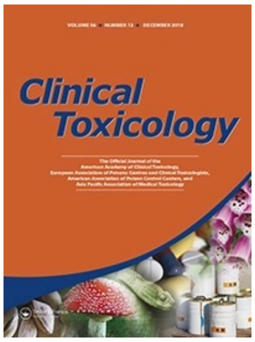

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Effect of age on the severity of chronic lithium poisoning

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ABSTRACT

Objectives: Severe lithium toxicity is commonly observed in older people. We aimed to determine the extent to which age is associated with increased severity of chronic lithium poisoning and of which a range of possible factors might explain the associations.

Method: We did a retrospective review of patients aged ≥15 years old with serum lithium concentrations ≥1.3 mmol/L from three hospitals. Clinical details, treatment and outcomes were recorded. eGFR, creatinine and lithium clearance were calculated. The severity of lithium toxicity was graded into five categories (Amdisen score). ANOVA was used to quantify the association between age and severity. Spearman correlation coefficient was used to explore relationships between age and different factors expected to alter severity. Ordinal regression analysis was used to determine the interdependence of age and these factors and age on severity of lithium toxicity.

Results: From 2008–2018, there were 242 patients with a median age of 56.5 years (IQR: 41–69). There were 156 females (64%). There was a statistically significant association between Amdisen severity scores and age ($p = .0004$). The median calculated eGFR was 65 mL/min/1.73 m^2 (IQR: 41–91) with a corresponding estimated lithium clearance of 18 mL/min (IQR: 13.8–22.8). There was no correlation of age with initial serum lithium concentration ($p = .76$). There was a strong correlation between age and estimated lithium clearance ($r = -0.72$, 95% CI: −0.78 to −0.66, $p < .001$), lithium daily dose ($r = -0.65$, 95% CI: −0.72 to −0.57, $p < .0001$) and lithium concentration/dose ($r = 0.62$, 95% CI: 0.53–0.69, $p < .0001$). There was a weak correlation between age and infection ($r = 0.18$, 95% CI: 0.04–0.31, $p = .009$) and drug interactions ($r = 0.25$, 95% CI: 0.11–0.37, $p = .0003$). Ordinal regression indicated the independent predictors for severity of lithium toxicity were lithium concentration ($p < .0001$) and lithium clearance ($p = .03$) adjusted for age and dose.

Conclusions: Despite lower lithium doses, older patients had more severe toxicity. Increased severity of lithium toxicity in the elderly is largely explainable by decreased lithium clearance from multiple factors such as age-related decline in renal function, drug interactions and infection.

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Chronic lithium toxicity; age; chronic lithium poisoning; risk factors

Introduction

Despite medical advances and the emergence of new drugs, lithium remains the gold standard for the treatment and prophylaxis of bipolar affective disorder as stated in clinical practice guidelines of over 12 countries and international bodies [1]. This recommendation is applied across all age groups including the elderly [2]. Bipolar disorder occurs across adult life but most case series of lithium toxicity are dominated by older people [3]. Lithium elimination is entirely renally dependent. Renal impairment due to lithium nephrotoxicity, reduced renal function with old age [4] or other kidney diseases, requires a dose reduction to avoid higher serum lithium and subsequent risk of toxicity [5]. In the general population, glomerular filtration rate (GFR) is estimated to decline at a rate of 6.3 mL/min/1.73 m^2 per decade [6]. In addition, elderly patients are more likely to have comorbidities and take concurrent medications that might alter renal function or lithium clearance including diuretics, angiotensin-converting enzyme inhibitors, angiotensin-II receptor blockers, non-steroidal anti-inflammatory drugs, anti-depressants, anti-psychotics and anti-epileptics [7]. Precipitating factors such as infection, fever, dehydration [8] and decreased fluid intake are likely to be more common in the older age group [3]. All these factors lead to higher lithium concentrations, but there might also be factors related to the ageing brain that would lead to more severe toxicity. This study aimed to determine the extent to which increased age is associated with increased severity of chronic lithium poisoning and what factors might explain the association.

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Supplemental data for this article can be accessed here.

