Lithium fingerstick whole blood analysis – results mental healthcare clinic test

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Goal of study

Aim of this study is (**A**) to perform a method comparison between the Medimate and the Siemens ADVIA 1800 Chemistry system (the reference) and (**B**) to examine the capability of the Medimate to measure lithium in fingerstick whole blood reliably at mental healthcare clinic.

This test is part of the larger validation study conducted at home and at physician's office. This validation study is approved by the Medical Ethical Committee Twente in the Netherlands with reference number: NL62392.044.17.

Introduction Medimate

Lithium is globally used to treat and prevent manic or depressive episodes in bipolar disorder. The drug has a small therapeutic window and is potentially a toxic substance. Since differences between therapeutic and toxic levels are small, close monitoring of lithium concentration is required.

The Medimate is primarily intended to assess the lithium concentration in blood. Figure 1 shows how a measurement is performed. Specifications of the Medimate are given in table 1. In addition, the Medimate is able to perform a quality control of the applied blood sample due to its ability to detect hemolysis. If light or severe hemolysis is detected, then respectively a warning or automatic rejection of the measurement will follow.

Table 1: Specifications of Medimate

Medimate	Analytes	Serum	Fingerstick	Users
• Multireader (reusable measurement apparatus) • Lab-chip (disposable cartridge)	• **Lithium** • Creatinine • Potassium	• Yes • Yes • Yes	• Yes • Yes • No	• Healthcare professionals (point-of-care) • Lithium users (self-test)

Study design

Two tests were performed; (**A**) a method comparison and (**B**) a reliability test.

A: Method comparison
The method comparison test was performed according to CLSI EP-9 A3*[1]. For this test fingerstick whole blood and venous whole blood were collected of 53 subjects to measure lithium levels on respectively the Medimate (the test method) and the Siemens ADVIA 1800 Chemistry system (the reference, standard method). Inclusion criteria were: (i) the time between a Medimate measurement and venous blood collection is less than 3 hours and (ii) a Medimate measurement is performed within 10 to 16 hours after medication (lithium) intake.

B: Reliability test
Three nurse practitioners of the mental healthcare clinic GGz in Eindhoven were requested to test the performance of the Medimate at the clinic. Each nurse practitioner performed one measurement series. Each series covered five different days of three consecutive lithium measurements. For each lithium measurement a fingerstick sample was obtained. Nurse practitioners were requested to perform these measurements by subjects within 11,5 to 14 hours after medication (lithium) intake. Including multiple subjects for different days was allowed.

The reliability test was solely focused on assessing precision, therefore no reference measurements were performed. In this way non-biased test results were obtained providing optimal performance information without any external disturbances (stress and external influence).

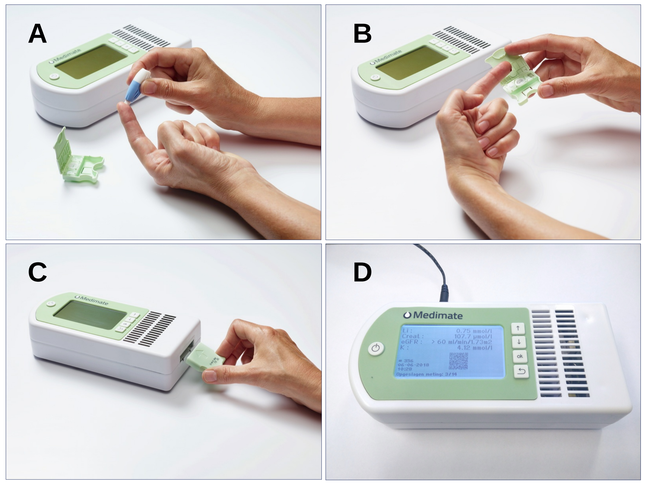

Figure 1: Measurement steps. **A.** Perform fingerstick, **B.** Apply blood droplet on cartridge, **C.** Insert cartridge, **D.** Readout result after 8 minutes

Acceptance criteria

Several parties have provided acceptance criteria for the performance of lithium measurements, see table 2. These acceptance criteria are quantified in the Total Error Allowable (TEA). Similar to the CLSI Evaluation protocols*[2] the TEA is separated into error budgets. Two error budgets are discriminated: the precision budget (one for random error deviation) and the accuracy budget (one for systematic error / bias).

A: For the method comparison the specifications are based on (i) the TEA of the Medimate accounting for +/- 10% or 0,10 mmol/L, (ii) the TEA of the ADVIA Chemistry system accounting for 4,8% and (iii) the time difference between fingerstick and venous blood collection. The TEA for this study is the combined TEAs and is chosen to meet +/-0,15 mmol/l or 15% with a 95% confidence interval.

B: For the reliability test, the precision budget to meet the Total Allowable Error is 0,06 mmol/l or 6% with a 95% confidence interval. The standard deviation should be less than half the precision budget (less than 0,03 mmol/l or 3%).

