Falsely Elevated Glucose Concentrations in Peritoneal Dialysis Patients Using Icodextrin

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Background: Peritoneal dialysis (PD) is used as an alternative to hemodialysis in end-stage renal disease (ESRD). Icodextrin has been used as a hyperosmotic agent in PD. The aim of the study was to assess two different point-of-care testing (POCT) glucose strips, affected and not affected by icodextrin, with serum glucose concentrations of the patients using and not using icodextrin. **Methods:** Fifty-two chronic ambulatory peritoneal dialysis (CAPD) patients using icodextrin (Extraneal[®]) and 20 CAPD patients using another hyperosmotic fluid (Dianeal[®]) were included in the study. Duplicate capillary and serum glucose concentrations were measured with two different POCT glucose strips and central laboratory hexokinase method. Assay principles of glucose strips were based on glucose dehydrogenase–pyrroloquinoline quinone

(GDH-PQQ) and a mutant variant of GDH (Mut Q-GDH). The results of both strips were compared with those of hexokinase method. **Results:** Regression equations between POCT and hexokinase methods in icodextrin group were $y = 2.55x + 1.12$ mmol/l and $y = 1.057x + 0.16$ mmol/l for the GDH-PQQ and Mut Q-GDH methods, respectively. The mean difference between the results of hexokinase and those of GDH-PQQ and Mut Q-GDH in icodextrin group was 3.41 ± 1.56 and 0.72 ± 0.64 mmol/l, respectively. However, the mean differences were found much lower in the control group; 0.64 mmol/l for GDH-PQQ and 0.52 mmol/l for Mut Q-GDH. **Conclusion:** Compared to GDH-PQQ, glucose strips of Mut Q-GDH correlated better with hexokinase method in PD patients using icodextrin. J. Clin. Lab. Anal. 30:506–509, 2016. © 2015 Wiley Periodicals, Inc.

Key words: glucose; icodextrin; interference; peritoneal dialysis; point-of-care testing

Abbreviations

ESRD	= end-stage renal disease
GDH	= glucose dehydrogenase
GDH-PQQ	= GDH–pyrroloquinoline quinone
Mut Q-GDH	= mutant variant of GDH
PD	= peritoneal dialysis

INTRODUCTION

Peritoneal dialysis (PD) is one of the primary treatments in end-stage renal disease (ESRD) patients. In the PD, a hyperosmotic fluid is introduced into the abdomen and the peritoneum is used as a dialysis membrane. PD fluids are prepared to mimic normal plasma with glucose as the main osmotic agent in the fluid (1). However, the use of glucose in high concentrations in the PD fluids has direct

deleterious effects on peritoneal structures and undesirable metabolic effects on the body. Hence, as an alternative to glucose, a soluble cornstarch-derived glucose polymer, icodextrin, has been commonly used as an osmotic agent for more than 15 years (2).

In PD, 20–30% of icodextrin is absorbed by systemic circulation and metabolized by alpha-amylase to oligosaccharides, such as maltose, maltotriose, and maltotetraose

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(3). In the presence of maltose, falsely elevated results could be obtained with the glucose strips using bacterial glucose dehydrogenases (GDHs) possessing pyrrolo-quinoline quinone as their prosthetic group (GDH-PQQ) (4). To avoid this problem, a new method with a mutant variant of GDH (Mut Q-GDH) has been developed (5). Bacterial nicotinamide adenine dinucleotide (NAD) or NAD phosphate (NADP) and flavin adenine dinucleotide (FAD) dependent GDH have also been developed for glucose strips (6). These GDH enzymes also have broad substrate specificity and catalyze galactose, xylose, fructose, and disaccharides (7). All of these GDH enzymes (GDH-PQQ, GDH-NAD(P), and GDH-FAD) are still used with many commercial glucose meters (8).

The aims of this study were to compare differences in glucose concentrations measured simultaneously using GDH-PQQ and MutQ-GDH strips and core laboratory hexokinase method in PD patients using and not using icodextrin, and to evaluate the performances of strips according to the international standards and clinical practice guidelines.

