Renal replacement therapy associated with lithium nephrotoxicity in New Zealand

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ABSTRACT

AIM: To document the numbers and characteristics of New Zealand patients commencing renal replacement therapy because of end-stage kidney disease attributed to lithium treatment, and to calculate incidence rates.

METHOD: Data on such patients were provided by the Australia and New Zealand Dialysis and Transplant Registry from the start of the Registry in 1977 until 2013. Numbers of patients prescribed lithium in the community were provided by the Ministry of Health for 2009–2013; earlier years had fewer than 96% of prescriptions for lithium linked to individuals by their unique National Health Index number. Time trends were analysed by linear, logistic and Poisson regression. Incidence rates were also calculated for five-year periods.

RESULTS: Thirty-five new patients were located with ‘lithium toxicity’ as their primary renal disease, starting the year after ‘lithium toxicity’ was included in the standard list (1995). A broader search for lithium within ‘other’ causes and ‘other’ comorbidities did not yield further patients. The mean age at the start of renal replacement therapy was 61.1 years (SD 9.2). Twenty-five patients were female. For 1996 onwards, new patient numbers increased on average by 8% per year (95% CI 1 to 15%) and incidence rates increased by 7% per year (95% CI 0 to 14%), an approximate doubling per decade. From 2007–2011, the average annual incidence per million population was 0.74 (95% CI 0.43 to 1.21) for New Zealand, similar to that reported elsewhere: 0.78 (95% CI 0.67 to 0.90) for Australia and 0.91 (95% CI 0.50 to 1.52) for southern Sweden. Prescription rates across the three countries were also similar. In New Zealand between 2009 and 2013, over 7,500 patients were prescribed lithium each year.

CONCLUSION: Dosing and monitoring of patients prescribed lithium should follow guidelines, not only to avoid future psychiatric episodes and acute toxicity but also because such adherence may reduce uncommon but serious outcomes of long-term treatment such as end-stage kidney disease.

In their 2012 review of the science and practice of lithium therapy, Mahli et al state that, “Its use in bipolar disorder is under-appreciated, particularly as it has the best evidence for prophylaxis, qualifying it perhaps as the only true mood stabilizer currently available”. Nonetheless, they acknowledge that in patients treated with lithium, renal function can become impaired and that even end-stage kidney disease (ESKD) can occur, although they point out that the increased occurrence of ESKD may in part be due to other risk factors associated with bipolar disorder. In 2014, a large UK retrospective cohort study of general practice patients with bipolar disorder compared those ever treated with lithium with non-users and, after adjusting for age, gender, comorbidities and poly-pharmacy, found the relative hazard for ESKD for patients treated with lithium was 2.7 (estimate using validated lithium exposure). The absolute increase in risk varied by age and by time since first diagnosis (a proxy for time on lithium). The absolute increase in risk of ESKD was low at 0.15% in those under 50 years of age but 2.3% in those over 50. The increase in risk of renal impairment was 0.95% in those under 50 and 8% in those over 50. Swedish studies indicate that patients on renal replacement therapy whose ESKD is attributed to lithium treatment have been treated with lithium for at least a decade and have reached ESKD twenty to thirty years after lithium was started. The UK general practice study had no patients followed for more
than 20 years, suggesting that their estimates of absolute risk increases due to lithium will underestimate those for patients followed up for thirty or more years.

In Australia and New Zealand, every renal unit contributes data on all patients treated for ESKD to the Australia and New Zealand Dialysis and Transplant Registry (ANZDATA) (www.anzdata.org.au/), which was set up in 1977. In April, 1995, ‘lithium toxicity’ (Code 019) was added to the standard list of options for primary renal disease. Prior to that, lithium toxicity could have been listed under the ‘other’ category for primary renal disease. In addition, ‘lithium toxicity’ could at any time have been recorded under ‘other’ comorbidity.

Roxanas et al have reported on all Australian patients commencing renal replacement therapy (dialysis or transplant) whose ESKD was attributed to treatment with lithium. They found a total of 187 new patients with incidence rates increasing steadily over five-year periods, from 0.02 per million population per year in 1987–1991 to 0.78 in 2007–2011.

