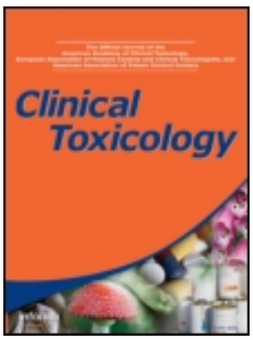

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CLINICAL RESEARCH

Lithium poisoning in the intensive care unit: predictive factors of severity and indications for extracorporeal toxin removal to improve outcome

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ABSTRACT

Context: Lithium is responsible for life-threatening poisoning, not consistently improved by extracorporeal toxin removal (ECTR).

Objective: Our aim was to identify predictive factors on admission of poisoning severity and based on an evaluation of practice, report indications for ECTR susceptible to improve outcome

Methods: We performed a retrospective cohort study including all lithium-poisoned patients admitted to the ICU in a university hospital. The usual clinical, biological and toxicological variables were collected. Poisoning severity was defined by seizures, catecholamine infusion, mechanical ventilation >48 h and/or fatality. Univariate followed by multiple logistic regression analyses were performed to identify prognosticators of poisoning severity and ECTR use.

Results: From 1992 to 2013, 128 lithium-poisoned patients including acutely (10%), acute-on-chronically (63%) and chronically poisoned patients (27%) were included. The presumed ingested dose of lithium was 17.0 g [8.0–24.5] (median [25th–75th percentiles]). Serum lithium concentrations were 2.6 mmol/l [1.5–4.6], 2.8 mmol/l [1.8–4.5] and 2.8 mmol/l [2.1–3.0] on admission, peaking at 3.6 mmol/l [2.6; 6.2], 4.3 mmol/l [2.4; 6.2] and 2.8 mmol/l [2.1; 3.1] in the three groups, respectively. Severe poisoning occurred in 48 patients (38%) including four fatalities. Using the regression analysis, predictive factors of poisoning severity were Glasgow coma score ≤10 (Odds ratio (OR), 11.1; 95% confidence interval (CI), [4.1–33.3], $p < 0.0001$) and lithium concentration ≥5.2 mmol/l (OR, 6.0; CI, [1.7–25.5], $p = 0.005$). Ninety-eight patients (77%) developed acute kidney injury according to KDIGO criteria and 22 (17%) were treated with ECTR. Peak lithium concentration ≥5.2 mmol/l (OR, 22.4; CI, [6.4–96.4]; $p < 0.0001$) and peak creatinine concentration ≥200 µmol/l (OR, 5.0; CI, [1.4–19.2]; $p = 0.01$) were associated with ECTR use. Only 21/46 patients who presented one of these two criteria were actually treated with ECTR. More significant neurological impairment persisted on discharge in patients not treated with ECTR ($p = 0.0007$) despite not significantly shorter length of ICU stay.

Conclusions: Lithium poisoning is responsible for severe impairments but rare fatalities. Severity can be predicted on admission using Glasgow coma score and lithium concentration. Our results suggest that ECTR could be indicated if serum lithium ≥5.2 mmol/l or creatinine ≥200 µmol/l.

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Introduction

Poisoning with lithium, the first-line treatment for bipolar disorders,[1] is rare, with 6,850 cases and seven fatalities reported by the American Association of Poison Control Centers in 2013.[2] Lithium poisoning may be responsible for life-threatening toxicity requiring intensive care unit (ICU) admission.[3] Three patterns have been well-described including acute (acute ingestion by a non-treated patient), acute-on-chronic (acute ingestion by a treated patient) and chronic poisoning (progressive overdose in a treated patient).[4] While acute poisoning rarely induces symptoms despite the ingestion of large amounts of lithium, acute-on-chronic and chronic poisonings result in severe toxicity.[4–6] Lithium accumulation in the brain following prolonged exposure has been hypothesized to explain the heterogeneous observed features in lithium-poisoned patients.[7–9] To date, data on severe lithium-poisonings are rare.[3,4,6,10–22]

Given lithium pharmacokinetics (i.e., no protein binding, low volume of distribution, absence of metabolism, and exclusively renal clearance),[23] hemodialysis represents the method of choice to enhance lithium elimination and continuous renal replacement therapy is an acceptable alternative.[24] However, extracorporeal toxin removal (ECTR) indications and benefits remain controversial, based on experts' opinions since no clear poisoning prognostic indicators have been demonstrated.[24,25] Consistently, there is no evidence from randomized controlled trials to neither support nor refute the use of hemodialysis in the management of patients with lithium poisoning.[26] ECTR may prevent severe toxicity in patients at risk of exhibiting elevated serum lithium concentrations, but may not efficiently reverse the observed neurotoxicity in those severely symptomatic. The aim of our study were (1) to describe lithium-poisoned patients admitted to the ICU; (2) to identify parameters on

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admission associated with severe poisoning; (3) to report criteria associated with ECTR use based on an evaluation of practice; and (4) to assess ECTR impact on patients' neurological status on ICU discharge.

