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The clinical characteristics and correlates of lithium toxicity in a tertiary referral centre

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Abstract:

Introduction: Lithium is a medication indicated for the treatment of bipolar disorder and in treatment resistant depression, with a narrow therapeutic index. Overdose, either acute or chronic can result in neurological symptoms, requiring dialysis and admission to intensive care in some cases. Lithium toxicity is avoidable with careful monitoring. However, we have noted several recent cases of lithium toxicity in our local service and thus sought to investigate this issue in a more systematic manner.

Aim: We aimed to quantify the incidence of lithium toxicity in our local population over a single year and identify the patients most at risk. We also aimed to generate clinical recommendations on the prevention of lithium toxicity to improve patient safety.

Method: We identified the incidence of lithium toxicity in our local population, by searching the hospital pathology database for patients with serum lithium levels greater than 1.0mmol/L. We examined the available clinical notes for these patients.

Results: We identified 74 serum lithium readings above 1.0mmol/L measured in 44 individual patients. The highest recorded level was 3.2mmol/L. Of these, eleven patients were aged 65 years or older. Hospital admission was required in 14 cases. There was missing data of note: 29.5% had no renal function/eGFR measurement at time of toxicity and 52.3% without a baseline eGFR.

Conclusion: Lithium toxicity is common in our population. Given the narrow therapeutic index, this demonstrates the need for careful monitoring and prescribing, especially patients aged 65 and over.

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Introduction

Cade initially described the use of lithium in 1949 [1]. Lithium is a medication with a strong evidence base for the prophylaxis of bipolar affective disorder, treatment of mania/hypomania and augmentation in treatment-resistant depressive disorder. It is clinically effective at plasma concentrations of 0.4-0.8mmol/L. Lithium has a narrow therapeutic index of 0.4-0.8mmol/L, with 0.6-0.8 mmol/L preferred for optimal clinical efficacy. Above 1.5mmol/L, it produces a wide range of toxic effects [2], although clinical lithium toxicity has been reported at 'normal serum' levels [3].

Lithium toxicity is rare, but may occur for several reasons, including its use in a cohort already at risk of overdose, inadequate monitoring of lithium use, and rapid onset of any factors which reduce renal excretion of lithium. Lithium is excreted unchanged through the kidneys; hence, its serum level depends on renal function and is affected by polypharmacy. Lithium excretion is a function of renal sufficiency [4, 5]. Salt depletion, dehydration or diuretics all increase serum lithium levels as well as some common medications such as angiotensin converting enzyme (ACE) inhibitors, non-steroidal anti-inflammatory drugs (NSAIDs), and diuretics.

Lithium toxicity may be either acute or chronic and could potentially lead to serious adverse effects, affecting the central nervous system, cardiovascular system, gastrointestinal system and renal system [6]. Intentional overdose with lithium is another reason for presentation to the hospital with acute lithium toxicity. Symptoms range from nausea, vomiting and diarrhoea to life-threatening features like coma, convulsions and potentially death at dangerously high lithium plasma levels.

The risk of developing lithium toxicity can be reduced by guideline-based monitoring of plasma lithium levels, and psycho-education about lithium therapy. Current guidelines recommend that lithium levels be checked one week following initiation or dose change. Once therapeutic level is achieved, levels can be repeated 3-monthly for the first year and 6-monthly thereafter (or 3-monthly for people who are at high risk of developing toxicity). Renal and thyroid function tests need to be tested at baseline and repeated every 6 months [7, 8]. These tests allow for early detection of declining function. Where renal function is moderately impaired (stage 3a or 3b: eGFR = 30-59), renal function should be monitored every 3 months and a referral to nephrology is indicated in stage 3b if heavy proteinuria (or proteinuria and haematuria) is present, or if there has been a rapid decline in eGFR (NICE 2008). In severe renal failure (stages 4 and 5; eGFR<29) lithium is usually contraindicated, and a nephrology opinion is required [2]. Discontinuation of lithium may not halt the decline in renal function [8,9].

