From drug level to personalized dosing and treatment

Dr. Nynke Jager, hospital pharmacist-clinical pharmacologist
KKGT Division
Short introduction – Nynke Jager

Hospital Pharmacist – Clinical Pharmacologist

Focus on antimicrobial treatment and laboratory/TDM

Board member KKGT, coordinator QA scheme antibiotic drugs

Kwaliteitsbewaking Klinische Geneesmiddelanalyse en Toxicologie = Quality Assessment of Clinical Drug Concentration Analysis and Toxicology
Disclosure

- The speaker has a financial relationship with Pfizer (consultancy)
Total testing process

Traditional proficiency testing
From drug level to personalized dosing
Do you provide a clinical case with the analytical sample?

A. No, only the analytical phase is covered

B. Yes, a clinical case (post-analytical phase) is provided

C. Yes, a clinical case requiring an answer for both pre-analytical (what analysis should be done) and post-analytical phase is provided
Aim KKGT/ SKML

Provide a tool for quality improvement in the analysis and interpretation of drug concentrations: Laboratories/hospitals can assess the performance of their TDM process and identify where the process needs to be improved.

SKML and KKGT stand for uniform interpretation of medical laboratory diagnostics.
Pre-analytical phase

Can the clinical question be answered by measuring the drug concentration?

Radboudumc
Therapeutic drug monitoring
Individualize dosing regimens based on measured drug concentrations, to optimize exposure
Participoll – What are prerequisites for useful TDM?

A. Drug effect can be easily monitored, for example blood pressure
B. Treatment will be stopped within a few days
C. There is a wide interpatient variability in exposure
D. There is a defined relation between exposure and effect
E. A and B
F. C and D
G. A, B, C and D
Participoll - answer
A. Drug effect can be easily monitored, for example blood pressure
B. Treatment will be stopped within a few days
C. There is a wide interpatient variability in exposure
D. There is a defined relation between exposure and effect
Interpatient variability
Variability in exposure

Cefotaxime Dosing Optimization in Neonates

100 neonates: cefotaxime 50 mg/kg

Licensed dosing regimens are for populations, not individuals

Leroux et al, Antimicrobial Agents and Chemotherapy 2016
Therapeutic window (relation exposure – effect)
From drug level to personalized dosing
Therapeutic drug monitoring
Proficiency testing in practice - KKGT

- Half of the samples is accompanied by a clinical case

  TDM and toxicology

- Developed by an expert in the field (‘vakinhoudelijk deskundige’)

- Sent to all participating laboratories

- Participants receive a score (0, 1 or 2 points), and the explanation of the case by the expert in the field.
Toxicology

Pre-analytical phase: which test(s) will you perform?

ANAMNESE
U wordt om 22:00 uur gebeld door de dienstzitting chirurg. Er zijn zojuist 52 bottenjes met onbekende stof (niet allemaal intact) chirurgisch uit het maagdarmkanaal van een patiënt verwijderd. Graag toxicologisch onderzoek.

Achtergrond:
De 28-jarige toets werd s'ochtend om 06:00 uur door de ambulance naar de SEH gebracht na een ongeluk. Later kon de patiënt een flesje XTC hebben gebruikt. Thuismedication: Ehanine 1id70mg.

Op de SEH werd een beeld gezien van opwindingsgedrag met toename van de hartslag, hypertensie, en een milde hyperthermie waarvoor diazepam en onvoldoende effect. Toxineen in urine was positief op AMP, METH, BENZ. Patiënt is overgeslagen naar een psychiater in kamer.

Om 18:30 welden door de verbalisatie gecocementeerd bij THCA waarneembaar succesvol is gereanimeerd. Op de röntgenfoto's waren bottenjes in het maagdarmkanaal zichtbaar waarna met spoed is overgegaan tot chirurgische interventie.

Graag toxicologisch onderzoek en uw advies voor behandeling.