Materials and methods

Study setting and design

This retrospective study was conducted in an 18-bed medical and toxicological ICU in an 850-bed tertiary university hospital in Paris, France. Patients with lithium poisoning admitted from January 1993 to December 2013 were selected using our toxicological laboratory database. Patients with at least one serum lithium concentration >1.5 mmol/l measured during the ICU stay were included in the study. Lithium poisoning was managed at the discretion of the physicians in charge. The review board of the French Society of Critical Care Medicine approved the study (CE-SRLF 13-53). Consent from the patients was not required.

Data collection and measurements

On admission, the data collected included: demographics (age, gender, morbidities), lithium poisoning history (presumed ingested dose, formulation, co-ingestants, patterns of exposure, triggers of poisoning in chronic exposure), clinical data (symptoms, vital signs, physical examination, 24h-urine output), biological data (ICU admission and peak concentrations of serum creatinine and lithium) and ICU management (gastrointestinal decontamination, fluids during the first 24 h, mechanical ventilation, ECTR). The new simplified acute physiology score (SAPS II), a routine tool used to predict ICU patient's probability of death, was calculated on ICU admission.[27] Two abstractors blinded to the study objectives collected the data from the patients' records. Lithium quantification was performed using inductively coupled plasma mass spectrometry (Elan DRCe Perkin Elmer, Courtaboeuf, France; limit of quantification: 0.6 nmol/l).

Definitions

Grading of clinical features related to lithium toxicity was assessed using Hansen and Amdisen's criteria,[3] as follows: grade 0, if asymptomatic; grade 1, in the presence of any of nausea, vomiting, tremor, hyperreflexia, agitation, muscle weakness, ataxia or drowsiness; grade 2 in the presence of stupor, rigidity or hypotension; and grade 3 in the presence of coma, seizures, myoclonia or cardiovascular instability. Lithium poisoning was defined as severe in the presence of at least one of the following conditions: (1) seizures; (2) catecholamine infusion; (3) mechanical ventilation lasting >48 h; and (4) fatality onset in the ICU. These conditions were chosen to facilitate the retrospective recognition of Hansen and Amdisen's grade 3 in the medical records. Consistently, cardiovascular instability was defined by catecholamine use and significant consciousness impairment by mechanical ventilation requirement >48 h to focus at lithium-related coma and try to overcome any confounding contribution of sedative co-ingestants. Acute kidney injury (AKI) was assessed according to the Kidney Disease Improving Global Outcomes criteria (KDIGO) that graded severity in three stages according to serum creatinine, urine output and need for renal replacement therapy.[28] Persistent loss of kidney function (i.e. for >4 weeks) and end-stage renal disease were defined according to the Risk Injury Failure Loss and End stage (RIFLE) criteria.[29]

Statistics

Continuous variables are expressed as medians [25th; 75th percentiles] and categorical variables as numbers and percentages. Comparisons between groups were performed using Kruskal–Wallis tests or Mann–Whitney *U*-tests (for continuous variables) and Fisher's exact tests (for categorical variables, performed with 2×2 or 2×3 tables as required). Significant variables at a 5%-threshold and variables usually suggested as being associated with severe lithium poisoning (i.e. pattern of lithium poisoning and lithium formulation) or ECTR requirement (i.e. kidney function, level of consciousness, seizure onset, catecholamine use and serum lithium concentration) were considered in a single multiple logistic regression after further data selection to remove parameters strongly correlated or clinically irrelevant. Continuous variables were considered both directly and after conversion into a binary variable using a threshold determined by a receiver operating characteristic (ROC) curve analysis. The obtained model was then simplified by a backward step regression based on the Akaike's Information Criteria.[30] A variable was considered in the final model if it significantly improved the model fit using a likelihood ratio test. Results are expressed as odds ratios (OR) with their 95% confidence intervals (CI). The model quality was checked using the specificity, sensitivity, positive and negative predictive values and accuracy (proportion of well predicted cases) after using the best threshold based on ROC curves. The best threshold was defined as the value that lead to the point on the ROC curve closest to the perfection (i.e., sensitivity = specificity = 1, at the upper left corner), with equal weight given to sensitivity and specificity. All these parameters are given with their exact 95% confidence intervals. Regarding factors associated with ECTR use, we built a decision tree to maximize the sensitivity and limit the number of missed cases treated with ECTR. All analyses were made using R version 3.0 and suitable additional packages (pROC, car).

Results

Poisoning characteristics, management and outcome

Characteristics

From January 1993 to December 2013, 128 lithium-poisoned patients (male/female ratio, 0.7; SAPS II, 30 [19; 44]) were included in the study, consisting of acute ($N = 12$, 10%), acute-on-chronic ($N = 81$, 64%), and chronic ($N = 35$, 26%) poisonings (Table 1). The median age (46 years [35; 55] in the

whole population) was significantly higher in the chronic poisoning group ($p < 0.001$).

In cases of acute lithium ingestion ($N = 93$), the presumed ingested dose was 17.0 g [8.0; 24.5], involving a sustained release formulation in 67 patients (72%). Time from ingestion to ICU admission was 8.3 h [4.0; 26.0]. Co-ingestions were observed in half of the patients ($N = 46$, 50%) including benzodiazepines ($N = 23$, 50%), antipsychotics ($N = 11$, 24%), ethanol ($N = 10$, 22%), and serotonin reuptake inhibitors ($N = 6$, 13%). No significant cardiotoxic co-ingestion was reported. In the chronically poisoned patients ($N = 35$), lithium overdose was attributed to either renal failure ($N = 23$, 66%) or to the recent increase in lithium dose regimen ($N = 4$, 11%). Several non-exclusive factors may have contributed to renal failure responsible for lithium overdose including urinary tract obstruction ($N = 3$, 13%), recent use of non-steroidal anti-inflammatory drugs ($N = 4$; 17%), angiotensin-converting-enzyme inhibitors ($N = 14$, 61%) and diuretics ($N = 8$, 35%).