Despite clear guidelines, a UK based study found that only 30% of mental health trusts met targets for lithium monitoring [11]. A local audit found that less than 20% of patients had monitoring in line with best practice guidelines (Dunne, 2017, in press).

The incidence of lithium toxicity was found to be approximately 5.4 cases per 100,000 per year in Cork, Ireland [12]. A retrospective, observational study of cases of lithium toxicity reported to the California Poisons Control System from 2003- 2007, reported 502 hospitalised cases due to lithium toxicity in the five year period [13]. Inadequate monitoring and management of lithium therapy could potentially lead to life-threatening risks as well as undesired economic consequences on the health service. In the UK, between 2003 and 2008, there were 567 incident reports received concerning lithium therapy with two cases indicating severe harm. Between 1995 and 2004, the NHS Litigation Authority acted on two fatal incidents as well as 12 cases of severe harm incidents relating to the use of lithium [14]. Locally, over a period of 6 years between 2004 and 2010, the Clinical Indemnity Scheme under the State Claims Agency in Ireland recorded 1,106 reports relating to medication incidents in mental health, of which 7.7% related to treatment with lithium [15]. These incidents could be mitigated with proper education and monitoring in patients receiving lithium therapy.

There is little data regarding the incidence of lithium toxicity in our local population. The aim of this study is to investigate the incidence and clinical associations of lithium toxicity in the Galway and Mayo population in 2016.

Method

This was a retrospective study, which analysed clinical and laboratory data, which was collected as part of routine clinical care. In collaboration with the hospital laboratory services at GUH, we identified patients through the hospital laboratory information system, which includes lithium levels for patients residing in the West Galway and Mayo region and who presented for medical attention in hospitals or community primary care centres.

Patients with serum lithium level greater than 1.0mmol/L over the 12 month period of 1st January to 31st December 2016 were included in this study: we chose this level, lower than the traditional cut off for toxicity of 1.5 mmol/L to reflect newer guidelines for the management of patients on lithium at a trough serum level of 0.6 to 0.8mmol/L [7]. NICE guidelines recommend a brief trial of levels between 0.8 to 1.0mmol/L only where the person has had a relapse while taking lithium in the past or has sub-threshold symptoms with functional impairment despite lithium at levels of 0.6 to 0.8mmol/L [7].

Demographic and clinical characteristics of these patients were obtained from their respective psychiatry clinical notes and electronic discharge summaries: age, gender, diagnosis (in accordance with ICD-10 criteria), frequency of serum lithium level sampling, thyroid and renal function monitoring were obtained. Where available, we also recorded the cause of overdose in this subset of patients. We also identified patients who required hospital admission as well as those who required input during their admission from the Liaison Psychiatry team.

Data were entered into SPSS. Basic statistical data on demographic and clinical variables were calculated and bivariate data were analysed. Chi square and T-test analyses were used where data were separated by age. The findings were then interpreted and presented in the form of summary tables.

This study was granted ethical approval by the Clinical Research Ethics Committee of the Saolta Hospital Group.

Results

We identified 74 serum lithium levels above 1.0mmol/L from 44 individual patients (26 patients had one elevated lithium only: the remainder had multiple levels above 1.0mmol/L some within the same day). Table 1 summarises the demographic and clinical characteristics of patients included in this study. Of 44 patients, 32 (72.7%) were aged less than 65 years while the remaining patients were ≥ 65 years of age. There were similar number of female (n=21) and male (n=23) patients. Of the 26 whose diagnoses were recorded, 17 had bipolar affective disorder, three had schizoaffective disorder and six were diagnosed with recurrent depressive disorder. Diagnosis and indication for lithium therapy could not be obtained for 18 patients, who did not have a medical or psychiatric file available for review at the hospital. When we compared the demographic and clinical characteristics of those patients for whom we had complete data with those with partial data only (missing diagnosis), there were no significant differences between the two groups in terms of age, serum lithium, or eGFR.

