Assessment of the practicability and analytical performance of a point-of-care affinity chromatography haemoglobin A₁c analyser for use in the non-laboratory setting

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Abstract

Background Haemoglobin A₁c (HbA₁c) is a pivotal pathology test used around the world for the long-term management of patients with diabetes. Point-of-care testing (POCT) provides a convenient means for conducting HbA₁c testing outside the laboratory.

Methods The practicability and analytical performance of the Micromat II POCT HbA₁c analyser (Bio-Rad Laboratories, USA), which has affinity chromatography as its methods principle, was evaluated in Australia and compared with the DCA 2000 POCT device (Bayer Australia) and a laboratory-based high-performance liquid chromatography (HPLC) method.

Results Overall between-day imprecision over 10 days was 1.9% for the laboratory HPLC method, 2.2% for the DCA 2000 and 7.0% for the Micromat II. In a second study over the same time period, the Micromat II’s imprecision was 6.4%. The mean difference between the Micromat II and the laboratory method in a patient comparison (n = 100) was −0.25% (lower and upper limits of agreement −1.79 to 1.30).

Conclusions The imprecision obtained with the Micromat II was inferior to both the DCA 2000 and laboratory methods and did not meet current internationally accepted precision goals for this analyte. The Micromat II’s poor imprecision can be explained by the high degree of technical expertise needed to perform the test; its use by non-laboratory health professionals such as nurses and Aboriginal health workers in rural and remote Australia cannot be recommended.


Introduction

Diabetes mellitus, with its associated long-term microvascular complications, is a major global health problem. The measurement of haemoglobin A₁c (HbA₁c) provides an assessment of glycaemic control over the preceding three months and is a pivotal pathology test for the long-term management of patients with diabetes. The analytical imperative for precise and accurate HbA₁c measurements arises from its clinical use in tracking changes in glycaemic control over time and determining whether patients have achieved, Australia clinical targets.

In Australia, the DCA 2000 point-of-care analyser (Bayer Australia, Melbourne, Australia) has been used widely in rural and remote locations and in indigenous and non-indigenous health settings for monitoring HbA₁c levels through point-of-care testing (POCT) models including the national Quality Assurance for Aboriginal Medical Services (QAAMS) Programme and the Diabetes Management Along the Mallee Track project.² The DCA 2000 measures HbA₁c by immunnoassay on 1 μL of capillary whole blood in 6 min and, in these programmes, this instrument has proven reliable and analytically sound in the hands of non-laboratory POCT operators.

In 2002 a new POCT HbA₁c analyser, the Micromat II (Bio-Rad Laboratories, CA, USA), was introduced into Australia. The small bench-top device uses affinity chromatography to measure HbA₁c on 10 μL of capillary whole blood in approximately 5 min. This study was conducted to determine its practicability and
analytical performance relative to the DCA 2000 analyser and a laboratory-based high-performance liquid chromatography (HPLC) method, and to assess its potential application as a POCT HbA1c analyser in rural and remote Australia.

Methods

Analytical principle of Micromat II POCT haemoglobin A1c method

The capillary blood sample was initially diluted, lysed to release haemoglobin, mixed with a boronate affinity resin to bind the glycated haemoglobin fraction, and then loaded onto the Micromat II analyser. The non-glycated fraction was collected in an optical chamber and the total haemoglobin concentration determined spectrophotometrically. The bound HbA1c fraction was washed and eluted, and its concentration also was measured spectrophotometrically. The HbA1c fraction was expressed as a percentage of the total haemoglobin.

The Micromat II method is not subject to interference by uraemia or the haemoglobin variants HbS, HbC and HbF and, like the DCA 2000, is traceable to the Diabetes Control and Complications Trial reference method.

Comparative POCT and laboratory methods

At the SouthPath laboratory at Flinders Medical Centre, Adelaide, comparative POCT and laboratory HbA1c measurements were performed using the Bayer DCA 2000 and cation-exchange HPLC with a Pharmacia Mono-S column, respectively.

Assessment of precision

Between-day imprecision was assessed using daily analysis of three patient samples with HbA1c concentrations of 5.5%, 6.9% and 9.8% over a 10-day period. An HbA1c of less than 6% generally indicates a person does not have diabetes; an HbA1c of 7% is a target for optimal glycaemic control in patients with diabetes, while an HbA1c of 10% is reflective of a person with diabetes whose glycaemic control is poor. A second assessment of imprecision was also made with the Micromat II only, using three further patient samples with similar HbA1c concentrations across the same time period.

