Original Contributions

Blood Draw Barriers for Treatment with Clozapine and Development of a Point-of-Care Monitoring Device

Deanna L. Kelly 1, Hadar Ben-Yoav 2,3, Gregory F. Payne 4,5, Thomas E. Winkler 2,4, Sheryl E. Chocron 2,4, Eunkyoung Kim 5, Christopher Kitchen 1, Veronika Stock 1, Gopal Vyas 1, Raymond C. Love 6, Heidi J. Wehring 1, Kelli M. Sullivan 1, Stephanie Feldman 1, Fang Liu 1, Robert P. McMahon 1, Reza Ghodssi 2,3,4

Abstract

Background: While clozapine (CLZ) is the most effective antipsychotic drug for schizophrenia treatment, it remains underused. In order to understand the barriers of frequent blood draws for white blood cell counts (WBCs) and clozapine levels, we developed a psychiatrist survey and began an integrative approach of designing a point-of-care device that could eventually have real-time monitoring with immediate results. Methods: We ascertained barriers related to CLZ management and the acceptance of possible solutions by sending an anonymous survey to physicians in psychiatric practice (n=860). In parallel, we tested CLZ sensing using a prototype point-of-care monitoring device. Results: 255 responses were included in the survey results. The two barriers receiving mean scores with the highest agreement as being a significant barrier were patient nonadherence to blood work and blood work’s burden on the patient (out of 28). Among nine solutions, the ability to obtain lab results in the physician’s office or pharmacy was top ranked (mean±sd Likert scale [4.0±1.0]). Physicians responded that a point-of-care device to measure blood levels and WBCs would improve care and increase CLZ use. Residents ranked point-of-care devices higher than older physicians (4.07±0.87 vs. 3.47±1.08, p<0.0001). Also, the prototype device was able to detect CLZ reliably in 1.6, 8.2, and 16.3 μg/mL buffered solutions. Discussion: Survey results demonstrate physicians’ desire for point-of-care monitoring technology, particularly among younger prescribers. Prototype sensor results identify that CLZ can be detected and integrated for future device development. Future development will also include integration of WBCs for a complete detection device.

Key Words: Clozapine, Antipsychotic, Medication Underutilization, Sensing Lab-on-a-Chip, Point-of-Care, Therapeutic Drug Monitoring (TDM)

Introduction

Schizophrenia is one of the most challenging and complex psychiatric disorders that afflicts humans. It is a devastating illness that affects 1% of the population worldwide. The burden of the disorder is high, with the estimated direct and indirect costs of the illness (2002 figures) exceeding $60 billion annually (1). Currently there is no cure for the disorder and lifelong treatment with antipsychotics is recommended (2). Clozapine (CLZ) is the most effective antipsychotic treatment for chronic and treatment-refractory patients with schizophrenia. It is the only antipsychotic that has been FDA approved for treatment-resistant schizophrenia, and it provides effective treatment even when patients do not respond to other second-generation antipsychotics (3). No existing first- or second-generation antipsychotic is as effective as CLZ monotherapy in treatment-resistant patients (2, 4-7).
Point-of-Care Monitoring of Clozapine

Current evidence-based pharmacologic guidelines for the treatment of schizophrenia recommend prescribing CLZ for individuals who are unresponsive or partially responsive to first-line medications, which is up to 40% of patients with schizophrenia (8). Despite the overwhelming evidence of the superior effectiveness of CLZ compared to other antipsychotics in treatment-resistant schizophrenia, prescription rates for CLZ in the U.S. are far lower than the estimated prevalence of treatment-resistant schizophrenia (9-12). There are many possible barriers to using CLZ and a few reports have noted the most significant barriers to be the registration process, tolerability and side effects, and nonadherence to blood draws (13, 14). Also, lack of education and experience with CLZ serves as a barrier, as psychiatrists have been reported to overestimate the actual risk of agranulocytosis (15) and underestimate how well patients like taking it (16).

One of the most frequently identified barriers known is the issue around frequent blood work needed to effectively manage this medication. In current practice, CLZ patients have many blood draws to monitor white blood cell (WBC) counts for agranulocytosis, a rare but potentially fatal side effect. Since WBCs need to be monitored weekly for six months, the addition of separate blood draws to measure CLZ levels involves considerable inconvenience to the patient on a weekly basis. CLZ is the only antipsychotic whose efficacy has been predicted by blood measurement (17-22). In addition, the Schizophrenia Patient Outcomes Research Team (PORT) guidelines recommend that blood level monitoring be performed to aim for optimal therapeutic response (2). Blood levels can also help in identifying medication nonadherence, which is a widespread problem in people with psychiatric disorders, as nonadherence can make it more difficult to re-achieve a response on relapse (23) and nonadherence is associated with relapse and possibility for hospitalization or even suicide (24, 25). Blood levels provide important guidance during acute illness and changes in smoking patterns that could lead to large fluctuations—both high and low—leading to relapse or toxicity (26-32). Currently, however, despite these blood draws as standard of care, they are frequently overlooked (2) or, due to the lag time of results and the infrequent psychiatry visits, the utility is often less limited than ideal.

