A Clinician's Guide to Monitoring Kidney Function in Lithium-Treated Patients

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Objective: Bipolar disorder treatment guidelines recommend kidney-function monitoring at regular intervals for patients taking lithium, but they tend not to provide specifics with regard to what to measure and how to ensure that the results most accurately reflect true kidney function. This overview clarifies those practical aspects of monitoring that are often overlooked or misunderstood.

Data Sources: Utilized English language materials were obtained by PubMed searches (1970–2009), from the Lithium Information Center database, and from books. Search terms included *lithium, kidney function, creatinine, creatinine clearance, GFR, GFR prediction equations, albuminuria,* and *urine concentration.*

Data Synthesis: Urine osmolality most accurately reflects urine concentrating ability, although specific gravity is usually adequate for clinical purposes. Serum creatinine concentration can be influenced by extrarenal factors, but even when these are controlled, it remains a less than ideal measure of glomerular filtration rate (GFR). Prediction equations are used commonly to estimate GFR and are an advance over serum creatinine alone, but even they are not as useful when GFR is only mildly impaired. Urine albumin measurement is important, but it requires greater standardization and sensitivity to maximize its potential.

Conclusions: The safe and effective use of lithium requires regular monitoring of kidney function. Doing so effectively requires knowledge of what to measure, how to ensure accurate results, and how to properly interpret them.

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A middle-aged man with bipolar disorder had been maintained on lithium carbonate for many years. In 1992, on a dose of 900 mg per day, the man's serum level was 0.6 mEq/L and the serum creatinine was 1.1 mg/dL. Sometime shortly thereafter, the dose was increased to 1,200 mg per day. According to office records, the next serum lithium level, which was 1.4 mEq/L, was not obtained until 2000. No laboratory studies were done for another 3 years until the patient was hospitalized with lithium toxicity–serum level 3.8 mEq/L, serum creatinine 3.9 mg/dL. Kidney function had not been assessed since 1992. Lithium was stopped and alternative therapy instituted, but 4 years later the serum creatinine remained elevated at 3.7 mg/dL. The clinician was faulted for inadequate monitoring of serum lithium levels and kidney function. Because of the paucity of monitoring, it was unresolved whether the impaired kidney function evolved gradually and ultimately caused the lithium toxicity or whether the toxicity itself was the cause of the impaired kidney function. Unfortunately, failure to adequately monitor kidney function in patients taking lithium is not a rare event. A study in Paris over an 8-year period found that 41% of 1,179 lithium-treated patients failed to have even a single serum creatinine determination.[1]

Periodic monitoring of kidney function in patients taking lithium is essential. The American Psychiatric Association Treatment Guideline for Bipolar Disorder states that kidney function should be assessed "every 2–3 months during the first 6 months of treatment" and subsequently "every 6 months to 1 year in stable patients."[2(p21)] The Canadian Network for Mood and Anxiety Treatments Bipolar Disorder Guidelines state that "plasma creatinine concentrations should be measured at least annually in those on lithium therapy."[3(p48)] The National Institute for Health and Clinical Excellence (NICE) Bipolar Guideline[4] recommends kidney function testing every 6 months. Most recently, the International Society for Bipolar Disorders (ISBD) consensus guidelines for the safety monitoring of bipolar disorder treatments recommended "urea and creatinine every 3–6 months for the duration of treatment."[5(p565)]

While these and other guidelines are consistent in recommending frequent monitoring of kidney function in patients taking lithium, issues remain about what to monitor, how to insure accurate results, how to interpret results, and how to manage abnormalities.

DATA SOURCES

Utilized English language materials were obtained by PubMed searches (1970–2009), from the Lithium Information Center database, and from books. Search terms included *lithium*, *kidney function*, *creatinine*, *creatinine clearance*, *GFR*, *GFR prediction equations*, *albuminuria*, and *urine concentration*.

DATA SYNTHESIS

Urine Concentration and Volume

Impaired urinary concentrating ability and polyuria (nephrogenic diabetes insipidus) are acknowledged lithium side effects. Urine concentration is measured most accurately by determining osmolality, which is a reflection of the

number of particles in solution. In routine practice, however, measuring specific gravity is a simpler and usually acceptable surrogate, although the presence of large molecules (protein, glucose, etc) may lead to inaccuracies. Urine volume is easily measured, but adequacy of collection can be problematic.[6] For example, when used in the formula to calculate creatinine clearance, an incomplete 24-hour collection will result in a falsely low clearance, while a collection in excess of 24 hours will do just the opposite. Also, if polyuria is severe, collection and transport can be problematic for outpatients (as exemplified by one of my patients, who managed to deliver over 11 L of urine to the laboratory).