In the whole patient population, the serum lithium concentration on admission was 2.8 mmol/l [1.9; 4.1] and peaked at 3.2 mmol/l [2.3; 5.4]. The peak lithium concentration was significantly higher in the acutely and acute-on-chronically in comparison to the chronically poisoned patients ($p = 0.008$). In the acute and acute-on-chronically poisoned patients, peak lithium was measured 23.5 h [10.0; 44.5] after the ingestion (26.0 h [10.6; 45.4] in case of sustained vs. 18.0 h [5.3; 38.9] in case of immediate release formulations, $p = 0.08$).

The proportion of patients who developed grade 2–3 toxicity according to Hansen and Amdisen's criteria was higher in the chronic than in the acute and acute-on-chronic poisoning groups ($p = 0.003$, Table 2). Glasgow coma score (GCS, 14 [11; 15] in the whole population) on ICU admission as well as the worst GCS during ICU stay (12 [7; 14]) did not significantly differ between the three groups. Following acute overdose, time from the ingestion to the worst GCS was 10.6 h [5.0; 50.0]. Onset of seizures ($N = 11$, 9%) was not significantly different between the three groups. Electroencephalograms (available in 58 patients) showed slow rhythms ($N = 40$, 69%) and subclinical seizures ($N = 3$, 5%). Cardiovascular complications included collapse/shock ($N = 25$, 20%), asystole ($N = 3$, 2%), sudden bradycardia ($N = 3$, 2%; including one patient with third-degree atrioventricular block and two patients with sinoatrial block) with no significant differences between the three groups. According to the KDIGO's criteria, 98 patients (77%) developed acute kidney injury, more frequently in the chronic poisoning

Table 1. Toxicants and poisoning patterns in 128 lithium-poisoned patients admitted to the intensive care unit.

	Acute poisoning ($N = 12$)	Acute-on-chronic poisoning ($N = 81$)	Chronic poisoning ($N = 35$)	p value[b]
Presumed lithium ingested dose (g)	10.0 [8.0; 25.0][a]	18.5 [8.0; 25.0]	–	0.7
Sustained release formulation of lithium, *N* (%)	8 (66)	59 (73)	20 (57)	0.2
Co-ingested toxicants, *N* (%)	7 (58)	39 (48)	–	0.5
- Ethanol	1 (8)	9 (11)	–	1.0
- Benzodiazepines	3 (25)	20 (25)	–	1.0
- Antipsychotics	2 (16)	9 (11)	–	0.6
- Serotonin reuptake inhibitors	0 (0)	6 (7)		1.0
Lithium concentrations (mmol/l)				
- On admission	2.6 [1.5; 4.6]	2.8 [1.8; 4.5]	2.8 [2.1; 3.0]	0.8
- Peak	3.6 [2.6; 6.2]	4.3 [2.4; 6.2]	2.8 [2.1; 3.1]	**0.0008**

Bold values represent significant differences.
[a]Median [25th; 75th percentiles]
[b]Fisher's exact tests were used to compare categorical variables and Kruskal–Wallis tests to compare continuous variables.

Table 2. Neurologic complications in 128 lithium-poisoned patients admitted to the intensive care unit.

	Acute poisoning ($N = 12$)	Acute-on-chronic poisoning ($N = 81$)	Chronic poisoning ($N = 35$)	p value[b]
Hansen and Amdisen's score				
Grades 2–3, *N* (%)	9 (75)	60 (74)	35 (100)	**0.003**
Grades 0–1, *N* (%)	3 (25)	21 (26)	0 (0)	
Glasgow coma score				
On admission	14 [10; 15][a]	14 [10; 15]	13 [11; 14]	0.3
Worst value during hospitalization	13 [6; 15]	11 [6; 15]	13 [10; 14]	0.5
Neurological impairment features				
- Drowsiness, *N* (%)	4 (33)	37 (30)	20 (57)	**0.009**
- Hyperreflexia, *N* (%)	5 (42)	24 (30)	14 (40)	0.5
- Agitation, *N* (%)	2 (16)	11 (14)	6 (17)	0.9
- Tremor, *N* (%)	4 (33)	32 (40)	24 (69)	**0.01**
- Ataxia, *N* (%)	0 (0)	4 (5)	4 (11)	0.2
- Stupor, *N* (%)	4 (33)	36 (45)	32 (91)	**0.001**
- Dysarthria, *N* (%)	1 (8)	11 (14)	10 (29)	**0.009**
- Myoclonus, *N* (%)	3 (25)	10 (12)	13 (37)	**0.007**
- Rigidity, *N* (%)	4 (33)	8 (10)	14 (40)	**0.001**
- Hypertonia, *N* (%)	5 (42)	16 (19)	20 (57)	**0.001**
- Coma, *N* (%)	6 (50)	33 (42)	6 (17)	**0.002**
- Seizures, *N* (%)	0 (0)	6 (7)	5 (11)	0.5
Neurological recovery on discharge, *N* (%)	9 (75)	69 (85)	22 (63)	**0.02**

Bold values represent significant differences.
[a]Median [25th; 75th percentiles]
[b]Fisher's exact tests were used to compare categorical variables and Kruskal–Wallis tests to compare continuous variables.

