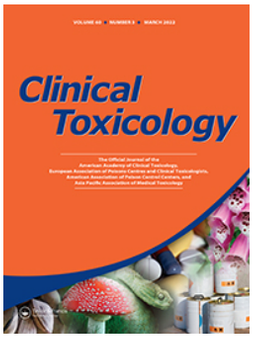

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CLINICAL RESEARCH

Validation of a nomogram used to predict lithium concentration in overdose

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ABSTRACT

Introduction: Extracorporeal Treatment (ECTR) is an essential component in management of severe lithium toxicity. The Extracorporeal Treatments in Poisoning (EXTRIP) group's suggested indications for ECTR include "if the expected time to obtain a [Li+] < 1.0mEq/L with optimal management is >36h". Buckley et al. developed a lithium nomogram which could help predict the fall in lithium concentrations for chronic poisoning. Our aim is to externally validate the lithium nomogram in a cohort of cases with chronic accumulation and acute on chronic lithium poisoning.

Methods: A retrospective analysis of suspected cases of chronic accumulation and acute on chronic lithium poisoning referred to our Toxicology Unit from May 2013 to 2020 was performed.

Results: Out of 51 cases, 29 cases of chronic accumulation and eight cases of acute on chronic poisoning were analysed after excluding 14 cases who required haemodialysis. In chronic accumulation cases, the nomogram correctly identified 10 out of 14 patients whose [Li+] failed to drop below 1.0 mmol/L by 36 h (sensitivity 71.4% [95% CI 42 − 92%]), and 8 out of 15 patients whose [Li+] dropped below 1.0 mmol/L by 36 h (specificity 53.3% [95% CI 27 − 78%]), resulting in the positive predictive value (PPV) of 58.8%, negative predictive value (NPV) of 66.7% and accuracy of 62.1%.

Conclusions: Our study shows that the lithium nomogram is moderately sensitive at identifying patients with chronic lithium accumulation who will have a serum lithium concentration >1 mmol/L at 36 h without ECTR.

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Lithium nomogram; chronic lithium toxicity; chronic accumulation of lithium

Introduction

Lithium is the oldest and only agent used specifically for the treatment of bipolar disorder [1]. Although effective in treatment and prevention of relapse from bipolar disorder, lithium is well known for its toxicity [2]. Three distinct patterns of lithium toxicity are recognised: "acute poisoning" in patients not previously receiving lithium, "acute on chronic poisoning" in the setting of current lithium treatment and "chronic accumulation" which arises insidiously in patients on therapeutic doses of lithium [3].

Lithium has a narrow therapeutic index [4]. Regular biochemical monitoring is required to ensure therapeutic serum concentrations and regular clinical assessment is performed to monitor for development of neurological toxicity [5]. For patients with chronic lithium accumulation, clinical features of toxicity may develop slowly and go unnoticed for an extended period [6].

Treatment of lithium toxicity is influenced by the severity of neurologic impairment and the extent of acute kidney injury (AKI). In addition to withholding lithium and nephrotoxic agents, serial clinical assessment, biochemical monitoring and intravenous rehydration are most important in the management of lithium toxicity [6,7]. Gastrointestinal decontamination by whole bowel irrigation may be performed in acute overdose with extended-release formulation [7]. Treatment may also include rehydration, correction of electrolyte abnormalities and extracorporeal treatment (ECTR) to enhance lithium clearance [6,7]. While ECTR is the key intervention in severely poisoned patients, the indications for this in the context of the abovementioned lithium toxicity scenarios are unclear and clinical practice is variable [7,8]. Furthermore, while ECTR removes lithium more rapidly in patients with AKI, the efficacy of ECTR in reducing morbidity for lithium poisoned patients is unclear [8].

The Extracorporeal Treatments in Poisoning (EXTRIP) Workgroup has developed recommendations for extracorporeal removal of lithium [9]. One of the suggested indications (level 2D) is to dialyse "if the expected time to obtain a [Li+] < 1.0 mEq/L with optimal management is more than 36 h" [9]. Buckley et al. developed a nomogram to predict the rate of fall of lithium concentration after acute on chronic poisoning and chronic lithium accumulation and a treatment flow chart to address this [10]. Our study aims to externally validate the lithium nomogram and its ability to predict lithium concentrations based on kidney function. We also analysed the usefulness of Buckley et al.'s flowchart in our chronic accumulation cases.

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Supplemental data for this article can be accessed here.