MATERIAL AND METHODS

Fifty-two PD patients (25 men and 27 women, aged 27–81 [mean age: 49 years]) using icodextrin (Extraneal, Baxter Healthcare Corp., Deerfield, IL, USA) were included as the icodextrin group. The control group consisted of 20 PD patients (ten men and ten women, aged 21–76 [mean age: 46 years]) using PD4 Dianeal (Mediflex, Eczacıbasi, Turkey). The subjects in both the groups were stable PD patients. The study was approved by the Institutional Review Board of Ankara Training and Research Hospital. The patients have signed informed consent. Simultaneous serum and capillary glucose measurements were performed in these patients in core laboratory and PD unit.

For simultaneous measurements without delay, we used two glucose meters with the same model (Accu-Chek Inform II [Roche Diagnostics, Indianapolis, IN]). Duplicate capillary glucose measurements were done by two different glucose strips (two measurements with each strip), one based on GDH-PQQ, the other based on Mut Q-GDH (Accu-Chek Performa, Roche Diagnostics). Within 5 min after capillary glucose measurements, blood was drawn intravenously into plain evacuated tubes (BD Vacutainer SST, BD Franklin Lakes NJ) for core laboratory glucose measurements. After sera were separated by centrifugation at $1,300 \times g$ for 10 min, serum glucose concentrations were measured in duplicate (one sample from each patient and two measurements in each sample) by a hexokinase method (Olympus AU 2700, Olympus Life and Material Science Europa GmbH, Hamburg, Germany) within 30 min after blood collection. Hematocrit was determined

with a Coulter LH 750 analyzer (Beckman-Coulter, Inc., Fullerton, CA).

Within-laboratory coefficients of variation (CVs) ($n = 21$) of low-level (2.5 mmol/l) and high-level (17.0 mmol/l) controls were 3.2% and 4.1% for GDH-PQQ and 2.6% and 3.3% for Mut Q-GDH. Strips were calibrated equivalent to plasma according to a National Institute of Standards and Technology (NIST) standard (SRM 965). Within-laboratory CVs of the core laboratory glucose method was 3.59% ($n = 21$) for low-level (5.63 mmol/l) and 3.35% for high-level control (13.0 mmol/l). The system was calibrated with a human serum based calibrator traceable to the NIST standard SRM 965. Both types of strips were calibrated equivalent to plasma.

Deming regression analysis was performed between glucose meters' and core laboratory's glucose data. Concordance correlation coefficients (CCCs) of the strips were determined against the reference method. The difference between Mut Q-GDH and GDH-PQQ strips was evaluated by paired *t*-test. Statistical analyses were performed by MedCalc version 9 (Ostend, Belgium).

In icodextrin group, regression equations between strips and hexokinase methods were $y = 2.55x$ (95% CI: 1.6–3.5) + 1.12 (95% CI: 0.9–1.2) mmol/l and $y = 1.057x$ (95% CI: 0.96–1.6) + 0.16 (95% CI: –0.4 to 0.8) mmol/l for the GDH-PQQ and Mut-Q GDH strips, respectively. When the results of glucose meters were compared with hexokinase method, the mean differences were 3.41 ± 1.56 mmol/l and 0.72 ± 0.64 mmol/l for GDH-PQQ and Mut Q-GDH strips in icodextrin group, respectively. These differences were 0.64 mmol/l and 0.52 mmol/l for GDH-PQQ and Mut Q-GDH in PD4 Dianeal group, respectively.

Significantly higher glucose results were obtained by GDH-PQQ strips than those of Mut Q-GDH ($P < 0.001$) and hexokinase method ($P < 0.001$) in the icodextrin group. The differences were not statistically significant among the methods in the control group.

The CCCs of two strips against the reference were 0.75 and 0.85 for GDH-PQQ and Mut Q-GDH, respectively. Hematocrit values of icodextrin and control groups were similar ($38.3\% \pm 4.2$ and $38.4\% \pm 3.7$, respectively; $P > 0.05$).

The present study shows that MutQ-GDH give relatively more acceptable results than GDH-PQQ as compared to the hexokinase method in the PD patients using icodextrin. Falsely high serum glucose concentrations with GDH-PQQ strips may result from the presence of icodextrin metabolites. Plasma concentrations of these metabolites have progressively risen with peak values reached by the end of the dwelling (9, 10). According to pharmacokinetics studies, the steady-state plasma concentration of icodextrin and its metabolites was achieved within 7–10 days (9). During this period, falsely elevated

