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Case Report

A Case Study of Administering Lithium to a Senior Who is Bipolar and Who Also has Chronic Kidney Disease Using an Innovative Treatment Method

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ABSTRACT

The case follows the treatment of a woman from age 73 to age 83 who was bipolar and who also had Chronic Kidney Disease (CKD). During the study, the eGFR dropped from 43 to below 20. Initially the treatment was fairly standard but highlighted the difficulty of knowing when to reduce the lithium dose before undesired mood changes occurred. In phase 2 of the treatment, the usual monthly blood serum test is combined with a new concept of a monthly running average eGFR to decide when to reduce the lithium dose. A new way of administering lithium was created which was used when the patient's daily dose of lithium reached 300mg a day. In place of a fixed daily dose of lithium, a fixed average daily dose of lithium over a short cyclic pattern was used. The daily dose varies within the repeatable cycle but is smoothed out by the long half-life of lithium. The new method allows for the reduction of the lithium dose by small amounts, less than the minimum strength 150mg capsule used in North America or the 100mg tablet used in Europe. The method has been successfully used for several years with the patient's moods stable and lithium toxicity avoided. The patient is currently on an average daily dose of 187mg a day with an eGFR less than 20.

Background

Prior to the case study, the patient's doctor had tried switching her to epival and also to respiridone but she did not respond to either. Her psychiatrist then set the target lithium plasma level to be .9mmol/L, achieved on a daily dose of lithium of 750mg, and, just before retiring, told her that she had to stay on lithium for the rest of her life.

This case started in March of 2012 when the patient was released from a Florida hospital after spending five days being treated for a serious case of lithium toxicity. Upon discharge from the hospital, she was told by the doctors that she should not take lithium anymore. The patient was about to turn 73 and had an eGFR of 43, an indicator of CKD.

The patient's status at the start of the treatment was as follows:

- The hospital had stopped all of her lithium;
- She was told not to go back on lithium by the hospital doctors;
- She had no psychiatrist;
- She was in Florida at her winter home and could not have a meeting with her Canadian doctors.

The author became the person in charge of the patient's bipolar disorder medication.

Phase I of the Treatment

It was decided to continue to use lithium because she had not responded to the use of other mood disorder medications. There were two questions that needed to be answered before any treatment could begin. The first was to decide what the target blood serum level of lithium should be and the second was to determine what lithium dose should be used.

In 2005 Young [1] published that lithium toxicity could occur if the lithium level of the elderly was over 0.1mmol/L. In 2010, Shulman [2] published a paper saying that lithium levels over .8mmol/L for the elderly could result in undesirable mood changes. Both papers used the new minimum of the therapeutic region to be 0.4mmol/L.

To calculate a new target for the lithium blood serum level for the patient, the following facts were considered. The therapeutic region for those at age 60 or older was now considered to be 0.4-0.8mmol/L with a midpoint of 0.6mmol/L. The patient was 73 with CKD, so the therapeutic range should definitely be no higher than for a person who was only bipolar. The new target for the patient's blood serum level was decided to be 0.6mmol/L, the mid-point of the recently discovered therapeutic range.

While in the hospital with lithium toxicity, the patient had been taken off lithium for five days. The lithium level had dropped from .9mmol/L to .6mmol/L by the time she was discharged from the hospital, and her moods were normal. Reducing the lithium level to .6mmol/L would entail a drop of one third in the blood serum level of lithium from what it had been. To match this drop in the blood serum level, it was thought that the lithium dose should also drop by one third, which would be a reduction of 250mg from 750mg to 500mg per day. A drop of 250 mg was not possible because the smallest capsule available for lithium was 150 mg and daily drug doses had to be reduced in steps of 150mg. It was decided to reduce the daily lithium dose to 450 mg, a drop of 300mg. After treatment was started, the patient's moods continued to be stabilised.

From 2012-06-19 to 2013-06-17, the monthly eGFR readings were 43, 41, 45, 41, 37, 47, 48, 43. The monthly eGFR varied too much to be a good indicator of the kidney's status. To better understand what was happening with the kidneys, it was decided to record a running monthly average eGFR, averaged over the last five or six monthly blood tests. The average eGFR proved to be a much better indicator of the deterioration of the kidneys and could be used when deciding to reduce the daily lithium dose.