Materials and methods

A retrospective analysis of cases of chronic accumulation and acute on chronic lithium poisoning referred to the Monash Health Toxicology Unit from May 2013 to 2020 was performed. The Monash Toxicology Unit covers five hospitals including three adult and one paediatric emergency department. Acute on chronic poisoning was defined as patients who had taken an acute overdose whilst on lithium therapy. Chronic accumulation was defined as patients developing toxicity while taking therapeutic doses of lithium.

The inclusion criteria included: patients aged 18 years or above, peak [Li+] more than 1.0 mmol/L and at least two documented [Li+] with the minimal requirement of one on arrival and one at or after 32 h from the first [Li+], initial creatinine recorded and definitions for acute on chronic poisoning or chronic accumulation fulfilled. To reflect the true 36 h [Li+] in patients who did not have [Li+] performed exactly at 36 h, we extrapolated the concentration from the available data, since lithium is known to exhibit linear pharmacokinetics [11]. A time-concentration graph was plotted for each individual case, and a 36 h [Li+] was extrapolated from this, based on serial lithium concentrations. For patients who were dialysed, we utilised the pre-dialysis [Li+] and eGFR to determine whether this would determine a [Li+] > 1 mmol/L at 36 h if dialysis had not been performed.

The exclusion criteria included: paediatric patients (age < 18 years), patients whose medical records did not contain the data needed to determine if EXTRIP criteria were met, those with peak [Li+] less than or equal to 1.0 mmol/L, and no serial [Li+] available, or where the repeat [Li+] was taken earlier than 32 h from the time of first concentration result.

Patient data collection included: demographics, including age and gender, serial lithium concentrations, creatinine, estimated glomerular filtration rate (eGFR), lithium dose and formulation of lithium ingested in cases of acute on chronic poisoning, recorded interventions to reduce the lithium concentration and time for lithium concentration to be <1.0 mmol/L. Presenting complaints, grade of neurotoxicity, clinical outcome data including neurological status upon discharge or medical clearance and medical length of stay (LOS) were also collected in chronic accumulation patients.

The Pathology department of our health service uses the CKD-EPI formula to calculate the eGFR and reports value of less than or equal to 90 mL/min/1.73 m^2, in line with the revised recommendations from the Australasian Creatinine Consensus Working Group [12]. For patients whose eGFR was reported above 90 mL/min/1.73 m^2, eGFR values were calculated using an eGFR calculator from Kidney Health Australia which also uses the CKD-EPI formula involving patient age, sex and creatinine concentration [13].

GraphPad Prism version 9.0.1 (GraphPad, San Diego, CA) was used for statistical analysis. We divided our patients into different groups (Li > 1.4@36 h, Li 1–1.4@36 h, Li < 1@36 h, dialysed patients) when plotting our patients on the nomogram consistent with Buckley et al.'s depiction of their patients [10]. A contingency table analysis was performed to determine sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV) and accuracy as per the results from the analysis of the graphs.

For both acute on chronic poisoning and chronic accumulation cases, we performed two contingency table analyses each: with and without cases receiving haemodialysis. Lithium half-lives before and during haemodialysis for chronic accumulation cases receiving haemodialysis were calculated using the Cornell University Drug Half Life calculator [14] assuming first-order elimination kinetics.

We applied the flowchart criteria suggested by Buckley et al. and EXTRIP recommended indications for ECTR to all our chronic-accumulation cases [9,10]. Further analyses including central nervous system (CNS) toxicity, initial creatinine and eGFR, peak [Li+], neurological outcome upon medical clearance or discharge and medical LOS were made for cases meeting these criteria. The CNS toxicity in these cases was graded as per Hansen and Amdisen grading [15].

Results

Ninety-four presentations of lithium poisoning were identified within the selected timeframe. Fifty-one (54%) presentations met the inclusion criteria. Out of 51 lithium poisonings, 39 cases of chronic accumulation and 12 cases of acute on chronic poisoning were identified. Ten out of 39 chronic accumulation cases and four out of 12 acute on chronic poisoning cases received ECTR (Supplementary Figure 1). Demographics and clinical characteristics of non-dialysed patients with lithium poisoning are reported in Table 1.

In acute on chronic poisoning cases who were not dialysed, the nomogram correctly identified two out of five patients whose [Li+] failed to drop below 1.0 mmol/L by 36 h (sensitivity 40% [95% CI 5–85%]) and three out of three patients whose [Li+] dropped below 1.0 mmol/L by 36 h (specificity 100% [95% CI 29–100%]) (Figure 1 and Table 2). For this cohort PPV, NPV and accuracy were 100%, 50% [95% CI 33–67%] and 62.5% [95% CI 25–92%], respectively. When dialysed acute on chronic poisoning patients were included

Table 1. Demographics and clinical characteristics of non-dialysed patients with lithium poisoning.

