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Using a fingerstick test for haematological monitoring in patients treated with clozapine

Matthew Atkins, Philip McGuire, Bhirundra Balgobin, Pravinkumar Patel and David Taylor

Abstract

Background Treatment with clozapine requires regular blood monitoring in order to minimise the risk of agranulocytosis. The demands on patients and clinicians associated with monitoring may be reduced by using point-of-care, as opposed to lab-based assessments. We assessed the utility of a device that can measure white blood cell (WBC) and neutrophil counts by capillary fingerstick blood.

Method The performance of a small, portable device (HemoCue® WBC DIFF System) was compared with that of a widely used laboratory analyser (ADVIA® 2120i) for measuring WBC and neutrophil counts. Patients with schizophrenia who were being treated with clozapine ($n = 201$) provided a fingerstick capillary sample and a venous sample for the respective assays.

Results WBC counts and neutrophil counts from venous blood as determined by ADVIA 2120i, ranged from 3.0×10^9/l to 19.5×10^9/l, and 1.2×10^9/l to 15.9×10^9/l, respectively. There was a strong correlation between the results from venous and the capillary sample methods (WBC: $R = 0.89$, neutrophil: $R = 0.92$). By Passing–Bablok regression analysis, the slope of the association between ADVIA® 2120i and HemoCue WBC DIFF for WBC was 1.0 [95% confidence interval (CI) 0.944–1.086], with intercept at –0.9 (95% CI –1.43 to –0.45). For neutrophils, the slope was 0.870 (95% CI 0.817–0.923), with intercept at –0.19 (95% CI –0.43 to 0.02). Overall, mean biases of -0.95×10^9/l for WBC, and -0.91×10^9/l for neutrophils were observed for the capillary blood method compared with the venous blood method. Below the clinical cutoff intervals for clozapine monitoring WBC ($<3.5 \times 10^9$/l) and neutrophils ($<1.5 \times 10^9$/l) these biases were -1.1×10^9/l for WBC, and -0.25×10^9/l for neutrophils.

Conclusion Results from the capillary blood HemoCue WBC DIFF analyser compared well with the venous blood ADVIA 2120i analyser for determining WBC and neutrophil counts. There was a slight overall bias, with the capillary method reporting lower values for both measures. Fingerstick point-of-care analysis is suitable for monitoring blood counts in patients on clozapine, although confirmatory standard venous testing is recommended for test results falling below accepted thresholds.

Keywords: Clozapine, Schizophrenia, capillary blood sample, finger stick, point of care

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Correspondence to:
Matthew Atkins
Pharmacy Department, South London and Maudsley NHS Foundation Trust, London, UK
Maudsley Hospital, Denmark Hill, London SE5 8AZ, UK
Institute of Pharmaceutical Science, Kings College, London
matthew.atkins@slam.nhs.uk

Philip McGuire
Institute of Psychiatry , King's College, London, UK
National Institute of Health Research Biomedical Research Centre at SLaM NHS Trust, London, UK

Bhirundra Balgobin
Clozapine Clinic, South London and Maudsley NHS Foundation Trust, London, UK

Pravinkumar Patel
Pharmacy Department, South London and Maudsley NHS Foundation Trust, London, UK

David Taylor
Pharmacy Department, South London and Maudsley NHS Foundation Trust, London, UK
Institute of Pharmaceutical Science, Kings College, London

Introduction

Clozapine is the most effective treatment for schizophrenia,[1] and the only treatment that is effective in the subgroup of patients with treatment resistance.[2] However, its use is limited by the risk of agranulocytosis, which occurs in around 0.4% of the those treated.[3] If undetected this can be fatal, and treatment usually entails regular monitoring of the patient's white blood cell (WBC) and neutrophil counts, with venous blood samples sent to a laboratory for haematology analysis, and the results entered into a monitoring database. These databases are configured with critical cutoff limits which alert clinic teams when counts fall below a given safety level. The frequency of monitoring is dependent upon the time a patient has been taking clozapine: monitoring is usually weekly in the first 18 weeks of

treatment, fortnightly from weeks 19 to 52, then monthly thereafter.[4]

Many patients dislike the requirement for repeated venous blood sampling[5] and frequently cite this as a reason for refusing or stopping clozapine. The need for venous blood monitoring also places logistical demands on the clinical team, and this can deter clinicians from prescribing clozapine.[6]

However, recent advancements in capillary blood technologies associated with devices that perform blood cell counting,[7] and reliable testing of capillary blood taken from fingerstick samples may help to address these issues.[8] The present study evaluated the performance and acceptability of the HemoCue® WBC DIFF System (HemoCue AB, Kuvettgaten 1, SE-262 71, Angelholm, Sweden), which measures WBC and the five-part white cell differential from 10 µl of fingerstick whole blood in less than 5 min. The HemoCue WBC DIFF System is a small portable device designed specifically for use at the point of care.