Table 3. Kidney function in 128 lithium-poisoned patients admitted to the intensive care unit.

	Acute poisoning ($N = 12$)	Acute-on-chronic poisoning ($N = 81$)	Chronic poisoning ($N = 35$)	p value[b]
Preexisting chronic renal failure N (%)	0 (0)	1 (1)	4 (11)	**0.03**
Serum creatinine concentration (µmol/l)				
On admission	84 [65; 207][a]	80 [68; 100]	169 [109; 280]	**<0.0001**
Peak	93 [70; 322]	87 [72; 122]	169 [109; 280]	**<0.0001**
On discharge	65 [61; 77]	66 [57; 82]	89 [68; 104]	**0.0008**
MDRD GRF (ml/min)				
On admission	85 [34; 132]	95 [75; 120]	37 [21; 65]	**<0.0001**
Lowest value	75 [20; 129]	90 [61; 116]	37 [21; 65]	**<0.0001**
On discharge	128 [106; 139]	124 [94; 145]	78 [66; 112]	**<0.0001**
Urine output during the first 24 h (ml)	1900 [1450; 4775]	2000 [1200; 2800]	1812 [1200; 2800]	0.7
KDIGO criteria, N (%)				
Stage 1	3 (25)	29 (36)	10 (28)	
Stage 2	2 (17)	22 (27)	13 (37)	**0.03**
Stage 3	4 (33)	7 (9)	8 (23)	
Acute kidney injury	9 (75)	58 (72)	31 (88)	**0.03**

Bold values represent significant differences.
[a]Median [25th; 75th percentiles]
[b]Fisher's exact tests were used to compare categorical variables and Kruskal–Wallis tests to compare continuous variables; MDRD: modification of diet in renal disease study equation; GRF: glomerular rate filtration; KDIGO: kidney disease improving global outcomes.[16]

Table 4. Management and outcome of 128 lithium-poisoned patients admitted to the intensive care unit.

	Acute poisoning ($N = 12$)	Acute-on-chronic poisoning ($N = 81$)	Chronic poisoning ($N = 35$)	p value[b]
Gastrointestinal decontamination, N (%)	7 (58)	49 (60)	1 (3)	**0.001**
- Whole bowel irrigation, N (%)	2 (17)	35 (43)	1 (3)	**0.0003**
- Gastric lavage, N (%)	5 (42)	13 (16)	0 (0)	**0.003**
- Activated charcoal, N (%)	2 (17)	10 (12)	0 (0)	0.06
- Sodium polystyrene sulfonate, N (%)	0 (0)	2 (2)	0 (0)	0.6
Fluids during the first 24 h (ml)	3500 [2800; 4750][a]	3000 [2500; 4000]	3000 [2500; 4000]	0.4
Mechanical ventilation,	6 (50)	37 (46)	6 (17)	**0.01**
Duration (days), N (%)	0.5 [0; 5]	0 [0; 4]	0 [0; 0]	**0.03**
Extracorporeal toxin removal, N (%)	2 (17)	17 (21)	3 (9)	0.3
Outcome				
Death, N (%)	0 (0)	4 (5)	0 (0)	0.3
Persistent neurotoxicity on discharge, N (%)	3 (25)	8 (10)	13 (37)	**0.02**
Length of hospital stay (days)	2.5 [1.5; 8.0]	4.0 [2.0; 8.0]	9.0 [4.0; 14.5]	**0.004**

Bold values represent significant differences.
[a]Median [25th; 75th percentiles]
[b]Fisher's exact tests were used to compare categorical variables and Kruskal–Wallis tests to compare continuous variables.

group ($p = 0.03$, Table 3). Admission and peak serum creatinine concentrations were 87 µmol/l [72; 167] and 100 µmol/l [75; 178] in the whole population, respectively. Using univariate analysis, both parameters were significantly higher in the chronic poisoning group ($p = 0.0001$). Other complications included aspiration pneumonia ($N = 44$, 34%), acute respiratory distress syndrome ($N = 5$, 4%), rhabdomyolysis ($N = 12$, 9%), and reversible nephrogenic diabetes mellitus ($N = 13$, 10%, only occurring in the acute-on-chronically and chronically poisoned patients).

Management

Poisoning management is given in Table 4. Fluids during the first 24 h did not significantly differ between the three groups. Mechanical ventilation was more frequently required in the acute and acute-on-chronic poisonings ($p = 0.01$). Veno-arterial extracorporeal membrane oxygenation ($N = 1$, 1%) was required in one patient with refractory cardiovascular failure. ECTR ($N = 22$, 17%) consisted of intermittent hemodialysis ($N = 12$, 54%), continuous veno-venous hemodiafiltration ($N = 6$, 28%) or both techniques successively performed ($N = 4$, 18%). Time from ICU admission to ECTR was 23.0 h [6.0; 38.0]. No significant differences in ECTR use were observed between the three groups.