The highest recorded lithium level was 3.2mmol/L with mean level of 1.4 (SD 0.5) mmol/L. The majority of patients had renal function tests performed, with mean baseline eGFR of 70.6ml/min. The mean eGFR in patients with lithium toxicity was 62.9ml/min. Of the studied patients, 39 (88.6%) had some degree of renal impairment prior to onset of episode of toxicity. Almost 90% of the patients had thyroid function tests done. Thirty patients were treated for their lithium toxicity as outpatients, while 14 required hospital admission. Of these, six patients (43%) received input from Liaison psychiatry team during their admission.

Table 2 demonstrates the difference in demographic and clinical characteristics of patients aged ≤ 64 and ≥ 65 years. Despite the lower baseline eGFR in the over 65 group, 25% of the patients did not have renal function tests performed when they developed toxicity. At toxicity, the older patient group developed a significantly lower eGFR level of 52.7ml/min compared to the younger age group (66.5 ml/min; $p=0.045$).

Table 3 demonstrates clinical and demographic characteristics of patients with serum lithium levels above and below 1.5 mmol/L. Patients with serum lithium levels above 1.5mmol/L were more likely to be hospitalised (61.5%) than those with lower lithium levels (19.4%; $p = 0.009$). Patients with higher serum lithium levels were more likely to be referred to the liaison psychiatry team ($p = 0.006$). We noted that 40% of patients with levels

greater than 1.5mmol/L have no record of attending hospital. There were no significant differences between groups when we excluded patients who presented with intentional self-poisoning. There were no deaths directly attributable to lithium toxicity.

Discussion

In this study, we identified the incidence of lithium toxicity over one year and examined the demographics and clinical characteristics of those 44 patients with recorded lithium levels over 1.0mmol/L. The highest recorded lithium level was 3.2mmol/L with mean level of 1.4 (SD 0.5) mmol/L. The majority of patients studied were aged less than 65 years. This may reflect clinicians' higher threshold for commencing lithium in the elderly population, or perhaps medically necessary discontinuation of lithium in later life due to the development of the sequelae of long-term lithium use such as nephrotoxicity. Moreover, as elderly patients tend to seek medical attention more frequently than younger patients, rising lithium levels may have been detected sooner, and interventions put in place before they develop toxicity. There were similar proportion of males and females in our cohort, which is not consistent with most studies [16]. This may be due to our small patient number included in this study.

We were unable to identify the clinical diagnosis for 18 of 44 patients. These patients were generally out of area and we had no access to their mental health records, however we have no reason to suspect that their clinical characteristics would differ from those whom we had more detailed information. Four of the twelve patients were managed by their GPs in the community. One patient, for whom a chart was available did not have an Axis I mental health diagnosis. Patients with borderline personality disorder may be prescribed lithium to manage emotional lability [17].

Lithium levels above 2.5mmol/L are potentially fatal [4]. We identified four patients with levels equal to or greater than this. This is a significant number in the space of one year for our catchment area, considering that frequent serum lithium level monitoring should prevent these events. However, two of these high levels were attributed to self-poisoning. Our highest recorded lithium level in the database was 3.2mmol/L. The toxic level was attributed to the addition of a thiazide diuretic to the patient's medication regime, an agent known to reduce renal clearance of lithium, thereby increasing plasma lithium levels [18]. Co-prescription of medications known to interact with lithium are frequently reported in patients who presented with lithium toxicity as reported by Dennison. Their study found that 49% of patients were co-prescribed drugs that interact with lithium: 21.3% were prescribed diuretics [11]. A Canadian study similarly reported an elevated increased risk of lithium toxicity among patients concomitantly prescribed loop diuretics or ACE inhibitors [158]. A seven-year prospective study of lithium levels among hospitalised patients found an incidence of lithium toxicity (defined as ≥ 1.5 mmol/L) of 6.8% in 2210 hospital admissions where lithium was administered. Less than 30% of patients with toxic levels showed signs of toxicity, and excess levels were more commonly seen in female and elderly patients [19]. A Californian study published in 2010 described a large cohort of lithium overdose hospitalised patients and found 629 cases of lithium toxicity per 5 years, with 80% requiring hospitalisation. The majority were the consequence of chronic overdose, and many required haemodialysis [11].

