Making Sense of Numbers and Ratios

The Laboratory’s Role in Pain Management Result Interpretation

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AACC Mass Spectrometry in the Clinical Laboratory

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Contact Information

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• ARUP Institute for Clinical and Experimental Pathology
• University of Utah
  – Department of Pathology
Objectives

• Explain the differences between quantitative and qualitative testing

• Differentiate between compound identification, quantitation and confirmation

• Compare the screen with reflex approach with targeted screening for pain management testing

• Judge the utility of urine drug testing for compliance in the pain management setting
The Clinical Goal for Testing

Pain Management Context

- Minimizing risk to maximize patient benefit
  - Monitoring Compliance
  - Detecting illicit use

<table>
<thead>
<tr>
<th>Risk Category</th>
<th>Recommended Frequency of Testing (per year) - UDT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low</td>
<td>≥ 1</td>
</tr>
<tr>
<td>Moderate</td>
<td>≥ 2</td>
</tr>
<tr>
<td>High</td>
<td>≥ 3 or 4</td>
</tr>
<tr>
<td>Aberrant Behavior</td>
<td>At visit</td>
</tr>
</tbody>
</table>
The Laboratory’s Goal for Testing

Pain Management Context

• High quality testing
  – AMRs; Cross-reactivity (IA); TAT; QC; cutoffs; etc.
• Well-designed testing menu
  – Metabolites; Free vs. Conjugated vs. Total
• Easy to interpret reports
  – Data overload; Physicians are not pharmacologists
• Development of a test that actually gets ordered
  – Welcome to clinical mass spectrometry!
Outline

• Quantitative and qualitative testing

• Compound identification, quantitation and confirmation

• Screen with reflex versus targeted

• Urine drug testing for compliance in the pain management setting
Positivity Rates: Clinical vs. Workplace Testing

Clinical Testing
• Nov – Dec 2011
• 77% positivity rate
• < 5% false positives

Workplace Testing
• Typical estimates
  – < 5% positivity rate
Screen w/ Reflex:
Pain Management Reality

Sample Collected

Screen w/ reflex ordered

Positive
Mass Spec confirmation
Positive
Report out Concentration
Negative
Report out Negative

Negative
Stop
Report out Negative
# Traditional Screening Assay Design

### SAMHSA Cutoffs
- Marijuana – 50 ng/mL
- Cocaine – 150 ng/mL
- Opiates – 2000 ng/mL
- 6-AM – 10 ng/mL
- PCP – 25 ng/mL
- AMP/MAMP – 500 ng/mL
- MDMA – 500 ng/mL

### Factors not considered
- Appropriate cutoffs
- Drugs of interest
- TAT
- Quantitative vs. Qualitative results
- Population
**Negative Screen Result:**

**Poor Population Resolution**

**High Risk Patient**

<table>
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<th>Result</th>
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Positive Screen Result: Poor Analyte Resolution

- **Rx:**
  - Hydrocodone
  - Oxycodone

- **Interpretations**
  - Compliant?
  - Diversion?
  - Heroin?

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Screen with Reflex Summary

- One-size-fits-all solution that doesn’t fit
- Delayed TAT
- Initial screen result that is often useless
- Unnecessary confirmation testing
Outline

• Quantitative and qualitative testing

• Compound identification, quantitation and confirmation

• Screen with reflex versus targeted

• Urine drug testing for compliance in the pain management setting
Confirmation Testing

Yes, no, maybe?

- True confirmation testing means that the identity of a drug has been determined by two different methods
  - e.g., an immunoassay “screen” and then a mass spectrometry “confirm”
- For routine clinical testing, absolute identification is needed – *but not usually by two different methods!*
Confirmation Testing

When?

- Non-specific screening method used
  - e.g., immunoassay for opiates

Interpretation:
- Morphine only?
- 6-AM?
- All of them?
- None of them?

“You need this reflexed to confirmation.”
A Sensitive, Qualitative (Targeted) Screen by LC-TOF/MS

- Broad range of compounds
- Adequate sensitivity
  - on par with current confirmatory methods
- Parent drug and metabolites to aid interpretation
- TAT less than classic screen w/ reflex
- One and done (no need for confirmation)
Confirmation Testing

*With LC-TOF this is not required!!*

• Drugs are individually identified
  – Absolute identification with the *first* test

**Interpretation:**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>Morphine</td>
<td>NOT FOUND</td>
</tr>
<tr>
<td>6-AM</td>
<td>NOT FOUND</td>
</tr>
<tr>
<td>Hydrocodone</td>
<td>PRESENT</td>
</tr>
<tr>
<td>Codeine</td>
<td>NOT FOUND</td>
</tr>
</tbody>
</table>

“Positive for hydrocodone. No need for further testing.”
Benefits of an LC-TOF/MS Targeted Screen

- Sensitivity & Specificity on par with classic confirmatory methods
- Individual compound identification
- Elimination of cross-reactivity complications
- Drug/metabolite pairs for interpretations
- Drug abuse testing conducted concurrently for high risk populations
- Relatively easy integration of new targets
- “Reflex to Quantitation” still possible when needed
Outline

• Quantitative and qualitative testing

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Quantitative vs. Qualitative

When? Why?

