VALIDATION (CLINICAL USE) AND COMPARISON OF THE FIRST LITHIUM ANALYSER FOR POINT-OF-CARE-TESTING (MEDIMATE MINILAB®) WITH THE INFINITY™ LITHIUM ANALYSIS APPLICATION ON THE ROCHE MODULAR ANALYTICS® P800 MODULE.

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March 27th, 2014

Version 0.3

This version is concept and waiting for approval of the Clinical Pharmacology department.

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INTRODUCTION

Lithium therapy is indicated in the treatment of manic episodes of Bipolar Disorder. Lithium is also indicated as a maintenance treatment for individuals with a diagnosis of Bipolar Disorder. Maintenance therapy reduces the frequency of manic episodes and diminishes the intensity of those episodes which may occur. (Typical symptoms of mania include pressure of speech, motor hyperactivity, reduced need for sleep, flight of ideas, grandiosity, elation, poor judgment, aggressiveness, and possibly hostility). When given to a patient experiencing a manic episode, Lithium may produce a normalization of symptomatology within 1 to 3 weeks.

During maintenance treatment the lithium plasma level should be between 0.6 and 1.2 mmol/l. Levels above 1.5 mmol/l can be toxic and levels exceeding 2.0 mmol/l will induce serious neurological symptoms (e.g. fasciculation's, twitching, clonic movements, pathologic reflexes, dizziness, confusion, epileptiform seizures, loss of consciousness, stupor, coma).

It is clear that the therapeutic range is small and toxic levels can easily be reached. Toxic levels are a medical emergency and require immediate intervention to prevent permanent damage. Therefore it is essential to monitor lithium plasma levels in treated patients and to adjust the dosing accordingly. In case of overdosing symptoms a stat lithium analysis is indicated to start treatment as soon as possible.

A stat lithium analysis requires blood collection, transport to the lab, sample preparation and analysis and finally communication to report the result. Although this process is fairly well controlled, it imposes a lag time that is not beneficial for the patient. A point-of-care-testing (POCT) system for lithium analysis could solve this problem and in addition would be an aid to the psychiatrist when the lithium analysis can be done during a consultation: the lithium result can be discussed with the patient in addition to the dosing adjustment, when needed.

For a lithium POCT system to be incorporated in the daily care for these patients, the results must be comparable to the lab results. In addition, the results should be available to both the psychiatrist and the clinical pharmacologist in an electronic patient file for monitoring and consulting purposes. Preferably, the POCT generated results should be send directly through an electronic connection to the database of an information system that is accessible by the psychiatrist and the clinical pharmacist (not necessarily the same information system). The

electronic and otherwise generated cumulative patient lab results should incorporate both the POCT as well as the routine lab plasma lithium results (with the POCT results tagged as such).

This report describes the analytical evaluations done to answer the following questions:

Can lithium results obtained through POCT in whole blood using the lithium analyzer Medimate Minilab®, be interpreted clinically?

Is the analytical performance of the lithium analyzer Madimate Minilab® comparable to the routine lab method of the Medical Center Leeuwarden?

MATERIALS

The instrument, named the Medimate Minilab®, consists of a Multireader and disposable lab-chips, and is manufactured by Medimate BV, Enschede, the Netherlands. A picture of the Minilab is shown in Figure 1. The instrument measures concentrations of certain substances in the whole blood, serum or urine, i.e. lithium. The Minilab is shown in Figure 2. The measurement does not require any calibration and little to no maintenance.

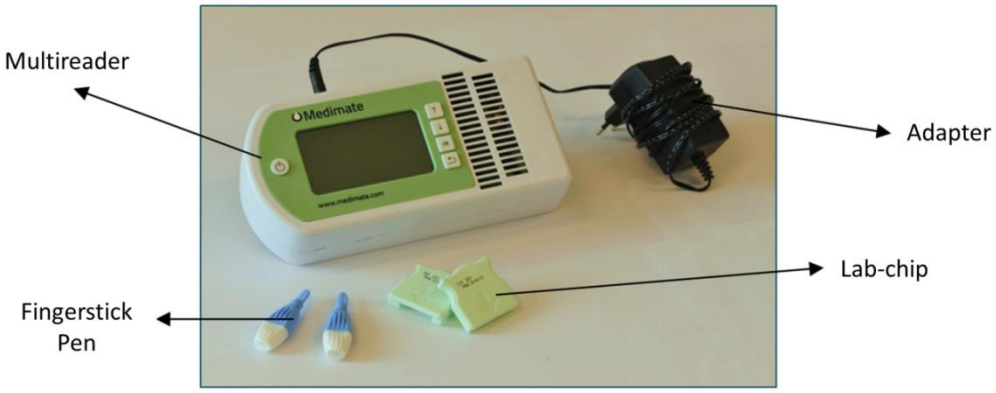

Figure 1: The Medimate Minilab®.

