Singapore Med J 2003 Vol 44(1) : 008-011

Comparison of Four Point-of-Care HbA1c Analytical Systems against Central Laboratory Analysis

R C Hawkins

ABSTRACT

Objective: To assess four commercially available point-of-care HbA1c analytical systems with respect to (1) inaccuracy against the central laboratory HbA1c method and (2) imprecision against the HbA1c analytical goal of coefficient of variation < 3%.

Methods: Analytical inaccuracy was assessed by analysis of 110 patient samples on all five analytical platforms (Biorad Diastat, Drew DS5, Bayer DCA 2000, Nycomed Nycocard and Roche Tinaquant (used in central lab)). Analytical imprecision was assessed by analysis of two levels of patient sample four times daily for six days, as well as analysis of two levels of commercial control.

Results: Deming linear regression for agreement: Diastat=0.98 * Tinaquant + 0.36; DS5=1.23* Tinaquant-0.65; DCA2000=0.95 * Tinaquant + 0.63; Nycocard=0.94 * Tinaquant + 0.92. Analytical coefficients of variation (CVs) at Tinaquant HbA1c levels of 6.2-10.8% were: Tinaquant 0.8-1.1%, Diastat 1.6-6.6%, DCA2000 2.6-7.2%, DS5 5.1-11.7%, Nycocard 8.5-15.3%. Two HbE samples gave elevated HbA1c results with the DS5 method.

Conclusions: The Diastat and DCA2000 systems gave the best performance with acceptable imprecision and good agreement with both the central lab and each other. The DS5 was less precise with a significant positive bias compared to the other methods and interference from HbE, while the Nycocard system showed the poorest precision in the evaluation. The Diastat and DCA2000 systems appear to be satisfactory analytical alternatives to both central laboratory (Tinaquant) testing and each other.

Keywords: Glycated haemoglobin, HbA1c, POCT, diabetes mellitus

Singapore Med J 2003 Vol 44(1):008-011

Department of Pathology and Laboratory Medicine
Tan Tock Seng Hospital
11 Jalan Tan Tock Seng
Singapore 308433

R C Hawkins, MB ChB, FRCPA
Consultant Chemical Pathologist

Correspondence to:
Dr R C Hawkins
Tel: (65) 6357 8943
Fax: (65) 6253 6507
Email: Robert_Hawkins@ttsh.com.sg

INTRODUCTION

Glycated haemoglobin (or HbA1c) is increasingly used as an index of mean glycaemia, a measurement of risk of diabetic complications and a quality assurance indicator to assess the quality of diabetes care[1]. Glycated haemoglobin measurement is recommended by the Singapore MOH Clinical Practice Guidelines[2] and the American Diabetes Association[3] for the monitoring of all patients with diabetes. Specific HbA1c goals have been defined as targets for diabetic treatment in Singapore. With over 30 different glycated haemoglobin methodologies available, it is important to ensure that all HbA1c results used for patient management are reliable and comparable between testing sites (clinics and laboratories). In addition to central laboratory HbA1c measurement, there is now a variety of point-of-care testing (POCT) devices allowing measurement in the clinic setting. These offer great convenience to clinician and patient and are increasingly popular in the polyclinics, restructured hospitals and private sector. Here I describe the evaluation of four POCT HbA1c assay systems available in Singapore, in comparison with the Roche Tinaquant HbA1c system used in the laboratory at Tan Tock Seng Hospital. The Tinaquant method is the popular HbA1c method used in Singaporean laboratories and is presently used by 10 laboratories (including five hospitals).

METHODS

Analytical inaccuracy was assessed by analysis of 110 patient samples on all five analytical platforms (Biorad Diastat, Drew DS5, Bayer DCA 2000, Nycomed Nycocard and Roche Tinaquant). Bland-Altman plots were prepared to assess bias and Deming model linear regression performed to describe agreement. Analytical imprecision was assessed by analysis of two levels of patient sample run twice in the morning and afternoon daily for six days, as well as analysis of two levels of commercial control. Within-run, between-run, between-day and total imprecision were calculated. All statistical data

Table I. Imprecision of HbA1c assays as coefficients of variation (%).