	Chronic accumulation ($n = 29$)	Acute on chronic poisoning ($n = 8$)
Median age (range)	55 years (21–86)	31 years (16–68)
Female % (n)	65 (19)	62.5 (5)
Slow-release formulation % (n)	Not available due to inadequate documentation	50 (4)
Median ingested dose (IQR)	Not applicable	5.4 g (1.5, 22.5)
Median [Li+] on arrival (IQR)	1.98 mmol/L (1.57, 2.29)	1.82 mmol/L (0.99, 2.57)
Median Cr on arrival (IQR)	89 μmol/L (77, 153)	67 μmol/L (62, 81)
Median peak [Li+] (IQR)	1.98 mmol/L (1.63, 2.29)	2.47 mmol/L (1.97, 3.33)
Median time to reach [Li+] < 1.0 mmol/L (IQR)	42 h (34, 67.5)	57 h (36.7, 65.2)

in the analysis (Figure 1 and Supplementary Table 1), the sensitivity and accuracy were increased to 66.7% and 75%, respectively.

In chronic accumulation cases who were not dialysed, the nomogram correctly identified 10 out of 14 patients whose [Li+] failed to drop below 1.0 mmol/L by 36 h (sensitivity 71.4% [95% CI 42–92%]), and 8 out of 15 patients whose [Li+] dropped below 1.0 mmol/L by 36 h (specificity 53.3% [95% CI 27–78%]) resulting in PPV 58.8% [95% CI 43–73%], NPV 66.7% [95% CI 44–84%] and accuracy 62.1% [95% CI 42–79%] (Figure 2 and Table 3). When dialysed chronic accumulation cases were included in the analysis (10 additional cases), the nomogram correctly predicted all patients who required dialysis resulting in an improved sensitivity of 83% [95% CI 63–95], PPV 74% [95% CI 62–84%] and accuracy 71.7% [95% CI 55–85%] (Figure 2 and Table 4).

Regarding patients who were dialysed, all dialysed acute on chronic poisoning patients had [Li+] > 1 mmol/L at or after 36 h while five out of 10 dialysed chronic accumulation patients had [Li+] > 1 mmol/L at or after 36 h despite undergoing dialysis. Plots of serum lithium concentration and its relationship to time from the first measured lithium concentration in non-dialysed and dialysed chronic accumulation cases are provided in Figures 3 and 4, respectively. For dialysed chronic accumulation cases, half-lives of lithium before dialysis and during dialysis were calculated and are reported in Table 5.

We also applied the EXTRIP recommended indications for ECTR [9] and the flow chart criteria from Buckley et al. [10] to all our chronic accumulation cases. Thirty-nine cases were included. A total of 28 cases met EXTRIP recommended indications (Figure 5) and 26 cases met Buckley flowchart criteria (Figure 6). Only 10 of these cases in our cohort were dialysed, and both EXTRIP and Buckley flow chart criteria identified these patients. Hansen and Amdisen neurotoxicity grades were applied to all patients meeting one or both criteria (Figures 5 and 6). Selected clinical, biochemical features and outcomes of the chronic accumulation patients meeting either EXTRIP or Buckley et al.'s criteria can be found in Tables 5 (dialysed patients) and 6 (non-dialysed patients). Of note, there was one chronic accumulation patient with grade-3 CNS toxicity who was not dialysed due to complex intercurrent medical problems and was palliated (Table 6). In our dialysed cohort, five (50%) out of 10 patients had grade-1 neurotoxicity, while three (30%) had grade-3 neurotoxicity (Table 5).

Discussion

The selection of treatment modalities for severe lithium poisoning can be variable, especially the decision to perform ECTR in patients with chronic accumulation and neurotoxicity. Various recommendations have been published, and further refined to more accurately identify patients who may benefit from extracorporeal lithium removal [9,10,16].

Buckley et al. reported that the lithium nomogram accurately predicted all patients who developed neurological sequelae and who required dialysis, and all but two patients who still had lithium >1.4 mmol/L at 36 h in their chronic accumulation cohort [10]. Our study showed the lithium nomogram did not identify all cases of chronic lithium accumulation with neurotoxicity that had a lithium concentration >1.0 mmol/L at 36 h and may have had benefit from ECTR. However, when we included chronic accumulation patients who received dialysis into our analysis, the nomogram showed improvement in sensitivity 83%, PPV 74% and accuracy 71% (Table 4). More information on these patients including half-life of lithium (before ECTR and average half-

