A Novel, Point-of-Care Test for Lithium Levels: Description and Reliability

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Background: Lithium is a highly effective agent for numerous psychiatric disorders but requires therapeutic monitoring because of its narrow therapeutic index. This article describes a novel instant blood test that will facilitate the routine monitoring process.

Method: This instant blood test allows the clinician to take a finger-stick sample of whole blood and determine the plasma lithium level in a 2-minute period. This new test is compared with standard laboratory measurements for lithium in human subjects. The reliability of the new test is reported as agreement with standard laboratory values in 3 studies involving a total of 269 subjects.

Results: The test demonstrates extremely high reliability (r = 0.962, 0.928, 0.983 for studies 1–3, respectively) for the measurement of serum and plasma lithium levels as compared with standard laboratory measures.

Conclusion: This new test is reliable and offers unique advantages over standard laboratory procedures for measuring lithium levels in patients.

(J Clin Psychiatry 2004;65:652–655)

Received Dec. 29, 2003; accepted March 24, 2004. From ReliaLAB, Inc., Basking Ridge, N.J. (Dr. Glazer); Uptown Research Institute, Chicago, Ill. (Drs. Sonnenberg and Reinstein); and Akers Biosciences, Thorofare, N.J. (Dr. Akers).

This project was funded by Akers Biosciences, Thorofare, N.J., and ReliaLAB Inc., Basking Ridge, N.J.

Dr. Glazer is President and Chief Medical Officer of and a major stock shareholder in ReliaLAB. Dr. Akers is President and Chief Executive Officer of, a major stock shareholder in, and has patents in application for Akers Biosciences, Inc.

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Lithium is the first modern recognized treatment for bipolar disorder and has served a unique role for this and other conditions for over 30 years.[1] It became U.S. Food and Drug Administration (FDA)–approved for treating acute manic episodes in 1970, and currently it shares this status with chlorpromazine (1973), divalproex (1995), and several atypical antipsychotic agents. Lithium became approved for maintenance therapy in 1974 for those patients who had experienced manic symptoms, and it was the only FDA-approved drug with that status until lamotrigine was recently approved for this indication. All clinical practice guidelines recommend lithium as the first-line agent for acute and prophylactic treatment of manic and mixed states, bipolar depression, and rapid cycling.[2–5] While lithium has been joined by a number of other agents found to be efficacious for the treatment of aspects of bipolar disorder,[6] it is still thus far the only mood stabilizer with substantial evidence for reducing the risk of suicide during long-term treatment.[7]

Lithium has a narrow therapeutic range (0.4–1.4 mEq/L) and therefore requires routine ongoing clinical monitoring because numerous conditions can alter lithium levels.[1] For example, drug interactions with other medications that affect renal function (e.g., nonsteroidal anti-inflammatory drugs, diuretics, angiotensin-converting enzyme inhibitors) or shifts in body fluid compartments resulting from episodes of crash dieting, strenuous exercise, hot climate, pregnancy, or vomiting and/or diarrhea can alter a patient's blood lithium level and result in toxicity or loss of efficacy. Thus, with a narrow therapeutic index, lithium levels are monitored to (1) identify and/or prevent potential toxicity associated with high levels, e.g., tremors, gastrointestinal disturbance, decreased coordination, and possible seizures and coma; (2) assure ongoing efficacy and effectiveness, including the prevention of suicidal behavior; and (3) monitor the patient's adherence to the prescribed regimen. The package insert recommendation[8] is that lithium level determinations occur twice per week during the acute phase until the level and clinical condition of the patient have been stabilized. Then, in uncomplicated cases receiving maintenance therapy during remission, lithium levels should be monitored at least every 2 months. The guidelines from the American Psychiatric Association recommend maintenance monitoring at least every 6 months.[4]

It is likely that the requirement for monitoring has dampened lithium's use, perhaps below what might be appropriate given the evidence base to support its effectiveness.[9] Determination of lithium levels involves relatively complex laboratory methods such as flame photometry, ion-selective electrode analysis, and atomic absorption spectrophotometry, which require venipuncture, transport

of the sample to a laboratory, analysis, and communication of results back to the clinicians. This process can be time-consuming (hours to days) and could be replaced by a rapid, point-of-care testing method. Here we report on the development of such a test.*

METHOD

Description of the Test

The test is a diagnostic device intended for the accurate measurement of blood lithium levels at the point of contact with the patient, e.g., office, clinic. It consists of 3 key components starting with the Blood Cell Separator.

A Blood Cell Separator separates whole-blood cells from the liquid fraction. This separation is achieved through the attraction and capture of blood cells from a whole-blood specimen by a lectin-coated membrane. The residual plasma fraction continues to flow laterally to the tip of the membrane, at which time a bulb pipette that has been inserted into a designated hole in the separator fills vertically to a controlled volume of 0.2 µL.

The collected 0.2-µL specimen of plasma is then added to the second component of the device: a prefilled reagent micro-cuvette. The reagent is a colorimetric reagent substance of which the active ingredient is a porphyrin compound that is highly specific and sensitive to lithium. The porphyrin compound is known to absorb light at 505 nm. This absorbance is increased by lithium concentration and is linear from 0.1 to 2.5 mEq/L of lithium.