We hypothesized that among many barriers to care, better ways to monitor real-time treatment with CLZ could make this medication more acceptable and widely utilized. Thus, we developed a survey for psychiatrists to better understand the impact of blood work and other barriers on CLZ use. At the same time, we began a collaboration between the School of Medicine and the Department of Engineering to begin to...
test and develop ways to provide technology as a solution to monitoring of CLZ (33). The research plan was to also ascertain how psychiatrists feel about technological aids to help with blood draws. In particular, we focused on point-of-care (POC) monitoring devices. POC testing devices are based on lab-on-a-chip (LOC) sensing micro-systems that provide numerous advantages in clinical diagnostics, environmental monitoring, and biomedical research fields (34-38). The ideal LOC will combine the ability to provide real-time monitoring of WBC and CLZ levels to the physicians with minimal invasiveness and immediate results. Here we focus on the novel development of technology to detect the CLZ levels. Technology for WBC detection is available and other techniques by our group are currently also under development, but these are not the focus of this paper. Others have reported that using types of POC devices for hematological monitoring leads to less discomfort and inconvenience in patients with schizophrenia (39). Our group, along with many schizophrenia treatment experts, believes that CLZ is grossly underutilized in the U.S. and improving acceptability and accessibility could significantly improve outcomes for schizophrenia patients (10-12, 40-46). This paper presents barriers, and identifies one advancement that may help improve outcomes of people in need of CLZ treatment.

Methods

Questionnaire Survey

We prepared an anonymous survey questionnaire sent to psychiatrists (psychiatry residents, fellows, psychiatrists) in the state of Maryland. This survey asked a series of questions on a 5-point Likert scale (1=strongly disagree, 5=strongly agree) regarding the barriers related to CLZ use, blood draw issues with CLZ, and the physician’s interest and willingness to use novel technology and point-of-care devices to monitor CLZ. In addition, the survey solicited the physicians’ willingness to increase the utilization of CLZ if LOC technology was available. This survey was sent to 860 physicians in the state of Maryland and response was anonymously returned by mail or web-based Survey Monkey®. Respondents were recruited from different settings including University of Maryland and Medical System and affiliates, Department of Health and Mental Hygiene State facilities, the Sheppard Pratt Health System, through direct research of community facilities and prescribers, and through the Maryland Psychiatric Society. The survey consisted of 56 questions: 12 demographic, 28 related to barrier perception, 9 related to solutions, 6 related to a POC device, 1 open-ended text. Here we report on data related to the POC device and blood draws primarily (47, 48). The anonymous protocol was determined exempt by the University of Maryland and the Department of Health and Mental Hygiene Institutional Review Boards.

Lab-On-A-Chip Sensor for Clozapine Detection

Following the results of the survey from physicians, we developed a prototype for a POC LOC sensor to detect CLZ. This was performed between a collaboration of investigators from the University of Maryland-Baltimore and College Park campuses (Maryland Psychiatric Research Center and the Institute for Systems Research at the School of Engineering). The integrated LOC device is composed of two components (see Figure 1): a sensor (an array of sensor electrodes in the bottom part) and a testing chamber (three parallel chambers in the top part). Because a bare gold electrode does not produce an adequate signal, we have been testing the amplification of the electrical signal of CLZ using chi-
Point-of-Care Monitoring of Clozapine

CHI660D single channel potentiostat from CH Instruments. All electrochemical tests were carried out using a similarly recorded using buffered solution with only 25 µM sensing signals (range of -0.4 V to +0.7 V, scan rate of 0.02 V/s, scan resolution of 0.001 V). Background signals were similarly recorded using buffered solution with only 25 µM HARu. All electrochemical tests were carried out using a CHI660D single channel potentiostat from CH Instruments (Austin, TX). All voltages were denoted versus the relevant reference electrode half-cell potential. The initial establishment of the feasibility to detect CLZ was tested with buffer solutions containing various concentrations of CLZ.

