Review of Adverse Events Associated With False Glucose Readings Measured by GDH-PQQ–Based Glucose Test Strips in the Presence of Interfering Sugars

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OBJECTIVE — To assess the implications of falsely elevated glucose readings measured with glucose dehydrogenase pyrroloquinolinequinone (GDH-PQQ) test strips.

RESEARCH DESIGN AND METHODS — We conducted a review of the Food and Drug Administration's Manufacturer and User Facility Device Experience database and medical literature for adverse events (AEs) associated with falsely elevated glucose readings with GDH-PQQ test strips in the presence of interfering sugars.

RESULTS — Eighty-two reports were identified: 16 (20%) were associated with death, 46 (56%) with severe hypoglycemia, and 12 (15%) with nonsevere hypoglycemia. In eight reports (10%), the AE was not described. Forty-two events (51%) occurred in the U.S. Although most events occurred in hospitalized patients, at least 14 (17%) occurred in outpatients. Agents most commonly associated with AEs were icodextrin-containing peritoneal dialysate and maltose-containing intravenous immune globulin.

CONCLUSIONS — GDH-PQQ test strips pose a safety risk to insulin-using patients treated with agents containing or metabolized to interfering sugars.

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Enzymes play a critical role in measuring blood glucose. Following blood application, glucose tests strips utilize enzymes to selectively catalyze the oxidation of glucose. In many systems, the product of the enzyme reaction is detected electrochemically, using a meter to convert the measured current into a glucose value.

Currently available glucose test strip enzymes include glucose oxidase (GOx), dehydrogenase (GDH) nicotinamide adenine dinucleotide (GDH-NAD), GDH flavin adenine dinucleotide (GDH-FAD), and GDH pyrroloquinolinequinone (GDH-PQQ). GDH-PQQ (referring to native GDH-PQQ not mutants of GDH-PQQ) is not glucose specific. As such, in addition to reacting with glucose, it reacts with other sugars (maltose, galactose, and xylose). Systems that utilize GDH-PQQ test strips may therefore report falsely elevated glucose readings in blood samples from patients treated with agents containing or metabolized to these sugars.

Over the past 10 years, reports have appeared of GDH-PQQ–related falsely elevated glucose readings resulting in insulin overdose and adverse events (AEs), including severe hypoglycemia and death. This brief report provides a comprehensive assessment of AEs associated with falsely elevated glucose readings measured with GDH-PQQ test strips in the presence of interfering sugars.

RESEARCH DESIGN AND METHODS

— A query of the Food and Drug Administration's (FDA's) Manufacturer and User Facility Device Experience (MAUDE) database was conducted in August, 2009. This database contains voluntary reports since June 1993, user facility reports since 1991, distributor reports since 1993, and manufacturer reports since August 1996 (available at http://www.fda.gov/cdrh/maude.html). The search was limited to codes for glucose-monitoring products and was further limited by searching for the following key words: maltose, galactose, xylose, icodextrin, extraneal, peritoneal dialysis, immunoglobulin, intravenous immune globulin (IVIG), globulin, Octagam, Intragam, Gamimune N, WinRho SDF, HepaGam B, abatacept, Orencia, Adept Solution, maltodextrin, galactosemia, tositumomab, and Bexxar. Each report was assessed by the authors to identify AEs associated with GDH-PQQ test strips and an interfering agent or disorder.

Combinations of the same key words were used to search Ovid and PubMed databases for AEs. Each retrieved article was assessed by the authors, and the article's references were searched for additional reports. Reports were categorized by type of AE and agent or condition associated with the event. AEs appearing in both MAUDE and literature databases were counted once.

RESULTS

— The MAUDE database and literature search yielded 61 and 21 unique cases of GDH-PQQ–related AEs, respectively (see supplementary references in the online appendix [available at http://care.diabetesjournals.org/cgi/content/full/dc09-1822/DC1]). Table 1 summarizes the AEs by severity and associated agent or condition. Of 82 AEs, 16 (20%) were associated with death and 46 (56%) with severe hypoglycemia (4 resulting in permanent injury). Most events (78%) were associated with the use of icodextrin-based peritoneal dialysis (PD) solution and 13% with a maltose-containing IVIG. In two reports, the false glucose reading was associated with galactosemia.