Method

Patient sample

The study involved a consecutive series of patients ($n = 201$) attending a clozapine monitoring clinic in the South London and Maudsley NHS Foundation trust as part of their routine clinical care, during a 10-week period starting in November 2019. All had a clinical diagnosis of schizophrenia and of treatment resistance and were being managed in the community.

Testing procedure

On arrival, patients were asked if they would be willing to provide a fingerstick capillary sample for testing in addition to the venous blood sample that was normally collected. All those who were approached agreed. Capillary whole blood and venous blood samples were thus collected from $n = 201$ patients during the same visit.

Analytical methods

Venous blood samples (3 ml) were transported to a central laboratory at King's College Hospital where a full blood count was performed on an automated ADVIA® 2120i analyser within 8 h of blood being taken. This was used as the reference standard method.

Capillary whole blood (10 µl) was collected into a disposable microcuvette, drawn into the cavity by capillary action. A haemolysing agent lysed the red cells in the microcuvette and a staining agent coloured the white cells. This microcuvette was then inserted into HemoCue WBC DIFF analyser in the clinic by a trained operator. The HemoCue WBC DIFF analyser took several images of the stained white cells, and cells were then counted as a total and classified into their five-part differential. Quantitative measurements of total WBC and neutrophil counts were thus provided in less than 5 min.

Statistical analysis

A Passing–Bablok regression[9] analysis was conducted for all results of the method comparisons. The regressions were generated using the validated EP Evaluator version 12 software (Data Innovations, Burlington, VT, USA).

Results

Analytical method comparison

The WBC count assessed from venous blood using ADVIA 2120i ranged from 3.0×10^9/l to 19.5×10^9/l, while the neutrophil count ranged from 1.2×10^9/l to 15.9×10^9/l. Regression analysis revealed a close correlation within the patient group between the venous blood measurements and the capillary blood measurements from the HemoCue WBC device. The correlation coefficient for the WBC count was 0.89, with a slope of 1.0 (95% CI = 0.944–1.086) and an intercept of −0.90 (95% CI −1.43 to −0.45; Figure 1). The correlation coefficient for the neutrophil count was 0.92, with a slope of 0.87 (95% CI = 0.817−0.923) and an intercept of −0.19 (95% CI −0.43 to 0.02; Figure 2). The mean analytical method bias for HemoCue was -0.95×10^9/l (−13.5%) for the WBC count, and -0.91×10^9/l (−20.54%) for the neutrophil count.

Discussion

The data indicate that the HemoCue WBC analyser provided similar results to the current 'gold standard' method for the measurement of WBC and neutrophil counts. The correlations in relation to the standard measure for both WBC and neutrophil counts (WBC: $R = 0.89$; neutrophils: $R = 0.92$) were high enough to be clinically acceptable. The present findings suggest that the correlation between the results of the respective

