Medimate Mini-lab Lithium validation results part 1
Internal validation serum and fingerstick

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Introduction

Lithium is globally used to treat and prevent manic or depressive episodes in bipolar disorder. The drug has a small therapeutic window, and is in potention a toxic substance. Since the difference between therapeutic window and a toxic concentration is small, close monitoring of the lithium concentration is necessary.

The Medimate Minilab makes it possible to assess the lithium concentration in serum as well as fingerstick whole blood. The system is suitable for professional and self test use.

The Medimate Minilab combines a measurement apparatus called the Multireader and a disposable cartridge called the lab-chip. A measurement is performed after applying the sample at the lab-chip and inserting the lab-chip into the Multireader. The device detects the lab-chip and performs the measurement. After 9 minutes the Multireader displays the measured lithium concentration, see Figure 1.

The test results are part of an extensive validation study approved by the Medical Ethical Committee Twente in the Netherlands with reference number: NL34961.044.10

The objective of the study was to establish the performance of the Medimate Minilab .

Method

Multiple validation experiments are conducted in house. The tests that characterizes the performance are described here.

The Multireader is calibrated against the Flame Photometer IL 943 which uses flame absorption emission spectroscopy and is used as the reference standard. Except for the analytical specificity study all studies are carried out with human samples. Where required, K-EDTA is used as anticoagulant. To obtain high lithium levels samples are spiked with lithiumchloride. CLSI evaluation protocols were followed as much as possible.

Evaluated tests are reproducibility, linearity, lower limits, method comparison, shelf life and analytical specificity. More studies are carried out but are not included in this overview, these are: repeatibility studies under normal conditions, precision studies under extreme conditions, batch and multireader equivalence.

Acceptance criteria

The Dgrhoads table for total allowable error[1] provides acceptance criteria from several different parties for lithium monitoring in serum, see Table 1.
As the Medimate Minilab is intented to be equivalent with serum these acceptance criteria are used for serum as well as for fingerstick whole blood.

1. Allowable total error database, www.dgrhoads.com.

Figure 1:Photo of Medimate minilab measurement steps. 1. Perform fingerstick, 2. Apply blood droplet, 3. Insert Cartridge, 4. Readout result

Criteria	Reference	Repeatibility	Reproducibility	Meth Comp	Shelf life
+/- 20% or 0.3 mmol/L	CLIA, WLSH, CAP, AAB	PASS	PASS	PASS	1 year
+/- 15% or 0.3 mmol/L	NYS	PASS	PASS	PASS	1 year
0.2 mmol/L	RCPA	PASS	PASS	PASS	1 year
10% of 0,1 mmol/l serum 15% of 0,15 mmol/l fingerstick	Medimate	PASS	PASS	PASS	1 year

Table 1: Third party performance criteria and evaluation results.
Abbreviations: CLIA '88 Proficiency Testing Limits: U.S. Federal Register, WSLH: Wisconsin State Laboratory of Hygiene, CAP: College of American Pathologists, AAB: American Association of Bioanalysts, NYS: New York State Department of Health, RCPA: Royal College of Pathologists of Australasia.

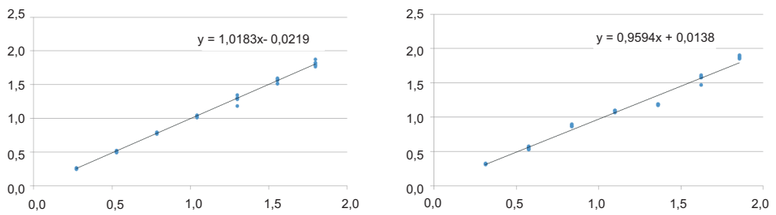

Figure 2: Linearity results: Left serum, right fingerstick. X-axis: Lithium [mmol/l] reference, Y-axis: Lithium [mmol/l] Medimate Mini-lab results

