Received: 15 August 2019 | Revised: 7 September 2019 | Accepted: 28 September 2019

DOI: 10.1111/bcp.14149

COMMENTARY

Evidence-based recommendations for haemodialysis in lithium-poisoned patients: Getting from where we are to where we want to be

Robert S. Hoffman

Division of Medical Toxicology, Ronald O. Perelman Department of Emergency Medicine, NYU School of Medicine, New York, New York

Correspondence
Robert S. Hoffman, Division of Medical Toxicology, Ronald O. Perelman Department of Emergency Medicine, NYU School of Medicine, 455 First Avenue, Room 123, New York, NY 10016.
Email: robert.hoffman@nyumc.org

Although lithium is the first-line pharmacologic intervention for the management of bipolar disorder,[1] its use is hampered by both an exceedingly narrow therapeutic index and by lithium's ability to injure its own organ of elimination—the kidney. Unfortunately, these factors make toxicity inevitable for many patients. Early attempts to treat lithium toxicity in the 1960s included forced diuresis, urinary alkalinization, and aminophylline but were minimally effective in severely poisoned patients.[2] At that time, only twenty years since the first use of haemodialysis in a poisoned patient,[3] the potential benefits of haemodialysis in poisoning were just being explored and not systematically studied. However, recognizing the limitations of conventional therapies and the potential benefit of haemodialysis, in 1969, two lithium-poisoned patients were dialysed in an attempt to alleviate their toxicity; one lived[4] and the other died.[5]

While lithium toxicity seems ideally suited for extracorporeal toxin removal (ECTR), given its low atomic weight, small volume of distribution, negligible protein binding, and exclusive reliance on renal elimination,[6] translating drug removal into actual clinical outcomes in poisoned patients is challenging. This is especially true given lithium's complex pharmacology. For other toxins commonly treated with ECTR, such as methanol or ethylene glycol, timely toxin removal is equivalent to cure because the toxin's metabolites are directly injurious to tissues. In contrast, lithium's complex and as of yet incompletely elucidated mechanism of action involves intracellular secondary and tertiary messengers[7] whose alterations sometimes persist long after the serum lithium concentration is negligible.[8]

Regrettably, there are no controlled trials of ECTR in lithium poisoned animals or humans. As such, based primarily on the surrogate marker of a falling drug concentration paired with largely anecdotal evidence of clinical improvement, thousands of lithium-poisoned patients have been treated with some form of ECTR, either intermittent haemodialysis or continual renal replacement therapy (CRRT).[9] In fact, lithium is among the top 10 most commonly dialysed toxins in the US, Canada, Denmark, and the UK and ranks second in the US and Denmark only behind ethylene glycol and salicylates, respectively.[9]

Given the lack of definitive controlled trials, the large numbers of poisoned patients, the severity of toxicity that sometimes leads to death or irreversible neurological injury, and the proven ability of ECTR to rapidly lower lithium concentrations, it is only reasonable that some guidance is provided to clinicians. The goal of this guidance is to help bedside providers select patients for whom the benefits of ECTR are likely to outweigh the risks and costs of the procedure. That guidance should ideally be based on evidence.

There are many ways to evaluate evidence and provide recommendations; every consultant, textbook chapter, review paper, and online reference makes recommendations that are ideally based on some assessment of existing data and are often tempered in some way by the expert clinical experiences of the authors. At one extreme is the evidenced-based approach taken by the Cochrane group. Though Cochrane correctly concluded that there are no randomized controlled human trials to inform the decision to perform haemodialysis in lithium-poisoned patients, their focused methodology prevented them for offering any clinical decision support.[10] In contrast, the Extracorporeal Treatments In Poisoning (EXTRIP) workgroup (https://www.extrip-workgroup.org) assembled a multidisciplinary team of international experts (including toxicologists, pharmacologists, nephrologists, intensivists, and methodologists) who reviewed the entirety of the existing literature and used a sound, transparent, and reproducible evidence and consensus-based methodology to offer their best recommendations for ECTR in lithium-poisoned patients.[11] Despite achieving consensus on many items, the low level of available evidence created the significant likelihood of imprecision around the clinical conditions and laboratory values used as criteria to either suggest or recommend ECTR for a given patient.

