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Clozapine blood level assessment using a point-of-care device: feasibility and reliability

Shiri Kamhi-Nesher, Sharon Taub, Shikma Halimi, Maria Frenkel, Mahmud Azam, Gil Bormant, Helena Isakov, Dikla Radzinsky, Abraham Weizman and Amir Krivoy

Abstract

Background: Therapeutic drug monitoring (TDM) is useful to assess clozapine adherence and optimize treatment. However, analysis of venous blood levels by liquid chromatography tandem mass spectrometry (LC-MS/MS) is often logistically complicated and process time is prolonged.

Objective: To assess the feasibility and reliability of a new point-of-care device, (MyCare™ Insite), using capillary blood for clozapine therapeutic monitoring.

Methods: Matched venous and capillary blood samples were collected from patients treated with clozapine on a stable dose. Samples were analyzed by LC-MS/MS and MyCare Insite Clozapine Test. Clozapine plasma levels were compared between methods using linear regression model. Both patients and treatment team completed questionnaires about the feasibility of blood sampling.

Results: Of the total sample (44 patients, 61% males, mean age 43 ± 12 years), mean daily clozapine dose was 293 ± 134 mg/day. Linear regression model demonstrated high correlation with $R^2 = 0.83$ ($p < 0.0001$) and mean difference of 26 ± 162 ng/ml. More than 60% of the patients found the clozapine TDM to be important. Most of the participants (58%) favored the capillary sampling and 11% claimed that testing method would affect their adherence to TDM. Moreover, a larger portion (72%) strongly preferred to be tested at the office rather than at the lab.

Conclusions: The point-of-care device offers an accessible and satisfactory measurement of clozapine blood levels. Both patients and healthcare providers reported preference for capillary sampling as well as for the in-office TDM procedure. The immediate results provided by the device can facilitate rapid and informed clinical decisions and therefore improve clozapine treatment outcomes.

Keywords: clozapine, schizophrenia, point of care, therapeutic drug monitoring

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Correspondence to:
Shiri Kamhi-Nesher
Geha Mental Health Center, 1 Helsinki street, P.O. Box 102, Petah-Tikva 49100, Israel
Sackler Faculty of Medicine, Tel-Aviv University, Tel-Aviv, Israel
sknesher@clalit.org.il

Sharon Taub
Geha Mental Health Center, 1 Helsinki street, P.O. Box 102, Petah-Tikva 49100, Israel
Sackler Faculty of Medicine, Tel-Aviv University, Tel-Aviv, Israel
shar.taub@gmail.com

Shikma Halimi
Maria Frenkel
Mahmud Azam
Gil Bormant
Helena Isakov
Dikla Radzinsky
Abraham Weizman
Amir Krivoy
Geha Mental Health Center, Petah-Tikva, Israel
Sackler Faculty of Medicine, Tel-Aviv University, Tel-Aviv, Israel

Introduction

Clozapine is a unique and effective antipsychotic compound and is known as the most efficient agent for treatment resistant schizophrenia (TRS). It is estimated that as many as 30% of individuals with schizophrenia meet the criteria for TRS and clozapine is considered valuable in 30–75% of this subgroup.[1,2] Clozapine is not only highly effective; it is also associated with reduced mortality in comparison with other antipsychotic treatments, as demonstrated repeatedly.[3,4] However, clozapine use is associated with barriers and the compound is underused in spite of its notable advantages.[2,5] Complex pharmacodynamic profile and fear of severe side effects are among those barriers.[6]

Measuring serum drug levels is available for many psychopharmacologic agents, including mood

stabilizers, tricyclic antidepressants, and several antipsychotic drugs, including clozapine.[7] Therapeutic drug monitoring (TDM) offers many advantages such as reflecting adherence to treatment, a crucial issue in schizophrenia treatment where adherence is estimated to be less than 50%,[8] assisting customized dosing decisions, and avoiding drug toxicity. Serum drug levels are affected by age, medical conditions, genetics, drug-drug interactions, and pharmacokinetic variability; all can differ immensely between patients and during the patient's life course.[7] Clozapine blood levels are correlated with clinical outcome: response is associated with blood levels above 350 ng/ml,[9,10] whereas levels higher than 600 ng/ml might be associated with increased risk to develop side effects.[10] Yet, measuring clozapine levels is complicated and often avoided. The current available customary analytic method of liquid chromatography tandem mass spectrometry (LC-MS/MS) requires transportation to a special lab and a multistep analysis process that may take several days.[11]

New and advanced technologies can enable rapid and easier ways to measure clozapine blood levels. MyCare™ Insite by Saladax is a new point-of-care (POC) immunoassay method using capillary blood sampling. This method offers three main advantages: (1) The analysis requires capillary blood instead of venous blood, which is preferred by both caregivers and patients.[12] (2) The test is conducted as an in-office procedure, with no need for laboratory outsourcing. (3) The results of the test are received immediately on the spot in less than 7 minutes. Preliminary results of this novel POC device were recently published,[11] demonstrating the validity of clozapine blood level measurements.