Assessment of accuracy

Blood samples were collected from 100 patients with and without diabetes (median HbA1c 7%; range 4.6–20.1%) and were analysed over a 10-day period by the three methods, according to the manufacturer's specifications. Agreement between methods was assessed by Passing Bablock regression analysis and Bland–Altman plots using the Analyse-It statistical package (Analyse-It Software Ltd, Leeds, UK).

Results

Assessment of precision

The between-day imprecision recorded by each instrument for the three different patient HbA1c levels is shown in Table 1.

The overall between-day imprecision was 1.9% for the laboratory HPLC method, 2.2% for the DCA 2000 and 7.0% for the Micromat II. Due to the poor imprecision exhibited by the Micromat II, a second precision study was undertaken for this instrument using three further patient samples with HbA1c concentrations of 5.4, 6.9 and 9.7%. The overall imprecision recorded by the Micromat II for these samples was 6.4%.

Assessment of accuracy

The Passing Bablock correlation coefficient ($r$) was 0.94 for the Micromat II versus the laboratory method, and 0.96 for the DCA 2000 versus the laboratory. Using Bland–Altman analysis, the mean difference between the Micromat II and the laboratory method was $-0.25\%$ (lower and upper limits of agreement [LOA] $-1.79$ to $1.30$) (Figure 1). For the DCA 2000 and the laboratory method, mean difference was $-0.36\%$ (LOA $-1.34$ to $0.62$).

Table 1 Between-day imprecision observed at three different HbA1c concentrations

<table>
<thead>
<tr>
<th>Analysers</th>
<th>Patient HbA1c concentration (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>5.5</td>
</tr>
<tr>
<td>HPLC MonoS</td>
<td>2.2</td>
</tr>
<tr>
<td>Bayer DCA 2000</td>
<td>3.1</td>
</tr>
<tr>
<td>Micromat II</td>
<td>9.0</td>
</tr>
</tbody>
</table>

Figure 1 Bland–Altman difference plot for comparing the Micromat II versus the laboratory-based cation exchange HPLC method
Discussion

This study investigated the analytical performance of a POCT analyser for HbA1c that used affinity chromatography as its methods principle and compared it with current POCT and laboratory benchmarks. The overall between-day imprecision obtained with the Micromat II across two separate precision studies (6.7%) was inferior to both the DCA 2000 and laboratory methods and did not meet internationally accepted precision goals for this analyte (less than 3%). Tight imprecision is critically important when monitoring glycaemic control in diabetes patients over time, and this clinical requirement demands that POCT HbA1c methods must exhibit precision equivalent to laboratory-based HbA1c methods. Methods with poor imprecision (or high degree of analytical noise) can potentially mask clinically significant changes in glycaemic status and their use in the POCT environment cannot be recommended. The poor imprecision exhibited by the Micromat II in our hands can largely be explained by the high degree of technical expertise needed to perform the test. There are a number of manual steps requiring precise timing and the POCT operator is not able to leave the instrument during the entire reaction sequence.

Accuracy of HbA1c measurement is important because there are set targets for the management of diabetes; for example, an HbA1c of 7% or less is considered to represent optimal glycaemic control in a diabetes patient. The mean bias observed with the Micromat II was slightly less than that observed for the DCA 2000 in this study; however, the LOA between the POCT device and the laboratory method were much tighter with the DCA 2000 compared with the Micromat II. This evaluation represents the fourth patient comparison between the DCA 2000 and the laboratory undertaken by our group (two being conducted in laboratory settings and two in field settings). The overall bias recorded by the DCA 2000 relative to the MonoS laboratory method across these four studies was 0.08% (-0.36% present study, 0.18% [LOA -0.9 to 1.2] in a previous unpublished laboratory comparison [n = 42], -0.1% [LOA -1.1 to 0.8] in field study 1 [n = 39] and -0.02% [LOA -0.65 to 0.61] in field study 2 [n = 118]).

The Micromat II system is innovative in its design, using a well-established methods principle of affinity chromatography and is not subject to interference by uraemia or haemoglobin variants. Other POCT HbA1c devices available in the market (such as the Cholestech GDX and Provalis Glycosol HbA1c tester) also use a methods principle identical to that of Micromat II. Like the Micromat II, poor imprecision was also observed with the Cholestech GDX device in a recently published study.

In conclusion, the poor imprecision observed with the Micromat II, together with the labour-intensive and technically demanding nature of its test procedure, severely limits the device’s practicability in the community setting. Its use by non-laboratory health professionals such as nurses and Aboriginal health workers in rural and remote Australia cannot be recommended, based on the results of this study.

References


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