The third key component of the system is a Photometric Reader designed to measure the absorbance of a solution contained in a micro-cuvette and to report concentrations from 0 to 2.5 mEq/L of lithium on the reader's display system. The amount of lithium bound to the reagent is measured by knowing how much light is sent to the solution containing plasma and reagent and how much is received by the photometric reader, which is programmed to calculate absorbance with the equation $A = 2\text{-}\log\%T$, where A is absorbance and T is transmission.

With the Photometric Reader in position, a 50-µL whole-blood specimen (taken from a finger stick) is applied to a well on the separator where the blood separates automatically into a bulb pipette that fills with the required volume of plasma. The filled bulb pipette is then removed and its contents discharged into the prefilled micro-cuvette, which is then placed in the photometer. The reader is activated to obtain the lithium reading on the sample, and the lithium level is displayed. The device is battery-operated, and the entire procedure takes about 2 minutes to complete.

*The brand name for this test is the InstaRead Lithium System.

Determining Reliability of the Test

We tested the clinical performance of the test by comparing its accuracy in whole blood, serum, and plasma with reference methods utilized currently in commercial laboratories. Three separate clinical evaluations were performed: the first evaluation (N = 200) was conducted in a clinical laboratory setting; 2 other evaluations (N = 40 and N = 29) occurred in clinical, "point-of-care" settings. When human subjects were tested directly, they signed informed consent statements and all identifying information was removed from the data collection process.

In all 3 studies, results from the comparative testing were analyzed by least-squares regression analysis.

Study 1. New test (venipuncture) compared with standard lab procedure (venipuncture). In the first study, the test was evaluated at 2 clinical laboratories in Miami, Fla. Demographic and clinical descriptors for these laboratory samples were unavailable. Two hundred venous whole-blood samples were collected in neutral (no anticoagulants) blood collection tubes, processed to serum within 4 hours of collection, and aliquoted for comparative testing with the laboratory's routine method for lithium analysis reflectance spectrophotometry (Vitros Chemistry System, Johnson & Johnson Clinical Diagnostics, Inc., Rochester, N.Y.). A number of samples were included from non–lithium-treated patients to assess detection of levels in the lower limits. Other samples were spiked with extra lithium in order to test levels in the toxic range (> 1.4 mEq/L).

Study 2. New test (finger stick) compared with standard lab procedure (venipuncture). The Uptown Research Institute in Chicago, Ill., evaluated the instant test in 40 psychiatric patients treated in 2 intermediate care facilities. The mean age of the patient population was 47.0 years (range, 30–71 years). Thirty-three patients (83%) were male; 18 were Caucasian (45%), 19 were African American (48%), and 3 were Hispanic (7.5%). All patients resided in 1 of 2 intermediate care facilities for the mentally ill. Clinical diagnoses included bipolar disorder (47%), schizoaffective disorder (47%), and schizophrenia (3%). All patients had been previously hospitalized for mental illness, and their average treatment history exceeded 10 years. The site staff was trained to implement the test before the evaluation was initiated, and all samples and materials were handled and disposed of following appropriate biohazard procedures. After signed informed consent was obtained, 40 finger-stick samples from patients were assayed by the instant test, and venous blood was collected into a neutral tube and processed to serum, which was assayed by atomic absorption (Perkin Elmer Instruments, Shelton, Conn.) at a reference laboratory.

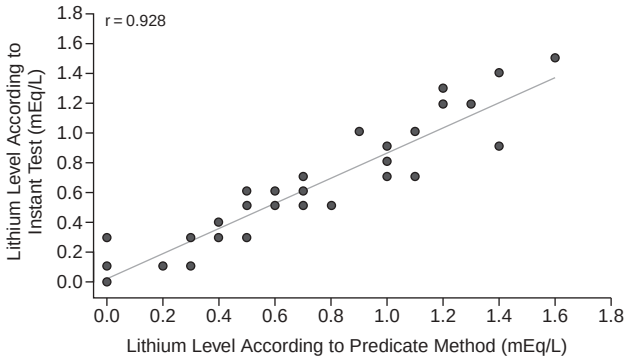
Study 3. Pre-prepared spiked whole blood: new test compared with standard lab procedure. The third study involved prepared whole-blood samples delivered to

Table 1. Summary Statistics: Test-Retest Reliability for 3 Studies Comparing Tests for Lithium Levels

Study	Description	N	Slope	Y-Intercept	Correlation (r)
1 (laboratory)	New test (venipuncture) vs standard (venipuncture)	200	0.998	–0.02	0.962
2 (outpatient psychiatry)	New test (finger stick) vs standard (venipuncture)	40	0.847	0.02	0.928
3 (outpatient oncology)	Spiked venipuncture samples: new test vs standard	29	0.833	0.05	0.983

Oncology Associates in Miami, Fla., an outpatient oncology practice, for testing. Here, an office staff member who normally performs in-office testing used the test to measure 29 pre-prepared whole-blood samples that had been collected in EDTA anticoagulated tubes and spiked with lithium ranging from approximately 0.1 to 3.0 mEq/L (NB: the reportable range has been limited to 2.5 mEq/L). The samples were separated into 2 aliquots: one aliquot was delivered to the office site for testing by the instant test; the second aliquot was processed to plasma and tested by the laboratory's chemistry analyzer (Vitros Chemistry System, Johnson & Johnson Clinical Diagnostics, Inc., Rochester, N.Y.). Patients were not identified in this study, so that demographic and clinical descriptors for these laboratory samples were unavailable.