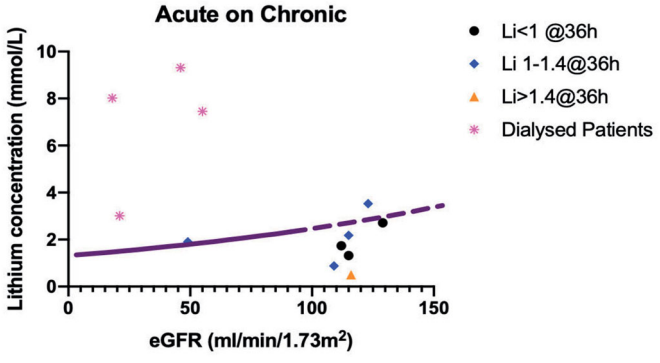

Figure 1. Arrival [Li+] *vs.* Arrival GFR of acute on chronic poisoning cases plotted on nomogram.

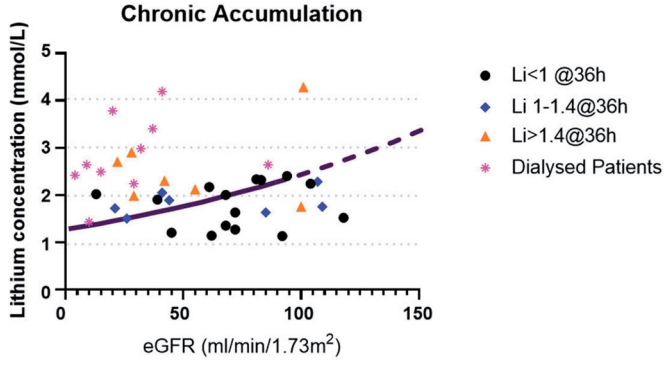

Figure 2. Arrival [Li+] *vs.* arrival GFR of all chronic accumulation cases plotted on nomogram.

Table 2. Contingency table analysis in non-dialysed acute on chronic poisoning cases.

	Actual 36 h [Li+] >= 1 mmol/L	Actual 36 h [Li+] < 1 mmol/L	Total	
Lithium nomogram predicted a 36 h [Li+] >= 1.0 mmol/L	2	0	2	PPV = 100%
Lithium nomogram predicted a 36 h [Li+] < 1.0 mmol/L	3	3	6	NPV = 50% (95% CI: 32.8 – 67.2%)
Total	5	3	8	
	Sensitivity = 40% (95% CI: 5.3 – 85.3%)	Specificity = 100% (95% CI: 29.2 – 100%)		Accuracy = 62.5% (95% CI: 24.5–91.5%)

Table 3. Contingency table analysis in non-dialysed chronic accumulation cases.

	Actual 36 h [Li+] >= 1 mmol/L	Actual 36 h [Li+] < 1 mmol/L	Total	
Lithium nomogram predicted a 36 h [Li+] >= 1.0 mmol/L	10	7	17	PPV = 58.8% (95% CI: 43.1–72.9%)
Lithium nomogram predicted a 36 h [Li+] < 1.0 mmol/L	4	8	12	NPV = 66.7% (95% CI: 43.5–83.9%)
Total	14	15	29	
	Sensitivity = 71.4% (95% CI: 41.9 – 91.6%)	Specificity = 53.3% (95% CI: 26.6 – 78.3%)		Accuracy = 62.1% (95% CI: 42.3–79.3%)

Table 4. Contingency table analysis in all chronic accumulation cases.

	Actual 36 h [Li+] >= 1 mmol/L	Actual 36 h [Li+] < 1 mmol/L	Total	
Lithium nomogram predicted a 36 h [Li+] >= 1.0 mmol/L	20	7	27	PPV = 74% (95% CI: 61.8 – 83.5%)
Lithium nomogram predicted a 36 h [Li+] < 1.0 mmol/L	4	8	12	NPV = 66.7% (95% CI: 42.1 – 84.6%)
Total	24	15	39	
	Sensitivity = 83.3% (95% CI: 62.6 – 95.3%)	Specificity = 53.3% (95% CI: 26.6 – 78.7%)		Accuracy = 71.7% (95% CI: 55.1 – 85%)

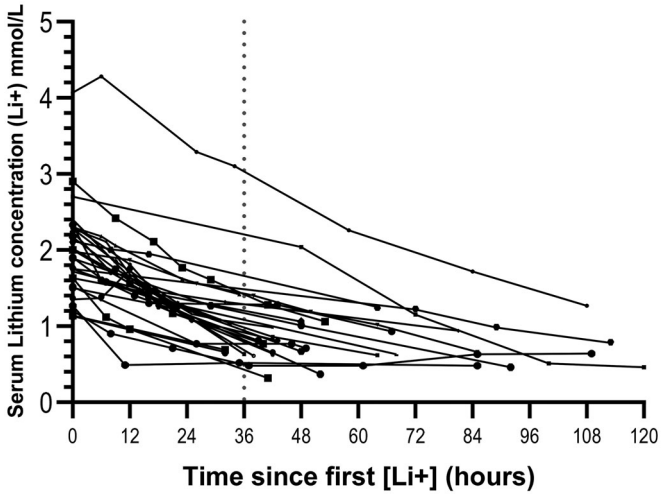

Figure 3. Summary of raw data for serial serum lithium concentration *vs.* time in non-dialysed chronic accumulation cases.