There have been no similar papers reporting the New Zealand experience. This paper reports numbers, characteristics, incidence and trends over time for New Zealand.

Method

A de-identified data extract of new patients commencing renal replacement therapy in New Zealand as a result of lithium treatment was provided by The Australia and New Zealand Dialysis and Transplant Registry (ANZDATA). An initial search was carried out only for those with lithium toxicity (code 019) listed under “Primary Renal Disease” (this code was added in April, 1995). A second broader search looked for mention of lithium under ‘other’ disorders and ‘other’ comorbidity and covered the whole period since the start of the Registry in 1977 until 2013, the last year for which data collection was complete and checked. ANZDATA also provided annual estimates of the total New Zealand population so that crude incidence rates could be calculated.

The Ministry of Health (personal communication) provided annual numbers of patients who had Pharmaceutical Management Agency (PHARMAC)-subsidised, community-dispensed lithium for the period 2009–2013. In this period the proportion of lithium dispensing records which included a unique National Health Index (NHI) number increased from 96% to 98% which meant that the number of individuals dispensed lithium in the community could be ascertained with a high degree of accuracy. The NHI is a unique patient identifier number assigned to all people accessing universally available health care in New Zealand. Note that all available forms of lithium prescribed are eligible for PHARMAC subsidy.

Analyses were carried out in SAS/STAT 12.1 (www.sas.com), apart from calculation of confidence intervals for some proportions for which OpenEPI (http://www.openepi.com/Proportion/Proportion.htm) was used with mid-P exact values. Descriptive statistics were calculated and some 95% confidence intervals. All p values were two-tailed. Poisson regression was used to investigate trends over time with the number of new patients in each year as the dependent variable and the year as the predictor. For analysis of incidence rates the population for each year was added as an offset. Trends over time were also investigated using linear regression with the age of each new patient as the dependent variable and using logistic regression with sex (female) as the dependent variable. Crude incidence rates were calculated annually and also averaged over five years by using the number of new patients over that period divided by the middle year population (the population increase was approximately linear). Given the small numbers of new patients within a five year period, age-standardised incidences were not calculated.

Results

Thirty-five new patients were found with lithium toxicity as the Primary Renal Disease. The broader search including ‘other’ disorders and ‘other’ comorbidity did not yield any additional patients. Initial treatment for 20 of these patients was Continuous Ambulatory Peritoneal Dialysis (CAPD), Hospital Haemodialysis (HD) for 12, and three patients received a pre-emptive transplant.
The mean age at the start of renal replacement therapy was 61.1 years (SD = 9.2) with the median at 63 (IQR 55-68). The number under 65 was 19 (54%) with a further four aged 65. Twenty-five patients were female: 71% (95% CI 55 to 84). While significantly different from a 50/50 distribution (p=.01) the New Zealand sex distribution did not differ significantly (p=.18) from that for Australian incident cases with lithium toxicity (111/187, 59% female, 95% CI 52 to 66%, p=.01 for comparison with 50/50). The mean age for New Zealand female patients was 62.4 (SD 9.1) and 57.8 (SD 9.2) for males, a non-significant difference of 4.6 years (95% CI -2.3 to 11.5; p=.19). Age at commencement of renal replacement therapy did not increase over time (slope per year of 0.22, SE=0.34, p=.45) nor did the proportion of females change (slope per year of log odds of -0.06, SE=0.09, p=.47).

Late referral, being referred to a renal unit less than three months before the start of renal replacement therapy, occurred only early in the series. The Registry records ‘racial origin’: 33 patients were ‘caucasoid’ and two were Māori. Only three patients were born outside New Zealand, all in the UK.

