Trends and Challenges in Therapeutic Drug Monitoring: Is LC/MS the Solution?

Paul J. Jannetto, Ph.D., DABCC, FACB, MT(ASCP)
Mayo Clinic
Director, Toxicology & Drug Monitoring Laboratory
Director, Metals Laboratory

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• None

Objectives
After this session, the attendee will be able to:
• Summarize some of the technical considerations, logistics, clinical issues, financial and regulatory requirements that are important when determining if TDM tests can or should be performed using mass spectrometry.
• Illustrate the advantages and disadvantages of using LC/MS/MS for TDM tests in the clinical laboratory.
• Assess future opportunities for TDM testing using mass spectrometry and list current clinical applications.
Outline

Trends and Challenges in TDM: Is LC/MS the Solution?

Important Factors to Consider:

1) Analytical/Technical Issues
   A. Capacity for Growth/Expandable Test Menu
   B. Required Method Performance Criteria
      • Specificity
      • Sensitivity
   C. Logistics
      • Labor/Staffing
      • Availability of Standards, QC, Proficiency Testing Material

2) Clinical/Financial Issues
   A. TAT (Clinical need vs. Market driven)
   B. Cost/Reimbursement
   C. Legal/Regulatory issues

3) Clinical Examples

Why is TDM still important?

• Drug Utilization:
  • >3.7 billion prescriptions filled in US 2011
  • From 1999 to 2009, # prescriptions increased 39%, w/ only 9% pop. growth
  • >10% Americans use 5 or more drugs

• Indications:
  • Personalization of dosage
  • Avoidance/detection of toxicity
  • Investigation of non-response
  • Identification of non-compliance

Traditional TDM Targets
w/ FDA approved Immunoassays

• Anticoagulants:
  • Phenprocoumon
  • Phenindione
  • Phenprocoumon-like agents
  • Novel anticoagulants

• Cardioactive drugs:
  • Diltiazem
  • Verapamil
  • Antagonists

• Antibiotics:
  • Amikacin
  • Gentamicin
  • Tobramycin
  • Vancomycin

• Anti-asthmatic:
  • Theophylline
  • Caffeine

• Anti-depressants:
  • Lithium

• Immunosuppressants:
  • Cyclosporine
  • Tacrolimus
  • Sirolimus

• Anti-neoplastic drugs:
  • Methotrexate

• Analgesics:
  • Acetaminophen
  • Salicylate
TDM Trends:
The Move to LC/MS or LC/MS/MS

• Analytical/Technical Considerations:
  1. Future growth and ability to measure evolving targets/new medications
     • Example: Anti-epileptic drugs (AEDs)

<table>
<thead>
<tr>
<th>Generation</th>
<th>Drug</th>
<th>Year FDA approved</th>
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<tbody>
<tr>
<td>First</td>
<td>Phenobarbital</td>
<td>1939</td>
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<tr>
<td></td>
<td>Phenytoin</td>
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<tr>
<td></td>
<td>Carbamazepine</td>
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<tr>
<td></td>
<td>Valproate</td>
<td></td>
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<tr>
<td>Second</td>
<td>Lamotrigine</td>
<td>1994-2005</td>
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<tr>
<td></td>
<td>Topiramate</td>
<td></td>
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<tr>
<td></td>
<td>Oxcarbazepine</td>
<td></td>
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<tr>
<td>Third</td>
<td>Gabapentin</td>
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<tr>
<td></td>
<td>Zonisamide</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Lacosamide</td>
<td>2008-present</td>
</tr>
<tr>
<td></td>
<td>Eslicarbazepine</td>
<td>(Rogiclar)</td>
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</tbody>
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Clinical Example #1: Lacosamide

Lacosamide (3rd Generation AED)

• FDA approved for adjunctive therapy for partial seizures
• MOA: enhances the slow inactivation of voltage-gated Na+ channels

• Pharmacokinetic parameters:
  • 100% Bioavailable
  • Tmax: 1-2 hours
  • Elimination half-life: 12-16 hours
  • Protein binding: 90%
  • Minimal drug-drug interaction

• TDM:
  • CNS toxicity associated w/ high drug concentrations
  • Reference interval: 10-20 mg/L
  • Indications for TDM:
    • Hepatic or renal disease
    • Overdose
    • Compliance