Figure 2: Performing a measurement on the Medimate Minilab®. A finger stick is performed with the finger stick pen (a), after which the blood droplet from the finger is applied to the Lab-chip (b). Then the Lab-chip is inserted into the Multireader (c) and finally after a few minutes the concentration value is shown on the screen (d).

ANALYTICAL EVALUATION AND METHOD

The Medimate Minilab® is compared to the Infinity™ method (Thermo Fisher Scientific, New York, United States of America) applied on the P800 module of the Roche Modular Analytics® (Roche Diagnostics GmbH, Mannheim, Germany) to investigate the possibility to use the Minilab as a point of care device as an add on to the clinical lithium measurement of the Modular. First a method comparison study is performed to indicate if the lithium measurement on the Modular by a serum sample is comparable to the fingerstick sample of the Minilab. Second a linearity study is performed to investigate the behavior in the high range and to investigate a potential offset between the Modular and the Minilab.

Medimate has published two test reports based on the performance of the Medimate Minilab®. The first test report, *Lithium Validation Report version 1.02 2013-12-12,* is the report about the internal evaluation by Medimate and the second test report, *2014-02-05 v1.0 Analytical validation of Point of Care analysis of Lithium.pdf*, is the external evaluation report by Medlon B.V. and Medical Spectrum Twente, both reports are used as input for the final evaluation described in this report.

The Total Allowable Error performance of the Medimate Minilab® is expected to be +/- 10% or 0,1 mmol/l for serum and +/- 15% or 0,15 mmol/l for capillary whole blood.

METHOD COMPARISON

The method comparison is performed with 28 patients on lithium therapy. All experiments are performed at a standard blood collection point by trained personnel. To evaluate the lithium level on the Modular a venous puncture is taken according to standard protocol. At the same time a fingerstick is performed to measure the lithium on the Minilab.

LINEARITY

To evaluate differences between Infinity™ method (Thermo Fisher Scientific, New York, United States of America) applied on the P800 module of the Roche Modular Analytics® (Roche Diagnostics GmbH, Mannheim, Germany) and the Medimate Minilab® extra reference measurements are performed on the reference method the Flame Photometer IL943 (MST laboratory, Enschede). The differences are investigated with respect to the IL943.

Two sample types are tested, venous serum and venous whole blood, each with 9 spiked lithium ranges from 0,30 to 4,00 mmol/L. Each level is measured in duplo on the Minilab and in single on the Modular. Zero level samples are obtained from a person not using lithium by a vena puncture. Serum is collected in anti-coagulation tubes and centrifuged. Whole blood is collected in K-EDTA collection tubes. High and low levels are spiked with lithium chloride solution. Both samples are verified by reference measurements. The samples are then pooled to get the intermediate lithium levels.

STATISTICS

Method comparison data is analyzed by Analyse-it, version 2.30 using Microsoft Excel. Linearity is analyzed in Microsoft Excel.

RESULTS AND DISCUSSION

METHOD COMPARISON

The results obtained are shown in Figure 3. The measurement range is 0,35 to 1,03.