<table>
<thead>
<tr>
<th>Component</th>
<th>Identiteit</th>
<th>Kwantiteit</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>+/-</td>
<td>code</td>
</tr>
<tr>
<td>2.</td>
<td></td>
<td>waarden</td>
</tr>
<tr>
<td>3.</td>
<td></td>
<td>eenheid</td>
</tr>
<tr>
<td>4.</td>
<td></td>
<td>code</td>
</tr>
<tr>
<td>5.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>6.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>7.</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Analytical phase: Results

<table>
<thead>
<tr>
<th>CODE</th>
<th>= AAS/AES</th>
<th>2 = EMIT</th>
<th>3 = FPIA</th>
<th>4 = GC</th>
<th>5 = GCMS</th>
</tr>
</thead>
<tbody>
<tr>
<td>6 = HPLC</td>
<td>7 = KMS</td>
<td>8 = LC/MS/MS</td>
<td>9 = SPECTR</td>
<td>10</td>
<td>10</td>
</tr>
</tbody>
</table>
Clinical cases – example TDM

Post analytical phase; from drug level to personalized dosing
Opportunities for participants

• Assess capability of clinicians to correctly interpret a measured concentration (i.e. performance of the process)
  • Additional training necessary?
  • Local protocols up to date?

• Discuss clinical cases within team of clinicians: learn from each other

• Important part of the training for hospital pharmacists (and other clinicians?)
Opportunities for SKML

Increase the impact of the proficiency testing by including pre- and post analytical processes.
Take home message

• Accurate measurement of concentrations is only a small part of the total testing process

• Participants: Clinical cases accompanying test samples are of value for assessment of a larger part of the testing process, i.e. daily clinical practice

• SKML: Including clinical cases will improve the impact and usefulness of proficiency testing
Questions?
TDM - criteria

• The patient is on the best drug
• The pharmacological response is not directly measurable
• Wide interpatient variability in pharmacokinetics
• The drug has a narrow therapeutic window (related to variability)
• Relationship between drug concentration and pharmacological response
• The drug can be measured in the desired biological matrix
• The duration of therapy is long enough for the patient to benefit from TDM
• TDM results influence the decision-making process

Het doel van de KKGT (Kwaliteitsbewaking Klinische Geneesmiddelanalyse en Toxicologie) is het bevorderen van de kwaliteit van de klinische geneesmiddelanalyse, de klinische toxicologie en de analyse van andere lichaamsvreemde stoffen in laboratoria, deel uitmakend van de gezondheidszorg. Tot deze gebieden worden ook gerekend de interpretatie van de analyseresultaten en de daaruit voortvloeiende klinische adviezen.

De KKGT tracht dit doel te bereiken door middel van het bereiden en versturen van monsters gespiket met geneesmiddel(len) die door de deelnemende laboratoria worden geanalyseerd en gerapporteerd. De resultaten worden statistisch geëvalueerd en gerapporteerd aan de deelnemende laboratoria. Daarnaast stelt de KKGT controlematerialen met bekende concentraties ter beschikking waarmee de eigen standaarden kunnen worden gecontroleerd.

### Rondzendingen

<table>
<thead>
<tr>
<th>Alcoholen/GHB</th>
<th>Anti-epileptica</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anti-epileptica vrije concentratie</td>
<td>Anti-HIV middelen</td>
</tr>
<tr>
<td>Antimicrobiële middelen</td>
<td>Antimicrobiële middelen 2</td>
</tr>
<tr>
<td>Antischimmel middelen</td>
<td>Antituberculose middelen</td>
</tr>
<tr>
<td>Antivirale middelen</td>
<td>Benzodiazepinen</td>
</tr>
<tr>
<td>Biologicals</td>
<td>Busulfan</td>
</tr>
<tr>
<td>Cardiaca</td>
<td>Drugs of Abuse</td>
</tr>
<tr>
<td>Geneesmiddelen afwisselend</td>
<td>Immunosuppressiva microsampling</td>
</tr>
<tr>
<td>Orale oncolytics</td>
<td>Pijnstillers</td>
</tr>
<tr>
<td>Psychofarmaca</td>
<td>Thiopurines</td>
</tr>
<tr>
<td>Toxicologie</td>
<td></td>
</tr>
</tbody>
</table>