Lacosamide continued

• Analytical /Technical Considerations:
  1. Clinical utility and need:
     • >250 requests/month
  2. Instrumentation:
     • No FDA-approved immunoassay available
     • Published HPLC and LC/MS/MS methods
  3. Logistics:
     • Staffing/Instrumentation capacity
     • Accessible materials:
       • Standards: Cerilliant
       • QC: Utah AED II
       • PT: LGC Standards Proficiency Testing

Lacosamide continued

• Clinical/Financial Considerations:
  1. TAT:
     • 2-4 days (send-out)
  2. Cost:
     • Send-out: >$250,000/year
     • In-house: >80% reduction in cost vs. send-out
  3. Legal/Regulatory Issues
     • Laboratory Developed Test (CLIA requirements)
     • No patent issues on TDM method or correlation of blood/serum levels and dosage

TDM Trends:
The Move to LC/MS or LC/MS/MS

• Analytical/Technical Considerations:
  1. Future growth and ability to measure evolving targets/new medications
     • Example: Anti-epileptic drugs (AEDs)
  2. Method Performance Requirements:
     • Example:
       • Specificity (Cross-reactivity) for IA vs. MS
       • Functional Sensitivity (LOQ)
Clinical Example #2: Methotrexate TDM Issues

Methotrexate TDM Issues
- Methotrexate is used to treat certain types of cancer of the breast, skin, head and neck, or lung. It is also used to treat severe psoriasis and rheumatoid arthritis
- Jan 2012 FDA approves Voraxaze
  - VORAXAZE (glucarpidase) is indicated for the treatment of toxic plasma methotrexate concentrations (>1 µM/L) in patients with delayed clearance due to impaired renal function.
  - Voraxaze Package Insert:
    5.3 WARNINGS AND PRECAUTIONS:
    Monitoring Methotrexate Concentration/Interference with Assay
    Methotrexate concentrations within 48 hours following administration of VORAXAZE can only be reliably measured by a chromatographic method. DAMPA (4-deoxy-4-formino-N-methylphthalic acid) is an inactive metabolite of methotrexate resulting from treatment with VORAXAZE. DAMPA interferes with the measurement of methotrexate concentration using immunoassays resulting in an erroneous measurement which overestimates the methotrexate concentration. Due to the long half-life of DAMPA (approximately 9 hours), measurement of methotrexate using immunoassays is unreliable for samples collected within 48 hours following VORAXAZE administration [see Clinical Pharmacology (12.3)].
    - Other issues with Methotrexate Immunoassay techniques:
      - Low-end precision (0.05 µM/L)

TDM Trends: The Move to LC/MS or LC/MS/MS
- Analytical/Technical Considerations:
  1. Future growth and ability to measure evolving targets/new medications
    - Example: Anti-epileptic drugs (AEDs)
  2. Method Performance Requirements:
    - Example:
      - Specificity (Cross-reactivity) for IA
      - Functional Sensitivity (LOQ)
  3. Logistics:
    - Equipment/Labor/Staffing
    - Availability of Standards, QC, PT material
Availability of Standards/QC Material

1. Source:
   • Commercial vs. Homemade

<table>
<thead>
<tr>
<th>Commercial vs. Homemade</th>
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<tr>
<td>Uniform, consistent</td>
<td>Some variability</td>
</tr>
<tr>
<td>More expensive</td>
<td>More affordable</td>
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Clinical Example #3: Tacrolimus

Instrumentation alone (MS) doesn’t solve everything

• Problem: Tacrolimus, and other immunosuppressants, are measured by a variety of LC/MS and immunoassay-based methods which are all independently calibrated without traceability to an accepted reference LC/MS method or standard tacrolimus reference material.
Misconceptions about Mass Spectrometry

- "Mass spectrometry is always the reference method/gold standard"
- "Mass spectrometry will always give the right answers"
- "Mass spectrometry is accurate / precise"

Mass spectrometry can be all of these, but ONLY if tests are carefully developed, validated, calibrated, QC’d, and have appropriate surveillance.

Isn’t LC/MS the GOLD Standard?