In the current study, we aimed to evaluate the feasibility of the POC analysis among both patients and healthcare practitioners. In addition, we aimed to corroborate and extend the initial data on the validity and accuracy of this innovative methodology, by comparison with the standard LC-MS/MS analysis.

Methods

Sample

Study population for this observational study included 44 subjects treated at Geha Mental Health Center during the years 2019–2020. The sample included both inpatients and patients treated in the day care unit, in a public mental health center in Israel that belongs to Clalit Health Services (CHS) health care organization. According to the inclusion criteria all participants were (1) adults aged over 18 years. (2) Diagnosed with schizophrenia, schizoaffective disorder, or other psychotic conditions. (3) Prescribed clozapine for at least 4 weeks at a stable dose at study entry. (4) Capable to provide a written informed consent. The study was approved by the institutional review board (approval number: 0007-19-GEH). Due to the exploratory nature of the study, the results obtained from the POC device were not available during medical decision-making.

Study procedures

Following provision of written informed consent to take part in the study, participants were asked to provide a finger-prick capillary blood sample for testing in addition to the regular venous blood sample that was collected in the same session. Samples were collected in the morning (08:00), before breakfast and the morning dose administration. The intrapatient results of the 2 adjacent assays, the LC-MS/MS and Insite POC test, were later analyzed and compared.

Testing protocol. Venous sample: Each venous sample, containing 5 ml of blood in an EDTA test tube, was centrifuged to separate the plasma. The frozen plasma (at −20°) was later sent to the toxicology lab at 'Carmel' medical center (Haifa, Israel) for analysis by the standard LC-MS/MS technology.

Capillary sample: An additional capillary sample, containing 0.01 ml of blood, was retrieved from the fourth finger of the nondominant hand of each participant. Each collected whole- blood sample was tested via the MyCare™ Insite POC device using the MyCare Clozapine Test. The MyCare Clozapine immunoassay is based on an antigen- antibody reaction causing nanoparticle aggregation that is measured photometrically. The entire procedure was performed by a trained health care professional (physician or a nurse) at the clinic room within minutes.

Feasibility evaluation. All participants were requested to complete a questionnaire regarding the test usability and their personal TDM preference. The questionnaire also included a series of questions regarding adherence to treatment, habits (tobacco use and caffeine consumption, etc.) and adverse effects under clozapine treatment. A

second questionnaire, designated for the treating team (six treating physicians), was composed of clinical global assessment of each patient. In addition, the physicians were requested to evaluate their own experience with the POC device.

Statistical analysis

Clozapine blood levels were compared between methods using linear regression. Significance was set at $p < 0.05$. Computer software used for data analysis was SPSS for Windows, version 20.0 (IBM Corp. Armonk, NY, USA).

Results

Sample characteristics

The sample included 44 patients, 61% males, mean age 43 ± 12 years, mean body weight was 80 ± 16 kg and 41% of the participants reported cigarette smoking (Table 1). Mean daily clozapine dose was 293 ± 134 mg/day (ranging between 50 and 600 mg/day) (Table 1) with one-fourth of the patients prescribed a daily clozapine dose above 350 mg/day. According to clinical global assessment, most of the patients (79%) presented moderate to severe psychotic symptoms as well as negative symptoms. Moderate-to-severe side-effects were reported by 44% of them, more than evaluated by the treatment team.

Table 1. Characteristics of the patient sample ($n = 44$).

Characteristic	Result	%	SD	Range
Sex				
Male	27	61		
Female	17	39		
Mean age (years)	43		12	18–71
Mean weight (kg)	79.7		15.5	
Smoking tobacco	18	41		
Mean clozapine dose (mg/day)	292.6		133.6	50–600

SD, standard deviation.

