Effect of amiloride on lithium-induced chronic nephropathy.

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(1) to establish the effect of adding amiloride to lithium- treatment on the progression of renal insufficiency in patients with lithium- nephropathy (2) to answer the question whether adding amiloride to the use of lithium has the same effect as...

Ethical review	Approved WMO
Status	Recruiting
Health condition type	Nephropathies
Study type	Interventional

Summary

ID

NL-OMON33899

Source
ToetsingOnline

Brief title
Amiloride and lithium nephropathy

Condition

- Nephropathies

Synonym
lithium nephropathy

Research involving
Human

Sponsors and support

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

Intervention

Keyword: amiloride, lithium, nephropathy

Outcome measures

Primary outcome

The result of combining lithium with amiloride should be reflected in a change

in the course of de plasma creatinine concentration (at least cutting in half

the slope of the plasma creatinine concentration) within 9 months.

Secondary outcome

Does not apply.

Study description

Background summary

Twenty percent of the patients on chronic lithium treatment develop a chronic and sometimes progressive nephropathy (1,2). At a certain point the question arises whether the use of lithium must cease to prevent progression of the nephropathy. Data concerning the effect of ending lithium-use on the progression of nephropathy related to chronic lithium-use are scarce.
In a group of 24 patients Lepkifker et al. found a mean plasma creatinine of 176 umol/l (values between 132 and 339 umol). In 12 patients decreasing the lithiumdosage resulted in a reduction of plasma creatinine levels tot values in the upper end of the normal interval. In three patients the plasma creatinine concentration did not change. In 9 patients however the plasma creatinine concentration continued to increase in spite of cessation of the use of lithium (3). Presne et al. found that when lithium-use was stopped, the creatinine-clearance improved in 5 out of 7 patients, when the level of the creatinine clearance at that point was above 40 ml/min. In a group of 18 patients with a creatinine clearance lower than 40 ml/min, however, in 12 patients the creatinine clearance went on deteriorating, in spite of stopping lithium (4).
Markowitz et al. found the nephropathy to be irreversible and progressive when the plasma creatinine concentration at the time of stopping lithium was 220 umol/l or higher (5). Gitlin et al. recommend tot cease the use of lithium at plasma creatinine levels ~140 umol/l, however without giving sufficient direct evidence (6). Data mentioned above seem to suggest that amelioration or

stabilisation of renal function might still be obtained when lithium is stopped at a plasma creatinine concentration of 150- 200 umol/l. Lithium remains first choice in the maintenance treatment of bipolar disorders (7) and is proven to be more effective than e.g. carbamazepine (8). Consequences of stopping lithium may be quite substantial. Other psychotropic drugs tend to be less effective, especially in bipolar depression, consequently resulting in temporary or permanent psychiatric instability (9). Furthermore, evidence has been found that lithium decreases attempts at suicide and suicide itself (10). Prevention of lithium induced nephropathy whilst continuing the use of lithium would thus prove to be a huge advantage.

The renal toxicity of lithium is in all probability a result of reabsorption of lithium in the collecting ducts of the kidney. In perfusion of isolated cortical collecting ducts, lithium administered from the luminal side prevents the effect of antidiuretic hormone (ADH) on the transport of water (11). In animals the administration of lithium causes a decrease in the concentrating capacity of the kidney within the hour (12,13). Pretreatment with amiloride prevents this effect of lithium (12). The above mentioned seems to suggest that lithium is transported through amiloride-sensitive luminal sodiumchannels in the collecting ducts and also that accumulation of lithium in these cells interferes with the effect of ADH on renal water transport. Micropuncture studies in rats directly confirmed the existence of amiloride- sensitive lithiumtransport in the distal nephron(14). In vitro studies in skin and bladder of amphibians confirm that lithium transport uses a mechanism that is capable of transporting lithium as well as sodium and that can be put to a stop by amiloride (15,16). In rats a toxic dosage of lithium causes necrosis of distal nephron cells within the hour (17). Plasma lithiumconcentrations within the therapeutic range bring on swelling of the cells in the cortical collecting ducts of the rat kidney within 3 days. After 7 days cellular hyperplasia is evident and elevated DNA-synthesis can be shown in autoradiography (18). Another rat-study showed dilatation and cell proliferation in the collecting ducts after three weeks, together with polyuria and polydipsia (19). In rats a 16- week exposure to lithium shows serious structural changes (interstitial fibrosis with dilatation and development of cysts in the distal nephron and tubular atrophy), together with a reduction of the glomerular filtration rate and renal concentrating capacity (20).
Patients that started lithium-treatment recently, developed a unique, specific lesion in distal tubuli and collecting ducts after just a few months of therapy (22). This 'acute' lesion in humans is identical to that seen in laboratory animals after lithium administration for several months. Patients treated with lithium during several years show both this 'acute' distal lesion and a chronic lesion including tubular atrophy, interstitial fibrosis and glomerular sclerosis. The latter suggests dat early distal lesions precede the chronic tubulo-interstitial nephritis.
Together the mentioned data suggest that amiloride- sensitive lithium transport is at the base of the continuum of early and late nephrotoxic effects of lithium. In this respect it is relevant that in patients on chronic lithium and

with renal diabetes insipidus, amiloride at least partly reduces polyuria and polydipsia (23). This implies that during continued use of lithium there is a still reversible nephrotoxic component which can be brought to a halt by amiloride.
Similarly it might be possible that amiloride could stop the progression of chronic tubulo- interstitial nephritis, but concerning this no data are available.
Our hypothesis is that the ongoing use of lithium combined with amiloride, which protects the cells of the distal nephron from accumulation of lithium, produces the same result as stopping the use of lithium.

