FDA/CDRH PUBLIC MEETING: Blood Glucose Meters

FDA Perspective - Public Health Notification:
Potentially Fatal Errors with GDH-PQQ Glucose Monitoring Technology

Courtney C. Harper, Ph.D.,
Director, Division of Chemistry and Toxicology Devices

• Office of in Vitro Diagnostic Device Evaluation and Safety
• Center for Devices and Radiological Health


Background

16-20 million Diabetics in US

Cost for diabetes management estimated at 150 billion dollars

Glucose meters:

• Available for more than 3 decades
• Revolutionized diabetes management
• Allow for better glycemic control by diabetics
• Have gotten smaller, faster, and more accurate over the years
Background

Methods:
• Glucose Oxidase
• Glucose dehydrogenase
  • PQQ
  • FAD
  • NAD

Glucose meters are used:
• By millions of diabetics at home
• In healthcare settings
  • Hospitals
  • Nursing homes
  • Physician’s offices
  • Emergency Departments
  • Emergency Response Units
Adverse Events - Injuries

Glucose meters have one of the highest number of device adverse events reported per year

• Device Reporting:
  • Events/malfunctions generally under-reported – particularly for OTC devices
  • Limitations of database – data analysis difficult

• Thousands of Medical Device Reports (MDRs) sent each year
  • >12,000 reports/year
  • Billions of tests performed per year
## Adverse Events - Injuries

- 12,672 serious injuries reported from 2004-2008

<table>
<thead>
<tr>
<th>Injury</th>
<th>% of Reports with Injury</th>
<th>Number of reports with Injury</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment with medication(s)</td>
<td>44.67%</td>
<td>5662</td>
</tr>
<tr>
<td>Hospitalization required</td>
<td>42.74%</td>
<td>5417</td>
</tr>
<tr>
<td>Therapy/non-surgical treatment</td>
<td>40.06%</td>
<td>5077</td>
</tr>
<tr>
<td>Blood glucose, low</td>
<td>25.05%</td>
<td>3175</td>
</tr>
<tr>
<td>Hypoglycemia</td>
<td>23.30%</td>
<td>2953</td>
</tr>
<tr>
<td>Consciousness, loss of</td>
<td>20.03%</td>
<td>2538</td>
</tr>
<tr>
<td>Blood glucose, high</td>
<td>13.93%</td>
<td>1766</td>
</tr>
<tr>
<td>Shaking/tremors</td>
<td>13.33%</td>
<td>1689</td>
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<tr>
<td>Dizziness</td>
<td>11.60%</td>
<td>1470</td>
</tr>
<tr>
<td>Hyperglycemia</td>
<td>7.42%</td>
<td>941</td>
</tr>
</tbody>
</table>
Adverse Events - Deaths

1992-2009: 100 deaths associated with glucose meters reported

- Unknown cause (34)
- Meter malfunction (11)
- False High Results (11)
- Diabetic Ketoacidosis (8)
- Maltose/non-glucose interference (13)
- Use on Critically Ill Patient (6)
- False Low results (6)
- Possible Medication Interference (5)
- Renal patient (2)
- Dehydration (1)
- Hyperosmolar Hyperglycemia (1)
- Feeding tube –glucose (1)
- Neonatal death (1)
GDH-PQQ Issue

Glucose Dehydrogenase – Pyrroloquinoline quinone (GDH-PQQ)
- Technology marketed for ~20 years
- GDH-PQQ is non-selective for glucose – also detects maltose, xylose, galactose, ...
- Several years ago, drug/therapeutic products were approved that contain these other sugars as components
- GDH-PQQ test systems used on patients receiving these drugs give falsely high results
- There have been deaths and serious injuries when patients have been treated based on these results (e.g., severe hypoglycemic events)
- Devices warn against this use

Different types of drugs involved. For example:
- Extraneal (icodextrin) peritoneal dialysis solution
- Some IV Immunoglobulins
Previous Actions

2005
• FDA MedWatch Safety Alert - Parenteral Maltose/Parenteral Galactose/Oral Xylose-Containing Products

2006
• FDA Patient Safety News - “Avoiding Glucose Monitoring Errors in Patients Receiving Other Sugars”

2008
• ISMP article published CDER
• Fatal Iatrogenic Hypoglycemia: Falsely Elevated Blood Glucose Readings with a Point-of-Care Meter Due to a Maltose-Containing Intravenous Immune Globulin Product published, CBER
• Patient Safety News - September

2009
• Extraneal Black Box Warning added, CDER
PQQ-Related Reports

• 1997-2009 - FDA received 13 reports of death associated with GDH-PQQ glucose test strips

• The deaths occurred in healthcare facilities

• 6 of the 13 deaths have occurred since 2008 despite FDA’s efforts to communicate the risk

• 10 of the 13 patients were receiving Extraneal (icodextrin) peritoneal dialysis solution for renal failure.