TDM preferences and test feasibility

When asked about their point of view and preferences regarding TDM, more than 60% of the patients declared TDM of clozapine to be of importance to them. Almost half (49%) of the patients preferred frequent TDM testing (medium or higher frequency of TDM). Most of the participants (58%) favored the capillary blood sampling, with 11% claiming that testing method would affect their adherence to TDM. Moreover, a larger portion (72%) strongly preferred to be tested in the physician's office rather than the lab. Treatment team (81%) also preferred the capillary testing and predicted most patients would prefer it (Figure 1).

Clozapine blood levels

Treating physicians predicted that most patients (62%) would present clozapine blood levels detectable but below the therapeutic threshold, 35% of the participants would be within therapeutic range and only few (3%) were predicted to have clozapine level higher than the range. Analyzing blood samples found the blood level of 57% and 64% of the sample to be below the therapeutic threshold by the LC-MS/MS and the POC device, respectively. Therapeutic blood levels of clozapine (range 350–650 ng/ml) were found in 18% and 21% of the patient's samples, with the two methods, respectively. Clozapine blood levels above the upper limit of the therapeutic threshold (above 650 ng/ml) were found in 25% and 16% of the sample, respectively.

Test validity

Linear regression model of TDM measurements from the two methods demonstrated high correlation with $R^2 = 0.83$ ($p < 0.0001$) and mean difference (LC-MS/MS minus POC) of 26 ± 162 ng/ml (median of 4.5 ng/ml) (Figure 2). Concordance rate between samples according to categories was found to be 96% for levels below 350 ng/dl, 62.5% for levels between 350 and 650 ng/ml, and 63.6% for levels above 650 ng/dl (Table 2).

Discussion

In this study, we aimed to assess the feasibility and validity of a novel rapid TDM immunoassay which is performed as an office-based procedure. Our main findings were that most caregivers and patients prefer this testing method over the 'gold standard' assay and that the new device provides valid clozapine blood level results.

Our results regarding test validity, with a satisfactory R^2 of 0.83 ($p < 0.0001$), are consistent with