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Study objective

(1) to establish the effect of adding amiloride to lithium- treatment on the progression of renal insufficiency in patients with lithium- nephropathy
(2) to answer the question whether adding amiloride to the use of lithium has the same effect as stopping lithium.

Study design

Patients.
Patients on chronic lithium therapy and with a progressive renal insufficiency, defined as a yearly rise in plasma creatinine of at least 10 umol/ l with a correlation coefficient of at least 0,85 and a maximum plasma creatinine concentration of 200 umol/l. Starting with a normal plasma creatinine concentration, this would imply a reduction of the creatinine clearance of ~10% per year. When these conditons are met there is a fair prospect of

reversibility and the result of an intervention on the development of the plasma creatinine concentration can well be studied. At inclusion patients should be normotensive, if necessary with antihypertensive medication.

- Group size estimation.
Our hypothesis is that the slope in the course of the plasma creatinine concentration wil be reduced from 20 +/- 13 umol per year to 10 +/- umol per year. Using a paired T-test this amounts to 15 patients per group.

- Protocol
Patients will be excluded that are unable to give informed consent.

- Randomisation:
Group I: stops lithium (actual dosage discontinued in three months, reduction with 1/3 every month)
Group II continues lithium in combination with amiloride.

- choice of alternative/ other moodstabiliser at the discretion of the psychiatrist (group I)

- Group II: administration of amiloride (20 mg once daily), together with lithium. Reduction of the lithiumdosage with 1/3 at the start of amiloride. Titration of the lithiumdosage till the usual target plasma lithium concentration is achieved at two consecutive weekly measurements. During this phase, plasma potassium will be checked weekly. In case of values > 5,5 mmol/l, an adequate dose of sodiumpolystyrenesulphate (Resonium) will be added to the medication. Since Resonium inhibits lithium- resorption the lithiumdosage must be elevated under regular check ups of the plasma lithium concentration.

- measurements at inclusion:
At start of the study (T 0, still at full lithium dosage) : biochemistry. MDRD (eGFR- formula). Urine- analysis to exclude other causes of renal pathology (sediment, micro- albuminuria, proteinuria, osmolarity), ECHO of the kidney's . Delta decline of plasma creatinine. Bloodpressure. Co- medication. Comorbidity. Psychiatric history, duration of lithium-use.

Interim- analysis
Analysis of our own (limited) cohort/ patientgroup (figure 1) showed an effect of stopping lithium within a period of 6 months. After cessation of lithium-use, or amiloride-addition in continued use of lithium plasma-kreatinineconcentration will be measured at quarterly intervals. In group II patients will cease using lithium (and amiloride) if no change is visible in the course of the plasma creatinineconcentration (at least cutting in half the slope of the plasma creatinine concentration) within 9 months.

Ending the study:
see interim-analysis.

Follow-up:
Group I (lithium stop): from the start of the reduction of the lithiumdosage, the plasma- creatinine concentration (and eGFR) and bloodpressure will be measured at quarterly intervals during a period of two years, as well as the psychiatric condition.

Group 2 (lithium with amiloride): from the start of the reduction of the lithiumdosage, the plasma- creatinine concentration (and eGFR), potassium- and lithiumconcentrations and bloodpressure will be measured at quarterly intervals during a period of two years, as well as the psychiatric condition.

Intervention

Group I: administration of amiloride (20 mg once daily), together with lithium. Reduction of the lithiumdosage with 1/3 at the start of amiloride. Titration of the lithiumdosage till the usual target plasma lithium concentration is achieved at two consecutive weekly measurements. During this phase, plasma potassium will be checked weekly. In case of values > 5,5 mmol/l, an adequate dose of sodiumpolystyrenesulphate (Resonium) will be added to the medication. Since Resonium inhibits lithium- resorption the lithiumdosage must be elevated under regular check ups of the plasma lithium concentration.

Study burden and risks

There is no burden which is considered to be greater than that of undergoing regular check ups which are usually done during lithium use.

Risk:

- there is a slight risk of elevated potassium levels during the start of amiloride. This will be anticipated by checking the blood potassium level 2-3 times during this period. If necessary, sodiumpolystyrenesulphate (Resonium) will be administered to reduce the potassium level. Since sodiumpolystyrenesulphate may lower lithium reabsorption, the dose of lithium may have to be increased. In this case, the plasma lithium concentration will be monitored more frequently.

- if there is no favourable effect of the intervention, renal function will continue to deteriorate in the lithium - amiloride group. Since lithium nephropathy progresses very slowly however, postponing the stopping of lithium (with its potentially severe psychiatric repercussions) will result in a minor, clinically irrelevant loss of renal function.

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

Patients on chronic lithium therapy and progressive renal function loss, defined as a plasma creatinine concentration increase of at least 10 umol/l/year during at least 5 years, a correlation coefficient of 0.85 on linear regression analysis and a maximum plasma creatinine value of 200 umol/l.

Exclusion criteria

Inability to give informed consent.

Study design

Design

Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Open (masking not used)
Control:	Active
Primary purpose:	Prevention

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	01-09-2009
Enrollment:	30
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	modamide
Generic name:	amiloride
Registration:	Yes - NL outside intended use

Ethics review

Approved WMO Date:	13-07-2009
Application type:	First submission
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	20-07-2009
Application type:	First submission
Review commission:	METC Brabant (Tilburg)

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

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

ID: 20246
Source: Nationaal Trial Register
Title:

In other registers

Register	ID
EudraCT	EUCTR2008-004746-81-NL
CCMO	NL24249.008.09
OMON	NL-OMON20246