Avoiding false potassium results due to hyperleukocytosis

We read with interest two recent related case reports regarding false potassium results in patients with very high white cell counts.^{1,2} In our laboratory, we have also seen both pseudohyperkalaemia and pseudohypokalaemia in the presence of major leukocytosis. In 2004, we reported a study in seven leukaemic children with white cell counts $>300 \times 10^9/L$.³ In four of these, the plasma potassium concentrations, measured after vacuum tube transport and centrifugation, were markedly higher than corresponding plasma potassium concentrations measured on a blood gas machine within 60 min of the samples being taken. For example, one patient with a white cell count of $812 \times 10^9/L$ had a plasma potassium concentration of 9.8 mmol/L after centrifugation with a corresponding potassium concentration measured using whole blood of 4.0 mmol/L. In 2006, we reported pseudohypokalaemia in a boy with myeloid leukaemia and a white cell count $>200 \times 10^9/L$.⁴ His centrifuged plasma potassium results were 1.4 and 1.2 mmol/L, with corresponding potassium concentrations measured using whole blood of 3.0 and 4.1 mmol/L. He had a marked metabolic alkalosis, so potassium may have moved into his white cells *ex vivo* at room temperature before his blood was centrifuged.

Leukaemic cells can be very fragile and easily break down either in the process of transport through a vacuum tube or while being centrifuged in the laboratory. Therefore, we feel that the most appropriate way of measuring potassium in patients with very high white cell counts ($>100 \times 10^9/L$) is to measure plasma potassium concentration using whole blood on a blood gas machine or a similar device. If there are any concerns about *ex vivo* haemolysis, this can be checked by centrifuging the sample after measurement. Although serum samples have been shown also to be free from this problem,¹ we are of the opinion that using whole blood is a much better and simpler approach, given the wide availability of blood gas machines in hospitals that admit such patients. In addition, the turnaround time using a blood gas machine is much quicker – an important consideration in this clinical situation.

For a number of years now, we have had this policy operating in our hospital, to good effect. It requires close cooperation between biochemistry and haematology departments to make sure that laboratory staff are quickly made aware of patients with white cell counts $>100 \times 10^9/L$. We feel that if such a policy were more widely adopted, the problem of false potassium results in the presence of major leukocytosis would go a long way to being solved.

DECLARATIONS

Conflict of interest: None.

Competing interest: None.

Guarantor: JC.

Tina Yen and John Coakley

Department of Clinical Biochemistry, The Children's Hospital at Westmead, Westmead, NSW 2145, Australia

Email: johnc2@chw.edu.au

DOI: 10.1258/acb.2010.010129

REFERENCES

- 1 Guiheneuf R, Vuillaume I, Mangalaboyi J, *et al.* Pneumatic transport is critical for leukaemic patients with major leukocytosis: what precautions to measure lactate dehydrogenase, potassium and aspartate aminotransferase? *Ann Clin Biochem* 2010;**47**:94–6
- 2 Polak R, Huisman A, Sikma MA, Kersting S. Spurious hypokalaemia and hypophosphataemia due to extreme hyperleukocytosis in a patient with a haematological malignancy. *Ann Clin Biochem* 2010;**47**:179–81
- 3 Coakley J, Shaw P. Pseudohyperkalaemia in patients with extremely high white cell counts. *Clin Biochem Rev* 2004;(Suppl.):S54
- 4 Coakley J, Bhadri V. An unusual case of factitious hypokalaemia. *Clin Biochem Rev* 2006;**27**(Suppl. (ii)):S31

Effect of non-glucose sugars and haematocrit on glucose measurements with Roche Accu-Chek Performa glucose strips

Point-of-care blood glucose meters based on glucose dehydrogenase (GDH) and pyrroloquinoline quinone (PQQ)-coupled reaction are subject to interference by non-glucose sugars¹ and icodextrin metabolites, chiefly maltose.²

Reports of treatment of spurious hyperglycaemia, arising from the interference, with insulin leading to life-threatening/fatal hypoglycaemia caused the Food and Drug Administration and others^{3–6} to issue safety notices to alert health professionals of the dangers of using GDH-PQQ-based glucose monitoring systems.

Roche Accu-Chek Advantage/Sensor Comfort glucose test strip (Roche Diagnostics, Basle, Switzerland) is based on GDH-PQQ reaction and is subject to positive interference by the non-glucose sugars mentioned in the safety notices.

Roche has now launched a successor glucose test strip called Accu-Chek Performa. Although the latter is still based on GDH-PQQ reaction, it is claimed that maltose interference has been eliminated and that blood glucose results are not significantly influenced by patients' haematocrit within the range of 10–65%.