While there is evidence that lithium reduces suicidal risk in patients with mood disorders [21], its narrow therapeutic index means it may be fatal in self-poisoning or intentional overdose. A study by Dyson et al of 68 admissions for lithium toxicity over a sixteen-year period, found that the majority (63%) were due to self-poisoning [22]. Psychiatrists who prescribe lithium should ultimately weigh the therapeutic benefits against the risks before prescribing lithium in view of the drug's potential dangers. In order to avoid lithium toxicity, NICE suggests that patients who are prescribed lithium are measured for plasma lithium level every three months for the first year and 6-monthly thereafter, unless a patient is at high risk of developing adverse effects from lithium in which they may need three-monthly monitoring [7]. It is important to consider the risk factors for developing renal failure, thyroid dysfunction and cardiovascular disease, before making decisions regarding maintenance treatment with lithium. A 2016 systematic review investigated the adherence to lithium monitoring guidelines in the United Kingdom and Ireland [11]. Their findings showed that no study in the review showed total adherence to every guideline. This is consistent with our study that suggests that lithium monitoring is not conducted in accordance with established guidelines.

Lithium is primarily excreted unchanged by the kidneys. Elderly patients may be more vulnerable to lithium toxicity as they were more likely to have some form of renal impairment at baseline as suggested by our findings, i.e. 11 out of 12 patients over age 65 had stage 2 and 3 chronic kidney disease at baseline. Elderly patients may have a longer duration of lithium treatment, resulting in an increased risk of renal impairment in

their later years, compounded by age-related decline in their renal function [23]. Studies in Scotland, Asia, and the Czech Republic found high rates of renal failure following lithium toxicity [19-21]. The course of renal impairment following the discontinuation of lithium is unpredictable, and cessation may not halt the decline in renal function [9].

Recognising the vulnerability to lithium toxicity in this age group, NICE recommends that older people have plasma lithium level monitoring every three months. As elderly patients tend to attend their GPs more frequently for routine medical check-ups, high lithium levels are more likely to be detected and treated before complications develop. In addition, elderly patients tend to be maintained on lower lithium dose [7]. Another study discussed the differences in the incidence of adverse lithium therapy effects in patients younger than and older than 65 years of age. Their study, similarly to ours, was retrospective. They found a significant difference in severity of side effects, more moderate to severe effects were seen in those older than 65 [27].

In a prospective study, Webb et al observed a decline in lithium toxicity over seven-year period as a result of education by a drug guidelines and education committee [20]. Measures such as the provision of a lithium alert card along with verbal and written information about lithium may reduce similar incidents in the future [14]. All prescribing clinicians should be aware of the guidelines in the area: this is particularly the case when patients are under the shared care of psychiatry and general practice. The guidelines for monitoring are all broadly similar – the main difference is that NICE and the Maudsley Guidelines suggest 6 monthly monitoring of lithium (3 monthly in the elderly) and the IMSN guidelines suggest 3 monthly monitoring of lithium levels for all (2,15, 29): the IMSN guidelines are summarised in table 4. In addition it may be helpful to have renal function as an automated electronic accompaniment to the laboratory report on serum lithium levels.

A small proportion of the patients admitted medically were referred for liaison psychiatry review during their admission. There are no guidelines in this area, beyond the National Clinical Programme in Self-Harm [28] which would suggest review for all patients presenting with self-poisoning – as was the case in our sample. We do not see it as necessary for all patients with levels $>1.0\text{mmol/L}$ to be seen, but those presenting with self-poisoning, extreme toxicity or a dramatic change in levels should be seen, and all cases should be discussed with the liaison psychiatry registrar.

