

Case Series

Does Renal Function Improve After Discontinuation of Lithium in Patients with Chronic Kidney Disease?

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Received: 06 August 2024

Accepted: 05 September 2024

Epub Ahead of Print: 04 December 2024

Published: 10 December 2024

DOI

10.25259/BJPSY_4_2024

Quick Response Code:



ABSTRACT

Lithium carbonate is widely used for the treatment of bipolar disorder as well as an augmenting agent in the treatment of unipolar depression. However, a significant percentage of patients develop chronic kidney disease (CKD) after long-term use. This case series attempted to look into whether the kidney function improved after discontinuation of lithium in patients who had already developed CKD.

Keywords: Lithium, Renal function, Glomerular filtration rate

INTRODUCTION

The efficacy of lithium is established in the treatment of bipolar disorder as well as an augmenting agent in the treatment of unipolar depression. A significant proportion of patients (15–20%) on long-term lithium therapy are known to develop chronic kidney disease (CKD).¹ However, in most patients, impaired renal functions could also be caused by many other factors, such as aging and chronic physical illnesses (diabetes, hypertension, etc.).² Fortunately, only a small proportion of patients on lithium progress to end-stage renal disease (ESRD); moreover, the use of lower therapeutic levels of lithium and regular monitoring over the past few decades might have reduced the risk of CKD and ESRD.³

Clinicians commonly encounter the situation when a patient on lithium therapy develops CKD, and they are asked whether to continue or discontinue lithium therapy. The decision requires careful assessments of the risks and benefits of the patient's physical and mental health.¹ One of the major determinants of the decision is the underlying assumption that either renal function will improve or the rate of decline will decrease. However, the existing evidence is inconclusive and contradictory.⁴

Presne et al.⁵ suggested that if lithium is stopped before creatinine clearance drops below 40 ml/min, it is reversible. However, if it drops below 25 ml/min, then it is not reversible. Their observations were based only on 11 subjects. In a study comprising elderly lithium-treated patients with CKD, Rej and colleagues⁶ retrospectively compared the renal function of 11 patients who had continued lithium; three of these patients had discontinued lithium due

to renal impairment. They reported that there was a non-statistically significant decrease in the mean estimated glomerular filtration rate (eGFR) in a subgroup of “continuers” in comparison to “discontinuers” after 5 years. This study only covered cases involving elderly patients where CKD is highly prevalent, and recovery from any renal insult might be very slow. Bocchetta *et al.*⁷ compared renal function outcomes of two groups of lithium-treated patients over 4 years after a reduction to an eGFR lower than 45 ml/min/1.73 m². The first group consisted of patients who had continued lithium at the same therapeutic range (54 patients). The second group comprised patients who had either discontinued lithium or had continued lithium at serum concentrations <0.5 mmol/l (45 patients). They did not find any significant differences between or within the groups. In this study, it was not clear as to what proportion of patients in the second group had continued lithium at concentrations <0.5 mmol/l. This proportion may be important given the somewhat counterintuitive evidence from animal studies that low serum lithium levels may have renal protective effects.⁸

Hence, the evidence base about the reversibility of renal adverse effects of lithium remains small and fraught with

uncertainty. Thus, further clarity is necessitated to guide our risk-benefit discussions with our patients.⁴ A starting point for such clarifications would be to have a clear answer to the question, “Do the renal function tests improve at all after lithium is discontinued?” To answer this question, we carried out a retrospective examination of renal function tests for 16 patients who had discontinued lithium due to CKD.

CASE SERIES

We screened the lithium register of a large mental health trust in England (about 1000 patients) for a list of patients who had discontinued lithium for up to a year prior to our sampling. We selected patients in the adult age range (18–65 years). The selected patients’ eGFRs were consistently below 60 ml/min/1.73 m² in the 3-month period that preceded its discontinuation and at the time of its discontinuation. We defined the “baseline” eGFR as the eGFR result of the patients in the month of lithium discontinuation. If a patient was found to have more than one eGFR result in the month of lithium discontinuation, then the average of the available results was taken as the “baseline” eGFR. Meanwhile, the “baseline” eGFR was taken from the last available eGFR value in case the

Table 1: Data for the 16 patients included in our series.

| Patients | Stated/Estimated age at the time of lithium discontinuation (Yrs) | Gender | “Baseline eGFR” ml/min/1.73 m ² | “Final eGFR” ml/min/1.73 m ² | Duration of follow-up after lithium discontinuation (months) | Required dialysis Y/N |
|---|---|--------|--|---|--|-----------------------|
| No significant change group (< -5 ml/min/1.73 m ² to < +5 ml/min/1.73 m ²) | | | | | | |
| Patient no: 1 | 57 | Female | 37 | 49 | 26 | N |
| Patient no: 2 | 47 | Female | 46 | 67 | 33 | N |
| Patient no: 3 | 59 | Female | 46 | 54 | 3 | N |
| Patient no: 4 | 39 | Female | 56 | 71 | 18 | N |
| Deterioration group (> -5 ml/min/1.73 m ²) | | | | | | |
| Patient no: 5 | 52 | Male | 37 | 26 | 52 | N |
| Patient no: 6 | 59 | Female | 45 | 38 | 30 | N |
| Patient no: 7 | 60 | Male | 43 | 35 | 18 | N |
| Patient no: 8 | 64 | Female | 56 | 43 | 18 | N |
| Improvement group (> +5 ml/min/1.73 m ²) | | | | | | |
| Patient no: 9 | 51 | Female | 56 | 51 | 33 | N |
| Patient no: 10 | 49 | Male | 48 | 53 | 22 | N |
| Patient no: 11 | 61 | Female | 46 | 51 | 32 | N |
| Patient no: 12 | 49 | Male | 50 | 49 | 23 | N |
| Patient no: 13 | 46 | Male | 50 | 50 | 20 | N |
| Patient no: 14 | 63 | Male | 34 | 33 | 20 | N |
| Patient no: 15 | 63 | Female | 51 | 49 | 8 | N |
| Patient no: 16 | 64 | Female | 47 | 46 | 3 | N |

e-GFR: Effective-Glomerular filtration rate, Y/N: Yes/No.

eGFR results in the month of lithium discontinuation were unavailable. In addition, we defined the “final” eGFR as the last available eGFR result for the patient.