Results

The test results of the method comparison and the reliability test are shown in Figure 2 and Table 3. For the method comparison in total 53 measurements were performed. One measurement was excluded because of medication intake between the venous blood collection and the Medimate measurement. For the reliability test 46 measurements were performed of which only one was outside specifications due to hemolysis of the sample. Both tests resulted in a test performance of 98%.

Conclusions

Measurements of lithium in fingerstick whole blood show excellent results for testing at healthcare clinic. For the method comparison the TAE is less than 0,15 mmol/l or 15%. And the precision budget of the TAE is less than 0,06 mmol/l or 6% for the reliability test. Therefore the acceptance criteria are met.

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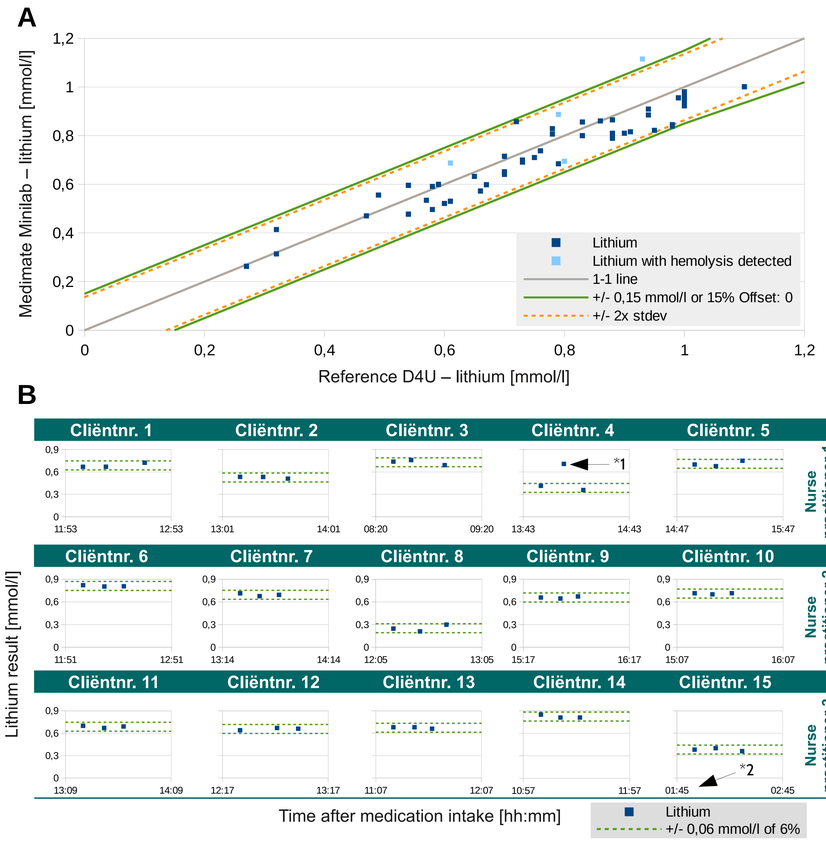

Figure 2: A) Results method comparison of the Medimate and the ADVIA 1800 Chemistry system (reference). Measurements indicating hemolysis are marked as light-blue. The orange, dashed lines indicate two times the standard deviation.
B) Results lithium fingerstick whole blood test at healthcare clinic. Three measurement series are plotted, each including five different days with three measurement results. 95% specification intervals are shown based on own average and specifications of +/- 6% or 0,06 mmol/l are shown. *1. Hemolysis detected, *2. Moment of medication intake possibly written down incorrectly or no lithium ingested.

Total Allowable Error	Third party reference	Method comparison
+/- 20% or 0,3 mmol/L	CLIA, WLSH, CAP, AAB	PASS
+/- 15% or 0,3 mmol/L	NYS	PASS
0,2 mmol/L	RCPA	PASS
+/- 10% or 0,10 mmol/L (fingerstick)	Medimate	PASS

Table 2: Third party performance criteria from the Rhoads Table for the Total Allowable Error.

Table 3: Results healthcare clinic test. For every test the pooled standard deviation is determined. This is the average of the residuals of all five days.

Test	Mean (mmol/L)	Number of measurements	Number of errors occured	Outside specifications (+/- 0,06 mmol/L or 6%)		Pooled stdev (mmol/L)	Pass criteria (mmol/L)	Evaluation
				Hemolysis detected	*No hemolysis detected*			
1	0,63	15	0	1	0	0,023	0,030	PASS
2	0,63	15	0	0	0	0,013	0,030	PASS
3	0,64	16	1 – no sample contact	0	0	0,012	0,030	PASS
Total	**0,63**	**46**	**1**	**1**	**0**	**0,016**	**0,030**	**PASS**

*[1] EP-9 A3 Method comparison and bias estimation using patient samples; Clinical and Laboratory Standards Institute, approved guideline – third edition, August 2013
*[2] EP21 Evaluation of Total Analytical Error for Quantitative Medical Laboratory Measurement Procedures, Clinical and Laboratory Standards Institute, 2-16