The limitations of this project include its design as a retrospective study, and its small sample size due to lithium toxicity being a rare occurrence. A further limitation of this study was the partial accessibility of clinical information of patients not seen within the Galway Mental Health Service. However, unlike a chart-based study, our use of the laboratory system used by the hospitals allowed easy identification of patients meeting our inclusion criteria. Other limitations are that we did not have access to a denominator for the total number of patients prescribed lithium and so could not calculate an incidence rate, for comparison with previous years or other areas/health services, and we only collected data for one year so could not test whether the incidence of lithium toxicity as identified in the hospital is changing over time.

Conclusion

Lithium is a commonly prescribed drug in psychiatry for the treatment of severe mental illness. However, it is associated with many adverse effects ranging from mild and self-limiting side effects to life-threatening adverse events. Given the narrow therapeutic index, this demonstrates the need for careful guideline-based prescribing and monitoring, especially in patients who are at high risk of developing lithium toxicity. Lithium toxicity outside of intentional overdose continues to occur regularly and may be related to inadequate implementation of safe guidelines around monitoring and unawareness of safe prescribing such as the co-prescription of ACE inhibitors. Clinicians therefore need to be vigilant, and to closely follow available clinical guidelines in the area. Further prospective research is required in this area.

Ethical Disclosure Statement

For this project we sought quality and integrity. We were in contact with no patients for the duration of the study. No identifiable patient data was used. Data was obtained via an electronic hospital laboratory system and was anonymised to ensure patient confidentiality. Data was stored on a fire-walled computer with coded access. Funding was obtained from the undergraduate research program at NUI Galway. No conflicts of interest existed in relation to this.

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Table 1: demographic and clinical characteristics		N=44
Age, mean (SD)		52.9 (17.7)
Age, n (%)	≤64	32 (72.7)
	≥65	12 (27.3)
Gender, n (%)	Female	21 (47.7)
	Male	23 (52.3)
Diagnosis, n (%)	Bipolar Affective Disorder	17 (38.6)
	Schizoaffective Disorder	3 (6.8)
	Recurrent Depressive Disorder	6 (13.6)
	Unknown	18 (40.9)
Serum Lithium level, mean (SD)		1.43 (0.48)
Renal function test performed, n (%)		39 (88.6)
Baseline eGFR ml/min, mean (SD)		70.6 (15.3)
Toxicity eGFR ml/min, mean (SD)		62.9 (18.8)
KDOQI renal failure stage (baseline)	Stage 1	12 (30.8)
	Stage 2	16 (41)
	Stage 3	11 (28.2)
	Stage 4	0 (0)
KDOQI renal failure stage (toxicity)	Stage 1	6 (15.4)
	Stage 2	18 (46.2)
	Stage 3	14 (35.9)
	Stage 4	1 (2.6)
Thyroid function test performed, n (%)		39 (88.6)
Requiring hospital admission, n (%)		14 (31.8)
Liaison psychiatry consult, n (% of adm)		6 (42.9)
Source, n (%)	Primary care	20 (45.5)
	OPD	14 (31.8)
	Inpatient	10 (22.7)