We selected an arbitrary difference of ± 5 ml/min/1.73 m² to denote what constitutes a “reasonable difference” between the “baseline” and “final” eGFR values to define “improvement” or “deterioration.” This study was approved by the trust’s audit and service evaluation department. Hence, approval from the ethics committee or patients’ consent was not required.

Out of the 456 patients on the Lithium register who had discontinued lithium, only 16 patients met our inclusion criteria. Table 1 presents the characteristics of the included patients along with the results.

The mean age of the patients was 55.2 ± 7.7 years. The patients included 10 females and 6 males. The median duration of follow-up after Lithium discontinuation was 21 months (range: 3–52 months). The results of four patients showed an “improvement” on their “baseline” eGFR. Their median “baseline” eGFR was 46 ml (range: 37–56 ml/min/1.73 m²). The median increase on the “baseline” eGFR was +13.5 (range: 8–21 ml/min/1.73 m²). The findings of an additional four patients revealed a “deterioration.” The median “baseline” eGFR for these patients was 44 (range: 37–56 ml/min/1.73 m²). The median decrease on their “baseline” eGFR was –9.5 (range: –7 to –13 ml/min/1.73 m²). The results for the remaining eight patients showed “no major difference” in their “baseline.” Median “baseline” eGFR for this group was 49 (range: 34–56 ml/min/1.73 m²). The median change on their “baseline” eGFR was –1 ml (range: –5 to +5 ml/min/1.73 m²).

DISCUSSION

The issue of renal impairment caused by lithium has been known since 1979.⁹ Over the years, case reports and small case series have shown inconsistent findings with regard to changes in renal function after discontinuation of lithium.^{9–13} Presne and colleagues⁵ had observed a relationship between creatinine clearance at the time of lithium discontinuation and renal function outcomes. However, in this study, we were unable to demonstrate a meaningful association between “baseline eGFR” and renal function outcomes from our data. Recently, Hoekstra *et al.*¹⁴ conducted a similar study. According to the findings, the majority of 13 patients with an eGFR of <60 ml/min either reported improvements in their renal functions or witnessed a decrease in the rate of decline. The patients with a mean eGFR of 32 ml/min continued to experience further deterioration. In their study, they also did not report the relevant comorbid physical health problems. In our sample, we cannot make any firm conclusion about the reversibility of renal impairment following the discontinuation of lithium.

The risk of CKD amongst lithium patients might be related to high lithium levels, duration of therapy, as well as the presence of other relevant comorbid disorders. However, the available literature does not consistently confirm the relationships. The only consistent finding is that episodes of Lithium toxicities are associated with a decline in renal function.¹ Presently, it is also not possible to identify patients who are at a high risk of developing CKD.³ There is some evidence that the presence of renal micro cysts on scans might also help attribute renal impairment to lithium and identify cases whose renal function might improve upon the discontinuation of lithium.¹⁵ As CKD is a common illness, we will continue to come across patients with CKD receiving lithium therapy. Hence, it is important for us to learn to use lithium safely in this group and make an evidence-based decision about the continuation/discontinuation of lithium.

Since relevant medical and family histories were unavailable for the patients in our series, we were not able to control for these confounding factors in our analysis. We also had a small number of patients in our series. Despite the limitation related to the sample size, our study provides preliminary data that renal impairment due to lithium might not improve even after the discontinuation of lithium. Hence, it is important to monitor patients’ renal function even after the discontinuation of lithium due to renal impairment. We utilized our definition of “improvement” as a means to make sense of the data obtained in our study. We also acknowledge that “improvement” may not necessarily translate to a clinically significant improvement.

CONCLUSION

Lithium is a widely prescribed medicine in psychiatry practice. Lithium is known to cause renal impairment after long term use and as index case series suggests the renal impairment may not reverse even after stopping lithium. Hence, caution should be exercised while prescribing lithium and monitoring of renal parameters should be done at regular intervals.

Ethical approval

The research/study approved by the Institutional Ethics Committee at College of Medicine and JNM Hospital, number COMJNMH/IEC/2022/3/7, dated 21th March 2022.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent.

Financial support and sponsorship

Nil.

Conflicts of interest

Kaustav Chakraborty is on the Editorial Board of the Journal.

Use of artificial intelligence (AI)-assisted technology for manuscript preparation

The authors confirm that there was no use of artificial intelligence (AI)-assisted technology for assisting in the writing or editing of the manuscript, and no images were manipulated using AI.

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How to cite this article: Gupta S, Alabi A, Goswami S, Sinha B, Chakraborty K. Does Renal Function Improve After Discontinuation of Lithium in Patients with Chronic Kidney Disease? *Bengal J Psychiatry.* 2024;29:48–51. doi: 10.25259/BJPSY_4_2024