In April 2015, after three years of stable blood serum levels near .6mmol/L, the blood serum level rose to .7, and the average eGFR dropped nearly 19 percent from 43 to 35. The reduction in the average eGFR indicated that the monthly blood test result of 0.7mmol/L for the lithium was not an anomaly. The lithium level was too near the maximum level of .8, and it seemed likely that the readings would continue to rise due to the reduced eGFR. It was decided that the daily dose should be reduced. The minimum possible reduction was by 150mg to 300mg per day. This was a drop of 33 percent in the daily dose and the patient's moods were closely monitored after the change.

At the end of phase 1 of the treatment, the patient's moods were stable on a 300mg daily dose of lithium, and the blood serum level was .6mmol/L.

Phase 2 of the Treatment

A further reduction in the daily dose from 300mg to 150mg would be a 50 percent decrease in the daily dose. Research was conducted to create a method of reducing the daily dose in steps of less than 150mg in order to prepare to be able to decrease the daily dose while keeping the patients moods stabilized and avoid lithium toxicity.

Lithium had been used for decades, and its half-life for bipolar patients was understood. Timor [3] reported that the half-life of lithium within plasma was 12 to 27 hours but referred to Okusa [4], who reported that the half-life depended on the persons age and the duration of the lithium therapy. Okusa reported that the half-life life can increase to as long as 58 hours in elderly individuals and for patients taking lithium chronically. The patient, in this case, had been on lithium therapy for 30 years and was in her seventies, so a long half-life was expected.

Using the suggested half-life of 58 hours, the amount of lithium in the system should have dropped by more than 80 percent after five days. When the patient was discharged from the hospital, having been off lithium for five days, the blood serum level had only dropped 33 percent. The implication of this was that a substantial amount of lithium, administered six or seven days before being discharged, was still in the blood. The patient's eGFR was 43. The conclusion is that the half-life of lithium for bipolar patients with CKD is very long. The new method of reducing the lithium dosage depends on the half-life of lithium being long. This is true for older patients, for those who have been on lithium therapy for a long time, and especially for those with CKD.

Instead of having a fixed daily dose of lithium, a repeating short cycle of doses that vary a little from day to day could be used. As long as the cycle length is no longer than five days, any slight changes from day to day would be smoothed out by the long half-life of lithium. For example, a person could take 300mg on day one and only 150mg the next day. The total lithium over the two days would be 450mg which is an average of 225mg per day. If the cycle is repeated over and over again, the average daily dose would be 225mg for any two adjacent days. The reduction in the lithium average daily dose from 300mg would be 75mg which would be safer than a reduction to 150mg.

An algorithm was developed that shows all possible fixed average daily dose cycles for reducing the lithium dose from 300mg to 150mg. There are only ten possible cyclic patterns, no longer than five days. When the current dose of 300mg a day needs to be reduced, it can be done in ten small steps, over time, before reaching a daily dose of 150mg.

The patient was getting near 80, and it was decided to change the target blood serum level to 0.55mmol/L. Later research proved that this was a wise decision.

At the beginning of 2017 when the patient was 77.8 years old, the monthly blood tests for the patient had the lithium levels starting to be in the range of .7 to .8. This was an indication that the average daily dose might need to be reduced. However the average eGFR was stable at about 34.9. Although the lithium level was, in the short term, too high, the patient's moods were stable. As long as the overall health of the patient stayed constant it was decided to not reduce the lithium just yet. Eight months later, the average eGFR finally dropped to 30 and it was decided to reduce the average daily dose to 225mg. This was the first opportunity to reduce the lithium dose by less than 180mg, using the new algorithm. This fairly large reduction in the lithium turned out to be too much as the daily lithium readings dropped to .4. The average daily dose was immediately increased to 250mg a day, and the lithium serum level became near the target level of .55mmol/L.

It was necessary to prevent reducing the lithium level by too much for future reductions. The general algorithm produced a choice of ten possible new average daily dose patterns with the choice of which reduction to use left up to the algorithm user. An app for smart phones was written that incorporated the general algorithm but which only suggested reductions in lithium of no more than ten percent of the patient's current average daily dose. The new app was used from this point on in treating the patient. Table 1 shows the results of using the app over the next five years.