Table 2: Clinical and demographic characteristics of patients aged below and over age 65 years				
		≤64	≥65	P
Gender, n (%)	Female	13 (40.6)	8 (66.7)	0.124 ^a
	Male	19 (59.4)	4 (52.3)	
Diagnosis, n (%)	Bipolar Affective Disorder	14 (43.8)	3 (25.0)	0.085 ^a
	Schizoaffective Disorder	3 (9.4)	0 (0.0)	
	Recurrent Depressive Disorder	2 (6.3)	4 (33.3)	
	Unknown	13 (40.6)	5 (41.7)	
Serum Lithium level, mean (SD)		1.5 (0.55)	1.25 (0.12)	0.123 ^b
Renal function test performed, n (%)		22 (69)	9 (75)	0.286 ^c
Baseline eGFR ml/min, mean (SD)		75.2 (14.7)	59 (9.8)	<0.001^b
Toxicity eGFR ml/min, mean (SD)		66.5 (19.1)	52.7 (14.3)	0.045 ^b
KDOQI renal failure stage at baseline	Stage 1	12 (42.9)	0 (0)	<0.001^a
	Stage 2	13 (46.4)	3 (27.3)	
	Stage 3	3 (10.7)	8 (72.7)	
	Stage 4	0 (0.0)	0 (0.0)	
KDOQI renal failure stage at time of toxicity	Stage 1	6 (20.1)	0 (0)	0.057 ^a
	Stage 2	15 (51.7)	3 (30)	
	Stage 3	7 (24.1)	7 (70)	
	Stage 4	1 (3.4)	0 (0.0)	
Thyroid function test performed, n (%)		28 (87.5)	11 (91.7)	0.583 ^c
Requiring hospital admission, n (%)		11 (34.4)	3 (25.0)	0.417 ^c
Liaison psychiatry consult, n (% of adm)		4 (36.4)	2 (67)	0.529 ^c

^a = chi square; ^b = independent sample t-test; ^c = Fisher's test

		Serum Lithium ≤1.4mmol/L n= 31	Serum Lithium ≥1.5mmo/L n = 13	P
Gender, n (%)	Female	16 (51.6)	5 (38.5)	0.426 ^a
	Male	15 (48.4)	8 (61.5)	
Diagnosis, n (%)	Bipolar Affective Disorder	12 (38.7)	5 (38.5)	0.477 ^c
	Schizoaffective Disorder	1 (3.2)	2 (15.4)	
	Recurrent Depressive Disorder	5 (16.1)	1 (7.7)	
	Unknown	13 (41.9)	5 (38.5)	
Age, mean (SD)		55.2 (18.9)	47.5 (13.6)	0.192 ^b
Renal function test performed within 6 months, n (%)		23 (74.2)	9 (62.9)	0.736 ^a
Baseline eGFR ml/min, mean (SD)		68.6 (14.5)	66 (15.9)	0.734 ^b
Toxicity eGFR ml/min, mean (SD)		64.0 (19.0)	60.9 (27.8)	0.725 ^b
KDOQI renal failure stage at baseline	Stage 1	4 (25)	1 (20)	0.974 ^c
	Stage 2	6 (37.5)	2 (40)	
	Stage 3	6 (37.5)	2 (40)	
	Stage 4	0 (0)	0 (0)	
KDOQI renal failure stage at time of toxicity	Stage 1	5 (22.7)	3 (33.3)	0.365 ^c
	Stage 2	6 (27.3)	2 (22.2)	
	Stage 3	11 (50)	3 (33.3)	
	Stage 4	0 (0)	1 (11.1)	
Thyroid function test performed within 6 months, n (%)		28 (90.3)	8 (61.5)	0.024^a
Requiring hospital admission, n (%)		6 (19.4)	8 (61.5)	0.006^a
Liaison psychiatry consult, n (% of adm)		1 (3.2)	5 (38.5)	0.002^a

^a = chi square; ^b = independent sample t-test; ^c = Fisher's test

Baseline	Information (verbal and written) on lithium, including side-effects and symptoms of toxicity, pregnancy if applicable. Risk of manic relapse on sudden discontinuation.	
	Height, weight, BMI	
	Renal function incl eGFR, thyroid function. Full blood count if indicated	
	ECG	
	Lithium levels weekly until stable in range 0.6 -0.8 mmol/L	
Monitoring once stable	Renal function	6 monthly More frequently if declining renal function
	Thyroid function	6 monthly
	Weight /BMI	Annually
	Blood pressure, glucose	Annually
	Lipid profile	Annually for patients aged >40y