Serum Creatinine

Serum creatinine is a critical component of kidney-function monitoring, whether used alone or in formulas to estimate or calculate creatinine clearance. The predominant source of creatinine in the body is degradation of muscle creatine; therefore, total muscle mass is the major determinant of serum creatinine. In general, men generate more creatinine than woman, the elderly less than youth, the infirm less than the healthy, and so on. Obviously, changes in muscle mass over time will result in changes in serum creatinine that have nothing to do with kidney function. Diet can also affect serum creatinine concentrations, particularly from the ingestion of cooked meat. As summarized by Levey et al,[6] creatinine generation is decreased by 10%–30% if meat intake is reduced or eliminated. Also, cooking converts creatine to creatinine, thereby increasing creatinine intake. The ever-popular use of creatine dietary supplements can be another external cause of elevated serum creatinine levels.[7] Another extrarenal factor to be avoided is dehydration because it can cause varying degrees of reversible prerenal azotemia. Those with lithium-induced polyuria may find it difficult to remain adequately hydrated. Prolonged heavy exercise can have a 2-pronged effect on serum creatinine—muscle breakdown and dehydration. The "perfect storm" for a nonrenal disease-related increase in serum creatinine (and decrease in calculated creatinine clearance) would be a muscular man using high-dose creatine supplements who eats a charbroiled 20-ounce porterhouse steak and runs a marathon. Patients must minimize these potentially contaminating extrarenal factors when having serum creatinine measured if the test is to have any value as a measure of kidney function.

Another factor accounting for serum creatinine variability is lack of measurement standardization.[8–10] A number of different assays are available, including the Jaffé and modified Jaffé colorimetric assays and enzymatic techniques. The former tend to overestimate serum creatinine in healthy individuals by 20%–30% because they also measure noncreatinine chromogens, while the latter do not. One can appreciate that between laboratories, or even within a laboratory, choice of assay used can be a source of variation. Clinicians must be aware that the range of normal for serum creatinine may vary considerably because of this and other factors. Efforts are under way to reduce interlaboratory variation in creatinine assay calibration by implementing use of a standardized reference material.[10–12] According to Coresh et al,[13] calibration bias in serum creatinine measurement is common and especially problematic when estimating glomerular filtration rate (GFR) in the mildly and moderately decreased range. Both assay standardization and eliminating nonrenal variables will contribute greatly to the value of serum creatinine as a useful indicator of kidney function both when used alone and for calculation of creatinine clearance and estimated GFR (eGFR).

Glomerular Filtration Rate

Serum creatinine concentration, while easily and inexpensively measured, is a gross and often inaccurate indicator of GFR. It is especially insensitive with regard to milder degrees of renal insufficiency and may remain within the range of normal despite substantial reduction in GFR.[6] At the other extreme is inulin clearance, the so-called gold standard, which is time-consuming, cumbersome and expensive, and, therefore, confined primarily to research purposes. The same can be said for the use of other exogenous markers such as iohexol, iothalamate, and chromium 51-labeled ethylenediaminetetraacetic acid (^{51}Cr-EDTA).[12] The 24-hour creatinine clearance has been an old standby for approximating GFR, although, as described above, collecting and transporting an accurate 24-hour urine specimen is often problematic.

The Kidney Disease Outcome Quality Initiative (K/DOQI) Clinical Practice Guidelines for Chronic Kidney Disease state that "estimates of GFR are the best overall indices of the level of kidney function"[14(pS76)] and recommend the use of prediction equations for this purpose. Furthermore, the guidelines state that the serum creatinine concentration should not be the sole measure of kidney function, that clinical laboratories should use a prediction equation to estimate GFR, and that these laboratories as well as autoanalyzer manufacturers should use an international standard to calibrate serum creatinine assays. Exceptional situations in which a 24-hour urine collection might be preferred over a prediction equation to estimate GFR include extremes in diet (creatine supplements, vegetarians) and muscle mass extremes (amputations, malnutrition, highly developed).