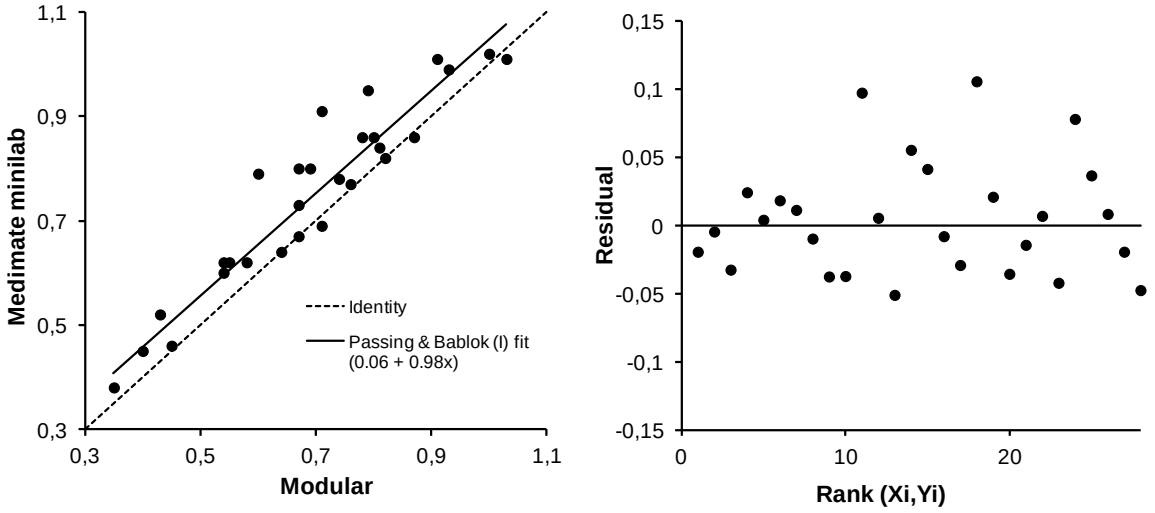

Figure 3: Left: Scatter plot with Passing & Bablok fit, X-axis lithium concentration in mmol/l as measured by the Modular, Y-axis lithium concentration in mmol/l as measured by the Minilab. Right: Residual plot, X-axis measurement number, Y-axis residual lithium concentration in mmol/l between Minilab and Modular.

Passing & Bablock fit indicates an offset of 0,06 and a proportional error of 0,98. Linear regression indicates an intercept of 0,091 and a slope of 0,952 with an R^2 of 0,89.

For the Minilab it is known that capillary measurements can give a small positive offset due to hemolysis of the sample possibly caused by a damaging the droplet during the fingerstick (we did not check for hemolysis in the capillary whole blood sample). This might explain why the largest differences are found solely at the positive side of the residual plot.

LINEARITY

According to protocol a concentration range from 0,3 to 4,0 mmol/l was made. The individual measurement results are shown in Table 1. Figure 4. show the measured lithium values versus the lithium target value. The spiked lithium value turned out to be a bit higher than intended.

From the results the linear fit, R and the mean difference can be derived. The results are shown in Table 2. As the R^2 is larger than 0,95 the data for the linear fit is found acceptable.

In Figure 4 it can be seen, especially for the whole blood levels, that the lower samples of the Minilab are more comparable to the Flame when compared to the higher levels. Because the measurements are acceptable without any correction, this is not further elaborated.

Table 1: Individual linearity test results

Method	Sample	Series	Lithium results per sample (mmol/L)
Flame *(reference)*	serum	1	0,40 ; 0,81 ; 1,32 ; 1,81 ; 2,33 ; 2,84 ; 3,34 ; 3,81 ; 4,38
		2	0,38 ; 0,79 ; 1,29 ; 1,79 ; 2,30 ; 2,81 ; 3,29 ; 3,70 ; 4,28
	plasma	1	0,36 ; 0,87 ; 1,44 ; 1,94 ; 2,49 ; 3,09 ; 3,64 ; 4,17 ; 4,66
		2	0,33 ; 0,86 ; 1,42 ; 1,90 ; 2,44 ; 3,05 ; 3,54 ; 4,08 ; 4,58
Minilab	serum	1	0,40 ; 0,83 ; 1,26 ; 1,83 ; 2,43 ; 2,86 ; 3,42 ; 3,76 ; 4,33
		2	0,38 ; 0,85 ; 1,32 ; 1,91 ; 2,37 ; 2,84 ; 3,45 ; 3,96 ; 4,51
	whole blood	1	0,37 ; 0,88 ; 1,34 ; 2,02 ; 2,61 ; 3,29 ; 3,71 ; 4,18 ; 4,94
		2	0,38 ; 0,89 ; 1,50 ; 2,08 ; 2,64 ; 3,21 ; 3,76 ; 4,26 ; 4,85
Modular	serum	1	0,31 ; 0,77 ; 1,24 ; 1,75 ; 2,23 ; 2,65 ; 3,19 ; 3,64 ; 4,10
	plasma	1	0,31 ; 0,87 ; 1,37 ; 1,84 ; 2,31 ; 2,88 ; 3,53 ; 3,98 ; 4,59