Including only the period 1996-2013, for which lithium toxicity was one of the listed options for Primary Renal Disease, numbers of new patients, which varied from 0-4 per year, increased on average by 8% per year (95% CI 1 to 15%, p=.03). The crude incidence rate per million population in New Zealand, which took account of population changes, increased by 7% per year (95% CI 0 to 14%, p=.057). Over a decade this corresponded to approximately a doubling of the numbers of new patients (ratio=2.11, 95% CI 1.08 to 4.12) and just under that for incidence (ratio=1.90, 95% CI 0.97 to 3.71). Over the whole period of the Registry since 1977 the increase was highly significant (p<.0001) for new patient numbers and for the incidence rate with a four-fold increase per decade for new patient numbers and 3.6 fold increase for incidence. However the absence of any lithium toxicity cases before 1996 may be because lithium toxicity was not listed under Primary Renal Disease, not because there were no such patients. From the data available it is not possible to distinguish these explanations, although the absence of additional patients from the broader search including ‘other’ disorders and ‘other’ comorbidity does suggest that there may not have been any missed from earlier years. Nonetheless the clinical awareness of lithium nephrotoxicity may have been low historically. Another possible factor is that there appear to have been changes over time in the ages accepted for Renal Replacement Therapy, regardless of Primary Renal Disease. In New Zealand no-one over 64 years was accepted until 1975, no-one over 74 years was accepted until 1987 and no-one over 84 years was accepted until 1997. Numbers for older age groups have been more stable from 2007–2012.

Incidence rates in New Zealand can be compared with those for Australia, and two regions in Sweden, although for the Swedish studies it is necessary to infer incidence from prevalence by comparing the numbers prevalent at the two time points plus any who died in between those times. Because of changes in incidence rates over time in Australia and in New Zealand it is important to ensure comparable time periods are used. For Australia over the period 2007-2011 the average annual incidence per million population was 0.78 (95% CI 0.67 to 0.90) and for New Zealand it was 0.74 (95% CI 0.43 to 1.21). For Sweden the estimate was 0.91 (95% CI 0.50 to 1.52) for the period 31/03/2005 to 1/12/2010. These are all very similar although rather imprecise for New Zealand and Sweden because of the small numbers of cases (16 and 14 respectively). The proportion of the population currently prescribed lithium also is not markedly different in the three countries. For New Zealand the numbers of patients prescribed lithium declined from 7,913 in 2009 to 7,641 in 2013 (personal communication, Ministry of Health), which corresponds to rates per million population of 1,846 down to 1,727, all under 0.2%. In 2011 in Australia the rate per million was calculated to be 1,150. In southern Sweden the rate was 1,255 in 2005 and 1,359 in 2010. Given the time from the start of lithium therapy until ESKD develops historical prescription data would be of interest, but is not available.
Discussion

This paper supplements a 2010 New Zealand Medsafe (Ministry of Health) prescriber alert about the renal dangers associated with long-term lithium use.\(^\text{10}\) That alert was based on voluntary reporting to the Centre for Adverse Reactions Monitoring (CARM) of nine cases of serious renal disease attributed to lithium, whether or not patients had commenced renal replacement therapy. In contrast this paper is based on all New Zealand patients who commenced renal replacement therapy with lithium toxicity listed as the Primary Renal Disease. A total of 35 new cases from 1996 to 2013 is not a large number. Nonetheless it is important to remember the burden each case imposes on the patient, family and on society. Just over half the patients were under 65 at the start of dialysis or the time of transplantation so that the tiredness and lack of energy which characterize very poor kidney function will have interfered with patients’ ability to work, as well as other aspects of their function over the years before as well as after renal replacement therapy was necessary. Furthermore dialysis is time-consuming and, particularly for home dialysis, dedication is required to carry it out correctly. The costs to society are not just reduction in employment. The annual cost to the health system of each dialysis patient is $30,000 to $60,000.\(^\text{11}\)

The increase over time in numbers of new patients (incident patients) and in incidence rates are similar to those reported for Australia.\(^\text{6}\) The increase may result from changes in lithium prescribing patterns since the 1970s such as the numbers of patients prescribed, the duration of treatment, the doses used and the monitoring regimes for both lithium levels and for kidney function. There also appears to have been increasing willingness over time to provide renal replacement therapy for older patients. An Australian study comparing deaths due to renal failure in 2003-2007 with ANZDATA enrolment indicated that about half of those who died of renal failure had never had renal replacement therapy.\(^\text{10}\) Of this untreated half, 20% were under 70 years of age. The likelihood of renal replacement was about 90% up to age 60 but declined sharply at older ages down to 4% for those aged 85 years and above.\(^\text{13}\)