We evaluated the Performa glucose test strips for interference from non-glucose sugars (fructose, galactose, lactose, maltose, mannose and xylose) and for the effect of blood haematocrit on blood glucose measurements. Throughout this study, glucose metabolism in heparinized whole venous blood was inhibited by adding DL-glyceraldehyde to a final concentration of 10 mmol/L⁷ and glucose results were reported as concentration of glucose in plasma.⁸

For the interference study, heparinized venous blood containing 10 mmol/L DL-glyceraldehyde was spiked with solution of non-glucose sugar to achieve the final concentrations of 0, 2.5, 5.0, 10.0, 15.0 and 20 mmol/L. The basal blood glucose concentration in these experiments was 5.2 mmol/L. After roller-mixing for 15 min at room temperature, glucose concentrations were determined with

the Performa strips on the Roche Accu-Chek Inform II glucose meter and with the hexokinase/glucose-6-phosphate dehydrogenase (HK/G-6-PDH) method on the Dimension XL analyser (Siemens Diagnostic Solutions, Deerfield, IL, USA). The level of interference, expressed as 'Found as Glucose' (Figure 1a), was calculated by subtracting the HK/G-6-PDH method result from the Accu-Chek result for the same sample.

Fructose and xylose showed no interference (Figure 1a). However, the presence of 1 mmol/L of maltose, mannose, lactose and galactose raised the glucose concentration by 0.09, 0.19, 0.19 and 0.34 mmol/L, respectively. Although the magnitude of interference by maltose with the Performa strip is considerably less than with its predecessor, 9% positive interference is still significant.

In order to study the effect of haematocrit, cellular and plasma proportions of the heparinized venous blood were adjusted to obtain haematocrits of 17.5–23.0%, 26.0–34.5%, 38.0–49.0%, 51.0–59.0% and 66.0–72.5%. Haematocrits were measured by capillary centrifugation in Hettich Haematokrit Centrifuge (NV Qlab SA, Vilvoorde, Belgium). Each haematocrit level was tested at mean

blood glucose concentration of 1.9, 4.0, 5.6, 7.8, 12.5 and 18.1 mmol/L. While the low blood glucose concentration (1.9 mmol/L) was achieved by allowing the heparinized whole blood, without DL-glyceraldehyde, to roll at room temperature until the desired concentration was reached, higher than the basal concentration was obtained by spiking with an appropriate volume of 1.11 mol/L glucose stock solution.

Figure 1b shows the percentage differences of glucose measurements with the Performa glucose strip compared with the HK/G-6-PDH method at different levels of haematocrit and blood glucose concentrations. The Performa results showed some degree of mutual dependency of haematocrit and glucose concentration. At all glucose concentrations and haematocrits of 17–59%, the Performa results were within $\pm 7\%$ of the reference method. When glucose concentration was 1.9 mmol/L and haematocrits were 23.0% and 34.5%, Performa gave 5.6% and 1.1% lower results, respectively, compared with the reference method. Thereafter, the Performa results were higher than the reference method (Figure 1b). At glucose concentrations of 12.5 and 18.1 mmol/L, the Performa results decreased with increasing haematocrit.

In summary, for haematocrits ranging from 17% to 59% and at all glucose concentrations tested, the Performa results were within $\pm 7\%$ of the reference method. Of the non-glucose sugars tested for interference, fructose and xylose showed no interference; maltose caused significant (9%); lactose and mannose substantial (both being 19%); and galactose severe (34%) positive interference.

DECLARATIONS

Competing interests: None.

Funding: None.

Ethical approval: No ethics committee approval was asked since no patient data or material were used.

Guarantor: ZZ.

Contributions: Concept and design: ZZ (and GC); performed the experiments: AF; data processing: AF and GC; and manuscript preparation: ZZ.

Annelies Fraeyman, Georges Claeys and Zahur Zaman

Department of Laboratory Medicine, University Hospitals Leuven, Herestraat 49, Leuven 3000, Belgium

Email: Zahur.zaman@uzleuven.be

DOI: 10.1258/acb.2010.010091

REFERENCES

- 1 Igarashi S, Ohtera T, Yoshida H, Witarto AB, Sode K. Construction and characterization of mutant water-soluble PQQ glucose dehydrogenases with altered K_m values-site-directed mutagenesis studies on the putative active site. *Biochem Biophys Res Commun* 1999;264:820–4
- 2 Garcia-Lopez E, Anderstam B, Heimbürger O, et al. Determination of high and low molecular weight molecules of icodextrin in plasma and dialysate, using gel filtration chromatography, in peritoneal dialysis patients. *Peritoneal Dial Int* 2005;25:181–91
- 3 FDA. Fatal Iatrogenic Hypoglycemia: Falsely Elevated Blood Glucose Readings with a Point-of-Care Meter Due to a Maltose-Containing Intravenous Immune