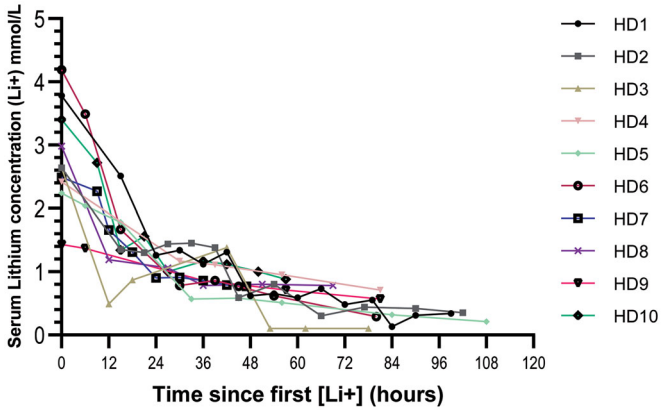

Figure 4. Summary of raw data for serial serum lithium concentration *vs.* time in dialysed chronic accumulation cases.

life during ECTR) and clinical outcome data can be found in Table 5.

DiSalvo et al. performed an external validation of the same lithium nomogram in 24 cases of chronic poisoning [17]. Their analysis revealed a sensitivity 91%, specificity 54%, PPV 63%, NPV 88% and accuracy 71% [17]. They concluded that the strong NPV might help identify patients for whom haemodialysis is unnecessary and that a larger prospective validation was required [17]. Vodovar et al. published a letter to editor where they also calculated sensitivity, specificity, NPV and PPV in Buckley et al.'s cohort [10,18]. For chronic accumulation, they reported sensitivity 59%, specificity 79%, PPV 77% and NPV 62% [18]. For acute on chronic poisoning, they reported sensitivity 95%, specificity 59%, PPV 46% and NPV 96% [18]. Vodovar et al.'s finding of a high NPV in acute on chronic poisoning and slightly above average NPV in chronic accumulation is contradictory to the findings of DiSalvo et al. Vodovar et al. stated that while Buckley et al. concluded that their nomogram should only be used in chronic accumulation patients, the performance of the nomogram was not as accurate in this cohort [19]. Nonetheless, for our acute on chronic poisoning cohort, the nomogram was not sensitive enough to identify most patients with a serum lithium concentration >1 mmol/L at 36 h without dialysis. Our findings support Buckley et al.'s recommendation that the nomogram should only be used in chronic accumulation cases [10].

The low sensitivity of the nomogram for acute on chronic poisoning cases may also be explained by the variability of pharmacokinetic parameters after acute lithium overdose. Absorption and distribution of lithium are often difficult to predict after ingestion of varying formulations in the setting of acute on chronic poisoning [9,19]. Due to prolonged absorption, peak lithium concentration can be delayed up to 12 h after acute poisoning with slow-release formulations [19]. In our acute on chronic poisoning cohort, 50% (4 out of 8) ingested a slow-released formulation (Table 1). The poor predictive value of a serum [Li+] < 1.0 mmol/L in this cohort, fits with this toxicokinetic principle, indicating the nomogram's low sensitivity for this cohort.

The biochemical criteria for chronic lithium accumulation can be variable and the serum lithium concentrations, although poorly correlating with clinical features of toxicity,

Table 5. Selected clinical and biochemical features of dialysed chronic accumulation patients.