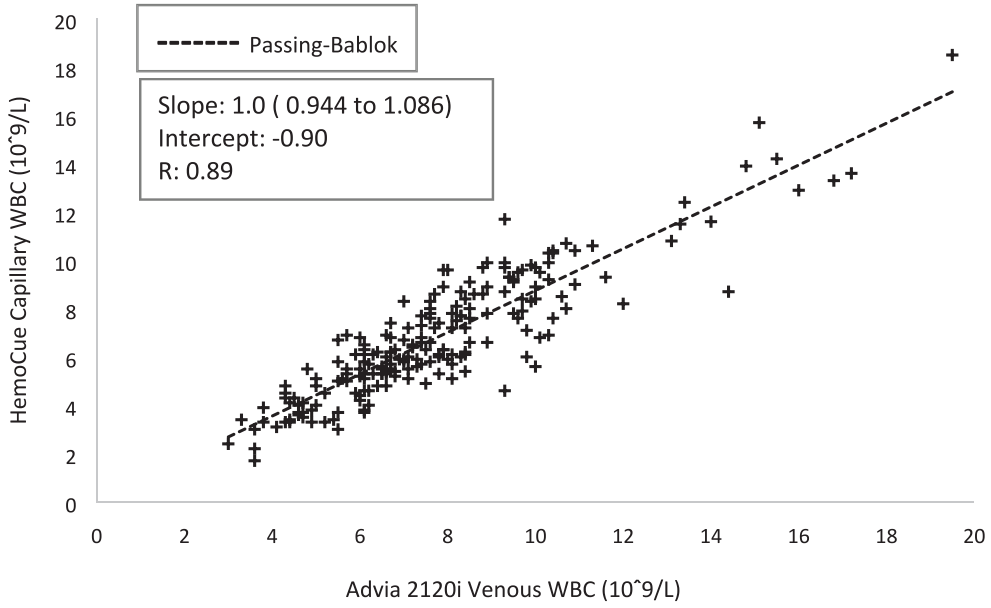

Figure 1. HemoCue® WBC (capillary whole blood) *versus* ADVIA® 2120i (venous whole blood) WBCs. ($n = 201$).

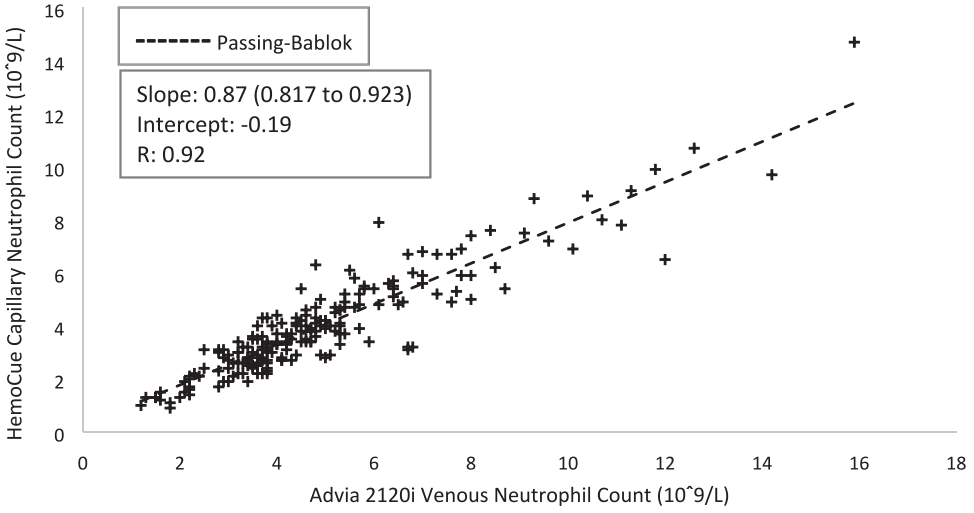

Figure 2. HemoCue® neutrophil POCT (capillary whole blood) *versus* ADVIA® 2120i (venous whole blood) neutrophil counts ($n = 201$).

methods is stronger than that reported in a previous study ($R = 0.772$ and $R = 0.817$ for the WBC and neutrophil counts, respectively). However, that study involved a smaller patient sample ($n = 60$), only a minority of whom ($n = 20$) were being treated with clozapine.[10]

Current UK monitoring practice uses defined clinical cutoff points for WBC and neutrophil counts ($< 3.5 \times 10^9$/l and $< 1.5 \times 10^9$/l, respectively), when intervention is required.[11] The HemoCue WBC method gave mean biases of -0.95×10^9/l for WBC count, and -0.91×10^9/l for the neutrophil count. These biases suggest that adjustments would be required to the way that results are interpreted if the HemoCue WBC method was to be used for clozapine monitoring in clinical practice.

One approach would be to use the mean biases associated with the HemoCue assay to adjust the clinical cutoffs for the WBC and neutrophil counts. Assuming a mean bias of -0.95×10^9/l for WBC count, the cutoff would be modified from $<3.5 \times 10^9$/l to $<2.55 \times 10^9$/l. For neutrophil count, assuming a mean bias of -0.91×10^9/l, the cutoff would be altered from $<1.5 \times 10^9$/l to $<0.59 \times 10^9$/l. However, measurement biases are not linear throughout the range of results obtained, and there is considerable variation in bias around the mean value. It is therefore possible that the application of new thresholds for the HemoCue device might miss results that would otherwise be subthreshold when measured using the standard method. In our sample, this would have occurred in 3 (of 201) patients. One of these patients had a WBC count of 3.4×10^9/l and a neutrophil count of 1.3×10^9/l by HemoCue, and WBC and neutrophil counts of 3.3×10^9/l and 1.3×10^9/l according to the standard assay. The second patient had a WBC count of 2.4×10^9/l by HemoCue, and 3.0×10^9/l by the standard measure. The third had a neutrophil count of 1.0×10^9/l by HemoCue and 1.2×10^9/l by the standard measure. These examples illustrate how some patients with low counts could be missed if the clinical cutoffs were adjusted according to the mean biases of the HemoCue measures.

