Overcoming Barriers to TDM: Information and the TDM Renaissance

How to integrate PK intelligence with routine clinical data

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Outline

- Importance of the right information for proper interpretation
- ‘Numbers only’ TDM is not effective
- Does the evidence support TDM outcomes?
- UNC-CERT initiative to develop Model TDM services in Pediatrics
- Our experience at Cincinnati Children’s

"Therapeutic Drug Monitoring is the measurement made in the laboratory of a parameter which, with appropriate interpretation, will directly influence prescribing procedures"  
IFCC/IA-TDMCT Joint Committee 1993

How should we do TDM?

- Not to check numbers or “Therapeutic Ranges”
- To describe and understand Drug PK/PD Behavior
- Collect informative data to use as Bayesian priors for designing model-based, individualized dosing regimens
- Change passive “Monitoring” to active “Management”

Phenytoin model-based interpretation

- Epilepsy pt (F, 33yr) 300 mg/kg/day
- Start iv -> po
- 10mg/L = "Therapeutic"
- Single numbers do not give the whole picture!

Does the evidence support TDM outcomes

- Methotrexate
- Aminoglycosides
- Other

Running a centralized TDM service

Specific Aims TDM Study
- Implementation of goal-oriented model-based dosing
- Pro-Active guidance vs. non-guided TDM
- Outcomes: clinical and economical benefits

Demographic data patients

<table>
<thead>
<tr>
<th>Variable</th>
<th>Intervention</th>
<th>Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total patients</td>
<td>207</td>
<td>225</td>
</tr>
<tr>
<td>Included patients</td>
<td>105</td>
<td>127</td>
</tr>
<tr>
<td>Infection on admission</td>
<td>48 (46%)</td>
<td>62 (49%)</td>
</tr>
<tr>
<td>Male / Female</td>
<td>50/55</td>
<td>67/60</td>
</tr>
<tr>
<td>Age (yr)</td>
<td>67.5 (± 17.5)</td>
<td>67.0 (± 17.2)</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>69.1 (± 13.2)</td>
<td>69.8 (± 17.5)</td>
</tr>
</tbody>
</table>

Distribution of Peaks & Troughs

Active Therapeutic Monitoring benefits patient outcome
Store and analyze data in our Heads, on Paper or in Computers
BUT – where’s the link?

UNC-CERT Project
Development of Model TDM services

- Establish policies to collect, interpret and report drug concentrations using a secure web-based data collection tool
- Develop educational materials and methods to teach proper TDM techniques in pediatrics
- Compare outcomes for no TDM, “numbers only” or consultation by the “model” TDM service

‘Eye Sis’: Integrating Clinical Information System (ICIS)
- COE – Clinical order Entry
- NetAccess - Lab Results
- Clinical Documentation – Patient Charting
- Med/IV Charting – electronic Medication Administration Record
- PACS – Picture Archiving and Communication System
- Toward single portal for all platforms

Data base structure at CCHMC

Development of Web-based tools

Web-based Liver Portal with Immunosuppressant TDM data
Over-use and over-interpretation of drug levels

- Fixed monitoring strategies often lead to bad decision making
- Treating the level rather than treating the patient
- No pharmacokinetic interpretation involved

Liver Transplant - case history

- 10 yr old African American boy
- Transplant 1998
- FK levels <1.5 µg/L at 4 mg bid
- Fluctuating levels between 1.5-5 µg/L
Q: Compliance – high clearance – other?

Liver Transplant - PK Evaluation

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PK model based interpretation

Samples and dosing information was collected on 15 patients (age 1-18 yr)
Most (10/15) were prescribed nelfinavir with widely varying dose: range 33 to 146 mg/Kg/day.
Measured blood levels in single samples were: none detected 9.9 µg/ml.
24% (6/25) of pediatric samples were “none detected” vs. 33% of adult samples (96/293)
Four patients with initially ND levels had multiple levels (one pre-dose and two post-dose samples) drawn over time

PI monitoring Columbus Children’s

Watson et al. Ther Drug Monit 2003 in press
Nelfinavir PK Model-based Interpretation

- Child (4 yr) receiving Nefavir 112 mg/Kg/day
- Trough "none detectable"
- Dose per G-tube – good compliance
- Medication being flushed with water - changed to formula
- On re-testing strain resistant to nefinavir

van Heeswijk et al. TDM 2002;24(4):487-91

Usefulness of Population PK models
Example: Nelfinavir

Conclusions...

- TDM informatics is still in its infancy
- Passive monitoring should be replaced by active Management
- Need better tools to link all clinical data to drug behavior (PK) data
- Need to develop tools to link patient info with Population PK, Pharmacogenetics (PG), Adverse Events and Clinical Effects (PD) data