Table 1. Reductions in average daily dose of lithium with age

Average daily dose	Age	Avg. eGFR
250	78.5	27.5
225	80.5	24.6
210	82.4	21
200	83.4	19.5
187	83.5	18.5

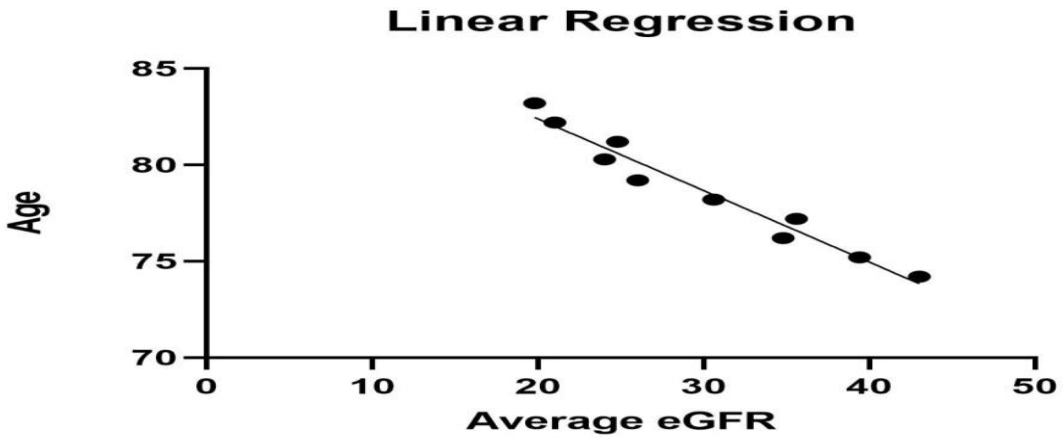
Table 1 shows all reductions in the average daily dose to be less than 10% of the current dose. The average eGFR steadily decreased from 27.5 to 18.5.

Graphing the monthly eGFR readings is not useful because of the way the eGFR jumps around. However, graphing the average eGFR is useful. Graph 1 shows the linear relationship (based on the data presented in Table 2) when graphing the average eGFR on an annual basis

Table 2. Data for Reduction of average eGFR with age

Avg. eGFR	Age
43	74.2
39.4	75.2
34.8	76.2
35.6	77.2
30.6	78.2
26	79.2
24	80.3
24.8	81.2
21	82.2
19.8	83.2

Graph 1. Regression line of the reduction of average eGFR with age



Graph 1 shows that the average eGFR reduces linearly with age. This implies that the average daily dose of lithium will need to be gradually reduced in small steps, not to reduce the target level for the lithium, but to maintain the current maintenance serum level as the average eGFR reduces.

The app can start at any blood serum level. Had the app been developed earlier in the case study, it could have been used when the patient's daily dose was 450mg. This would have avoided the risky large decrease from 450mg to 300mg a day.

Conclusions

The target blood serum level of lithium for patients who are bipolar and have CKD should be less than the mid-point of the plasma level for a patient of the same age who does not have CKD.

Once a patient's daily dose of lithium reaches 300mg a day, all reductions in the patient's lithium dose must use a fixed average daily dose rather than the fixed daily dose. It would not be possible to reduce the fixed daily dose from 300 mg to 150 mg without leaving the therapeutic region. Even dropping from 300mg to an average daily dose of 225mg had the lithium level in the blood dropping below 0.4mmol/L. and a small increase in the dose was initiated.

Blood tests should be done monthly to have a useful running average eGFR. The decision to reduce the lithium is made using the recent blood serum level and the changes in the average eGFR from the last reduction in lithium.

The average eGFR decreases in a linear way. The new app developed assists in safely reducing the lithium by only suggesting reductions in the lithium dose of no more than ten percent of the patient's current lithium dose.

For all bipolar patients, even those who do not have CKD, to improve the quality of life for the patient, the best lithium dose is the one that has the blood serum level near the minimum of the therapeutic range. For seniors and elderly patients, very small reductions in the lithium are required to achieve a lower blood serum level. Switching to fixed average daily doses assists in setting the maintenance dose where desired. The author recommends that physicians use the average daily lithium dose instead of a fixed daily dose for all patients once the fixed

daily dose gets to 900mg a day. To facilitate doctors make this change in treatments, the author has released an app called MedsReducer.

Declarations

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