		Tinaquant		Diastat		DCA 2000		DS5		Nycocard	
Patient	HbA1c (%)	6.8	10.3	7.6	10.4	7.0	10.2	8.8	11.7	7.0	10.8
Material	Total CV	1.1	1.0	1.6	2.2	2.6	2.9	5.7	5.1	8.5	8.6
	Within run CV	0.8	0.8	1.1	1.3	2.1	2.6	3.1	1.5	2.3	3.4
	Between run CV	0.7	0.6	0.0	1.1	0.0	0.0	0.3	2.3	5.8	4.5
	Between day CV	0.0	0.0	1.1	1.4	1.4	1.2	4.8	4.3	5.7	6.5
Commercial	HbA1c (%)	6.2	10.8	5.8	9.6	5.8	10.6	6.0	11.1	4.8	9.1
Material	Total CV	0.9	0.8	4.6	6.6	7.2	3.6	11.7	7.9	15.3	14.7

Table II. Deming linear regression parameters for y=m*x + c, mean bias and Pearson correlation coefficients r for HbA1c method comparisons (95% confidence intervals in brackets).

x	y	Slope (m)	Intercept (c)	Mean bias (y-x)	r
Tinaquant	Diastat	0.98 (0.34 - 1.01)	0.36 (0.01 - 0.71)	0.17 (0.07 - 0.27)	0.98 (0.97 - 0.99)
Tinaquant	DCA 2000	0.95 (0.92 - 0.98)	0.63 (0.36 - 0.90)	0.20 (0.12 - 0.27)	0.99 (0.98 - 0.99)
Tinaquant	DS 5	1.23 (1.14 - 1.33)	-0.65 (-1.49 - 0.19)	1.38 (1.16 - 1.59)	0.93 (0.90 - 0.95)
Tinaquant	Nycocard	0.94 (0.89 - 0.99)	0.92 (0.48 - 1.35)	0.40 (0.28 - 0.52)	0.96 (0.95 - 0.98)
Diastat	DCA 2000	0.96 (0.91 - 1.01)	0.37 (-0.7 - 0.82)	0.03 (-0.08 - 0.14)	0.97 (0.95 - 0.98)

was performed using Microsoft Excel and Analyse-It Statistical Add-on for Excel (Analyse-It Software Ltd, UK).

HbA1c methods

Tinaquant immunoassay: The sample used was 20 uL of EDTA whole blood. The test system uses a latex-enhanced competitive turbidimetric immunoassay for determining HbA1c in whole blood with a colorimetric assessment of total Hb. The test requires manual preparation of sample haemolysate before automated analysis on a Roche 917 clinical chemistry analyser. The automated measurement takes 10 minutes for the first result, with subsequent results at nine second intervals. Up to 110 samples can be loaded at one time.

DS5 ion exchange: The sample used was 20 uL of EDTA whole blood. The test system uses low pressure cation ion exchange chromatography in conjunction with gradient elution. The test requires manual preparation of sample haemolysate before automated analysis. The automated measurement takes five minutes for the first result, with subsequent results at six minute intervals. Up to 15 samples can be loaded at one time.

Diastat ion exchange: The sample used was 20 uL of EDTA whole blood. The test system uses low pressure cation ion exchange chromatography in conjunction with gradient elution. The test requires manual preparation of sample haemolysate before automated analysis. The automated measurement takes 10 minutes for the first result, with subsequent results at 11 minute intervals. Up to 15 samples can be loaded at one time.

DCA 2000 immunoassay: The sample used was 1 uL of EDTA whole blood. The test system uses latex immunoagglutination inhibition technology. No manual sample haemolysis step is needed. The automated measurement takes six minutes for analysis. Samples are loaded one at a time.

Nycocard immunoassay: The sample used was 5 uL of EDTA whole blood. The test system uses boronate affinity technology and entails a series of manual precipitation, application, washing and sample reading steps. The entire procedure takes approximately six to seven minutes. Samples are analysed one at a time. All testing was performed by the same technologist.

RESULTS

Data from the imprecision studies is summarised in Table I. The Tinaquant system was most precise, followed by the Diastat and DCA2000 assays. All three displayed CVs (coefficients of variation) of less than 3% using patient samples. The DS5 and Nycocard systems were less precise with CVs of 5.1-8.6% with patient samples.

For method comparison, the Tinaquant system was used as the reference method, based on its superior precision and its use in the central laboratory. Bias plots of the various methods against the Tinaquant method are shown in Figs. 1-4. Deming model linear regression parameters, mean bias and Pearson correlation coefficients are shown in Table II. Generally there was good mean agreement between the Tinaquant assay and Diastat, DCA 2000 and Nycocard assays. Additionally there is

Bias plots of POCT methods against lab method (Fig. 1-4) and DCA2000 against Diastat (Fig. 5) --- represents mean bias. * on Fig. 4 represents HbE samples.