Methods

We used retrospective data from the toxicology databases and New South Wales Health Pathology to identify patients from out-patients or in-patients who were on chronic lithium therapy and had recorded serum lithium levels ≥1.3 mmol/L with or without specific symptoms from the Prince of Wales Hospital, a tertiary teaching hospital and The Sutherland Hospital, a regional hospital (South Eastern Area Toxicology Service (SEATS), New South Wales Health Pathology (NSWHP)) and the Princess Alexandra Hospital, a tertiary teaching hospital in Queensland. Patients who had an acute or acute on chronic overdose of lithium were excluded from the study. Patients who had multiple presentations were included if there was a minimum gap of 2 months from a previous presentation. This is done so that serial lithium levels will not be analyzed again from the same presentation and that impaired renal function from a previous episode has time to recover. Regarding the lithium therapeutic range, there was a decrease in the recommended range in Australia from January 25, 2017 onwards, from 0.6–1.0 mmol/L to 0.5–0.8 mmol/L.

A preformatted data form was used to record patient demographics, lithium dose and concentrations, signs and symptoms of lithium toxicity, concurrent medications and outcomes. Drugs that interact with lithium (angiotensin converter enzyme inhibitors, angiotensin receptor blockers, non-steroidal anti-inflammatory drugs) and nephrotoxic drugs (cyclosporin, cisplatin, B-lactam antibiotics, amphotericin B) were recorded. Infections such as urinary tract infection or respiratory tract infection were obtained from the physicians' diagnosis. The severity of lithium toxicity was determined using the Hansen–Amdisen grading system [9] (Table 1). The duration of stay in the hospital, dialysis and ongoing sequelae following presentation were also determined from the review of medical records. Re-abstraction of 17 (7%) randomly selected patient charts was conducted and cross-checked by an objective third party to confirm the accuracy and reliability of initial data collection.

eGFR values were calculated using serum creatinine levels in accordance with the CKD-EPI formula [10]. Creatinine clearance (CrCL) was calculated using the Cockcroft Gault equation; then, lithium clearance was estimated using the following formula [11]:

$$\mathrm{LiCl}(\mathrm{mL/min}) = 0.161 \times \mathrm{CrCl}(\mathrm{mL/min}) + 6.47$$

Statistical analysis

ANOVA was used to determine whether there were any variation between the lithium severity score and age. Spearman correlation was used to determine whether there was an association between different factors and age. Ordinal regression was used to create a multifactor model for severity of lithium toxicity as defined by the Hansen–Amdisen grading system [9] and adjust for possible confounders. p values $<.05$ were deemed as statistically significant. Statistical analysis was conducted using the SPSS (Statistical Package for the Social Sciences) Statistics software (version 25) and GraphPad Prism (version 8.0.2).

The protocol was submitted to the Human Research Ethics Committee (HREC) and was assessed as a quality improvement project (Ref Number: 17/201). Consent from patients was not required.

Table 1. Lithium symptom severity score (LSSS) (adapted from Hansen, Amdisen [9,10]).

Score	Category	Symptoms
0	No features	
1	Mild	Nausea, vomiting, diarrhea, hyperreflexia, ataxia, tremor, muscle weakness, dysdiadochokinesia, dysarthria
2	Moderate	Hypotension, hypertonia, rigidity, sluggishness
3	Severe	Confusion, nystagmus, myoclonus, collapse, seizure
4	Death	

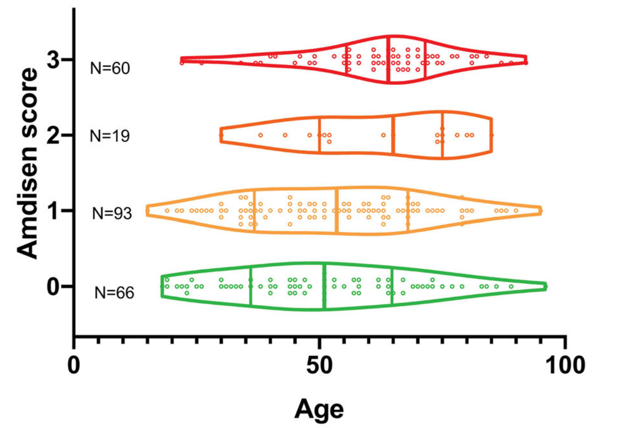

Figure 1. Violin plot of Amdisen score versus age. The violin plot showed the distribution of the categories of Amdisen scores by age. The lines represent median and interquartile range.