Outcome

Four patients died (3%) among the acute-on-chronically poisoned patients (Table 4). Three patients developed multiorgan failure and died <48 h after ICU admission: none of them received ECTR. One 80-year-old patient treated with ECTR died from massive stroke 3 weeks after ICU admission. Lithium concentrations were >6 mmol/L on admission in these four fatalities.

Length of ICU stay was 5.0 days [2.5; 10.5], significantly longer in the chronically lithium-poisoned patients ($p = 0.004$). Lithium-attributed neurotoxicity including confusion, dysarthria, hypertonia, myoclonus and ataxia persisted in 24 patients (20%) on ICU discharge, more frequently in the chronically lithium-poisoned patients ($p = 0.02$). Serum creatinine on ICU discharge was significantly higher in chronically vs. acute and acute-on-chronically poisoned patients ($p < 0.001$). However, no patient developed persistent loss of kidney function or end-stage renal disease.

Predictive factors of poisoning severity

Forty-eight patients (38%) developed severe features, as previously defined (Table 5). The proportion of multidrug poisoning was significantly higher in the severely lithium-poisoned

Table 5. Univariate analysis of predictors of severity in 128 lithium-poisoned patients on admission to the intensive care unit.

	Severe poisoning[a] ($N = 48$)	Non-severe poisoning ($N = 80$)	OR [95% CI]	p value[c]
Age (years)	44 [33; 55][b]	47 [36; 56]	1.0 [0.97; 1.02]	0.9
Gender (F/M), N (%)	54/46	63/36	1.5 [0.7; 3.3]	0.4
Poisoning pattern, N (%)				
Acute	5 (10)	7 (9)	0.9 [0.3; 3.3]	0.8
Acute-on-chronic	32 (67)	49 (61)	0.6 [0.2; 2.6]	
Chronic	11 (23)	24 (30)		
Chronic treatment, N (%)	43 (90)	73 (91)	0.8 [0.2; 3.5]	0.8
Co-ingested toxicants, N (%)	24 (50)	23 (29)	2.5 [1.1; 5.6]	**0.02**
Sustained release lithium formulation, N (%)	37 (77)	50 (62)	2.0 [0.8; 5.0]	0.1
Glasgow coma score ≤10, N (%)	23 (48)	7 (9)	10.0 [3.8; 20.0]	**<0.0001**
Serum lithium ≥5.2 mmol/l, N (%)	14 (29)	4 (5)	7.8 [2.6; 29.2]	**0.0002**
Serum creatinine ≥200 µmol/l, N (%)	15 (31)	8 (10)	2.8 [1.3; 5.8]	**0.006**

Bold values represent significant differences.
[a]Severity of poisoning was defined by the presence of at least one of the following conditions: (1) seizures; (2) catecholamine infusion; (3) mechanical ventilation lasting >48 h; and (4) fatality onset in the ICU.
[b]Median [25th; 75th percentiles].
[c]Fisher's exact tests were used to compare categorical variables and Mann–Whitney tests to compare continuous variables.

Table 6. Univariate analysis of predictors of extracorporeal toxin removal in 128 lithium-poisoned patients admitted to the intensive care unit.

	Dialysis ($n = 22$)	No dialysis ($n = 106$)	OR [95% CI]	p value[a]
Poisoning pattern, N (%)				
Acute	2 (9)	10 (9)	1.3 [0.31; 9.17]	0.3
Acute-on-chronic	17 (77)	64 (60)	0.47 [0.07; 3.93]	
Chronic	3 (14)	32 (30)		
Sustained release lithium formulation, N (%)	19 (86)	68 (66)	3.5 [0.9; 20.0]	**0.05**
Co-ingested toxicants, N (%)	11 (50)	36 (34)	1.93 [0.7; 5.46]	0.2
Preexisting chronic renal failure, N (%)	2 (9)	3 (3)	3.4 [0.27; 32.0]	0.2
Worst Glasgow coma score during hospitalization ≤6, N (%)	11(50)	18(17)	5.0 [2.0; 10.0]	**0.017**
Shock, N (%)	7 (31)	13 (12)	3.3 [0.9; 11.0]	**0.05**
Mechanical ventilation, N (%)	14 (63)	34 (33)	3.7 [1.3; 11.13]	**0.008**
Serum lithium ≥5.2 mmol/l, N (%)	12 (55)	15 (14)	7.3 [2.7; 20.3]	**<0.0001**
Serum creatinine ≥200 µmol/l, N (%)	18 (81)	14 (13)	29.6 [9.5; 114.6]	**<0.0001**

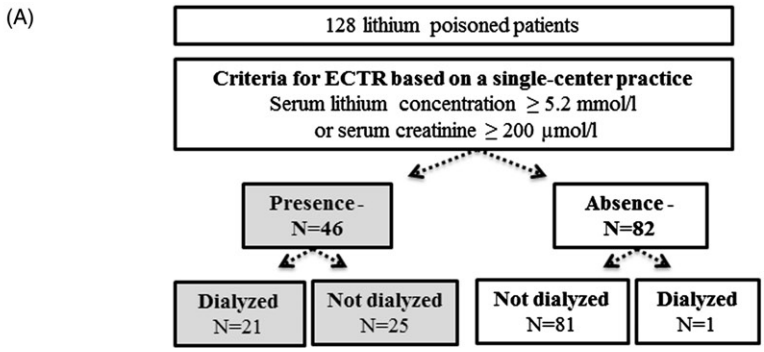
Bold values represent significant differences.
[a]Using Fisher's exact tests.