Fig. 1

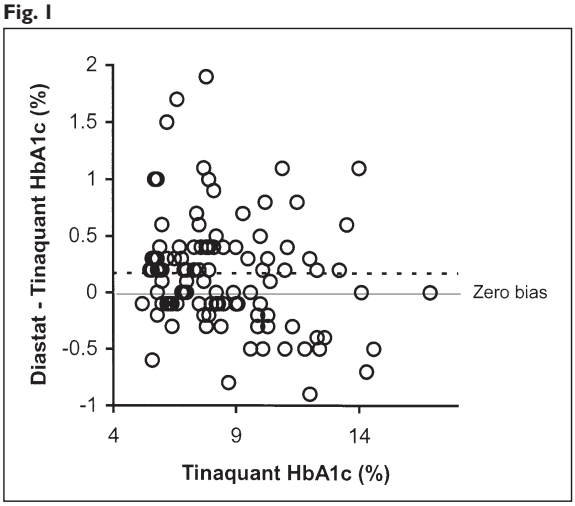


Fig. 2

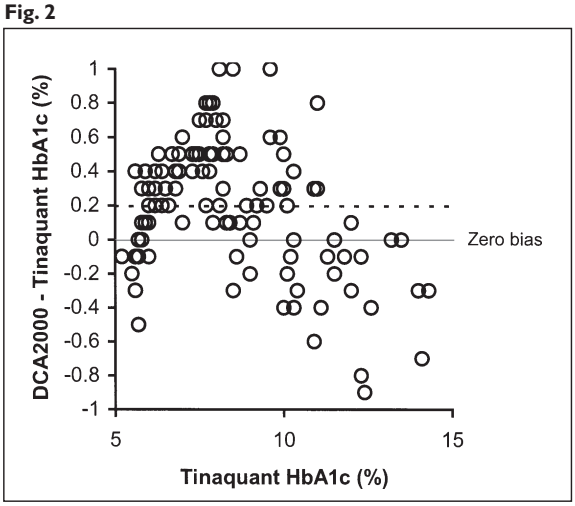


Fig. 3

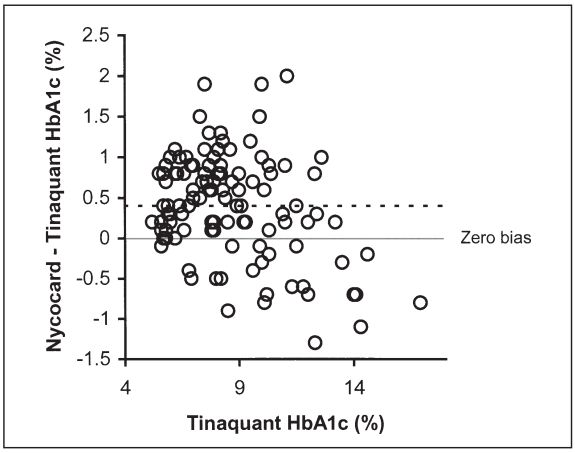


Fig. 4

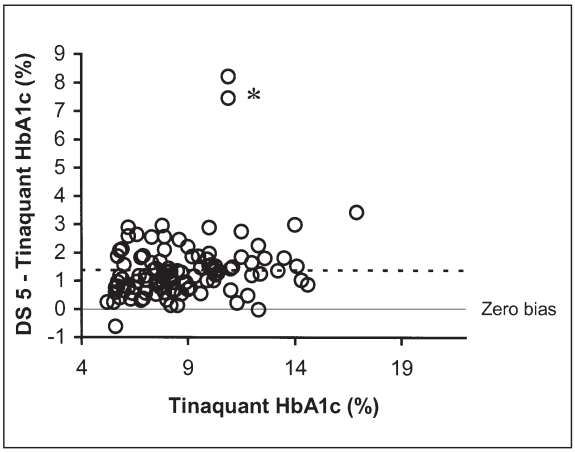
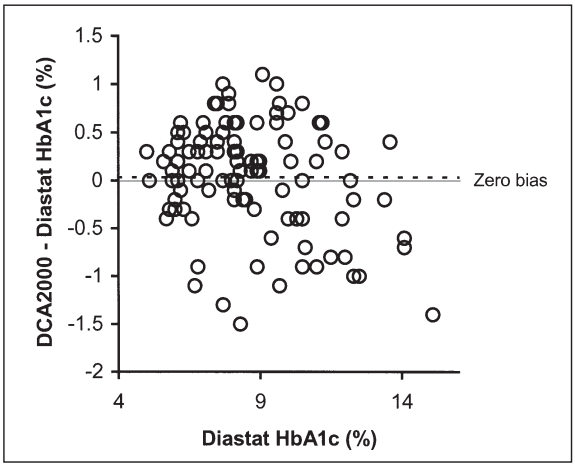


Fig. 5



excellent mean agreement between the Diastat and DCA 2000 systems (Fig. 5). The DS5 assay gives higher results than all other systems. Two patient samples which gave DS5 results an additional 6% higher than expected were subsequently identified as HbE trait cases.