Results

From 2008–2018, there were 364 patients with serum concentrations ≥1.3 mmol/L. A total of 122 were excluded due to insufficient medical records or being a second presentation within 2 months. As a result, 242 admissions with elevated serum lithium concentrations were studied. The median age of the patients was 56.5 years (range: 15–96, IQR: 41–69) and 156 were female (64%). Median lithium daily dose was 900 mg (range: 125–2500, IQR: 500–1250), and median concentration was 1.5 mmol/L (range: 1.3–4.8, IQR: 1.3–1.9). Four patients received hemodialysis. Median length of stay was 4 days (IQR: 1–11 days). One patient with a serum lithium concentration of 1.3 mmol/L died from pneumonia, renal failure and congestive cardiac failure, and this was thought not to be caused by lithium toxicity. There was a statistically significant association between different lithium toxicity severity scores and age as determined by ANOVA ($F(3,238)=6.3$, $p=.0004$) (Figure 1). There was also a significant correlation between serum lithium concentration and toxicity severity score ($r=0.34$, 95% CI: 0.2–0.45, $p<.0001$) (Figure 2). However, there was no correlation between initial

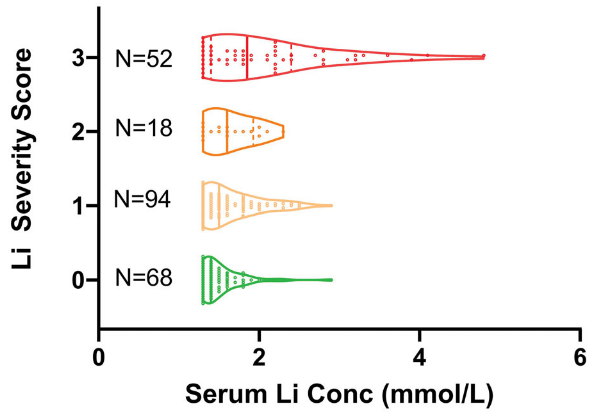

Figure 2. Violin plot of Amdisen score versus serum lithium concentrations. The violin plot showed the distribution of the categories of Amdisen scores by lithium concentration. The lines represent median and interquartile range.

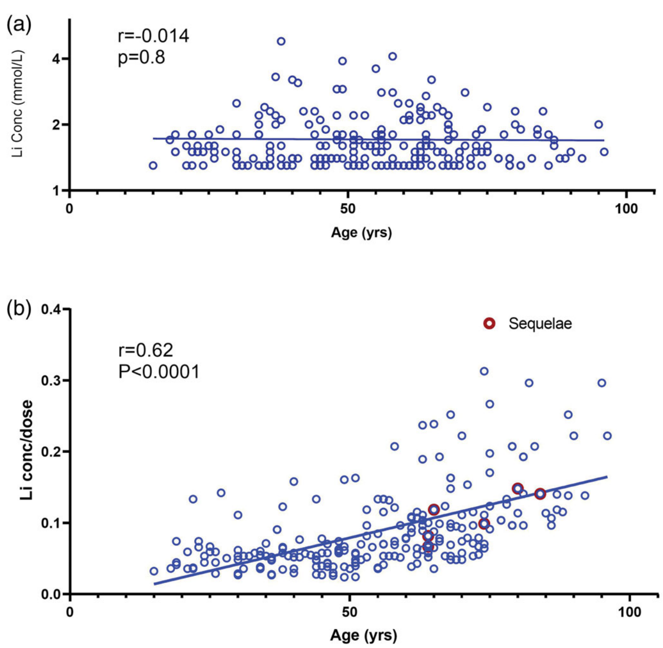

Figure 3. (a) Lithium concentration versus age; (b) Lithium concentration/dose versus age.