In adults, the prediction equations in most common use for estimating GFR are Cockcroft-Gault and Modification of Diet and Renal Disease (MDRD). The former requires serum creatinine, weight, age, and gender, while the 4-variable version of the latter utilizes serum creatinine, age, race (African-American or all other), and gender. Calculators are readily available on the internet if the clinical laboratory has not already provided a result. Other equations are available for children (such as Schwartz or Counahan-Barratt).[10]

A shortcoming of prediction equations is that they are less precise in the early stages of chronic kidney disease (stage 1—kidney damage with no GFR decrease; stage 2—kidney damage with mild GFR decrease [60–89 mL/min/1.73 m^2]).[10,15] Because of this lack of precision, values above 60 mL/min/1.73 m^2 are more appropriately reported only as > 60 rather than providing an exact number.[16] Stage 3 chronic

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Table 1. Monitoring Options

Test	Advantages	Disadvantages
Urine concentration ability		
Specific gravity	Easily measured on routine urinalysis	Less accurate than osmolarity
Osmolality	More accurate than specific gravity	More expensive Not necessary for routine monitoring
Urine volume (24-hour)	Quantitative evaluation of polyuria and proteinuria Calculation of creatinine clearance	Difficulty with accurate 24-hour collection
Serum creatinine	Easily, inexpensively measured Necessary for calculating estimated glomerular filtration rate (eGFR) and 24-hour creatinine clearance	Can be affected by diet, exercise, dehydration Less accurate in elderly Lack of measurement standardization Not a sensitive indicator of mild renal insufficiency
Blood urea nitrogen (BUN)		Less specific than serum creatinine
Glomerular filtration rate (GFR)		
Inulin clearance	Gold standard	Expensive, cumbersome, time-consuming, not practical
Creatinine clearance (24-hour)	Usually accurately reflects GFR	Accurate 24-hour urine collection problematic Dependent on serum creatinine
eGFR	Practical, easily calculated, more accurate than serum creatinine	Less precise in early stages of chronic kidney disease False-positives for Stage 3 chronic kidney disease Dependent on serum creatinine
Urine albumin	Easily and inexpensively measured by dipstick Easily quantitated by 24-hour collection	False-negatives with microalbuminuria Accurate 24-hour collection problematic

kidney disease is defined by a moderately decreased GFR of 30–59 mL/min/1.73 m^2 for at least 3 months with or without evidence of kidney change. While the stage 3 cutoff of < 60 mL/min/1.73 m^2 is used commonly as a call to action, detecting the onset of chronic kidney disease even earlier has great appeal. Furthermore, it is essential to remember that these prediction equations are dependent on the accuracy with which serum creatinine concentrations are measured.[10]

Recently, Glassock[17] focused on pitfalls associated with the use of GFR estimation equations. For example, he points out that the MDRD equations "suffer from both bias (systematic underestimation of true GFR) and imprecision (wide coefficient of variation), particularly at higher levels of GFR."[17(p1001)] Concern about the overdiagnosis of chronic stage 3 kidney disease using Cockcroft-Gault or MDRD equations is especially great in women and in the elderly. Prigent[10] summarized 4 studies of over 1,000 kidney transplant donors and reported that neither equation was validated and that neither was recommended for screening donors because of its tendency to underestimate GFR in this assumedly healthy population. The predictive performance of the Cockcroft-Gault and MDRD equations for estimating kidney function was evaluated in 2,095 adult Europeans whose GFR had been determined by ^{51}Cr-EDTA. About 20% of the adults whose actual GFR was > 60 mL/min/1.73 m^2 were misclassified as having stage 3 chronic kidney disease based on the prediction equations.[18]

All in all, prediction equations are far from ideal, but they have merit until something better comes along. Nonetheless, keep in mind the concern expressed by Glassock and Winearls that "A whirlwind of unjustified enthusiasm for the relatively newer methods of estimating glomerular filtration rate (eGFR) is blowing all over the world."[19(p1563)] While their statement applied to the use of eGFR for universal screening, they acknowledged that targeted screening of high-risk groups (eg, hypertension, diabetes) may be appropriate. Whether patients taking lithium would constitute such a high-risk group is worthy of consideration. A preliminary study suggested that the Chronic Kidney Disease Epidemiology Collaboration equation might provide greater accuracy at higher GFRs than the older equations.[20] Replacing serum creatinine in equations with another substance such as cystatin C is also under investigation.[10,12]