Fig. 1. Comparison of GDH-PQQ against hexokinase in icodextrin group ([A] $y = 2.55x$ [95% CI: 1.6–3.5] + 1.12 [95% CI: 0.9–1.2]) mmol/l and controls ([B] $y = 0.947x$ [95% CI: –2.201 to 3.613] + 0.705 [95% CI: 0.426–1.467 mmol/l]); comparison of Mut Q-GDH against hexokinase in icodextrin group ([C] $y = 1.057x$ [95% CI: 0.96–1.6] + 0.16 [95% CI: –0.4 to 0.8] mmol/l) and controls ([D] $y = 0.908x$ (0.731–1.085) + 0.611 [95% CI: –0.446 to 1.669]), respectively.

serum glucose concentrations are expected if glucose is measured with GDH-PQQ strips. Our study confirms the false elevation of serum glucose concentrations with a false increase of 3.41 ± 1.56 mmol/l in GDH-PQQ strips and there was no significant difference in the control group ($P = 0.698$). Despite other GDH enzymes have also broad substrate specificity (7), Huang et al. (4) compared the accuracy of mutant Q-GDH- and FAD-GDH-based blood glucose monitors and found excellent accuracy. Our findings also support the idea that icodextrin interferes with the measurement of glucose by GDH-PQQ-based strips. However, differently from Huang et al.'s study, we included a control group of PD patients using another PD solution (Dianeal) and compared the results according to Clinical and Laboratory Standards Institute (CLSI) and American Diabetes Association (ADA) standards as well as ISO 15197 standard.

Although hematocrit affects the glucose results of strips in general and POCT12-A3 recommends excluding data if blood samples have hematocrit values outside the manufacturer's specifications (11, 12), there is no subject with a hematocrit value outside the limits in our study population. Moreover, the hematocrit values are similar in both the groups, hence the difference between the groups can be interpreted independently from hematocrit values.

We compared results of both strips against hexokinase method according to the specifications of ISO, CLSI, and ADA standards. According to the ISO 15197, total analytical error of glucose meter must be within ± 0.83 mmol/l of the laboratory glucose concentrations for values < 5.55 mmol/l and $\pm 15\%$ at glucose concentrations ≥ 5.55 mmol/l. According to ADA, total analytical error must be $\leq 5\%$ for all levels. According to CLSI POCT12-A3, total analytical error must be within ± 0.67 mmol/l of the laboratory glucose concentrations for values < 5.55 mmol/l and within $\pm 12.5\%$ at glucose concentrations ≥ 5.55 mmol/l. We found that nearly all of the results with GDH-PQQ were out of the limits recommended by ISO, ADA, and CLSI POCT12-A3 (94.2% [$n = 49$] and 98.1% [$n = 51$], 96.1% [$n = 50$], respectively). Report of Perera et al. presents similar results in which an interference up to 79% was found by Accu Chek Performa (Roche Diagnostics, Indianapolis, IN, USA) (13). On the contrary, according to ISO, ADA, and CLSI POCT12-A3 criteria, our study shows that when Mut Q-GDH strips were considered, the rates of unacceptable results were 21.2% ($n = 11$), 69.2% ($n = 36$), 25% ($n = 13$) in the patient group and 12.5% ($n = 3$), 40% ($n = 8$), 0% ($n = 0$) in the control group. However, the more strict limits set out by the ADA, which allows a difference $< 5\%$, are unlikely to be

met even with the Mut Q-GDH strips (69.2% [$n = 36$] and 40.0% [$n = 8$] in patient and control groups, respectively).

Regression equation indicates an unacceptable positive proportional systematic error of GDH-PQQ strips. Positive proportional systematic error of Mut Q-GDH strips is much less than GDH-PQQ strips (Fig. 1). The constant systematic errors of both strips are roughly similar. CCC showed a poor agreement for both strips with core laboratory glucose results. Mut Q-GDH had a poor agreement (CCC = 0.85), while GDH-PQQ had the worst (CCC = 0.75). These values suggest that the results with GDH-PQQ lack accuracy when compared to the core laboratory method.

CONCLUSIONS

It should be noted that falsely elevated serum glucose concentrations can be obtained with the glucose strips based on GDH in PD patients using icodextrin. It is recommended for the Mut Q-GDH or non-GDH-based strips for the follow-up of PD patients using icodextrin. Additionally, still there is a confusion in the evaluation of glucose meters and strips, in general. Therefore, there is a need for a single guideline worldwide for analytical and clinical evaluation of glucose meters. Currently the laboratory specialists and clinicians should know the content of PD solutions and whether to include icodextrin or not.

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