DISCUSSION

It is recommended that HbA1c methods used should be certified by the National Glycohaemoglobin Standardisation Program (NGSP) as traceable to the Diabetes Control and Complications (DCCT) reference and that imprecision (CV) should be less than 5% (ideally <3%)[1]. All of the systems evaluated here are certified by NGSP as traceable to DCCT without any correction equation except for the DS5, which gives lower results and thus requires lot-specific correction factors to be entered manually into the instrument by the operator.

All the POCT systems showed poorer precision than the central laboratory method. Despite the good mean agreement between some methods seen in this evaluation, clinicians should take note of the wide discrepancy between methods seen for individual samples as illustrated by Fig. 1-5. They should be cautious when comparing results from different analytical platforms. Such variability is best minimised by consistent use of a single analytical system for a given patient.

Of the POCT systems evaluated, the Diastat and DCA2000 systems performed best, with acceptable imprecision (CV <3%) and good mean agreement with the central laboratory method and with each other. It should be noted that imprecision was assessed for only six days rather than the usual 20 used for method evaluations[4]; hence the total imprecision figures given here probably underestimate the true imprecision of the systems. Both of these systems would appear to be satisfactory analytical alternatives to both central laboratory (Tinaquant) testing and each other.

The DS5 system, which is very similar in technology to the Diastat but has a shorter analytical time, showed a positive bias compared to the other methods and was less precise than the Diastat and DCA 2000. The poorer precision may be due to the shorter analytical time leading to poorer separation of the HbA1c peak from the other Hb peaks in the sample. Interference from HbE is recognised as a potential problem for ion-exchange HbA1c assays but generally can be overcome if adjustments are made in the onboard instrument calculations[5]. HbE is the second most prevalent Hb variant in the world, with a prevalence as high as 30% in indigenous South East Asian populations[6]. The two unexpectedly raised HbA1c cases on the DS5 which proved to be HbE in this evaluation were both Malay and the prevalence of diabetes in Malays in Singapore is 11.3%[7]. This problem, together with the overall high bias and poor precision, makes this assay an unsuitable system for use in Singapore.

The Nycocard system gave the poorest precision of all the systems, reflecting the manual nature of the test. If multiple operators were performing the assay, as would be anticipated in a clinical setting, the expected imprecision would be even higher than seen in this evaluation involving a single technologist. The analytical results compared fairly well with the central laboratory method but the very poor precision of this assay makes this system unsuitable for clinical use.

CONCLUSION

POCT testing for HbA1c is of increasing interest to both clinicians and patients. Although factors such as cost, ease of use, speed of analysis and blood volume should be considered when choosing a suitable system, guaranteed result quality is mandatory and must not be sacrificed for patient or clinician convenience. Of the four systems evaluated here, only two (DCA2000 and Diastat) met the quality requirements for HbA1c testing. The DS5 system showed poorer precision, a positive bias and interference from HbE. The Nycocard system was unacceptably imprecise. The Diastat and DCA2000 systems appear satisfactory analytical alternatives to both central laboratory testing and each other. When used with a comprehensive quality assurance, training and documentation programme, these instruments can offer safe, convenient HbA1c POCT testing for diabetics to augment the services of the central laboratory.

ACKNOWLEDGEMENTS

I would like to thank Andrew Tse for performing the tests in this evaluation. I would also like to thank the following companies for gifts of reagents and loan of equipment: Alcare Pharmaceutical Pte Ltd (DCA 2000), Bio-Rad Laboratories (Singapore) Pte Ltd (Diastat), and All Eight Marketing Services Pte Ltd (Nycocard and DS5).

REFERENCES

1. Sacks DB, Bruns DE, Goldstein DE, Maclaren NK, McDonald JM, Parrott M. Guidelines and recommendations for laboratory analysis in the diagnosis and management of diabetes mellitus. Diabetes Care. 2002; 25:750-86.
2. Singapore Ministry of Health. Clinical Practice Guidelines: Diabetes Mellitus; 1999.
3. American Diabetes Association. Test of glycemia in diabetes. Diabetes Care. 2002; 25:S97-9.
4. National Committee for Clinical Laboratory Standards. Evaluation of precision performance of clinical chemistry devices. NCCLS Document EP5-T2, 1992.
5. Bry L, Chen PC, Sacks DB. Effects of Hemoglobin Variants and Chemically Modified Derivatives on Assays for Glycohemoglobin. Clin Chem. 2001; 47:153-63.
6. Beutler E. Disorders of hemoglobin. In: Fauci A, Braunwald E, Isselbacher K, et al., eds. Harrison s principles of internal medicine. 14th ed. New York: McGraw-Hill 1996; 645-52.
7. Singapore Ministry of Health National Health Survey 1998. Singapore: Ministry of Health; 1999.