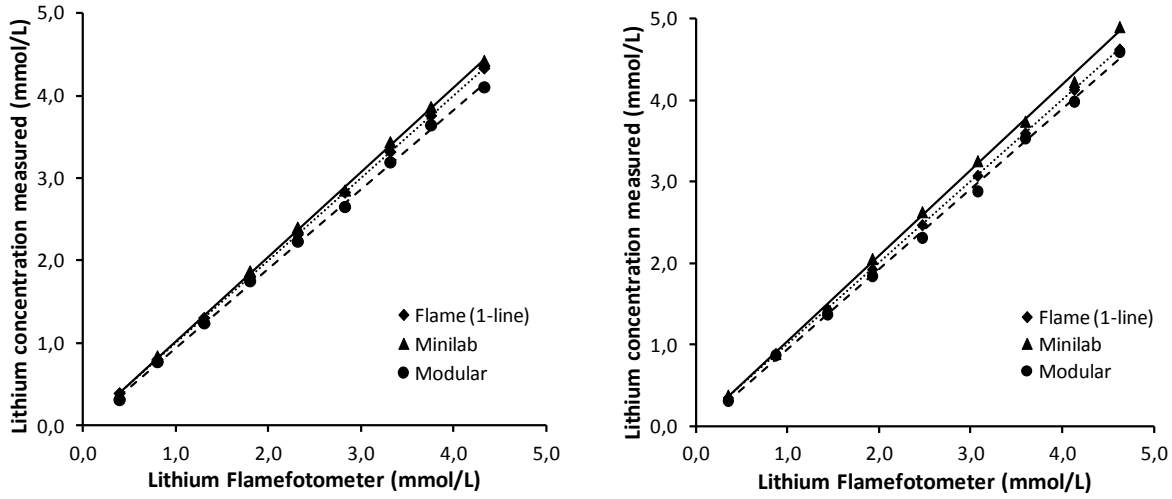

Figure 4: Linearity scatter plot for serum (left) and wholeblood / plasma (right). The X-axis is the average of the reference measurement on the IL943. The Y-axis is the lithium result from the Minilab (average) and Modular (single).

Tabel 2. Analysis results for the Minilab and the Modular when compared to the Flame.

Sample type	Device	Regression line	R^2	Diff
Serum	Minilab	1,026 x - 0,00	0,999	3%
	Modular	0,962 x - 0,02	0,999	-6%
Whole blood / Plasma	Minilab	1,048 x - 0,01	0,999	5%
	Modular	0,983 x - 0,04	0,998	-4%

CONCLUSION

The Medimate Minilab ® can be an add on to the Infinity™ method (Thermo Fisher Scientific, New York, United States of America) applied on the P800 module of the Roche Modular

Analytics® (Roche Diagnostics GmbH, Mannheim, Germany) taking into account that the Minilab gives a higher value as a result. The average difference is between 6% to 9% .

The method comparison indicate that there are no significant differences between the Modular and the Minilab and that both methods are comparable. A positive offset of 0,06 is observed.

From the linearity results it is derived that the lithium concentration measured by the Minilab is 4% higher compared to the Flame whereas the Modular is 5% lower. This gives a difference of 9% between the Modular and the Minilab.

No significant differences are found between the different sample types.

The Minilab and Modular are linear in the range 0,3 to 4,5 mmol/l.

Finally,

- The results described in this report did not show any reason to doubt the manufacturer claimed performance of the Multimate Minilab® with respect to lithium analysis. The analytical performance was comparable to the routine lab method.
- From a clinical point of view, the lithium results obtained with the Medimate Minilab® can be interpreted in line with the results obtained by the routine lab method (Infinity™ method (Thermo Fisher Scientific, New York, United States of America) applied on the P800 module of the Roche Modular Analytics® (Roche Diagnostics GmbH, Mannheim, Germany)). Cumulative patient records can depict both routine lab as well as Medimate Minilab® lithium results and a cumulative interpretation of the patient's lithium results can be made without distinguishing between both methods.
- These statements are true provided that the handling of the lab chips are adequately performed. Users should therefore be trained and certified by the lab before using the Medimate Minilab® in a clinical setting.