# Effect of amiloride on lithium-induced chronic nephropathy.

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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 with respect to the progression of renal...

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|---|---|
| **Ethische beoordeling** | Positief advies |
| **Status** | Werving gestart |
| **Type aandoening** | - |
| **Onderzoekstype** | Interventie onderzoek |

## Samenvatting

### ID

NL-OMON20246

**Bron**
NTR

**Aandoening**

lithiumnefropathie lithiumnephropathy

### Ondersteuning

**Primaire sponsor:** does not apply
**Overige ondersteuning:** fund=initiator=sponsor

### Onderzoeksproduct en/of interventie

### Uitkomstmaten

**Primaire uitkomstmaten**

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.

# Toelichting onderzoek

### Achtergrond van het onderzoek

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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**Doel van het onderzoek**

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 with respect to the progression of renal failure.

**Onderzoeksopzet**

Plasmacreatinine-concentration at inclusion and every three months during the following 2 years.

**Onderzoeksproduct en/of interventie**

Group I: stops lithium (actual dosage discontinued in three months, reduction with 1/3 every month).

Group II continues lithium in combination with amiloride.

# Contactpersonen

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# Deelname eisen

## Belangrijkste voorwaarden om deel te mogen nemen (Inclusiecriteria)

1. 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;

2. Patients must be normotensive (if necessary, with treatment).

## Belangrijkste redenen om niet deel te kunnen nemen (Exclusiecriteria)

1. Inability to give informed consent. (e.g. manic or depressiee episode, at discretion of psychiatrist);

2. Pregnancy.

# Onderzoeksopzet

## Opzet

| | |
|---|---|
| Type: | Interventie onderzoek |
| Onderzoeksmodel: | Parallel |
| Toewijzing: | Gerandomiseerd |
| Blindering: | Open / niet geblindeerd |
| Controle: | Geneesmiddel |

## Deelname

Nederland

| | |
|---|---|
| Status: | Werving gestart |
| (Verwachte) startdatum: | 01-10-2009 |

| | |
|---|---|
| Aantal proefpersonen: | 30 |
| Type: | Verwachte startdatum |

# Ethische beoordeling

Positief advies

| | |
|---|---|
| Datum: | 16-10-2009 |
| Soort: | Eerste indiening |

# Registraties

## Opgevolgd door onderstaande (mogelijk meer actuele) registratie

ID: 33899
Bron: ToetsingOnline
Titel:

## Andere (mogelijk minder actuele) registraties in dit register

Geen registraties gevonden.

## In overige registers

| Register | ID |
|---|---|
| NTR-new | NL1950 |
| NTR-old | NTR2068 |
| CCMO | NL24249.008.09 |
| ISRCTN | ISRCTN wordt niet meer aangevraagd. |
| OMON | NL-OMON33899 |

# Resultaten

**Samenvatting resultaten**
none