Number	Presenting complaint	Worst GCS[a]	Hansen and Amsiden CNS toxicity Grade	Initial creatinine (umol/L)	Initial eGFR (mL/min/1.73 m^2)	Initial [Li+] (mmol/L)	Peak [Li+] (mmol/L)	Lithium half-life prior to ECTR (h)	Average lithium half-life during ECTR (h)
1	Confusion, disorientation and 3 weeks of diarrhoea	14	3	308	20	3.78	3.78	30	9.3
2	Altered conscious state	8	3	600	9	2.64	2.64	Insufficient data	13.3
3	Confusion, ataxia and 1 week of diarrhoea	11	2	71	86	2.64	2.64	Insufficient data	5.6
4	Confusion, slurred speech, tremor and reduced oral intake	12	1	1174	4	2.42	2.42	Insufficient data	26
5	Confusion	14	1	156	29	2.24	2.24	48	7.3
6	Confusion, withdrawn and weight loss	14	1	117	41	4.19	4.19	22.7	11.6
7	Altered conscious state and hypothermia 33.1 °C	6	3	307	15	2.49	2.49	60	13.5
8	Altered conscious state, bradycardia 45/min and hypotension: systolic blood pressure 83 mmHg	12	2	151	32	2.98	2.98	Insufficient data	12.9
9	Confusion, increasing falls, known end-stage renal failure planned to commence dialysis in 2 months	14	1	392	10	1.43	1.43	168	7.4
10	Confusion, withdrawn and reduced oral intake	13	1	182	37	3.4	3.4	31	8

[a]GCS: Glasgow Coma Scale

are only to guide the risk of toxicity [3,9,19]. For our study, we included patients with a peak [Li+] > 1 mmol/L. This is to reflect the EXTRIP suggested indication (level 2 D) for which Buckley *et al.* developed the nomogram to determine if patients' [Li+] would reduce to < 1.0 mmol/L by 36 h with optimal treatment [9,10]. Four (10.2%) out of 39 of our chronic accumulation patients had peak [Li+] between 1.0 and 1.4 mmol/L and all of our acute on chronic cohort had peak [Li+] above 1.4 mmol/L. Notably, all four of the chronic accumulation patients whose peak [Li+] was between 1.0 and 1.4 mmol/L met EXTRIP recommended indications for ECTR (Table 6).

The flowchart suggested by Buckley et al. for chronic lithium accumulation does not quantify the degree or severity of the "signs of neurotoxicity" [10]. Therefore, when utilising this flowchart, all patients with any signs of CNS toxicity are regarded as meeting the criteria for dialysis. In our chronic accumulation cohort, if cases with grade-1 neurotoxicity were excluded, the flowchart would only recommend dialysis in three extra cases as opposed to 16 extra cases (Figure 6). Similarly, if we excluded cases of grade-1 neurotoxicity from our chronic accumulation cohort meeting EXTRIP recommended ECTR indications, there would only be four extra cases meeting the ECTR criteria as opposed to 18 extra cases (Figure 5). Interestingly, in our non-dialysed cohort, we did not identify clinically significant outcomes in patients with grade-2 neurotoxicity compared to those with grade-1 neurotoxicity meeting Buckley flowchart and/or EXTRIP recommended criteria (Table 6). This, however, is confounded by multiple clinical factors including patient past medical history, baseline functional status and nosocomial complications.

Limitations

Our study is limited by its retrospective nature. Some cases did not have blood collected for [Li+] exactly 36 h after the first blood test. Although obtaining a 36 h [Li+] is ideal in analysing the lithium nomogram, we are aware of the limitations of precise timing in clinical practice, and therefore a four-hour time window was chosen to account for this. To reflect the true 36 h [Li+], we extrapolated the concentration from the available data. Nevertheless, we excluded cases where serial [Li+] was taken less than 32 h after the first concentration, as we aimed for the closest estimated 36-h lithium concentration. Regarding the chronic accumulation patients who received dialysis, we extrapolated their pre-dialysis [Li+] to 36 h to assess whether this would exceed 1 mmol/L if dialysis had not been undertaken. Five out 10 patients (50%) in this cohort had an actual [Li+] < 1 mmol/L at 36 h which was confounded by the fact that they received the dialysis.

In most cases, Glasgow Coma Scale (GCS) and level of consciousness were recorded on arrival, but routine recording of other signs of neurotoxicity was sporadic which could lead to our study missing the subtle signs of neurotoxicity. Co-ingestants, such as benzodiazepines and antipsychotics can also affect the patients' neurological status [9]. For our