• 3 of the 13 patients were receiving maltose-containing substances
Problem

• Despite previous actions deaths still occurring
• Issue affects small minority of patients
  • Yet devastating effects when occurs
• Additional action warranted
  • How to send clear message without confusion?
  • Balance: safety warning / message that patients should keep testing
• FDA decided on a slightly stronger message and ongoing actions
  • Communication via new Public Health Notification
Public Health Notification: August 2009

• Raise the level of the recommendation

• Attempt to increase awareness of this problem

• Aimed at healthcare providers who use GDH-PQQ tests systems in their facilities
Nature of the problem

• When non-glucose sugars present, GDH-PQQ system will produce a false high glucose result

• May lead to inappropriate insulin dosing
  • May result in hypoglycemia, coma, or death
  • Hypoglycemia may go unrecognized

• Can occur anywhere
  • in-patient, out-patient healthcare facilities
  • at home
Nature of the problem

• Other glucose test strip technologies are not affected by the presence of non-glucose sugars.

• The unaffected methods are:
  - Glucose oxidase (GOD)
  - Glucose dehydrogenase nicotine adenine dinucleotide (GDH-NAD)
  - Glucose dehydrogenase flavin adenine dinucleotide (GDH-FAD)

• Laboratory-based blood glucose assays do not use GDH-PQQ methodology and are not subject to falsely elevated results from non-glucose sugars
Recommendations

1. Avoid using GDH-PQQ glucose test strips in healthcare facilities.

2. If your facility currently uses GDH-PQQ glucose test strips, NEVER use them on patients:
   - who are receiving interfering products, or
   - from whom or about whom you cannot obtain information regarding concomitant medication use (e.g., patients who are unresponsive or cannot adequately communicate)

Use ONLY laboratory-based glucose assays on these patients.
Recommendations

3. Determine whether patients are receiving interfering products on admission and periodically during their stay at your facility.

4. Educate staff and patients about the potential for falsely elevated glucose results in the presence of certain non-glucose sugars when using GDH-PQQ glucose test strips.

5. Consider using drug interaction alerts in computer order entry systems, patient profiles and charts to alert staff to the potential for falsely elevated glucose results.

6. Periodically verify glucose meter results with laboratory-based glucose assays if you are using GDH-PQQ test strips in patients who are not receiving interfering products.
Recommendations

Interfering products containing non-glucose sugars include:

• Extraneal (icodextrin) peritoneal dialysis solution
• Some Immunoglobulins:
  • Octagam 5%
  • Gamimune N 5%***
  • WinRho SDF Liquid
  • Vaccinia Immune Globulin Intravenous(Human)
  • HepaGamB
• Ocrenica (abatacept)
• Adept adhesion reduction solution (4% icodextrin)
• BEXXAR radioimmunotherapy agent
• Any product containing, or metabolized into maltose, galactose or xylose.

*** Within the U.S., Gamimune N 5% has not been manufactured since December 2005, and no lots are in distribution in the U.S.
PQQ-Related Reports

• Patients treated with insulin doses guided by falsely elevated results

• Test result values generated on GDH-PQQ test strips 3X to 15X higher than lab results. e.g.,:
  - GDH-PQQ result 200 mg/dL, lab result 19 mg/dL
  - GDH-PQQ result 193 mg/dL, lab result 8 mg/dL

• Serious patient injury (hypoglycemia, confusion, neurologic deterioration, severe hypoxia, brain damage, coma) occurred prior to death in some reports
Advice for Patients

http://www.fda.gov/MedicalDevices/Safety/AlertsandNotices/PatientAlerts/ucm177189.htm

- FDA published an Advice for Patients to accompany the PHN Recommendations

Diabetic patients who use any of the listed drug products should:

1. NEVER use GDH-PQQ glucose meters or test strips.

   Instead, use another type of glucose monitoring technology and continue to monitor your blood glucose as instructed by your healthcare provider.

2. Contact your healthcare provider if your results do not reflect the way you feel.

   Determine the type of glucose monitoring technology you are using by looking at the instructions that accompanied your meter or test strips, or at your meter’s box. If you can’t tell what kind of technology your meter and test strips use, ask your healthcare provider or pharmacist to help you find out, and/or contact the manufacturer of your meter and test strips.
Advice for Patients

General recommendations for all diabetic patients:

1. Continue testing your blood glucose as directed by your healthcare provider.

2. Use only test strips specified for your glucose meter.

3. Know the type of glucose monitoring technology you are using.

4. Know that GDH-PQQ meters and strips should NOT be used if you are using an interfering drug product or therapy.

5. Know that GDH-PQQ meters and strips are okay to use if you are not using an interfering drug product or therapy.

6. Know the medications you are taking and keep a current list of your medications. If you do not have a current list of medications, ask your healthcare provider to provide you with a list.
FDA is working with manufacturers to address patient safety problems with GDH-PQQ glucose test strips and will continue to monitor adverse events associated with these products.

In the meantime, FDA encourages all facilities and users to report adverse events associated with glucose meters (http://www.fda.gov/Safety/MedWatch/HowToReport/default.htm)
Awareness

**Problem:**
PQQ interference is known
PQQ interference is predictable
PQQ interference is preventable
but…
Awareness of the Problem = TOO LOW

**Goal:**
Address this issue without unintended harmful consequences
Challenges

• Past communication efforts have not had a lasting effect

• What more can FDA, healthcare providers, and industry do to prevent unnecessary deaths due to known interferences?