All "guidelines" (evidence-based and consensus-based recommendations) need to be re-evaluated and revised when necessary. In addition to periodic review over time, significant new data, a change in outcomes of interest, or development of new resources or therapies should trigger rapid revision.[12] Two recent papers in the Journal add to the evidence for ECTR in lithium poisoning by comparing locally derived decision rules to the EXTRIP criteria. In the first paper, Vodovar et al performed a retrospective analysis of lithium-poisoned patients from a single ICU in Paris.[13] They derived a simple set of clinical criteria and suggest that these new criteria outperform the EXTRIP criteria. Similarly, Buckley retrospectively analysed patients from three local hospitals and performed a toxicokinetic evaluation to identify patients whose lithium concentrations were likely to remain elevated for a prolonged period of time.[14] Both groups address parameters (the peak serum lithium concentration, prolonged lithium elimination, and individual patient factors) that were recognized decades ago as likely markers of morbidity[15] and were evaluated and included in the EXTRIP recommendations.[11]

Are these new papers sufficient to discard the existing EXTRIP recommendations? Both are retrospective case series and as such provide additional low quality evidence that must be taken into account. While their clinical decision rules are noteworthy, both analyses are limited by the circularity of validation in the same patients from which their decision analyses were derived. Because of this circularity, it is completely predictable that the internal validations performed will appear superior to external validation. Some additional concerns are over the choice of endpoints. Is intensive care unit length of stay or time to reduce the lithium concentration the most objective measures of outcome or would more patient-centred outcomes such as short-term neurological debility or long-term neurological dysfunction be more appropriate? Additionally, both papers interpret EXTRIP's criteria and make assumptions about meaning rather than requesting clarification. Furthermore, the work by Buckley uses a single point time estimate of the glomerular filtration rate (GFR) to predict outcome in a dynamic process. Some lithium toxic patients will have chronic kidney disease and have a static GFR over time, while many others will have pre-renal acute kidney injuries and have a GFR that rapidly improves with salt and water repletion. It is unclear how these two populations can be merged into a single calculation.

That being said, a cyclic iteration has begun with the ultimate output being the creation of clinically useful guidelines based on the best available evidence. For 45 years, patients with lithium poisoning were being treated with ECTR without any attempt to rigorously define either the indications for or the benefits of ECTR using controlled methodology. Recognizing that clinical decision making is challenging in the absence of high-quality evidence, the EXTRIP workgroup developed a framework from which to begin an evidence-based evaluation of the use of ECTR in lithium poisoning and provide practicing clinicians with guidance that might help facilitate patient care and ultimately improve outcomes. It should never be expected that the first iteration of EXTRIP's recommendations would stand as the ultimate decision tool. Rather, EXTRIP's work has stimulated research into an unsettled clinically relevant problem that essentially remained unstudied for half a century. If externally validated, the nomogram proposed by Buckley would help prospectively identify those high-risk patients with prolonged lithium elimination that were retrospectively recognized by Hansen and Amdisen 40 years ago as candidates for ECTR. Likewise, the revised criteria suggested by Vodovar et al might be a welcome simplification of EXTRIP's recommendations. In fact, both papers conclude that the EXTRIP criteria work, just that they are too broad. This is exactly the position that should have been taken in the first iteration of a guideline where the treatment is generally safe, widely available, and of limited expense. Both Vodovar's and Buckley's papers demonstrate that the EXTRIP criteria correctly identified every patient who needed ECTR in their cohorts. Additionally, both works inherently imply belief in a benefit of ECTR. It is now EXTRIP's turn to respond either with a validation of its own criteria based on newly gathered data, an attempt to validate the works by Vodovar and Buckley, and/or a potential revision based on a thorough consideration of these two papers (and potentially others) using EXTRIP's existing methodology.