patients ($p = 0.02$) in contrast to the proportions of sustained release formulations and chronic treatment. On admission, GCS was significantly lower (11 [7; 14] vs. 14 [13; 15], $p = 0.001$) and serum creatinine (110 µmol/l [79; 206] vs. 83 µmol/l [67; 123], $p = 0.01$) and lithium concentrations (2.8 mmol/l [1.7; 5.6] vs. 2.5 mmol/l [1.9; 3.6], $p = 0.03$) significantly higher in the severely poisoned patients. Similarly, the peak lithium (5.1 mmol/l [2.6; 13.6] vs. 2,2 mmol/l [2.2; 4.4], $p = 0.005$) and creatinine concentrations (134 µmol/l [86; 293] vs. 87 µmol/l [72; 128], $p = 0.003$) were significantly higher. Based on a multiple logistic regression analysis, GCS ≤10 (OR, 11.1; CI, [4.1; 33.3], $p < 0.0001$), and lithium concentration ≥5.2 mmol/l (OR, 6.0; CI, [1.7; 25.5], $p = 0.005$) on admission were associated with the onset of severe poisoning (sensitivity of 0.64 (CI, [0.49; 0.78]), specificity of 0.86 (CI, [0.78; 0.92]), positive predictive value of 0.74 (CI, [0.58; 0.86]), negative predictive value of 0.80 (CI, [0.70; 0.88]) and accuracy of 0.78 (CI, [0.71; 0.85])). Interestingly, severely lithium-poisoned patients stayed longer in the ICU (11.0 days [5.2; 20.8] vs. 3.0 days [2.0; 7.0], $p < 0.0001$) and more frequently presented persistent neurological impairment on discharge ($N = 18$, 37% vs. $N = 10$, 13%, $p = 0.001$).

Predictive factors of ECTR requirement

Patients who underwent ECTR had significantly lower GCS (7 [3; 10] vs. 13 [7; 15.0], $p = 0.0003$) and higher peak serum creatinine (205 µmol/l [9; 329] vs. 94 µmol/l [74; 141], $p = 0.009$) and lithium concentrations (6.4 mmol/l [5.6;10] vs. 3.0 mmol/l [2.1; 4.3], $p = 0.001$) during ICU stay (Table 6). Severe lithium-poisoned patients were more frequently treated with ECTR ($N = 18$, 38% vs. $N = 4$, 5%, $p < 0.0001$). Based on a multiple logistic regression analysis, peak lithium concentration ≥5.2 mmol/l (OR, 22.4; CI, [6.4; 96.4]; $p < 0.0001$) and peak creatinine concentration ≥200 µmol/l (OR, 5.0; [1.4; 19.2]; $p = 0.01$) were associated with ECTR use (sensitivity of 0.95 (CI, [0.77; 1.00]), specificity of 0.76 (CI, [0.67; 0.84]), positive predictive value of 0.45 (CI, [0.31; 0.61]), negative predictive value of 0.99 (CI, [0.93; 1.00]) and accuracy of 0.80 (CI, [0.73; 0.87])).

Forty-six patients (36%) presented at least one of our two criteria associated with ECTR use; however, only 21 were actually treated with ECTR. Figure 1 shows patient outcome according to their peak lithium and creatinine, the presence/absence of ECTR criteria and to the actual ECTR performed in the ICU. More significant neurological impairment including confusion, dysarthria, hypertonia, myoclonus and ataxia persisted on ICU discharge in the patients who were not treated with ECTR ($N = 12$, 54% vs. $N = 3$, 20%, $p = 0.0007$), despite less severe intoxication ($p = 0.02$), mechanical ventilation >48 h ($p < 0.001$) and need for catecholamine ($p < 0.05$). Additionally, no significant differences in gastrointestinal decontamination, fluid repletion and length of ICU stay were observed in these patients.



Death (N,%)	1 (5)	3 (12)	0 (0)	0
Neurologic impairments (N,%)	3 (15)*	12 (54)*	9 (11)	0
ICU stay (days)	14.0 [7.2-21.0]	9.0 [6.0-20.5]	4.0 [2.0-6.5]	3