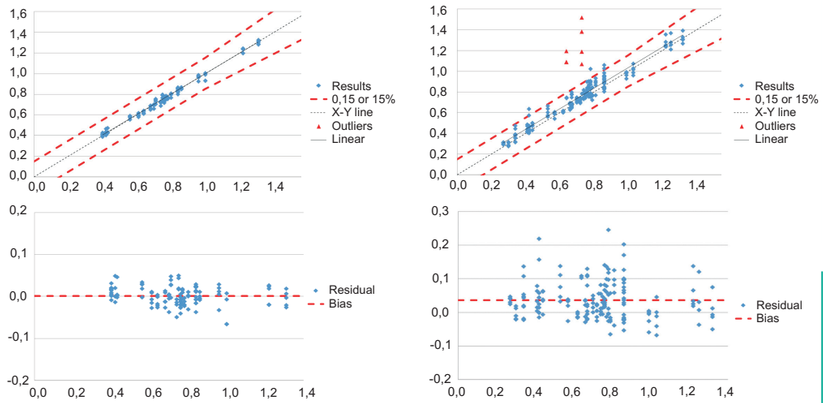

Figure 3: Method comparison results: Left serum, right fingerstick. Top: individual value plot, bottom: residual results.X-axis: Lithium [mmol/l] Il943 standard reference Y-axis: Lithium [mmol/l] Medimate Mini-lab results

Lithium results serum		
mmol/l	std.dev.	%cv
0,33	0,021	5,0
1,27	0,032	2,5
1,69	0,033	2,0
2,64	0,044	1,7

Lithium results fingerstick		
mmol/l	std.dev.	%cv
0,34	0,016	4,8
1,25	0,026	2,1
2,70	0,080	3,0
4,20	0,106	2,6

Table 2: Reproducibility results

Sodium mmol/l	Lithium deviation %
120	14
140	0
160	-14

Hemo-lysis %	Lithium deviation %
5	1,5
10	3,0
20	6,0

Table 3: lithium dependance for sodium and hemolysis

Results & Discussion

Reproducibility: 229 venous serum measurements were performed on 4 samples over 10 days, 2 locations, 9 disposable batches and 3 Multireaders, see table 2. 1 outlier was detected. 232 fingerstick K-EDTA whole blood measurements were performed on 4 samples over 1 days, 2 locations, 9 disposable batches and 10 Multireaders, no outliers were detected.
Linearity: Venous serum and fingerstick whole blood were found lineair in the range 0 – 10 mmol/l and 0 – 8 mmol/l respectively, see Figure 2.
Lower Limits: Limit of quantification for venous serum and fingerstick whole blood was tested at 0,25 for both.
Method comparison: All samples were verified against the average of 5 repetitive measurements at the Il943 Flame photometer, see Figure 3.
28 venous serum samples were tested with 5 repetitive measurements: $y = 0{,}982x + 0{,}0154$, $R^2 = 0{,}990$. Test results found were within the 0,1 mmol/l and 10% at 95% CI. Observed bias was 0,002mmol/l.
42 fingerstick whole blood samples were tested with 5 repetitive measurements, 5 droplets were used, each time from one fingerstick: $y = 0{,}9865x + 0{,}0455$, $R^2 = 0{,}954$. Test results were found within 0,15 mmol/l or 15% at 95% CI. Observed bias was 0,036 mmol/l.
Differences between fingerstick whole blood and venous serum are expected to come from different droplets with different individual hemolysis percentages as well as the difference between individual samples. Outliers observed are expected, but not confirmed, to come from ringed fingers. These are excluded from the protocol after confirmation tests were performed in house.
Shelf life: The shelf life was tested with 9 batches for 15 consecutive months. Each month more than 12 samples were analyzed. The deviations observed in average was smaller than 0,022 mmol/l and in standard deviation smaller than 0,029 mmol/l.
Analytical specificity: There is no significant Interference found for Kalium, Ammonium, Calcium, Magnesium, Zink, Ureum, Hemoglobin, Albumine, Creatinine, Billirubine, Iron, Lipid Index.
Sodium and hemolysis interference is found according to the following two equations. Examples are shown in Table 3.
Sodium: [Li_correction] = -0,7%*[Sodium deviation]
Hemolysis: [Li_correction] =2,8%*[Hemolysis percentage]

In Table 1 it is shown which venous serum criteria are met by the Multireader for serum and fingerstick whole blood.

Conclusions

Measurement results showed that the Medimate Multireader is very well capable to measure the Lithium concentration in venous serum and fingerstick whole blood within the general acceptance criteria.
Performance for serum is 10% or 0,10 mmol/l and for fingerstick 15% or 0,15 mmol/l.