Fifty-nine (72%) events occurred in an inpatient setting, 14 (17%) in an outpatient setting, and in 9 (11%) cases the

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Table 1—*AEs summarized by severity and associated agent or condition*

Agent/condition	Death	Severe hypoglycemia*	Nonsevere hypoglycemia	Type of injury in AE not reported	Total
Icodextrin (PD solution)	10	35	11	8	64
IVIG	3	7	1	0	11
Maltose-containing substance	1	2	0	0	3
Maltodextrin	1	0	0	0	1
Agent not reported	1	0	0	0	1
Galactosemia	0	2	0	0	2
Total	16	46	12	8	82

*Severe hypoglycemia defined as an event requiring assistance of another person to actively administer carbohydrate, glucagon, or other resuscitative actions.

setting was not documented. Half of the events (51%) occurred in the U.S. Other countries reporting AEs included Australia, Belgium, China, England, Holland, Israel, Japan, Saudi Arabia, Singapore, and South Africa.

CONCLUSIONS — Despite repeated warnings by regulatory agencies and manufactures, AEs associated with GDH-PQQ test strips have continued to occur. A recent FDA Public Health Notification reported 13 deaths associated with GDH-PQQ test strip interference from nonglucose sugars. Six of 13 deaths occurred after 2007 (1).

The most commonly implicated agent in our review was icodextrin-containing PD solution, which is used in treating end-stage renal disease, a condition with a heightened risk of hypoglycemia (2). Importantly, 12% of cases were associated with maltose-containing IVIG, which is used in several disorders including primary immune deficiency and idiopathic thrombocytopenia, and is reportedly used off label ~50% of the time. Over 150 off-label uses were recently described (3,4). Other maltose-containing agents that may interfere with GDH-PQQ test strips include abatacept (for rheumatoid arthritis), Adept Solution (for reduction of postsurgical adhesions), and tositumomab (for non-Hodgkin's lymphoma). Given the wide spectrum of disorders that may be treated with icodextrin or maltose-containing agents, health care providers across a range of specialties need to be familiar with this issue.

The majority of AEs in this review (71%) occurred in an inpatient setting. Based on similar findings, the FDA recently issued recommendations to "avoid using GDH-PQQ glucose test trips in healthcare facilities" (1). However, 18% of AEs in our review occurred in an outpatient setting (including 10 cases of severe hypoglycemia and one death). This is not unexpected since PD is primarily administered at home and IVIG infusions may be administered in a provider's office. This is therefore an issue that should be considered for patients in the outpatient setting as well as for hospitalized patients.

Because voluntary reports in MAUDE vary in detail and, unlike the published literature, may not always provide enough information for the reviewer to establish direct causality, we chose to report all AEs as device associated. It is important to note that the AEs summarized in this report likely represent a small fraction of the AEs that have actually occurred, as it is well accepted that significant underreporting of AEs occurs in databases that rely on spontaneous reporting, including the FDA's Adverse Event Reporting System and MAUDE (5–7).

A list of GDH-PQQ test strips has recently been published (1). The risk posed by these products must be balanced against the risk of available alternatives. Test strips using enzymes with higher glucose specificity are widely available. These include GOx, GDH-NAD, and GDH-FAD. These enzymes do not yield falsely elevated glucose readings in the presence of maltose and galactose (GDH-FAD does react with xylose). Although GOx-based test strips can be affected by varying oxygen levels and may exhibit chemical interferences common to most electrochemical systems, these limitations are not due to nonspecificity of the enzyme. We have found no reports of serious injury or death due to interferences with GOx, GDH-NAD, or GDH-FAD enzymes.

Findings in this report indicate that GDH-PQQ test strips pose an important safety risk to insulin-treated patients with diabetes undergoing therapies with agents containing or metabolized to interfering sugars. Health care professionals and patients must be aware of this risk and of known interfering agents and disorders.

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