Figure 1. Scatter Plot of Data From Study 2 Comparing Instant Test of Blood Lithium Level to Predicate Method (atomic absorption) in 40 Patients



RESULTS

Sensitivity, Linearity, and Precision of the New Test

Prior to the clinical studies reported here, a series of experiments were performed to evaluate the sensitivity, linearity, and precision of the new test. Specifically, the following tests were run:

- Within-day: 11 prepared samples, spanning the subtherapeutic to therapeutic ranges, were assayed in 7 replicates.
- Within-day and between-day: 2 clinical samples were assayed 10 times per day over 5 days. The samples contained low and high levels of lithium and were quantified by a reference laboratory.
- Within-day and between-day: EDTA plasma samples were assayed 10 times per day over 3 days. The samples contained low and high levels of lithium and were quantified by a reference laboratory.
- EDTA whole-blood spiked samples were assayed 20 times in 1 day by each of 2 operators using 2 different instant-test readers. Again, 2 levels representing low and high lithium levels were used.
- Two levels of controls, low and high, were assayed twice per day over 20 days.

The characteristics of the test are quite compatible with its use for determining serum or plasma lithium levels across the therapeutic range. These studies demonstrated that the assay was sensitive to 0.1 mEq/L, the assay was linear between 0.1 and 2.5 mEq/L, and precision estimates ranged from 0.00 to 0.08 standard deviations (SDs) when samples, targeted at various levels throughout the range, were assayed in multiple runs over multiple days. The percent coefficient of variation (%CV) of a control at ~1.5 mEq/L lithium was 6.4% when tested in 50 runs over 5 days (10 runs per day).

Reliability of the New Test

In all 3 studies (Table 1), there was excellent correlation between the new test and the standard laboratory procedure. In study 1, the correlation coefficient (r) for 200 patients was 0.962. In study 2, the mean lithium level was 0.61 mEq/L via the new test and 0.70 mEq/L via the standard laboratory method, and the regression analysis from the comparison of 40 subjects yielded an r-value of 0.928 (Figure 1). In study 3, the data demonstrated excellent agreement between the new test and the standard laboratory assay methods. The correlation coefficient was 0.983. In all 3 studies, the slopes and y-intercepts were close to 1 and 0, respectively.

DISCUSSION AND CONCLUSION

This article reports a new, self-contained, point-of-care device that demonstrates extremely high reliability for the measurement of whole blood, as compared with standard laboratory measures.

A previous study[10] had compared lithium assessments between an ion-selective electrode method and flame emission spectrometry and the authors noted that agreement was higher for venous than capillary blood. How-

ever, they did not study possible differences between collection methods within patients. Study 2 is, to our knowledge, the first to directly compare collection methods within patients, and the results indicate that lithium level assessments from capillary blood correlate highly with ones from venous blood.

While not new to medical practices, point-of-care devices have not been employed in psychiatric practice until now. This test will allow the attainment and evaluation of a finger-stick blood sample to occur at the point of care and as often as needed. It will provide treatment teams with accurate, real-time information about lithium level status, i.e., it will eliminate the time lag between the old venipuncture collection method and laboratory analysis. Since the provider will have the option of transcribing the test results in the permanent record, there will be less risk of transcription errors and greater assurance of optimal medical record documentation of the procedure.

This real-time option will enhance the precision of psychiatric practice. For example, in study 2, which included patients attending a clinic, there were several results between 0 and 0.5, indicating noncompliance with the therapeutic regimens. Clinicians were able to address this observation immediately with the patient, allowing for more effective interventions in comparison with what occurs in current practice, where the time lag reduces the option to work with the patient immediately when low or high blood lithium levels are detected. Additionally, rapid "toxicity" determinations in the office, especially in drug interactions and medical conditions associated with water loss or hot climates, may even be life saving and permit rapid and emergent interventions. From the patient's perspective, this new test will reduce the time required to participate in the lithium monitoring process (e.g., waiting for venipuncture, traveling to venipuncture sites away from location of clinical care) and will offer the option of a finger-stick blood draw in addition to the venipuncture method.

Point-of-care diagnostic in-office testing has radically advanced the practice of medicine by monitoring medications and management of disorders like diabetes, hyperlipidemia, and clotting diseases. The introduction of this new test is one of a number of new in-office diagnostics that will be made available to psychiatrists in the near future.

Drug names: chlorpromazine (Thorazine, Sonazine, and others), divalproex (Depakote), lamotrigine (Lamictal), lithium (Eskalith, Lithobid, and others).

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