• Will the amount of drug detected in the urine change management?
  – Remember to take urine concentration into account!
  – Quantitative value adds little when testing for compliance

Prescriptions:
Klonopin
Lortab

LC-TOF (Qualitative):
Clonazepam  
7-aminoclonazepam  
Hydrocodone

LC-MS/MS (Quantitative):
Clonazepam  64 ng/mL
7-aminoclonazepam  820 ng/mL
Hydrocodone  120 ng/mL

Q: Would the interpretation differ if clonazepam was 35 ng/mL? 
A: Not likely.

Q: What if hydrocodone was 250 ng/mL? 
A: Both values indicate compliance.
Quantitative vs. Qualitative


• Quantitation can help – sometimes
  – long $t_{1/2}$ for marijuana metabolites in a patient claiming to have abstained but still positive
    • Result 1 = 826 ng/mL (creatinine of 86 mg/dL)
    • Result 2 = 278 ng/mL (creatinine of 92 mg/dL)
    • Trend is downward = good!

• **Quantitation is still available when needed**

Q: Can’t I extrapolate back from a urine concentration and predict compliance with dose?
A: Unfortunately this has not proven to be reliable with routine testing in large and diverse populations.
Benefits of a Qualitative Assay

- Simpler testing strategy for multi-analyte tests
  - 67 drugs with 67 calibration curves??
- Reduced costs
- Addition of new analytes can be rapid
Limitations of a Qualitative Assay

- Quantitative results can be useful
- Accurate ratios are lost
  - Methamp/amp
  - Pharmaceutical tolerances for impurities
- Makes many physicians nervous
- Platform can cause reimbursement challenges
Quant vs. Qual Summary

- Absolute identification is required and can be done qualitatively
- Quantitation can be useful in select scenarios
- Quantitation in urine will not allow for partial vs. full compliance in the general population
Outline

• Quantitative and qualitative testing

• Compound identification, quantitation and confirmation

• Screen with reflex versus targeted

• Urine drug testing for compliance in the pain management setting
Interpreting Results

Easier said than done…

**Dry Lab Challenge**

**Case Summary and Interpretation**

A 41-year-old male with chronic low back pain came for a follow-up visit. The patient has a known right L5-S1 disc extrusion osteophyte complex and is being prescribed *Roxicet* (oxycodone + acetaminophen) and *Percocet* (oxycodone + acetaminophen).

**Medication List**

- LYRICA 150 mg p.o. b.i.d
- ROXICET/PERCOCET 5 per day p.r.n. pain
- VIAGRA p.r.n.

**Test Results**

<table>
<thead>
<tr>
<th>Screen Results</th>
<th>Confirmation Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Opiate screen NEGATIVE</td>
<td>Oxycode 2500 ng/mL, oxydormone 1500 ng/mL</td>
</tr>
<tr>
<td>Amphetamine screen POSITIVE</td>
<td>Amphetamine 2500 ng/mL</td>
</tr>
<tr>
<td>Benzo screen NEGATIVE</td>
<td>Lorazepam 4000 ng/mL</td>
</tr>
</tbody>
</table>

**Interpretation (Educational)**

<table>
<thead>
<tr>
<th>Result</th>
<th>No. of Respondents</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Toxicology results are inconsistent with prescribed medication</td>
<td>49</td>
<td>59.8</td>
</tr>
<tr>
<td>Toxicology results are consistent with prescribed medication</td>
<td>33</td>
<td>40.2</td>
</tr>
<tr>
<td>Additional prescription drugs present</td>
<td>74</td>
<td>90.2</td>
</tr>
<tr>
<td>Additional prescription drugs absent</td>
<td>8</td>
<td>9.8</td>
</tr>
<tr>
<td>Illicit drugs present</td>
<td>40</td>
<td>48.2</td>
</tr>
<tr>
<td>Illicit drugs absent</td>
<td>43</td>
<td>51.8</td>
</tr>
</tbody>
</table>
Physicians make mistakes too

*Common calls*

- “My patient is taking Klonopin but repeatedly screens negative for benzos.”
  - 7-aminoclonazepam vs. clonazepam
- “My patient is taking oxycodone but is negative for opioids. Is he diverting?”
  - Opiate IA vs. Oxycodone IA
- “My patient is taking Valium but is positive for 4 other drugs.”
  - Benzo metabolism
How can the lab help physicians?

• Open dialogue

• Tests designed to meet the needs of the population served

• Inclusion of metabolites and conjugates

• Enhanced reports – if you dare!
How can the lab help itself?

• Inclusion of metabolites
  – Enhances confidence in identification
    • Oxycodone
    • Oxycodone, oxymorphone, noroxycodone, noroxymorphone
  – Allow for higher LOQs

• Staff education
  – Instrumentation, metabolite patterns, interferences
  – Continued education
Key Points

- Rethink the screen with reflex paradigm
- Compound identification is key – quantitation is a separate aspect
- Qualitative results are often all that is needed
- Design testing with both physicians AND the staff in mind
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