Revisiting Icodextrin Masked Hypoglycemia – A Case Report

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Abstract: Icodextrin based peritoneal dialysis fluids are being commonly used, especially among diabetic patients. We report a lady with end stage renal disease due to diabetic nephropathy on Icodextrin based peritoneal dialysis, who had hypoglycemia that was masked by the interaction of Icodextrin metabolites with the point of source glucose testing by glucometer. However, potentially catastrophic complications of iatrogenic hypoglycemia were averted by confirmatory laboratory testing by method free of this interaction. This case emphasizes on the need for increased awareness among the patients and paramedical staff regarding this interaction to prevent potential life threatening iatrogenic hypoglycemia.

Key words: Icodextrin, Diabetes, Hypoglycaemia, Peritoneal dialysis, Maltose,

Introduction
Icodextrin (7.5% wt/vol) (Extraneal™; Baxter Healthcare, USA) solution contains a spectrum of high molecular weight polysaccharides (average molecular weight 16200 Daltons) that are minimally and slowly absorbed across the peritoneal membrane (1). Use of this solution to provide osmotic gradient in peritoneal dialysis fluid, results in a very low absorption leading to a better ultrafiltration as well as improved glycemic control in diabetic patients(1). Icodextrin PD solutions are being increasingly used in patients with diabetic nephropathy as the cause of ESRD(2). Use of Icodextrin is associated with significantly better cumulative technique survival(2). Net ultrafiltration volume is significantly higher in patients on icodextrin compared with the glucose solutions(2).

Case Report
A 61 years old lady with diabetic nephropathy related chronic kidney disease stage 5, presented in April 2011 at Christian Medical College, Vellore with end stage renal disease with fluid overload state. She was initially prescribed a total of 8 to 12 units of short acting insulin per day for adequate glycemic control and the daily blood glucose levels were monitored by point of source testing with Accu-Chek (Roche Diagnostics, Indianapolis, USA) glucometer. She was not on any oral hypoglycemic agents. The various options of renal replacement therapy (RRT) were discussed with the patient and she chose CAPD. Her baseline urine output was 700ml/day. She was given 3 sessions of hemodialysis (HD) for stabilization during the first week. Subsequently, a percutaneous swan-neck CAPD catheter was inserted PD fluid exchanges were started from the 2nd day after catheter insertion. She initially had poor ultrafiltration with three 8 hour dwells of 1.5% dextrose (D). Her PD prescription was changed to one dwell of 1.5%D and two dwells of 2.5%D, 8 hours each. With use of high concentrations of glucose solutions, she required much higher doses of insulin (a total of 70-80units of short acting insulin per day) for adequate glycemic control. The dose of insulin was titrated based on glucometer readings of blood glucose in the ward. She continued to have less PD output and a positive fluid balance, requiring a session of Ultrafiltration via the jugular catheter for an impending pulmonary edema. Considering the possibility of a high transporter status, the PD fluid prescription was changed to a three hour dwell of 2.5% D and two long dwells of 7.5%D for 10 hours each. With this, the net PD ultrafiltration was approximately 1000 ml per day and she no longer required sessions of HD. However, after changing to two long dwells with Icodextrin, D, with the reduction in glucose exposure it was expected that her glycemic control would be better and the insulin requirement may decrease. However, her blood glucose levels, as assessed by glucometer readings, continued to be on the rise and she was given higher doses of insulin (a total of 100 units of short acting plain insulin per day) aiming to achieve better “glycemic” control.

Two days later she complained of episodes of sweating, chills, tachycardia and restlessness. She also developed altered sensorium in the night time. The attending nurse had checked
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the blood glucose values by the glucometer (Accu-Chek, Roche Diagnostics, USA) and reported them to be 251 mg/dl. Due to the discordant results, the ward nurse had re-checked the blood glucose level in another glucometer (Ascensia Contour, Bayer HealthCare Diagnostic Division, USA), and was found to be 248 mg/dl. However feeling weak and hungry, and recognizing the similarity between the current episode and her past experience of hypoglycemic symptoms, the patient intuitively consumed a few biscuits and a sweet candy and subsequently felt immediate symptomatic relief. This was brought to notice of the doctors only the next day.

At this point interference of icodextrin with the glucometer assays was considered and all the subsequent assays for blood glucose were sent to the central biochemistry laboratory. The fasting glucose checked on the subsequent day using the glucometer was 157 mg/dl as against the value reported form the same blood sample from the central laboratory as 73 mg/dl. Subsequent insulin dose adjustments were made as per the values of blood glucose obtained from the central laboratory and the insulin requirements at the time of discharge was a total of 35 units of short acting insulin per day.