Blood Urea Nitrogen

Although blood urea nitrogen (BUN) concentration is part of a basic metabolic chemistry panel, it is a less specific measure of renal function than is serum creatinine. Unlike serum creatinine, BUN concentration is not used in formulas for calculating GFR. According to the Kidney Disease Outcomes Quality Initiative (K/DOQI) Clinical Practice Guidelines,[14] assessment of chronic kidney disease involves estimation of GFR and assessment of proteinuria. Consequently, BUN concentrations would not be considered essential to the monitoring of renal function in patients taking lithium.

Urine Albumin

A rare renal side effect of lithium is nephrotic syndrome, which is characterized by heavy proteinuria and is usually associated with focal segmental glomerulosclerosis or minimal change glomerulopathy. Proteinuria of this magnitude is easily detected by dipstick on routine urinalysis and can be quantitated with the gold standard 24-hour urine collection. Relying on a standard dipstick to detect lesser degrees of proteinuria can be associated with frequent false negatives, although microalbumin test strips are available that can detect low concentrations in a semiquantitative fashion.[21–24]

The role that quantification of low levels of urine albumin should play in the ongoing monitoring of patients on lithium has not been established. In fact, a recent editorial commented on the general state of urine albumin measurement, pointing out that "we use a wide range of nonstandardized measurement procedures" and that there "is inconsistency between laboratories regarding sample type, units of reporting, and reference intervals or cut points."[25(p1595)] There is a clear need

for standardization of urine albumin measurements.[24] Given the relative rarity of lithium-induced proteinuria, it is unclear if such determinations would contribute in a meaningful way to monitoring lithium-induced changes in kidney function. This is an issue that merits further study.

Recommendations

1. Do not assume that an abnormal kidney function test is due to lithium—association may be coincidental rather than causal. When there is more than 1 possible cause (eg, lithium and diabetes), the relative contribution of each may be difficult to establish.[26]
2. Assess kidney function with reasonable regularity. It should be at least twice yearly and more frequently in higher risk patients.
3. The pros and cons of monitoring options are summarized in the Table 1.
4. Choice of kidney function test may vary but should include serum creatinine to calculate eGFR and urinalysis to assess specific gravity and proteinuria. Prior to the test, extrarenal contributions to serum creatinine should be minimized by maintaining adequate hydration, avoiding strenuous exercise, and avoiding excessive meat ingestion and the use of creatine dietary supplements.
5. If eGFR is not provided by the laboratory, it should be calculated using an internet-available calculator. A single abnormal result (< 60 mL/min/1.73 m^2) requires confirmation. Morriss and Benjamin[27] provide practical advice on the correct use of eGFR in patients taking lithium that is based on the UK Consensus Conference on Early Chronic Kidney Disease.
6. Complaints of excessive fluid intake and urination should be quantitated by 24-hour urine volume.
7. Abnormalities in screening tests should lead to more comprehensive evaluation. An accurate 24-hour urine collection coupled with a serum creatinine determination can provide useful quantitative information with regard to volume, protein loss and creatinine clearance—all areas of interest when lithium is involved.
8. When in doubt, consult with a nephrologist—but be selective. There have been occasions when a nephrologist has instructed a patient to discontinue lithium immediately after having been confronted by an abnormal kidney function test. A risk-benefit analysis is a necessity and should involve the patient, prescribing physician, and consultant.

CONCLUSION

At one extreme, lithium has been portrayed as a nephrotoxic monster whose use should be considered only when all else has failed. The opposite extreme posits that its nephrotoxic potential is little different from the changes of kidney function that accompany normal aging. As is usually the case with extremes, reality lies somewhere in between. A study utilizing Swedish Registry for Active Treatment of Uremia[28] found the prevalence of renal replacement therapy (RRT) in the lithium-treated population to be 5.3%, which was 6-fold higher than in the general population. Likewise, patients with lithium-induced end-stage renal disease comprised 8.1% of the renal replacement therapy population. Monitoring kidney function at regular intervals is essential to the safe and effective use of the drug, but to do so effectively requires knowing what to measure, how to get the most accurate results, and how to interpret these results.

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