 hours. After voiding, 40 µg 1-desamino-8-D-arginine vasopressin (dDAVP) will be administered intranasally. Throughout the day, urine volume and maximal renal concentrating ability will be determined by measuring osmolality in urine collected every 60-120 minutes for a total duration of 6 hours. In addition, water intake, body weight, blood pressure and heart rate will be determined at two hour intervals. Patients with a clearly decreased maximal urinary osmolality (urine osmolality < 600 mosmol/kg) after dDAVP administration will be diagnosed as lithium induced nephrogenic diabetes insipidus. Finally, patients will be observed for possible adverse events of dDAVP.

Study burden and risks

Patients may be exposed to the risk of adverse effects as a consequence of their participation in this study. Adverse reactions occurring most often (but still infrequently) include transient headache, nausea, nasal congestion, rhinitis nosebleed, sore throat, cough, upper respiratory infections and flushing occasionally along with mild abdominal cramps. In addition, intranasal DDAVP at high dosage infrequently produce a slight elevation of blood pressure. Since dDAVP is administered only once, there is no prolonged action and development of severe adverse reactions is thus unlikely. Furthermore, many of these risks are substantially minimized by increased subject monitoring before, during, and after treatment. Although no treatment benefits can be guaranteed to the study participants, patients may be rewarded for participation in this study since the thorough evaluation may be more than the standard of care. In

addition, early recognition of an impaired urinary concentration may be helpful in selecting lithium treated patients at risk of severe nephrogenic diabetes insipidus and allow increased surveillance and an earlier start of treatment. Finally, information obtained from this study may improve the evaluation and care for patients with lithium induced NDI in the future.

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 with a mood disorder treated with lithium
men and women
age >= 18 years

Exclusion criteria

general contra-indications for participation in a trial:
inability to give informed consent
pregnancy
unstable psychiatric condition;alternative causes of (nephrogenic) diabetes insipidus:
hypo/hyperkalemia (plasma potassium < 3.5 or > 5.5 mmol/l)
severe hypercalcemia (albumin-corrected plasma calcium > 2.80 mmol/l)
hyperglycemia (plasma glucose > 10.0 mmol/l)
history of amyloidosis, Sjögren*s syndrome or Sickle cell anemia
previous treatment with ifosfamide
established primary polydipsia or central diabetes insipidus;contra-indications for dDAVP administration:
inability to comply with water restriction
renal insufficiency (GFR < 45 ml/min/1.73 m2)
hyponatremia (plasma sodium < 130 mmol/l) ;other:
concomitant treatment with desmopressin or democlocycline

Study design

Design

Study type: Observational invasive

Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Diagnostic

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	30-11-2012
Enrollment:	100
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Desmopressin nasal spray, 10 mg/ml
Generic name:	desmopressin (dDAVP)

Registration:	Yes - NL intended use

Ethics review

Approved WMO Date:	31-07-2012
Application type:	First submission
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	06-09-2012
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	EUCTR2012-001809-24-NL
CCMO	NL40450.091.12