How are laboratories in Ontario reporting lithium for therapeutic drug monitoring?

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ABSTRACT

Objective: Lithium is prescribed for long-term treatment of bipolar affective disorder. Serum levels are monitored to maintain a narrow therapeutic range. Lithium is mostly eliminated by the kidneys and a decline in renal function or drug interactions can lead to toxicity in chronic treatment, notably in the elderly. This study aimed to survey the current laboratory practices on lithium testing in Ontario.

Design and Methods: A questionnaire on laboratory practice for collection instructions, reporting of therapeutic ranges, and toxic levels for lithium was included with the IQMH DRUG proficiency testing survey in May 2017. Data was analyzed using MS Excel.

Results: From 162 survey respondents, 85 laboratories performed lithium testing and were included in the analysis. Although all reported methods were traceable to NIST materials, the therapeutic ranges varied from 0.4–0.8 mmol/L (lower) to 1.5–1.9 mmol/L, with 62% of laboratories using 0.6–1.2 mmol/L for adults. Only four laboratories provided lower therapeutic ranges specific to the elderly. Reported thresholds for toxic concentrations varied from 1.2–2.5 mmol/L. Of those 45% reported toxicity at >1.5 mmol/L. Only 50% of the laboratories indicated standardized collection instructions for trough levels, which would be necessary for appropriate result interpretation.

Conclusions: Despite a narrow therapeutic index for serum lithium, there is a significant variation in the therapeutic ranges and toxic levels. As the cohort of older adults on long-term lithium reaches old age, inadequate attention has been paid to the specific needs of older adults and the increased risk of toxicity.

INTRODUCTION

• Lithium is a drug prescribed for long-term treatment of affective disorders in patients of all ages.
• Therapeutic levels are monitored in many laboratories usually with automated assays.
• Lithium has a narrow therapeutic range and low therapeutic index requiring accurate and precise analytical methods.
• Clinical users have asked laboratories to provide a therapeutic range for lithium in elderly patients.

PHARMACOKINETICS

• Univalent cation
• Completely absorbed in about 8 h from upper GI
• Distributed in total body water 80%–90% Lig
• Distribution in brain 24 h delayed from blood
• CSF is 40% of serum levels due to transport by brain capillary endothelium and arachnoid membranes

HALF LIFE

• Lithium has variable half-life.
• After single dose half-life is 2–27 h, which increases up to 58 h in elderly and chronic lithium treatment.
• Factors altering half-life include: age of patient, duration of lithium therapy, and renal function.

ELIMINATION

• Almost entirely excreted by kidneys.
• 80% of filtered lithium is reabsorbed in proximal tubules and 20% in Loop of Henle and collecting ducts.
• Decreased GFR or increased proximal tubule reabsorption leads to increased serum lithium levels.

DOSE

• <50 y: 0.65 mmol/kg; >50 y: 0.50 mmol/kg; 70–79 y: 0.35 mmol/kg
• Between 50 and 80 years is a 50% decrease in dose versus age. Therefore, elderly require lower doses.

THERAPEUTIC RANGE FOR ELDERLY?

• Limited good studies on lithium in elderly bipolar disorder.
• Lithium has superior or similar efficacy to other mood stabilizers.
• Older adults more likely to have adverse effects.
• Low dose regimen with frequent monitoring recommended.

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DESIGN AND METHODS

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RESULTS

• After collection of the samples, 44 laboratories (53%) stated that they recorded the date of collection and 47 laboratories (57%) recorded the time of collection of the sample.
• Eight laboratories provided two concentrations as toxic: one level identifying as potentially toxic and the second higher level as toxic.
• Three laboratories reported a level of 1.5 mmol/L and five laboratories reported 2.0 mmol/L as potentially toxic, while a concentration as greater than 2.5 mmol/L was considered toxic.
• One laboratory reported a toxic range of greater than 1.0 mmol/L in patients greater than 65 years of age.
• Only seven out of 85 laboratories appear to call critical lithium results and the actual concentration at which it was called was variable.

ACCURACY

Manufacturer inserts of the most commonly used assays were reviewed for information on traceability. All manufacturers have calibrators traceable to four different NIST.

Manufacturer — Calibrator traceability
NIST Method for assigning concentrations to calibrators
ABBOTT
SRM959

Beckman Coulter
SRM329

Gravimetric

Ortho
SRM924

Atomic absorption

Beckman Coulter
SRM924a

Flame photometry

Siemens Aurova
SRM929a

Siemens Dimension Vista SRM924a
Gravimetric

Absolute Bias (mmol/mol) vs. AMM - DRUG 2012-2014

Absolute Bias (mmol/mol) vs. AMM - DRUG 2015-2017

CONCLUSIONS

• The majority of laboratories report a therapeutic range of 0.6–1.2 mmol/L, and report a toxic range in patients from >18 years of age.
• Reporting of a separate range for patients over 65 years is very limited. A lower range would be appropriate to account for the lower doses used, reduced renal function, and increased risk of adverse events in elderly patients.
• Considerable variability exists for collection instructions and reporting comments.
• Current PT performance shows most commercial lithium assays have agreement of ±0.05 mmol/L in the lower therapeutic range that could reliably monitor lithium in the elderly.