Results

Questionnaire Survey

We sent out 860 surveys and received back 277 (32% response). Two hundred fifty-five surveys were included in the final analyses as 16 were incomplete and 6 respondents declined participation, stating that they didn’t feel they could adequately respond. Table 1 lists the demographic features of the survey respondents. Among 28 listed barriers (clinical, nonclinical and side effects) to more frequent use of CLZ, the two that ranked highest were: 1) patients will likely be nonadherent to blood work (score 3.7±1.1) and 2) the burden of blood work on the patient (score 3.6±1.2) (see Table 2). Also, among nine potential solutions for increased CLZ use, CLZ levels and WBC measurement in the physician office or pharmacy was top ranked (4.0±1.0). Physicians agreed that a POC device would improve care and that it would increase their CLZ use, with a mean score of 3.9±1.0.

Agreement ratings were significantly higher for residents compared to older physicians, suggesting that residents are eager to use technology to improve patient care (4.07±0.87 vs. 3.47±1.08; t=3.40, df=340, p<0.0001). Among the types of devices suggested, 59% of physicians ranked a handheld device as the preferred monitoring modality. Among residents and younger physicians, 73% preferred a handheld device to monitor CLZ treatment (47).

Clozapine Detection with the Lab-On-A-Chip Sensor

The electrochemical signal of CLZ was recorded in the presence and absence of the catechol-modified chitosan system and the results are presented in Figure 3. An anodic current density peak at an electric potential of +0.4 V, as expected due to CLZ oxidation reaction, showed the amplification effect. A signal 2.5-fold higher compared to an unmodified bare electrode was determined, which is close to our previously determined 3-fold for millimeter-scale electrodes (33). The detection feasibility of 5 (1.6 µg/mL), 25 (8.2 µg/mL), and 50 (16.3 µg/mL) µM CLZ in buffered micro-liter solutions with the microelectrodes is shown in Figure 4. The calculated total oxidative charge generated between 0 and +0.7 V in the measured cyclic voltammograms reveals a positive CLZ dose-dependence. These results provide initial promise as the first step toward the development of a POC testing device based on a microfluidic LOC for CLZ detection.

Table 1

<table>
<thead>
<tr>
<th>Sex</th>
<th>Categories</th>
<th>Values</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Male</td>
<td>134 (53%)</td>
</tr>
<tr>
<td>Age*</td>
<td>25–35 years</td>
<td>48 (19%)</td>
</tr>
<tr>
<td></td>
<td>36–45 years</td>
<td>49 (19%)</td>
</tr>
<tr>
<td></td>
<td>46–55 years</td>
<td>56 (22%)</td>
</tr>
<tr>
<td></td>
<td>56–65 years</td>
<td>54 (21%)</td>
</tr>
<tr>
<td></td>
<td>65+ years</td>
<td>45 (18%)</td>
</tr>
<tr>
<td>Race†</td>
<td>White</td>
<td>185 (73%)</td>
</tr>
<tr>
<td>Years in Practice</td>
<td>Still in training</td>
<td>45 (18%)</td>
</tr>
<tr>
<td></td>
<td>1–10 years</td>
<td>44 (18%)</td>
</tr>
<tr>
<td></td>
<td>11–20 years</td>
<td>47 (19%)</td>
</tr>
<tr>
<td></td>
<td>20+ years</td>
<td>115 (45%)</td>
</tr>
<tr>
<td>Treatment of Psychotic Disorders</td>
<td>&gt;50% of patients</td>
<td>31 (12%)</td>
</tr>
<tr>
<td>Clozapine Prescribing</td>
<td>Ever</td>
<td>217 (85%)</td>
</tr>
<tr>
<td></td>
<td>Last Year</td>
<td>131 (61%)</td>
</tr>
</tbody>
</table>

*3 missing race; †4 missing years in practice.

tosan, a natural polymer, that is compatible with microfabrication (49), modified with a redox material catechol. The resulting catechol-modified chitosan sensor enables CLZ detection through a redox cycling mechanism. The grafted catechol moieties in the redox cycling system can participate in an electron transfer reaction and be inter-converted between oxidized (Q) and reduced (QH₂) forms (E₀=+0.2 V). CLZ (E₀=+0.4 V) is an electro-active species that can diffuse freely within the chitosan film. Upon the application of voltage values higher than its E₀ (overpotential conditions), CLZ is oxidized, followed by its reduction by the grafted QH₂ moieties, and re-oxidation at the electrode (see Figure 2A and 2C). This continuous CLZ reduction/oxidation cycle results from this use of CLZ as an oxidizing mediator (see Figure 2B). With such continuous redox reaction we hypothesize that the total charge transferred by CLZ oxidation is increased, amplifying the generated electrochemical current and improving the signal-to-noise ratio. Redox cycling system recovering to the reduced state is achieved by the application of negative potential in the presence of a reducing mediator, hexaammineruthenium(III) (HARu, E₀=-0.2 V of Ru⁶⁺/³⁺ reaction).