All clinicians want to make the best recommendations for patients under their care. As such, both groups of researchers should be encouraged to apply strict methodology to prospectively validate their findings and improve the evidence base. This will allow an internationally recognized multidisciplinary group whose work is endorsed by relevant stakeholders, such as EXTRIP, to refine and propagate clinical useful recommendations for extracorporeal treatments in lithium-poisoned patients. Finally, given the ambiguous benefits of ECTR in marginally poisoned patients, the hope for a randomized trial should not be abandoned.

COMPETING INTERESTS

Dr Hoffman is a co-chair of the Extracorporeal Treatments in Poisoning (EXTRIP) Workgroup. The opinions stated in this editorial are his own and should not be assumed to be reflective of the position of EXTRIP as a whole.

ORCID

Robert S. Hoffman https://orcid.org/0000-0002-0091-9573

REFERENCES

1. Hui TP, Kandola A, Shen L, et al. A systematic review and meta-analysis of clinical predictors of lithium response in bipolar disorder. *Acta Psychiatr Scand*. 2019;140(2):94-115.
2. Schou M, Amdisen A, Trap-Jensen J. Lithium poisoning. *Am J Psychiatry*. 1968;125(4):520-527.
3. Bywaters EG, Joekes AM. The artificial kidney; its clinical application in the treatment of traumatic anuria. *Proc R Soc Med*. 1948;41(7):420-426.
4. Amdisen A, Skjoldborg H. Haemodialysis for lithium poisoning. *Lancet*. 1969;2(7613):213.
5. Hawkins JB, Dorken PR. Lithium. *Lancet (London, England)*. 1969;1(7599):839-840.
6. Ghannoum M, Hoffman RS, Gosselin S, Nolin TD, Lavergne V, Roberts DM. Use of extracorporeal treatments in the management of poisonings. *Kidney Int*. 2018;94(4):682-688.

7. Pagani R, Gasparini A, Ielmini M, et al. Twenty years of lithium pharmacogenetics: a systematic review. *Psychiatry Res*. 2019;278: 42-50.
8. Adityanjee MKR, Thampy A. The syndrome of irreversible lithium-effectuated neurotoxicity. *Clin Neuropharmacol*. 2005;28(1):38-49.
9. Ghannoum M, Lavergne V, Gosselin S, et al. Practice trends in the use of extracorporeal treatments for poisoning in four countries. *Semin Dial*. 2016;29(1):71-80.
10. Lavonas EJ, Buchanan J. Hemodialysis for lithium poisoning. *Cochrane Database Syst Rev*. 2015;9:1-23CD007951.
11. Decker BS, Goldfarb DS, Dargan PI, et al. Extracorporeal treatment for lithium poisoning: systematic review and recommendations from the EXTRIP workgroup. *Clin J Am Soc Nephrol*. 2015;10(5):875-887.
12. Committee on Standards for Developing Trustworthy Clinical Practice Guidelines. In: Graham R, Mancher M, Wolman DM, Greenfield S, eds. E. S*Clinical Practice Guidelines We Can Trust*. Washington, DC: National Academies Press; 2011.
13. Vodovar D, Beaune S, Langrand J, Vicaut E, Labat L, Megarbane B. Assessment of EXTRIP criteria for the decision of extracorporeal toxin removal in lithium poisoning. *Br J Clin Pharmacol*. 2019.
14. Buckley NA. Haemodialysis for Lithium Poisoning: translating EXTRIP recommendations into practical guidelines.
15. Hansen HE, Amdisen A. Lithium intoxication. (report of 23 cases and review of 100 cases from the literature). *Q J Med*. 1978;47(186): 123-144.