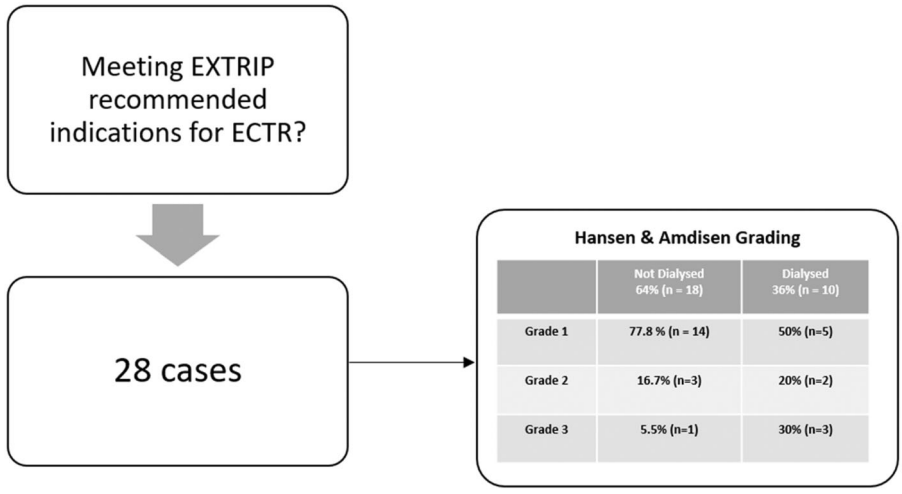

Figure 5. Application of EXTRIP's recommended indications for ECTR to chronic accumulation cases.

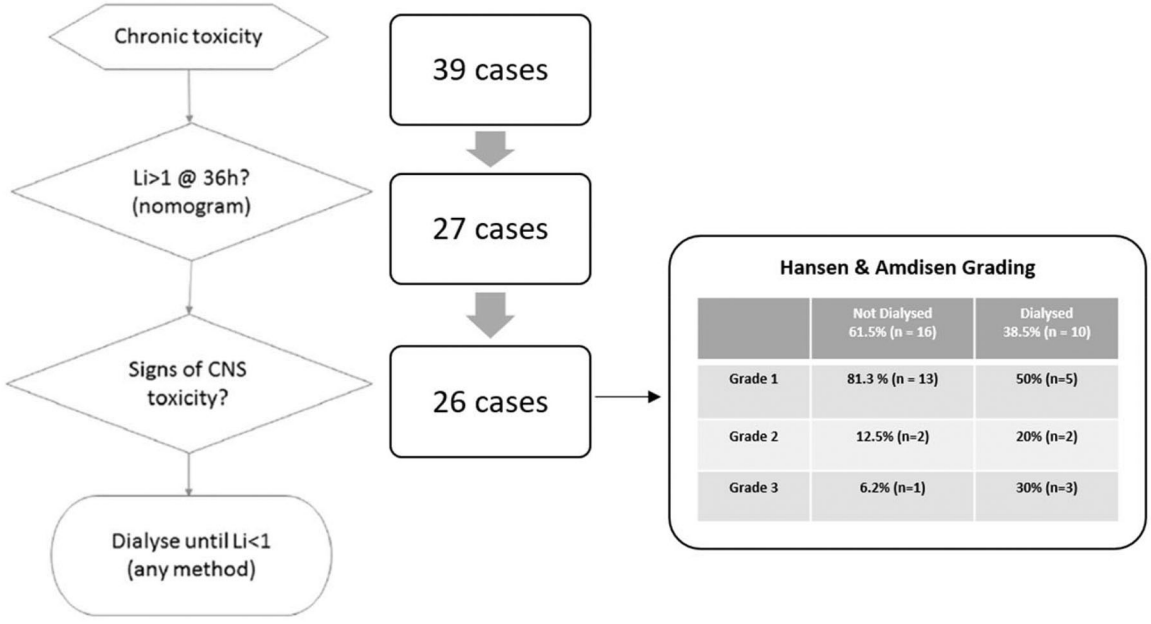

Figure 6. Application of Buckley et al.'s flow chart to chronic accumulation cases.

acute on chronic poisoning cohort, 91.7% (11 out of 12) of patients took co-ingestants. However, the neurotoxicity in this cohort was not analysed. In our chronic accumulation cohort, none had taken an acute overdose or a supratherapeutic ingestion. Regarding the dosage and formulation of lithium in all patients, we were only able to identify these based on the medical records.

All our patients had fluid rehydration as part of the first-line management of lithium poisoning. However, given that our study is retrospective, the exact amount of administered fluid which might have altered the clinical outcome was not controlled. Moreover, the toxicokinetic nature of lithium in poisoning is variable, especially in the setting of co-existing AKI [9,19] and the initial creatinine may underestimate the actual GFR affecting the accuracy of the nomogram. Regardless, the nomogram pertains to the arrival creatinine and lithium concentration and is not designed for re-stratification after fluid resuscitation.

When analysing the usefulness of the nomogram, especially for our acute on chronic cohort, the low case numbers may have affected the accuracy of the result. For chronic accumulation cases, when we included the patients who received dialysis in the contingency table analysis, the sensitivity and PPV were increased. In our opinion, within the limitations of this retrospective chart review, these patients received dialysis for multiple reasons, predominantly for altered conscious state and severe kidney impairment. Despite the correct prediction of the [Li+] at 36 h $>$ 1.0 mmol/L using the nomogram in this cohort, it is unlikely that it would have made an impact on the decision of ECTR.