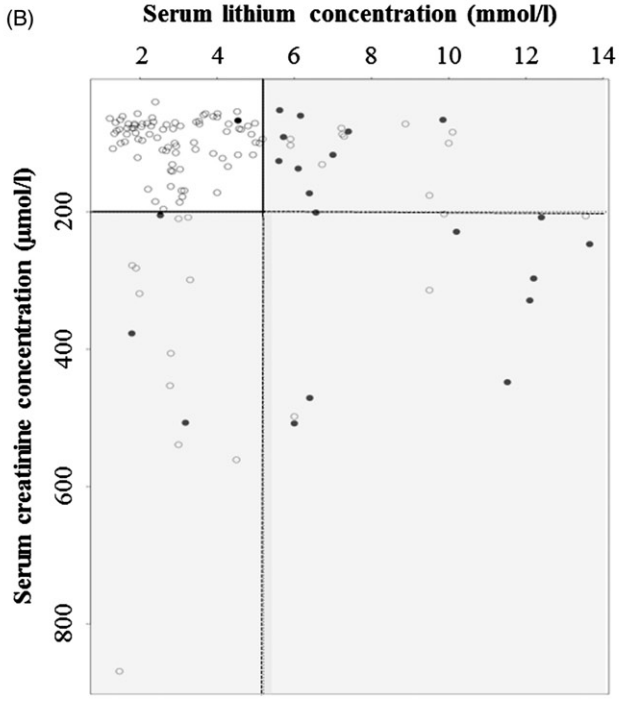


Figure 1. Extracorporeal toxin removal (ECTR) in 128 lithium-poisoned patients based on a single-centre experience. (A) Outcome according to the presence/absence of the ECTR criteria (i.e. serum lithium concentration ≥5.2 mmol/l or serum creatinine concentration ≥200 µmol/l) and the actual ECTR in the intensive care unit (ICU). Neurological impairment on ICU discharge included confusion, dysarthria, hypertonia, myoclonus and ataxia. (B) Patients were classified according to their peak lithium and creatinine concentrations and to the actual performance of ECTR (the black circles represent patients treated with ECTR and the white circles represent patients not treated with ECTR). *$p < 0.05$.

Discussion

We identified clinical parameters associated with poisoning severity and ECTR use in a series of 128 lithium-poisoned patients admitted to the ICU. Our data suggest that ECTR may significantly improve neurological status on ICU discharge in lithium-poisoned patients with serum lithium ≥5.2 mmol/l or creatinine ≥200 µmol/l.

Prediction of lithium poisoning severity

Prolonged exposure to lithium has been associated with poisoning severity based on the frequency of onset of Hansen and Amdisen's grades 2–3 in this subset of patients.[5] This relationship could be explained by the markedly delayed diagnosis, the higher rate of older poisoned patients with underlying brain susceptibilities [31] and the prolonged lithium half-life leading to enhanced brain exposure.[11,17] In our study, chronically poisoned patients more frequently presented Hansen and Amdisen's grades 2–3 in comparison to acutely and acute-on-chronically poisoned patients ($p = 0.003$, Table 2); however, chronic exposure was not identified as a significant prognostic indicator in our regression analysis. Several reasons may explain these discrepancies in comparison to Waring's study,[6] including a higher proportion of patients with chronic exposure in our study (91% vs. 40%) and greater severity of our acutely poisoned patients as supported by the mean value of the presumed lithium ingested

dose (10 g vs. 5 g) and peak lithium concentration (3.6 mmol/l vs. 2.4 mmol/l). Interestingly, chronically poisoned patients more frequently presented neurological impairments on ICU discharge ($p = 0.02$) despite significantly longer ICU stay ($p = 0.004$) and lower peak lithium concentrations ($p = 0.0008$). Moreover, death only occurred in the group of acute-on-chronically poisoned patients in our study.

In contrast to Waring et al.,[6] we choose not to consider the presumed ingested lithium dose in our analysis of poisoning severity since this data is not relevant in chronic poisoning and not reliable in patients with consciousness impairment. In our series, sustained release lithium formulation was not associated with increased poisoning severity. Such a relationship was previously suggested based on pharmacokinetic studies [23,32–35] but not definitively demonstrated by clinical studies. In massive ingestions involving sustained release tablets, delayed absorption may lead to gastro-intestinal drug reservoir responsible for successive lithium peaks in serum, promoted by food intake,[34,35] and consequently to prolonged brain exposure to elevated lithium concentrations. Our data did not support the worsening contribution of sustained release lithium formulation; however, as previously suggested,[22] the use of whole bowel irrigation in some of our patients who acutely ingested sustained release lithium may have limited its deleterious effects.

GCS $\leq$10 on admission was the strongest prognostic indicator evidenced in our series. However, due to the high incidence of co-ingested sedative drugs in our lithium poisonings, we tried to limit possible biases by using mechanical ventilation requirement during a period $>$48 h as criterion of poisoning severity, assuming that benzodiazepines and ethanol, the most frequently expected psychoactive co-ingestants, do not usually need prolonged ventilation.[36,37] Additionally, both substances are rarely involved in seizure onset and catecholamine requirement,[36] the two other criteria used to define poisoning severity in our study.

Lithium concentration $\geq$5.2 mmol/l on admission was the second prognostic indicator evidenced in our series, although controversial in the literature.[6,16] Interestingly, lithium concentrations were higher in our patients in comparison to other studies, suggesting that the prognostic value of serum lithium is more easily evidenced in studies including more severe patients.

Surprisingly, renal clearance impairment was not identified as an independent prognostic indicator based on our regression analysis, despite the major role of the kidneys in lithium elimination.[23] About 77% of our patients presented acute kidney injury during the first 24 h according to KDIGO's criteria, but significantly more frequently in the chronically poisoned patients, as expected (Table 3). Prolonged lithium therapy is associated with increased risk of reduced urinary concentrating ability, although, based on a meta-analysis, little evidence for a clinically significant reduction in renal function exists in most patients, and the risk of end-stage renal failure is low.[38] In lithium-treated patients, acute kidney injury as well as recent increase in lithium dose regimen triggers the onset of chronic poisoning.[5] Interestingly, none of our acute and acute-on-chronically poisoned patients developed further chronic renal failure, supporting the reversibility of renal injury induced by acute lithium exposure, assuming prompt and adequate fluid infusion and supportive care.