All chemicals were purchased from Sigma-Aldrich. All chemical testing solutions were prepared in phosphate buffer (PB; 0.1 M, pH 7). The electrochemical characterization technique cyclic voltammetry was used to record CLZ sensing signals (range of -0.4 V to +0.7 V, scan rate of 0.02 V/s, scan resolution of 0.001 V). Background signals were similarly recorded using buffered solution with only 25 µM HARu. All electrochemical tests were carried out using a CHI660D single channel potentiostat from CH Instruments.
Discussion

Here we presented an integrated approach to develop an engineered medical solution for CLZ treatment management. By understanding the barriers and identifying the technological needs, new paradigms will be established and will help design innovative and effective solutions. The results of this study demonstrate the need for POC testing technology, particularly among younger prescribers. Psychiatrists feel their use of CLZ is hindered by frequent blood draws and welcome technology that could advance the ease of sensing CLZ and WBC blood levels. In fact, our study shows that nonadherence to blood work is the top-rated barrier by practicing psychiatrists in the state of Maryland. Furthermore, the top-rated solution for improving CLZ use was the use of POC monitoring devices. We realize there are many barriers to care and many aspects to improve upon but have used this survey as the framework for developing POC technology.

A miniaturized prototype sensor for CLZ detection is developed as a model POC monitoring solution to overcome some of the barriers around blood draws. With this prototype, challenges related to sensor development such as sensitivity and detection limit—as well as compatibility with blood samples and integration of pretreatment steps—are identified. In future work, we will focus on defining specific technological requirements for improved sensitivity and better acceptance by users. The next level of a questionnaire will be conducted to evaluate usability factors (e.g., human factors, mode and place of use, and cost) that will impact this developing solution. The detection limit and the dynamic range of the sensor will be characterized in the next steps with relation to the required clinical range. Following performance characterization of the device with serum fluids, a flow system will be integrated to realize a fully autonomous micro-system for clinical monitoring of CLZ blood levels.

Table 2 Survey Results: Barriers and Device Feasibility

<table>
<thead>
<tr>
<th>Results Reported from Survey</th>
<th>Questions on Survey</th>
<th>Mean Value and SD from Likert Scale*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ten Top-Ranking Barriers</td>
<td>Patients likely nonadherent to blood work</td>
<td>3.7±1.1</td>
</tr>
<tr>
<td>(among 28)</td>
<td>Burden of blood draws on patient</td>
<td>3.6±1.2</td>
</tr>
<tr>
<td></td>
<td>More monitoring than other antipsychotics</td>
<td>3.2±1.2</td>
</tr>
<tr>
<td></td>
<td>Medication nonadherence</td>
<td>3.2±1.1</td>
</tr>
<tr>
<td></td>
<td>Risk of neutropenia</td>
<td>3.0±1.0</td>
</tr>
<tr>
<td></td>
<td>Risk of weight gain and associated complications</td>
<td>3.0±1.0</td>
</tr>
<tr>
<td></td>
<td>Delay in WBC may delay medication</td>
<td>2.8±1.2</td>
</tr>
<tr>
<td></td>
<td>Lack of structure to facilitate prescribing</td>
<td>2.8±1.4</td>
</tr>
<tr>
<td></td>
<td>Time spent administratively to start</td>
<td>2.7±1.2</td>
</tr>
<tr>
<td></td>
<td>Inpatient to outpatient disconnection</td>
<td>2.7±1.2</td>
</tr>
<tr>
<td>Five Top-Ranked Solutions</td>
<td>WBC and CLZ levels in office</td>
<td>4.0±1.1</td>
</tr>
<tr>
<td>(among 9)</td>
<td>WBC and CLZ levels at pharmacy</td>
<td>4.0±1.0</td>
</tr>
<tr>
<td></td>
<td>Centralized internet-based database for registration, results and other information</td>
<td>3.9±1.1</td>
</tr>
<tr>
<td></td>
<td>WBC and CLZ levels at home</td>
<td>3.8±1.2</td>
</tr>
<tr>
<td>Device Feasibility</td>
<td>Modified CLZ prescribing guidelines permitting less frequent blood draws</td>
<td>3.8±1.1</td>
</tr>
<tr>
<td>Interested in Using Handheld Monitoring Device</td>
<td>POC device would improve care</td>
<td>3.9±1.0</td>
</tr>
<tr>
<td></td>
<td>POC device with WBC would increase CLZ use</td>
<td>3.6±1.1</td>
</tr>
<tr>
<td></td>
<td>POC device with CLZ levels would increase CLZ use</td>
<td>3.3±1.0</td>
</tr>
<tr>
<td></td>
<td>Immediate transmitted results would increase use of CLZ</td>
<td>3.5±1.0</td>
</tr>
<tr>
<td></td>
<td>Type of device highest ranked</td>
<td>59% handheld</td>
</tr>
</tbody>
</table>