Epidemiological studies across a number of countries including New Zealand have found similar rates of bipolar disorder for males and females, in contrast to the higher female rates for depression,\(^\text{14-18}\) although a more recent cross-national study found that the male:female ratio depended on the type of bipolar disorder (BPI/BPII/subthreshold).\(^\text{19}\) Nonetheless a large UK general practice study\(^\text{2}\) found approximately a 60:40 female:male ratio for patients diagnosed with bipolar disorder regardless of treatment, and a 60:40 female:male ratio was also found among patients on lithium in Sweden.\(^\text{3}\) These ratios are close to those found among patients starting renal replacement therapy as a consequence of lithium treatment in New Zealand and also in Australia\(^\text{6}\) and in Sweden.\(^\text{20}\)

The strength of this study is that it contains complete national data from New Zealand. One weakness, however, is that the diagnosis of lithium toxicity is a clinical one with no pre-specified criteria and no means of checking this diagnosis. Moreover there is no information on the course of lithium treatment and whether or not there had been any episodes of acute lithium toxicity. This study is also limited for an understanding of the risk of ESKD following lithium treatment in that not all patients with ESKD do start renal replacement therapy.

Lithium is widely used to treat patients with bipolar disorder and there is much known about its efficacy, particularly for prophylaxis.\(^\text{1,21}\) In contrast, less is known about how to prevent renal damage from long-term treatment with lithium.\(^\text{1,2}\) Some Swedish psychiatrists are optimistic that the treatment and monitoring regime in place in Sweden for lithium since the early 1980s has been effective in preventing ESKD.\(^\text{20}\) None of the patients with ESKD that they located through their registry of patients on renal replacement therapy had commenced lithium treatment after 1980, although there were other renal replacement patients who had started lithium earlier. They do admit, however, that the time period covered and the size of the population studied
(population 2.8 million) may have been inadequate. Furthermore there may have been patients who did not go on to renal replacement therapy even though this is unusual for patients with ESKD in Sweden. Stopping lithium treatment is one option if kidney function begins to decline at more than the usual age-related rate: eGFR declines 1 mL/min/1.73m² per year after age 40. Such a decision requires careful consideration of how well the patient has been on lithium, potential suicide risk, and experience with other mood stabilisers. Nonetheless it is not known at what point stopping lithium prevents or at least slows the progression towards ESKD. Some patients who have stopped lithium have gone on to ESKD. Roxanas et al. recommend considering stopping lithium and switching to another mood stabiliser if two successive test results indicate declining renal function or if eGFR is < 45mL/min/1.73m². Sabiosky and Roxanas recommend referral to a nephrologist as soon as kidney function is of concern. This will prevent late referrals to renal units and provides patients with more time to adjust to the possible future need for renal replacement therapy. However it is not clear that early referral can markedly influence the continuing decline in renal function.

Another issue is the extent of variation in creatinine from blood test to blood test, which can make it difficult to ascertain trends in renal function. Psychiatrists and clinicians already stress to patients on lithium the need to avoid marked dehydration to prevent episodes of acute lithium toxicity, which may harm renal function. Nonetheless mild dehydration may often occur in these patients as duration of lithium treatment is associated with loss of renal concentrating ability. Therefore another practical recommendation is to instruct patients to make sure they are well hydrated before they present for blood tests, in order to remove one source of fluctuation in measurement of kidney function.

This paper documents the numbers of patients in New Zealand who have commenced renal replacement therapy following ESKD attributed to lithium treatment. Because of the decades required from the start of treatment to ESKD, the consequences of modern approaches to treatment with lithium will not be seen for many years. There are a number of guidelines about dose and monitoring to avoid or minimise acute toxicity and, while these are mainly based on consensus decisions, they represent the best advice currently available. Although the influence of dose and episodes of acute toxicity on the development of end-stage renal disease is not known it would be wise for these guidelines to be followed and future studies should elucidate the long term outcomes of their use. Little is known in New Zealand about current dosing, duration of treatment, and monitoring. One study based in the Canterbury District Health Board in 2009/2010 showed that the 2006 UK National Institute for Health and Clinical Excellence (NICE) recommendations for lithium levels and monitoring were often not met. This is of concern given that over 7,500 patients are treated with lithium annually in New Zealand.
VIEWPOINT

Competing interests: Nil

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