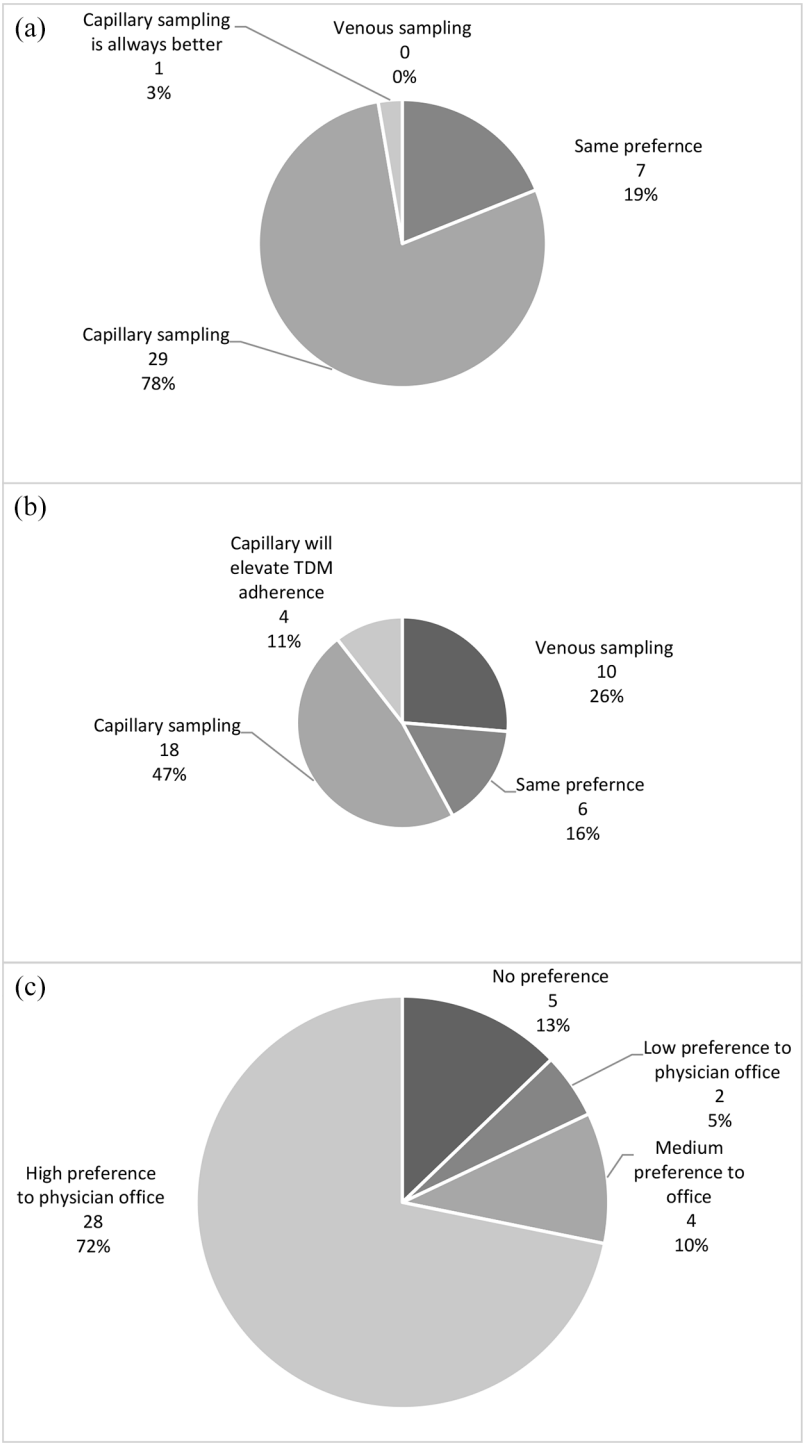

Figure 1. Therapeutic drug measurement preferences. (a) Preferred sampling method of treatment team ($n = 37$). (b) Preferred sampling method of patients ($n = 38$). (c) Preferred sampling setting of patients ($n = 39$).

a previous UK study regarding the same POC device.[11] The authors assessed clozapine blood levels of 309 patients by the two methods, the standard laboratory LC-MS/MS assay and the MyCare™ Insite device. Sample characteristics and inclusion criteria were similar to those applied in the UK study. The latter revealed similarity between the results obtained by the two methods, with correlation coefficient of 0.89 and a slope of 1.0 [95% confidence interval (CI) 0.9–1.0]. Within-patient differences between measures were ⩽10%.

In our study, agreement rate between the results obtained by the two methods was better with lower clozapine blood levels (96%) in comparison with higher levels (63%). This may imply that the results obtained by the POC tend to be lower compared with the results from the LC-MS/MS. These findings are comparable with the previous UK POC study.[11] As suggested by the authors, some variation between methods is expected due to use of different types of blood samples (venous plasma *versus* capillary whole blood)[13] and calibration calculations applied by the assay manufacturer to report plasma results from whole blood samples. In addition, it is important to note that the gold standard LS-MS/MS is not infallible and may be subjected to errors that may affect agreement rate.[14]

The current study, beyond confirming the test validity, evaluated user experience and testing method preferences. Patients and their treating physicians were queried regarding various aspects of TDM, testing procedure and personal viewpoints. The participants' responses reflect a clear trend in favor of Insite capillary testing, indicating that the POC device may contribute to increased TDM adherence. Another important clinical consideration is the immediacy and proximity of the assay, which makes the POC device useful to detect and prevent clozapine overdose.

Such preference is consistent with clozapine-treated patients and their practitioners' attitude toward other POC testing, as reported in a study of a portable capillary white blood count (WBC) monitoring device.[12] This is also in line with data on patients satisfaction with POC testing methods in general practice, like INR capillary testing for anticoagulation monitoring[15] and sugar blood level monitoring.[16] Capillary POC methods are gaining more interest and a new portable WBC device was recently compared well with the gold standard laboratory assay.[17] The possibility to combine POC WBC monitoring and TDM can be clinically-beneficial for clozapine- treated patients.