When applying the EXTRIP ECTR indications to our chronic accumulation cases, we only used the EXTRIP recommended indications (1D) [9]. We did not apply the EXTRIP suggested indications (2D) to our cohort since the "confusion" in the suggested indications (2D) could be used interchangeably with the "presence of decreased level of consciousness" in

Table 6. Neurotoxicity grading, treatment, biochemical and outcome data of non-dialysed chronic accumulation patients meeting EXTRIP and/or Buckley flowchart criteria[a].

Number	Hansen and Amdisen grading	Initial Creatinine (umol/L)	Initial eGFR (mL/min/1.73 m^2)	Peak [Li+] (mmol/L)	Treatment	Neurological outcome	Medical length of stay (days)	Met EXTRIP recommended indications (Y/N)	Met Buckley et al.'s flowchart criteria (Y/N)
1	1	247	22	2.7	IV[c] Fluid and withhold lithium	Mild ataxia upon discharge	4	Y	Y
2	1	77	75	1.13	IV Fluid and withhold lithium	Muscle weakness requiring gait aid	12	Y	N
3	1	200	26	1.5	IV Fluid and withhold lithium	Deceased from COPD[e] exacerbation	11	Y	Y
4	2	89	72	1.27	IV Fluid and withhold lithium	All symptoms resolved	7	Y	N
5	1	78	109	1.75	IV Fluid and withhold lithium	All symptoms resolved	5	Y	N
6	1	51	107	2.28	IV Fluid and withhold lithium	Mild tremor	6	Y	N
7	2	175	28	2.9	IV Fluid and withhold lithium	Resolved by day 4	7	Y	Y
8	1	122	41	2.11	IV Fluid and withhold lithium	Resolved by day 6	9	Y	Y
9	1	113	44	1.2	IV fluid, withhold lithium and HDU[d] monitoring	Improved, but below baseline	18	Y	N
10	2	329	13	2.02	IV Fluid and withhold lithium	Motor function improved on day 3, mild confusion upon discharge	11	Y	Y
11	1	89	60	2.17	IV Fluid and withhold lithium	Improved	3	Y	Y
12	3	137	44	1.89	IV Fluid and withhold lithium	Slow improvement, but deteriorated from another illness and was palliated[b]	28	Y	Y
13	1	187	21	1.72	IV Fluid and withhold lithium	Cognition below baseline	13	Y	Y
14	1	75	85	1.63	IV Fluid and withhold lithium	Motor function normal by day 3, slow cognitive improvement	7	Y	N
15	1	149	39	1.9	IV Fluid and withhold lithium	Symptoms resolved by day 18, prolonged admission due to sepsis	27	Y	Y
16	1	180	29	1.98	IV Fluid and withhold lithium	Improved by day 3	6	Y	Y
17	1	113	55	2.12	IV Fluid and withhold lithium	Improved by day 5, prolonged admission due to sepsis	36	Y	Y
18	1	86	62	1.14	IV Fluid and withhold lithium	Back to normal	5	Y	N
19	1	82	82	2.32	IV Fluid and withhold lithium	Resolved	1	N	Y
20	1	88	67	2.0	IV Fluid and withhold lithium	Resolved	3	N	Y
21	1	64	94	2.4	IV Fluid and withhold lithium	Resolved	4	N	Y
22	1	158	42	2.3	IV Fluid and withhold lithium	Resolved	2	N	Y
23	1	82	101	4.07	IV fluid, withhold lithium and HDU monitoring	Slow recovery	14	N	Y

[a]All chronic accumulation patients who had dialysis met both EXTRIP and Buckley flowchart criteria.
[b]The patient met criteria for ECTR but decided not to proceed due to severe multiple comorbidities.
[c]IV: intravenous; [d]HDU: high dependency unit; [e]COPD: chronic obstructive pulmonary disease

the recommended indications (1D) [9] showing no difference in our analysis. Due to the retrospective nature of the study, we were not able to determine the opinion of the consulting toxicologist or treating clinician at the time of their decision making on the suggested indication of "the expected time to obtain a [Li+] < 1.0 mEq/L is >36 h" (2D) [9]. Regardless, none of our chronic accumulation patients had a peak [Li+] > 5.0 mmol/L, a suggested indication (2D) [9].

Conclusion

Our study suggests that the lithium nomogram was moderately sensitive at predicting patients with chronic lithium accumulation who will have a serum lithium concentration > 1 mmol/L at 36 h without ECTR. Clinical judgement and CNS toxicity grading should be included in the decision algorithm when applying the proposed flowchart to consider intervention with ECTR.

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