ECTR indications in lithium poisoning

Our study showed that serum lithium concentration $\geq$5.2 mmol/l or serum creatinine concentration $\geq$200 µmol/l can reasonably be used to initiate ECTR in lithium-poisoned patients. It is noteworthy that only three chronically poisoned patients (lithium concentrations: 1.79, 2.53, and 3.16 mmol/l) were treated with ECTR. It is obvious that 5.2 mmol/L cannot be reached in this setting (range of the observed lithium concentrations: 1.2–3.16 mmol/l). Therefore, it is clear that ECTR indication in chronically poisoned patients should be based on the importance of renal failure. However, we cannot rule out that a specific threshold of lithium concentration could be identified in chronically poisoned patients, but our study was unable to define it.

While renal failure is the usually accepted criterion to indicate ECTR,[39–41] lithium concentration remains controversial with multiple suggested thresholds based on experts' opinions: $\geq$ 4.0,[39,42] $>$ 4.0,[41] $>$ 5[24] or $\geq$7.5 mmol/l[43] regardless of clinical features and poisoning pattern; $\geq$ 2.5,[39,42] $>$ 2.5 [41,44]or $>$4.0 mmol/l[43,45] in chronically exposed patients; and $>$4.0 mmol/l in combination with renal failure.[24] Jaeger et al. recommended determining the exact phase of lithium kinetics rather than using a concentration threshold to indicate ECTR.[4] Accordingly, increase in serum concentrations during the first hours corresponds to persisting lithium absorption, thus indicating the need for gastro-intestinal decontamination. Decrease in serum concentrations corresponds to lithium distribution with maintained elimination, thus precluding the need for emergency ECTR. In contrast, increase in the lithium elimination half-life evidently supports the indication for ECTR. These kinetic considerations explain the discrepancies between the different thresholds proposed in the literature.

Surprisingly, impairment of consciousness was not identified as an independent predictor of ECTR requirement in our study, despite it being a usual criterion based on experts' opinion.[24,39–45] However, in the patients who had or should have been treated with ECTR, GCS was significantly lower (7 [4; 12] vs. 14.0 [9; 15], $p = 0.001$) despite no significant differences in co-intoxication rate (25% vs. 30%, $p = 0.8$).

Usefulness of hemodialysis is based on kinetic studies demonstrating increased lithium elimination with reduced half-lives (3–6 h vs. 16–30 h) and enhanced clearance (80–120 vs. 15–20 ml/min) in patients with normal kidney function.[4,15–23] Continuous veno-venous hemodiafiltration is less effective than hemodialysis (resulting clearance: 20–50 ml).[46] However, the exact impact of ECTR on reversing and improving lithium-attributed neurotoxicity has never been demonstrated.[15,21,24] Our findings suggest that ECTR if performed according to our criteria may improve the patient's neurological status on ICU discharge.

Study strengths and limitations

Available data on severe lithium poisoning are limited due to the small number of studied patients (<50) and to the low proportion of severe cases (<20%) in the published case-series. The largest series (>150 cases) are poison center series, with multiple missing clinical and biological data items. In our study, we provided a broad description of severe lithium poisonings, detailing the different lithium-induced neurological, renal and cardiovascular complications in relation to the ingested amounts and serum concentrations. Although Hansen and Amdisen's scale is controversial especially for the acute overdoses,[16] we included a larger proportion of severe poisonings in comparison to previous studies (grades 2–3: 81% vs. ~20%).[6,16] Accordingly, peak lithium concentrations were more elevated in our study (mean value: 4.6 mmol/l) in comparison to previous series (<3.5 mmol/l).[3,4,6,16–20] Our single-centre retrospective study also has significant limitations. One major confounding factor is the elevated prevalence of co-ingestions; however, this corresponds to the accurate "real life" patient. Our study spans two decades; however, we do not believe that changes in ECTR machines and membranes may have affected our findings. We cannot rule out in the absence of a simple operational biomarker able to discriminate between the different patterns of lithium poisoning that some non-observant patients considered as acute-on-chronically poisoned were actually acutely poisoned. Additionally, criteria to recommend ECTR were determined based on our single-centre experience and long-term follow-up of symptomatic patients on discharge was not available. Further prospective external validation of these criteria is warranted to increase the model estimates and only a multicentric randomized study with prolonged neurological follow-up could definitively demonstrate ECTR's contribution to improving lithium-poisoned patients' outcome as suggested by the recent meta-analysis.[26]

Conclusion

Lithium poisoning is rare but frequently responsible for neurological, renal and cardiovascular impairment. Based on a single-centre evaluation of practice, we identified helpful criteria to predict poisoning severity and provide better indications for ECTR use. However, further prospective studies are needed to definitively identify patients in whom ECTR improves outcome.

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The authors report no declaration of interest. The authors alone are responsible for the content and writing of the paper.

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