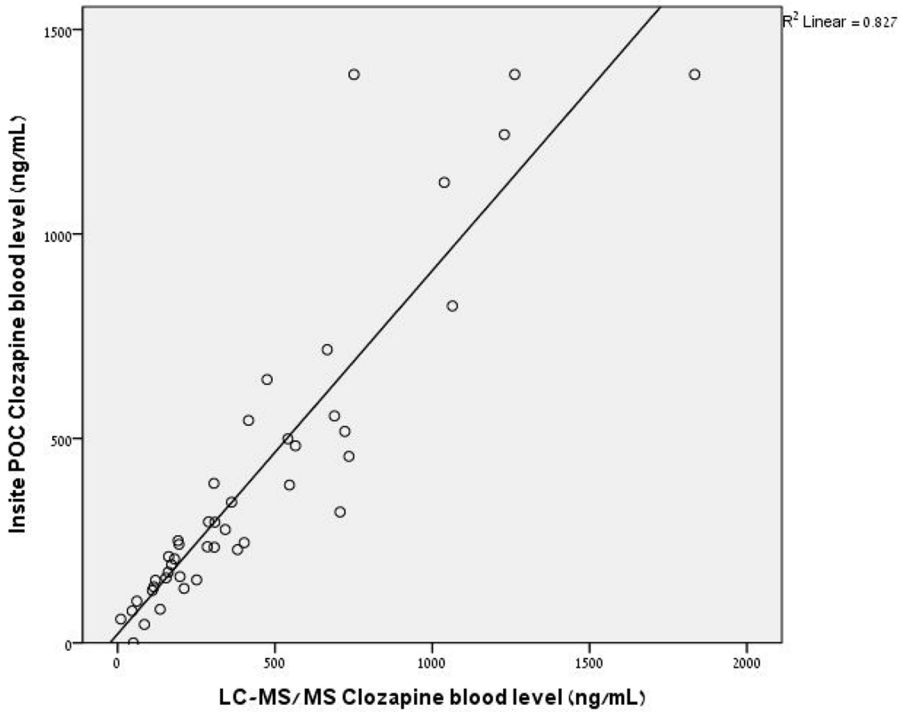

Figure 2. Comparison of the two assays using linear regression.
POC, point of care.

Table 2. The concordance rate between the two assays and clozapine blood levels (ng/ml).

Lab		Insite		
		<350	351–650	>650
	<350	96%		
	351–650		62.5%	
	>650			63.6%

In spite of the clear advantages, such as convenient application and instant results, the POC immunoassay is associated with several built-in drawbacks, which must be addressed. As mentioned, the results obtained are less accurate at higher drug levels. Furthermore, the test has a detection upper limit of 1390 ng/ml, which makes it less suitable to precisely measure clozapine overdose. Therefore, it is advisable to apply the same testing method when repeated measures are required per-patient and interpret the obtained results within the clinical context. Another technical disadvantage is lacking the ability to measure clozapine metabolite levels and specifically, norclozapine. The ratio of clozapine to norclozapine concentrations, which can be provided by the LC-MS/MS method, has been suggested to have clinical value in assessing recent compliance and pharmacokinetic changes,[18] however, evidence on this subject is conflicting.[19]

Study limitations

Study limitations are inherent to the small sample size of the current investigation. On one hand, due to the limited scope of the study, all samples were undertaken by a small team of trained device operators, hence contributing to its consistency. On the other hand, the small sample size may reflect on higher effect of the outlier results.

In addition, most of the sample measures (capillary as well as venous samples) detected clozapine

blood levels on the lower range. Test accuracy in the presence on higher clozapine blood levels should be studied more thoroughly in the future.

Further research, including larger samples of patients from diverse care settings and with various clinical characteristics, is essential to further evaluate both POC device feasibility and user experience.

Conclusions

In conclusion, clozapine TDM is a valuable tool to ascertain both efficacy and safety of treatment. The POC device offers a rapid, accessible, and satisfactory measure of clozapine blood levels. Both patients and healthcare providers reported preference of capillary sampling as well as the in-office TDM procedure. Using POC immunoassay may contribute to increase TDM adherence and therefore improving rate and outcome of clozapine treatment among this difficult-to-treat population.

Author contributions

Shiri Kamhi-Nesher: Conceptualization; Methodology; Validation; Writing – original draft.

Sharon Taub: Conceptualization; Formal analysis; Software; Writing – original draft.

Shikma Halimi: Investigation; Writing – review & editing

Maria Frenkel: Data curation; Investigation; Writing – review & editing.

Mahmud Azam: Investigation; Writing – review & editing.

Gil Bormant: Data curation; Investigation; Writing – review & editing.

Helena Isakov: Investigation; Project administration; Writing – review & editing.

Dikla Radzinsky: Methodology; Writing – review & editing.

Abraham Weizman: Conceptualization; Methodology; Supervision; Writing – review & editing.

Amir Krivoy: Conceptualization; Formal analysis; Methodology; Writing – original draft.

Conflict of interest statement

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ORCID iD

Sharon Taub https://orcid.org/0000-0002-6496-9350

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