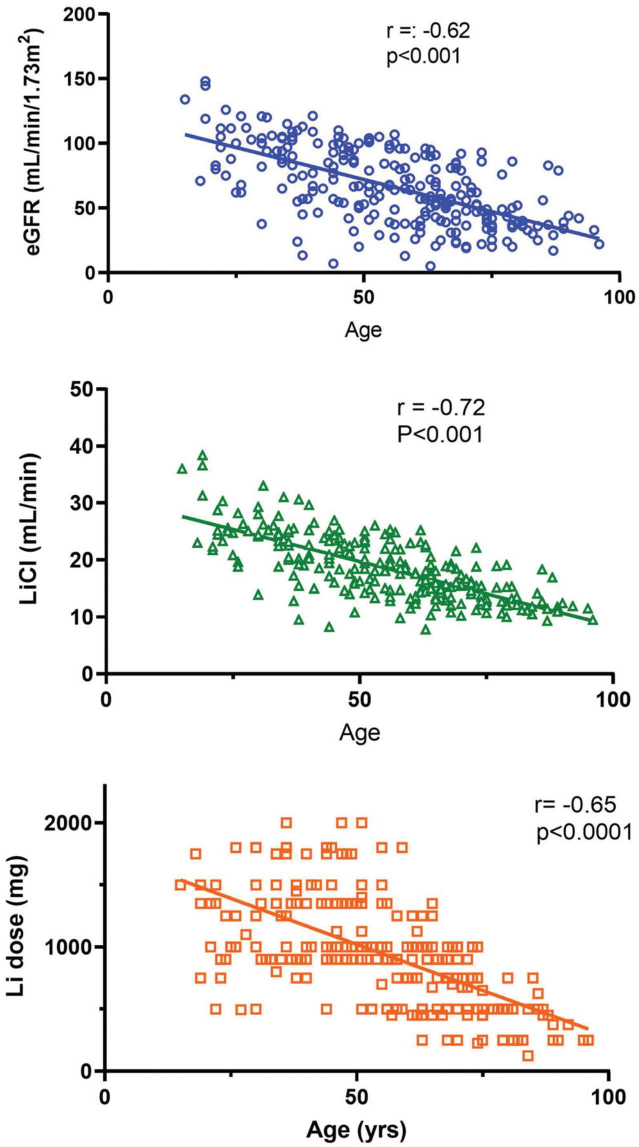

Figure 4. eGFR, lithium clearance and dose in relation to age. eGFR values were calculated using serum creatinine levels in accordance with the CKD-EPI formula. Lithium clearance was calculated as LiCl(mL/min)=0.161 × CrCl(mL/min)+6.47.

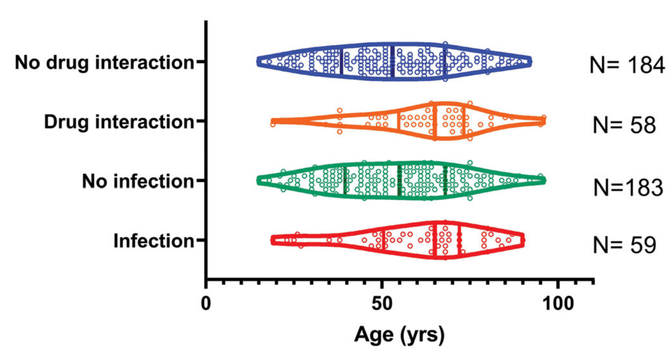

Figure 5. Violin plot of the number of patients who had and did not have drug interaction versus age and patients who were suspected to have infection or no infection versus age.Red solid lines represent median and inter-quartile range. Small circles represent age distribution with each category.

serum lithium concentration and age ($r = -0.02$, 95% CO: –0.11–0.15, $p = .76$) (Figure 3(a)).

The median calculated eGFR was 65 mL/min/1.73 m^2 (range: 5–148, IQR: 41–91). The estimated lithium clearance was 18 mL/min (range: 7.8–38.5, IQR: 13.8–22.8). As expected, the estimated lithium clearance based on the formulas we used correlated strongly with lithium dose/concentration, which at steady state would equal lithium clearance [$R = 0.6$ (95% CI: 0.51–0.68, $p < .0001$) (Supplementary Figure 1)].