The Move to LC/MS or LC/MS/MS, continued

- Clinical/Financial considerations:
  1. Clinical demand/utility
     - Examples:
       - Busulfan
       - Lenalidomide
       - Lacosamide
       - Dabigatran
       - Leflunomide
       - Posaconazole
       - Thiopurine Metabolites
       - Others
Clinical Example #4: Busulfan

New Formulations, Dosing Regimens, or Guidelines

- Busulfan:
  - Alkylating agent used in high doses for bone marrow ablation prior to allogeneic hematopoietic stem cell transplantation (HSCT) for Chronic Myelogenous Leukemia (CML)
  - Narrow therapeutic window:
    - High: Toxicity (Hepatic veno-occlusive disease)
    - Low: Increased incidence of graft rejection/relapse
  - Pharmacokinetic testing for IV dosing
Typical Busulfan Curve

- Determines drug exposure (Area Under the Curve AUC)
- Calculates drug clearance and dose adjustment
- Proven Utility:
  - Improved clinical outcomes (pediatric HSCT recipients)
  - Reduced toxicity
- No FDA-approved Immunoassay; Typically use LC/MS or GC/MS

The Move to LC/MS or LC/MS/MS, continued

- Clinical/Financial considerations:
  1. Clinical demand/utility
  2. TAT needs
    - Market driven vs. Clinical need

TAT and the Move to LC/MS

- Potential Limitations to Using LC/MS:
  - Batch analysis vs. Random Access
  - May require expensive/time-consuming sample preparation
  - Throughput

- Solutions/Trends to Improve Throughput:
  - UPLC (Ultra Performance Liquid Chromatography)
  - RapidFire
  - LDTD (Laser Diode Thermal Desorption)
**Option #1**
Conversion from HPLC to UPLC to Increase Throughput

- Why convert HPLC to UPLC?
  - Faster TAT (Cycle time)
  - Higher chromatographic resolution
  - Increased sensitivity
  - Lower injection volume (sample volume)
  - Less reagent/solvent
  - Same robustness as HPLC
  - Overall, increased capacity

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**Example of an HPLC Assay Converted to UPLC**

11 x’s the throughput
1/7th reagent volume

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**A UPLC-MS/MS Method for Analyzing Eight Drugs**

- Objective:
  - To improve the efficiency and quality of a HPLC-MS/MS method for eight drugs (Cocaine, BE, Coca-ethylene, Diphenhydramine, Methadone, EDDP, Chlorpheniramine, and Dextromethorphan)
- Benefits of converting to a UPLC-MS/MS method:
  - Shorter run time: Saved 4 hours per batch of 30 samples.
  - Better separation of components especially in forensic samples.
  - Less matrix effects which improves the accuracy of results as compared with HPLC-MS/MS.
  - Shorter dwell time in the UPLC-MS/MS method allows for more points across the peaks of the chromatograms ensuring better chromatographic results

By Tim Dahn, Marcie Larson, and Andrea Tarell, Ph.D./DABCC
Option #2
Using RapidFire® to Improve Throughput

http://www.youtube.com/watch?v=hJSm-p8_No4

Option #3
Using LDTD to Improve Throughput

http://www.youtube.com/watch?v=dNnfrfNyeZo

The Move to LC/MS or LC/MS/MS, continued

• Clinical/Financial considerations:
  1. Clinical demand/utility
  2. TAT needs
     • Market driven vs. Clinical need
  3. Cost/Reimbursement
Cost Savings/ROI
Using LC/MS/MS to Bring Tests In-Lab

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<tbody>
<tr>
<td>Levetiracetam (Keppra)</td>
<td>250</td>
<td>$35.00</td>
<td>$8,750.00</td>
<td>$5.00</td>
<td>$1,250.00</td>
<td>$7,500.00</td>
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The Move to LC/MS or LC/MS/MS, continued

• Clinical/Financial considerations:
  1. Clinical demand/utility
  2. TAT needs
     • Market driven vs. Clinical need
  3. Cost/Reimbursement
  4. Legal/Regulatory issues

Legal/Regulatory Issues

• Important to check for any Intellectual Property or Patent issues on TDM method or correlation of blood/serum levels and dosage.
• Understand how to satisfy CLIA requirements for validating LDTs
  • Sensitivity
  • Specificity
  • Carry-over
  • Accuracy
  • Precision
  • Etc……..
Why Switch to LC/MS for TDM?

Advantages
• Sensitivity
• Specificity
• Open/Expandable test menu
• Long-term cost savings
• Shorter TAT vs. Send-Out

Disadvantages
• High Complexity
• LDT regulations
• R&D tech/expertise
• Initial cost (need to buy 2)
• Staffing
• Batch tests

Summary
• LC/MS or LC/MS/MS is a viable option for TDM:

Trends:
• Labs continue to switch to LC/MS to bring new TDM assays in-house
  • Cost-effective
  • Better TAT

Challenges:
• Regulatory: New LDT regulations
• Personnel/Expertise

Questions & Discussion