Figure 1 (a) Interference of non-glucose sugars with glucose measurement using Performa Glucose strip on Roche Accu-Chek Inform II. ○, galactose; ▲, lactose; ◇, mannose; ●, maltose; △, fructose; and ◆, xylose. Basal blood glucose concentration was 5.17 mmol/L. (b) Effect of haematocrit on measurements of different levels of blood glucose compared with HK/G-6-PDH reference method. ●, 1.85 mmol/L glucose; △, 4.03 mmol/L glucose; ◆, 5.6 mmol/L glucose; ○, 7.82 mmol/L glucose; ◇, 12.45 mmol/L glucose; and ▲, 18.14 mmol/L glucose

- Globulin Product. See <http://www.fda.gov/BiologicsBloodVaccines/SafetyAvailability/ucm155099.htm> (last checked 18 June 2008)
- 4 FDA. FDA Public Health Notification: Potentially Fatal Errors with GDH-PQQ Glucose Monitoring Technology. See <http://www.fda.gov/medicaldevices/safety/alertsandnotices/publichealthnotifications/ucm176992.htm> (last checked 13 August 2009)
- 5 Lage C. Effect of icodextrin on laboratory measurements. *PDServe. Connection* 2004;8:1–3. See: [http://www.pdsolve.com/pdsolve/pdsolve.nsf/AttachmentsByTitle/PDF_PDserve%3AVol+8%2C+No+2/\\$FILE/Vol.+8+%232+comp.pdf](http://www.pdsolve.com/pdsolve/pdsolve.nsf/AttachmentsByTitle/PDF_PDserve%3AVol+8%2C+No+2/$FILE/Vol.+8+%232+comp.pdf) (last checked 14 July 2010)
- 6 Octapharma. *Important Drug Warning*. See: <http://www.octapharma.com/Australia/docs/FINAL%20Maltose%20WARNING%20Letter%2019-10-5%20Australia.pdf> (last checked 19 October 2005)
- 7 Landt M. Glyceraldehyde preserves glucose concentrations in whole blood specimens. *Clin Chem* 2000;46:1144–9
- 8 D'Orazio P, Burnett RW, Fogh Andersen N, *et al.* Approved IFCC recommendations on reporting results of blood glucose (abbreviated). *Clin Chem* 2005;51:1573–76

Clinical and regulatory standards for the evaluation of blood glucose monitoring systems

In response to Fraeyman *et al.*,¹ Roche blood glucose monitoring systems are fully compliant to all relevant regulatory approval standards and meet established clinical requirements. Blood glucose monitoring systems for hospital or home use available on the market are evaluated and approved according to the DIN EN ISO 15197:2003 standard. Manufacturers of blood glucose monitoring devices have to provide evidence of fulfillment of this standard to obtain clearance for their products. The DIN EN ISO standard states that '≥ 95% of the individual glucose results

should be within ± 0.83 mmol/L (15 mg/dL) of the results of the manufacturer's measurement procedure at glucose concentrations <4.2 mmol/L (75 mg/dL) and within $\pm 20\%$ of the results of the manufacturer's measurement procedure at glucose concentrations ≥ 4.2 mmol/L'.^{2,3} Hence, blood glucose monitoring systems evaluated and cleared according to this quality and regulatory standard deliver accurate results and are safe to use in a hospital and outpatient setting.

Due to its advanced chemistry and compliance with quality and regulatory standards, if used as directed the Accu-Chek Performa/Accu-Chek Inform II blood glucose monitoring systems provide accurate and precise results. Thus, the systems deliver a safe and reliable basis for day-to-day therapeutic decisions for hospital setting and home use.

H Franke

Roche Diagnostics GmbH Sandhofer Straße 116 D-68305 Mannheim

Email: roche_diabetes_care.global_communications@roche.com

DOI: 10.1258/acb.2010.010107

REFERENCES

- 1 Fraeyman A, Claeys G, Zaman Z. Effect of non-glucose sugars and haematocrit on glucose measurements with Roche Accu-Chek Performa glucose strips (Letter). *Ann Clin Biochem* 2010 (in press ACB-10-091.R1)
- 2 DIN EN ISO 15197. *In vitro* Diagnostic Test Systems-Requirements for Blood Glucose Monitoring Systems for Self-Testing in Managing Diabetes Mellitus (ISO 15197:2003). European Committee for Standardization, Brussels, 2003
- 3 Freckmann G, Baumstark A, Jendrike N, *et al.* System accuracy evaluation of 27 blood glucose monitoring systems according to DIN EN ISO 15197. *Diabetes Technol Therap* 2010;12:221ff