There was a significant negative correlation between eGFR and age ($r = -0.62$, 95% CI: –0.69 to –0.53, $p < .001$), lithium clearance and age ($r = -0.72$. 95% CI: –0.78 to –0.66, $p < .001$) (Figure 4), lithium daily dose and age ($r = -0.65$, 95% CI: –0.72 to –0.57, $p < .0001$) (Figure 4), lithium clearance and toxicity severity score ($r = -0.38$, 95% CI: –0.49 to –0.27, $p < .0001$). There were weak correlations between age and infection ($r = 0.18$, 95% CI: 0.04–0.31, $p = .009$) and drug interaction ($r = 0.25$, 95% CI: 0.11–0.37, $p = .0003$) (Figure 5). Finally, there was a positive correlation between the ratio of lithium concentration/dose and age ($r = 0.62$, 95% CI: 0.53–0.69, $p < .0001$) (Figure 3(b)).

Ordinal regression indicated age *per se* was not an independent risk factor for severe toxicity, but estimated lithium clearance ($p = .03$) was an additional risk to lithium concentration ($p < .0001$) when controlled for age and lithium dose (Nagelkerke Pseudo R^2: 0.26) (Supplementary Table 1).

Discussion

Our study showed that older people were at risk of developing more severe lithium toxicity despite taking lower doses of lithium and therefore having no higher average initial serum lithium concentrations. However, older people did have lower lithium clearance and poorer renal function and were more likely to be taking nephrotoxic drugs or have concurrent infections. The most notable finding was that reduced lithium clearance appeared to have an effect on severity beyond contributing to the initial level. Once this was accounted for, no further effect of age was apparent. This has significant potential implications as lithium clearance can be greatly enhanced with hemodialysis [12]. Endogenous lithium clearance is about 15–20 mL/min with normal renal function. Intermittent hemodialysis can increase lithium clearance 10-fold [12], even low intensity methods (e.g., continuous renal replacement therapy (CRRT)) will triple clearance [12].

As far as we know there have not been any clinical trials, cohort or observational studies that investigated the effect of age on chronic lithium toxicity [3]. It has been shown that lithium is associated with a twofold increase in chronic renal disease risk in older people (age >65 years) [13]. Moreover, increased duration of lithium use is associated with a higher risk of chronic renal disease [13]. This is important as it has been estimated that over 50% of patients with bipolar disorders and depression will be older than 60 years by 2030 [14].

Our study showed that the toxicity severity score increased with worsening renal function as defined by lithium clearance. Our result is contrary to another study that was performed in an ICU setting, which suggested that renal function was not an important predictor of lithium toxicity [15]. This could be explained by the fact that the study included 125 patients in three different categories of exposures, acute, acute on chronic and chronic, with the chronic category having only 35 patients. Patients with chronic lithium toxicity have worse renal function resulting in longer exposure to toxic lithium concentrations and hence be expected to develop more severe toxicity. Such considerations are much less important in acute or acute on chronic overdosing, which have less morbidity.

In our study, serum lithium concentration correlated with toxicity ($r = 0.41$, $p < .0001$). This is in agreement with other studies which showed that higher lithium concentrations increased the risk of severe toxicity [4,15]. In addition, it is suggested that there is marked interindividual variation in the brain-to-serum lithium concentration ratio which might cause some patients to be more susceptible [5].

The key limitation of this study was that it was retrospective and so excluded many patients who had insufficient records. We were also not able to consistently determine whether patients had thyroid or parathyroid disorders or nephrogenic diabetes insipidus from the patient records, and these might also be relevant risk factors.

Conclusion

Despite presenting with similar concentrations, older patients with chronic lithium toxicity had more severe clinical effects. This is likely to be multifactorial, with contributions from lower eGFR and lithium clearance, use of nephrotoxic drugs and concurrent infection. Lithium concentrations were also very important predictors for severe toxicity. Hemodialysis is known to greatly increase lithium clearance, but further research is required to determine whether this would reduce the increased risk of severe lithium toxicity in the elderly.

Disclosure statement

No potential conflict of interest was reported by the author(s).

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