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...

Ethical review	Positive opinion
Status	Recruiting
Health condition type	-
Study type	Interventional

Summary

ID

NL-OMON20246

Source
Nationaal Trial Register

Health condition

lithiumnefropathie lithiumnephropathy

Sponsors and support

Primary sponsor: does not apply
Source(s) of monetary or material Support: fund=initiator=sponsor

Intervention

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

N/A

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. References. 1. Boton R, Gaviria M, Batlle DC.: Prevalence, pathogenesis, and treatment of renal dysfunction associated with chronic lithium therapy. Am J Kidney Dis. 1987 Nov;10(5):329-45. 2. van Gerven HA, Boer WH. Chronische nierfunctiestoornissen bij gebruik van lithium. Ned Tijdschr Geneeskd. 2006 Aug 5;150(31):1715-8. 3. Lepkifker E, Sverdlik A, Iancu I, Ziv R, Segev S, Kotler M. : Renal insufficiency in long-term lithium treatment. J Clin Psychiatry. 2004 Jun;65(6):850-6. 4. Presne C, Fakhouri F, Noel LH, Stengel B, Even C, Kreis H, Mignon F, Grunfeld JP.: Lithium-induced nephropathy: Rate of progression and prognostic factors. Kidney Int. 2003 Aug;64(2):585-92. 5. Markowitz GS, Radhakrishnan J, Kambham N, Valeri AM, Hines WH, D'Agati VD. : Lithium nephrotoxicity: a progressive combined glomerular and tubulointerstitial nephropathy. J Am Soc Nephrol. 2000 Aug; 11(8):1439-48. 6. Gitlin M.: Lithium and the kidney: an updated review. Drug Saf. 1999 20(3):231-243. 7. Nolen, W.A., Kupka, R.W., Schulte, P.F.J., Knoppert-van der Klein, E.A.M., Honig, A., Reichart, C.G., Goossens, P.J.J., Daemen, P., Ravelli, D.J. (2008). Richtlijn Bipolaire Stoornissen, Nederlandse Vereniging voor Psychiatrie, Utrecht. 8. Hartong EG, Moleman P, Hoogduin CA, Broekman TG, Nolen WA; LitCar Group. Prophylactic efficacy of lithium versus carbamazepine in treatment-naive bipolar patients. J Clin Psychiatry. 2003; 64: 144-151. 9. Hartong EG (2006). Recidiefpreventie van bipolaire stoornis. Geneesmiddelenbulletin 40, 61-69 10. Baldessarini RJ, Tondo L, Davis P, Pompili M, Goodwin FK, Hennen J. Decreased risk of suicides and attempts during long-term lithium treatment: a meta-analytic review. Bipolar Disord. 2006; 8: 625-839. 11. Cogan E, Abramow M. Inhibition by lithium of the hydroosmotic action of vasopressin in the isolated perfused cortical collecting tubule of the rabbit. J Clin Invest. 1986 May;77(5):1507-14. 12. Webb RK,

Woodhall PB, Tisher CC, Robinson RR. Acute effects of lithium on the renal concentrating mechanism in a primate. Am J Physiol. 1975 Mar;228(3): 909-14. 13. Harris CA Jenner FA Some aspects of the inhibition of the action of antidiuretic hormone by lithium ions in the rat kidney and bladder of the toad Bufo Marinus. Brit J Pharmacol 44:223-232, 1972 14. Fransen R, Boer WH, Boer P, Koomans HA. Amiloride-sensitive lithium reabsorption in rats: a micropuncture study. J Pharmacol Exp Ther. 1992 Nov;263(2):646-50. 15. Leblanc G. Mechanism of lithium accumulation in the isolated frog skin epithelium. Pflugers Arch. 337: 1-18, (1972). 16. Herrera FC. Inhibition of lithium transport across toad bladder by amiloride. Am. J. Physiol. 222 (2): 499-502 (1972). 17. 9. Levine S, Saltzman A, Katof B, Meister A, Cooper TB. Prevention of lithium nephrotoxicity in a novel one-hour model in rats. Psychopharmacology (Berl). 1998 Jul;138(1):34-9. 18. 10. Jacobsen NO, Olesen OV, Thomsen K, Ottosen PD, Olsen S. Early changes in renal distal convoluted tubules and collecting ducts of lithium treated rats: light microscopy, enzyme histochemistry, and 3[H]-thymidine autoradiography. Lab Invest 46:298-305, 1982. 19. Kling MA, Fox JG, Johnston SM, Tolkoff-Rubin NE, Rubin RH, Colvin RB. Effects of long-term lithium administration on renal structure and function in rats. A distinctive tubular lesion. Lab Invest. 1984 May;50(5):526-35. 20. Ottosen PD, Sigh B, Kristensen J, Olsen S, Christensen S. Lithium induced interstitial nephropathy associated with chronic renal failure. Acta Path Immunol Scand 92: 447-454, 1984. 21. Walker RG, Escott M, Birchall I, Dowling JP, Kincaid-Smith P. Chronic progressive renal lesions induced by lithium. Kidney Int. 1986 Apr;29(4):875-81. 22. Burrows GD, Davies B, Kincaid - Smith P. Unique tubular lesion after lithium. Lancet, 7;1310 , 1978 23. Battle DC, von Riotte AB, Gaviria M, Grupp M. Amelioration of polyuria by amiloride in patients receiving long-term lithium therapy. N Engl J Med. 1985, 312: 408-14.

Study objective

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.

Study design

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

Intervention

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

Contacts

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Eligibility criteria

Inclusion criteria

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).

Exclusion criteria

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

Study design

Design

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

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	01-10-2009
Enrollment:	30
Type:	Anticipated

Ethics review

Positive opinion

Date:	16-10-2009
Application type:	First submission

Study registrations

Followed up by the following (possibly more current) registration

ID: 33899
Bron: ToetsingOnline
Titel:

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

No registrations found.

In other registers

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

Study results

Summary results
none