*Mean and SD of the Likert scale score reported. Results are listed in descending order with most agreement to statement listed at the top. This survey asked a series of questions on a 5-point Likert scale (1=strongly disagree, 5=strongly agree) regarding the barriers related to CLZ use, blood draw issues with CLZ, and physician’s interest and willingness to use novel technology and point-of-care devices to monitor CLZ. In addition, the survey solicited the physician’s willingness to increase the utilization of CLZ if lab-on-a-chip technology was available. Mean values above 3 indicate agreement with the statement, as 3 was neutral.
Point-of-Care Monitoring of Clozapine

Figure 3

Cyclic voltammograms in the presence and absence of CLZ with either bare unmodified (with CLZ dashed red; without CLZ dash-dot-dotted green) or catechol-modified chitosan (with CLZ solid black; without CLZ dash-dotted blue) electrodes. Arrows indicate CLZ oxidation peaks.

Figure 4

CLZ detection in 110 μL buffer solutions with 5, 25, and 50 μM concentrations. Y-axis values are the total oxidative charge calculated between 0 V and +0.7 V from measured cyclic voltammograms. Optimized biofabrication duration parameters of 210 and 50 seconds for chitosan electrodeposition and catechol grafting, respectively.

in schizophrenia patients. This device will allow treatment teams to perform analysis at the POC in a low-cost, fast, and straightforward way, aiming to guide CLZ dosages within the effective range (21), to decrease the patient’s burden, and to personalize medical care. To further reduce the burden of monitoring, we also plan to incorporate WBC monitoring into a fully miniaturized and portable instrument that can return both blood level monitoring and WBC detection in the same unit.

The main challenges that arise within micro-scale systems are the large deviations observed in CLZ detection and the overall lower sensing performance. Accurate control of system biofabrication is critical to overcome these challenges. Therefore, a comprehensive characterization of the microfluidic device architecture (e.g., electrodes and microfluidics geometry), the biofabrication process (e.g., chitosan electrodeposition and catechol grafting steps) and the sensing performance (e.g., sensitivity, selectivity, and compatibility with human serum) will be conducted in future studies to maximize the amplification performance and accuracy of the sensor. The main limitation to the survey was that only about one-third of all prescribers sent the surveys responded, which may overestimate favor of CLZ use or more motivated prescribers. However, understanding more about the
needs and solutions for prescribers is critical and the major-ity responding think they would benefit and patients would benefit by POC monitoring.

By addressing the need for real-time monitoring of blood antipsychotic levels, more rapid results can be available to help guide treatment. This approach could potentially reduce the cost and burden of monitoring, and increase the acceptability of psychiatric drug treatment to patients and prescribers. It will also aid in higher acceptability and treatment response. The incorporation of WBC counts would make an LOC biosensing device attractive for POC use, decreasing costs and patient burden and changing the paradigm of how we currently monitor psychiatric drug treatment. This novel application of LOC monitoring of psychiatric drug treatment can revolutionize and provide a new model for mental health disorder research. It is a first step in personalized medical care that millions of mental health patients could benefit from worldwide.

Acknowledgments

The authors would like to thank the Robert W. Deutsch Foundation, the Maryland Innovation Initiative (MII), the National Science Foundation, the Maryland Innovation Initiative (MII), the NSF Grant No. DGE0750616 for financial support. The authors likewise appreciate the support of the Maryland NanoCenter and its FabLab. The authors wish to also thank the bioengineering rotation students in MSAL: Bao-Ngoc Nguyen, Bharath Ramaswamy, Stephan Restaino, and Nicholas Woolsey and the undergraduate intern Gillian Costa for the useful discussions.

References


30. Espnes KA, Heimdal KO, Spigset O. A puzzling case of increased serum clo-
Point-of-Care Monitoring of Clozapine

Zapine levels in a patient with inflammation and infection. Ther Drug Monit 2012;34(5):489-492. doi: 10.1097/FTD.0b013e318266c662.