Discussion

There is an increasing acceptance of PD as a modality of RRT among Indian CKD patients. Currently more elderly and diabetic patients choose PD than in the past. Several factors such as fast transporting peritoneal membrane status, concern of glycemic control as well as peritoneal membrane preservation with use of high concentration dextrose solutions, and the declining price difference between the Dextrose and Icodextrin solutions, have resulted in increasing use of Icodextrin containing PD solutions, especially in diabetic PD patients.

Icodextrin is a glucose polymer derived from cornstarch. Icodextrin is not metabolized in the peritoneal cavity, but the polymer can move into the blood stream via the lymphatic system(3). Once in the blood stream, Icodextrin is hydrolyzed by circulating α-amylase into the oligosaccharides maltose and maltotriose, which accumulate due to a lack of circulating maltase(4). Hence the use of Icodextrin PD solution is often restricted to once or twice a day only, to avoid systemic accumulation(5). Accumulation of the Icodextrin metabolites in the systemic circulation is considered to be responsible for erroneous glucose values obtained in several point of source test glucometers.

Point of source test glucometers measure glucose levels by the glucose by various methods such as glucose dehydrogenase - pyrroloquinolinequinone (GDH-PQQ), glucose dye oxidoreductase (GDO), glucose dehydrogenase nicotinamide adenine dinucleotide (GDH-NAD), or glucose oxidase (GOx) methods. In the GDH-PQQ method, conversion of glucose to gluconic acid by the GDH enzyme results in reduction of NAD to NADH, and the amount of NADH measured by the glucometer is directly proportional to the blood sample's glucose concentration. However, the enzyme glucose dehydrogenase with coenzyme pyrroloquinolinequinone can react with the free reducing group of glucose located at the end of the maltose molecule, a breakdown product of icodextrin, producing additional NADH, and thus yielding an overestimation of blood glucose levels. A similar phenomenon is observed among tests using the GDO method.

However, glucose estimation using the glucokinase, hexokinase, or GDH-NAD methods does not exhibit this interaction. The Ascensia Contour (Bayer HealthCare Diagnostic Division, New York, USA) and the Accu-Chek (Roche Diagnostics, Indianapolis, USA), showed >60% higher glucose values than that obtained by the reference method. Both glucometers were based on the GDH-PQQ method(6). These glucometers should not be used in patients on CAPD using icodextrin as the exchange fluid. Serum glucose in the centralized laboratory is often measured using the standard hexokinase method which is not influenced by the maltose metabolites of Icodextrin(6).

Similar interactions are also observed with use of maltose or Xylose containing substances such as Human intravenous immunoglobulin, Rho(D) immune globulins and D-Xylose test (absorption tests for malabsorption). In addition to interfering with glucose estimation, Icodextrin is also known to result in underestimation of serum amylase activity, by the competitive action of Icodextrin metabolites as substrate in the amylase assay(7).

The US-FDA advices to “Use only test methods not affected by the presence of maltose, galactose, or D-xylose, such as glucose oxidase- or glucose hexokinase-based test methods. If GDH-based methods are used, find which cofactor is used in the test strip to determine whether the test strips are subject to interference or not. Make sure it is not a GDH-PQQ-based test strip.”(8)

If the potential interaction of the glucometer assay techniques with Icodextrin was missed in our case, the insulin dose would have been increased further with its attendant serious
complications including seizures and death. Although the effect of Icodextrin on glucose testing has been reported before, awareness of this potentially life threatening interaction among medical and paramedical staff is low(9). Icodextrin–glucometer interaction resulting in increased use of insulin is an important and easily preventable cause of hypoglycemia among diabetic PD patients(10). All patients on CAPD using Icodextrin as the CAPD fluid and the paramedical staff should be warned of the possibility of spuriously high glucose values obtained with the glucometers which use GDH-PQQ-based test strip. Preferably a list of such glucometers should be given to them to avoid checking blood sugar in these devices. They shall be advised to use glucometers which use GOx based strips such as LifeScan (OneTouch UltraLink) Nova (Biomedical Nova Max), or GDH-NAD based strips is Arkay (Glucocard X-meter).

Conclusion

Metabolites of Icodextrin cause spurious hyperglycemia which results in inappropriate dosing of insulin and can lead to life threatening hypoglycemia. Diabetic PD patients on Icodextrin should be instructed to check their glucose readings in devices that do not use the GDH-PQQ method, which exhibits this interaction. Awareness among the patients and paramedical staff regarding this interaction can avoid potential life threatening iatrogenic complications of missed hypoglycemia.

References