An alternative approach would be to avoid adjusting for the HemoCue-associated biases but ensure that any patient who had a WBC or neutrophil count on the HemoCue assay lower than the existing cutoff would then have a venous blood sample taken for measurement by the standard method. Of the 201 patients tested in the present study using the HemoCue method, 9 had both WBC and neutrophil counts below the cutoff ($<3.5 \times 10^9$/l and $<1.5 \times 10^9$/l, respectively), and 5 had a WBC count below the cutoff, but a normal neutrophil count. This suggests that 7% of the total sample (14 patients) would require an additional venous sample for testing by the standard method.

In the present study, of the nine patients in whom both the HemoCue WBC and neutrophil counts were below the respective thresholds, only three were found to be below the cutoffs when the counts were assessed using the standard measure. One patient had a WBC count $<3.5 \times 10^9$/l and a neutrophil count $<1.5 \times 10^9$/l, one had a WBC count $<3.5 \times 10^9$/l and a neutrophil count $>1.5 \times 10^9$/l, and one had a WBC count $>3.5 \times 10^9$/l and a neutrophil count $<1.5 \times 10^9$/l. Therefore, two of the nine patients requiring a venous blood test would need to have clinical intervention where neutrophil counts were $<1.5 \times 10^9$/l. Overall, in the second scenario 4.5% ($n=9$) of this study cohort would require a venous blood sample to be taken and sent for standard measure, of whom, 1% ($n=2$) would have needed actual clinical intervention. So, on average 4–5 patients in every 100 would require a venous blood sample to be taken, of which one would need to have changes made to their prescription of clozapine.

Our results suggest that one way that the HemoCue WBC method could be safely employed in clinical practice would be to use it as an initial screening test for neutropenia, with venous blood testing reserved for the minority of patients found to have low WBC or neutrophil counts. This would allow blood monitoring to be less invasive, and usually provide the patient with a result at the point of care, while ensuring that no patients who were neutropenic would be missed. Retaining the existing set of clinical cutoffs, as opposed to introducing new, adjusted ones, would avoid the risk of confusion and the misinterpretation of results.

The good correlations of both WBC and neutrophil counts seen in the present study compares well with a previous study in clozapine monitoring[10] and with other studies that also found them acceptable for use in practice for different clinical purposes.[7,12] Indeed, the rationale to repeat testing with a venous blood sample when counts fall below standard cutoffs has previously been described in the point-of-care device evaluated.[10]

Clozapine-induced agranulocytosis tends to follow a distinct pattern of a precipitous fall in neutrophil counts over a period of a week or so.[13–15] The use of a rapid and portable easy-to-use test offers the possibility of early detection of impending agranulocytosis *via* the prompt identification of an emerging pattern (perhaps using machine learning). This, allied with pharmacogenetic testing for high risk variants for blood dyscrasia,[16] would potentially allow clozapine treatment to be ceased before a neutrophil nadir is reached, so offering significant protection against the consequences of agranulocytosis.

This device can offer rapid access to the clozapine monitoring parameters of WBC and neutrophil counts. This could be applied to clinical practice where repeat venous sample

testing by traditional laboratory method ensues at defined cutoff points. It is likely that access to rapid fingerstick methods such as this will reduce prescribing barriers to, and the burden of, clozapine use.[2,3,8,17,18]

Conflict of interest statement

David Taylor has received personal fees from H Lundbeck and Janssen unrelated to this manuscript and has received consultancy payments from Mylan, a manufacturer of clozapine, again unrelated to this manuscript. He is the Editor-in-Chief of Therapeutic Advances in Psychopharmacology, therefore, the peer review process was managed by alternative members of the Board and the submitting Editor was not involved in the decision-making process.

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Ethics statement

This investigation was defined as a service development by our local Drug and Therapeutics Committee. Our trust policies dictate that medicines-related audits and service developments are considered by the Drug and Therapeutics and approved or modified by that committee. Ethical committee approval is only sought when it is considered appropriate by the Drug and Therapeutics Committee. In the case of this investigation, the committee approved it as a service development not requiring ethical committee approval or formal written consent from potential participants (SLAMDTC2020/3). All patients had the simple fingerstick procedure explained to them and were asked if they were willing to provide two samples. The reason for taking two samples (the testing of a new device) was also explained to them.

ORCID iDs

Matthew Atkins https://orcid.org/0000-0002-2898-8343

David Taylor https://orcid.org/0000-0002-2557-1710

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