FDA Perspective on Glycemic Control and Glucose Meters

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Glycemic Control

- Van den Berghe (2001)
  - Landmark TGC study
  - Mortality benefit in SICU
  - 80 – 110 mg/dL target
  - More hypoglycemia
  - POC blood gas analyzers,

- NICE-SUGAR (2009)
  - Increase in mortality in TGC group
  - No specified testing or patient management method
Glycemic Control

Why the difference?
What to do about it?

• Need accurate blood glucose measurement
  • What technology to use?
  • New technologies coming?

• More information better? (trends)
Blood glucose measurement technologies:

- Point of Care Blood glucose meters/devices
- Continuous/Near continuous measurement
- Next steps / Patient needs
There are multiple technologies currently used to measure blood glucose at the patient bedside:

- Small tabletop instruments (blood gas analyzers, etc.)
- Handheld (non-strip based) meters
- Over the Counter blood glucose meters
Standards for Clearance - POC

Small tabletop instruments - (blood gas analyzers, etc.)
Handheld (non-strip based) meters

- Evaluated like lab instruments (accuracy, precision, etc.)
- Testing performed in POC setting, by POC operators
Standards for Clearance - BGMS

- **Precision**
- **Linearity**
- **Interferences**
  - Endogenous substances (bilirubin, uric acid, etc.)
  - Drugs
  - Hematocrit, etc. etc.

- **Accuracy**
  - ISO 15197 (2003) - accuracy criteria *for Home Use meters*
  - ~100-150 samples tested
  - +/- 20% in samples >75 mg/dL glucose, +/- 15 mg/dL in samples <75 mg/dL glucose

- **Lay User studies**
  - Accuracy in the hands of lay users (within ISO 15197 criteria)-100 subjects
  - Labeling is evaluated for reading level (7th grade)
  - Human factors are considered in the review
BGMS Issues

- Meters assessed/cleared for OTC use – used in hospitals
  - Standards set for home use, no standards for other use
  - Currently no way to distinguish OTC from professional use
  - Automatically waived when OTC (no studies required)

- Studies are not sized to assess true field performance ("outliers" represent millions of tests)

- Little data gathered for hypoglycemic range

- Use in contraindicated populations (e.g., ICU, DKA)

- Use on multiple patients – risk of infection/transmission

- Limited hematocrit range (e.g., 20-60%, 30-55%)
Hospital BGMS – What is needed?

• Studies should be sized to assess true field performance

• The acceptable number of “outliers” should be well-defined and risk-based

• Additional data should be available for the hypoglycemic range

• Precision and accuracy should be evaluated in the intended use population to get realistic performance estimates
  - Use in different hospitalized populations should be assessed (e.g., ICU, DKA)
  - Accurate hematocrit range should reflect hospital population
  - Interference from common drugs/conditions should be well understood

• Meters should be designed/evaluated to reduce risk of infection/transmission
**Intended use:** Continuous (or near-continuous) measurement of blood glucose in hospitalized patients (esp. in ICU) to better enable glycemic control protocols

**Potential benefit:**

- Provide near real time data
- Can give trend information – more useful?
- Alarms can be designed for crisis avoidance
Design Considerations – Hospital CGMs

**Performance**
How low (or high) do these really need to go (quantitatively)?

**Sterility**
- Indwelling – sensor sterility/biocompatibility
- External – system sterility
- Use on multiple patients – risk of infection/transmission (reusable parts?)

**Anticoagulants**
- If needed, how much returned to patient?
- Clinical considerations?

**Calibration solutions**
- If used, contact with patient?
- Regulatory – drug safety potential
Glycemic Control

What is needed to achieve safe and effective glucose measurement that is:

- Accurate
- Reliable
- Economical
- Convenient
- Safe
- etc...?
How accurate do hospital meters need to be?

ISO 15197 (+/- 20% (or +/-15mg/dL below 75mg/dL))
- Standard intended for **home use glucose meters**
- **NOT** accurate enough for hospital use/GC protocols

Recent audience poll at DTS Hospital Diabetes Meeting:
within 10% from reference value
Accuracy

How accurate do hospital meters need to be?

Considerations:

• BGMS and CGM currently not as accurate as lab methods
• What range(s) of glucose concentrations most critical?
• How to assess accuracy in intended use population?
• No result better than wrong result? Acceptable error frequency?
How accurate do hospital meters need to be?

How to analyze the data?

- **Portable meters:**
  - Point accuracy to reference / total error

- **Continuous / Near-continuous:**
  - Point accuracy may not be good enough
  - Other ways to evaluate safety?
  - Clinical measures/parameters?
  - Clinically-based analytical limits?
  - Frequency of clinically significant differences?
How to facilitate development of new devices designed for hospital protocols?

Incremental development?

- If CGM devices not accurate enough yet, would trend information (without quantitative values) be better than nothing?
  - No glucose concentration given (trend graphs only)?
  - Dosing based on lab value, new device informs testing?

- What functionality needed first/most urgently?
Interferences

**Technology:**
- Established technology (e.g., glucose oxidase) – must address known interferences
- New technology – need full and complete assessment of interference potential

**Intended Use Population:**
- Clinical conditions, e.g., DKA
- Blood gases/acidity
- Drugs
- Relevant hematocrit range
- Altitude

**Endogenous substances:**
- Bilirubin
- Hemoglobin
- Albumin
- Immune system components, etc.
Clinical Evaluation

Safe Trial Design

First step = Feasibility data (for CGMs)
- Animal studies
- Healthy diabetics – get wider blood glucose range
- Evaluate adverse events (infections, clots, etc)

Next – Study in ICU/hospital population

Evaluate:
- Accuracy / Total Error in intended use population
  - Challenge = enough data in hypoglycemic range?
- Interferences
- Calibration frequency
- Measurement stability
- Failure rate
- Human factors
- Use in POC setting
Summary

• More accurate, more convenient devices needed to enable effective glycemic control protocols

• May need incremental improvements over time to enable faster access

• May need new approaches to data evaluation to assess safety and effectiveness of these devices
Questions?

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