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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  – Jess Becker

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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>&gt; 1</td>
</tr>
<tr>
<td>Moderate</td>
<td>&gt; 2</td>
</tr>
<tr>
<td>High</td>
<td>&gt; 3 or 4</td>
</tr>
<tr>
<td>Aberrant Behavior</td>
<td>All 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

Screen w/ Reflex Workflow
Screen w/ Reflex: Expectations

Sample Collected

Screen w/ reflex ordered

Positive

Mass Spec confirmation

Negative

Positive

Stop

Negative

Report out Negative

Report out Negative

Report out Concentration

Report out Negative

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

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Report out Negative

DATA: Dr. Gwendolyn McMillin; IMAGES: dietchange.com; confirmbiosciences.com
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

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**Negative Screen Result:**
**Poor Population Resolution**

<table>
<thead>
<tr>
<th>High Risk Patient</th>
<th>Pain Management Patient</th>
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<tr>
<td>AMPHETAMINE</td>
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<tr>
<td>BARBITURATES</td>
<td>BARBITURATES</td>
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<tr>
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<td>BENZODIAZEPINES</td>
</tr>
<tr>
<td>COCAINE</td>
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<tr>
<td>OPIATES</td>
<td>OPIATES</td>
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<tr>
<td>OXYCODONE</td>
<td>OXYCODONE</td>
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<tr>
<td>PCP</td>
<td>PCP</td>
</tr>
<tr>
<td>PROPOXYPHENE</td>
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<td>THC</td>
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Positive Screen Result: Poor Analyte Resolution

- Rx:
  - Hydrocodone
  - Oxycodone
- Interpretations
  - Compliant?
  - Diversion?
  - Heroin?

<table>
<thead>
<tr>
<th>Analyte</th>
<th>Result</th>
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</thead>
<tbody>
<tr>
<td>AMPHETAMINE</td>
<td>NEGATIVE</td>
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<tr>
<td>BARBITURATES</td>
<td>NEGATIVE</td>
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<tr>
<td>BENZODIAZEPINES</td>
<td>NEGATIVE</td>
</tr>
<tr>
<td>COCAINE</td>
<td>NEGATIVE</td>
</tr>
<tr>
<td>DRUGS</td>
<td>POSITIVE</td>
</tr>
<tr>
<td>OPIATES</td>
<td>POSITIVE</td>
</tr>
<tr>
<td>OXOCODONE</td>
<td>POSITIVE</td>
</tr>
<tr>
<td>PCP</td>
<td>NEGATIVE</td>
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<tr>
<td>PROPIONYPHENE</td>
<td>NEGATIVE</td>
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<tr>
<td>THC</td>
<td>NEGATIVE</td>
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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

<table>
<thead>
<tr>
<th>Interpretation:</th>
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<tbody>
<tr>
<td>Morphin</td>
</tr>
<tr>
<td>6-AM</td>
</tr>
<tr>
<td>Hydrocodone</td>
</tr>
<tr>
<td>Codeine</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
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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

<table>
<thead>
<tr>
<th>Prescription</th>
<th>LC-TOF (Qualitative):</th>
<th>LC-MS/MS (Quantitative):</th>
</tr>
</thead>
<tbody>
<tr>
<td>Klonopin</td>
<td>Clonazepam PRESENT</td>
<td>Clonazepam 64 ng/mL</td>
</tr>
<tr>
<td>Lortab</td>
<td>7-amino-clonazepam PRESENT</td>
<td>7-amino-clonazepam 820 ng/mL</td>
</tr>
<tr>
<td></td>
<td>Hydrocodone PRESENT</td>
<td>Hydrocodone 120 ng/mL</td>
</tr>
</tbody>
</table>

LC-TOF (Qualitative): Clonazepam PRESENT 7-amino-clonazepam PRESENT Hydrocodone PRESENT

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 t1/2 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
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Interpreting Results

Easier said than done...

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
    - Oxymorphone, noroxycodone, noroxymorphone
  - Allow for higher LOQs
- Staff education
  - Instrumentation, metabolite patterns, interferences
  - Continued education

Key Points

- Rethink the screen with reflex paradigm
- Correlation is a self
- Quality led
- Design testing with both physicians AND the staff in mind
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