Midazolam Measurement and Modelling using Matrix Samplers (The 4M’s Study)

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Importance of getting the dose right

“To ensure that drug efficacy is optimised for every age category and......

....ensure that dose selection is associated with an acceptable safety margin across the predicted range of drug exposures”
Background

Unlicensed and off label use of medicines in children very common

Risks: (i) Reduced Efficacy (ii) Toxicity
Why is data on drug dosing in children so poor?

Lack of Engagement by Pharmaceutical Industry

• Economics
• Too difficult

→ “guesstimate” correct doses

Left to Paediatricians
PK-PD studies & Drug licensing

Disease only occurs in children

Similar disease process in adults & children

Guidance for Industry

Exposure-Response Relationships — Study Design, Data Analysis, and Regulatory Applications
PK studies in children beset with ethical and technical challenges.

PK studies in children require

(i) Relatively large volumes of blood
(ii) Repeated venepuncture to obtain blood

Together (i) & (ii) are generally unacceptable to parents, researchers and ethics committees

‘POP-PK’ modelling techniques partly resolve the issue of obtaining multiple samples from patients for PK studies
EMA Guidelines

• ‘Per individual, the trial-related blood loss (including any losses in the manoeuvre) should not exceed 3 % of the total blood volume during a period of four weeks and should not exceed 1 % at any single time’ *

• Deviations from these recommendations must be justified
  
  • In neonates the total volume of blood is estimated at 80 to 90 ml/kg body weight
  • 3 % corresponds to 2.4 to 2.7 ml blood per kg body weight

*Doc. Ref. EMEA/536810/2008
PK studies in Infants & Children: Is DBS the answer?

- **DBS sampling**: Potential to overcome many of the practical and ethical issues surrounding blood sampling in children.

- **‘CUBS’ Study**: Caffeine PK study in neonates using DBS Methodology

Main issues
- High proportion of spoilt samples
- Haematocrit bias
VAMS tips and 4Ms study
The 4Ms Study: Why Midazolam?

- Used in children => ICU and peri-operatively - sedative, anxiolytic & amnesic agent

- Side effects => cardio-respiratory depression, withdrawal symptoms => Increased morbidity and mortality

Have we got the dose of Midazolam right for children?

*Ince et al => Suggests critical illness alters Midazolam PK? Due to SIRS*
Study Hypotheses

1. **Critical illness alters midazolam PK**

2. **In children administered IV drug VAMS tips and traditional wet samples provide equivalent blood Midazolam and 1-OH Midazolam (active metabolite) concentration measurements**
Patient Population and Blood Sampling

- Children between 1 month and 16 years, administered IV Midazolam (Bolus dose +/- Continuous infusion)

- Blood Sampling:
  1. Opportunistic samples: Extra blood collected when sampling blood for routine clinical tests
  2. Scavenged samples: Blood collected for routine clinical laboratory tests but no longer needed
  3. An extra blood sample for research purposes

All blood collected in EDTA tubes prior to adsorption onto VAMS tips

Blood adsorbed onto 3 different VAMS tips for each PK time point
Study Blood Sample Management

- VAMS tips stored in bespoke cartridges containing desiccants at room temperature
- Wet blood samples stored in dedicated study freezer at -20°C
- Samples stored on clinical site for up to 90 days prior to assay at GSK laboratories (Ware, UK)
- Blood midazolam and 1-OH Midazolam concentrations are analysed by HPLC / MS
Data: April 2015 - Sept 2016

Age Distribution of Children Recruited into the Study

N = 93
Data: April 2015 - Sept 2016

Gender Distribution & Illness Severity of Children Recruited into the Study

N = 93

- PICU Group 61
- ES Group 32
Recruitment & Illness Severity

Number

Time (Months)

Expected

Actual

Theatre group
PICU group
Midazolam concentrations in patients

$N = 56$ patients, $N = 199$ time points

<table>
<thead>
<tr>
<th></th>
<th>PICU Group</th>
<th>ES Group</th>
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</thead>
<tbody>
<tr>
<td>Mean Midazolam Concentration (ng/ml)</td>
<td>322</td>
<td>28</td>
</tr>
<tr>
<td>Range Midazolam Concentration (ng/ml)</td>
<td>5 - 1987</td>
<td>5 - 161</td>
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</table>
1-OH Midazolam concentrations in patients

$N = 56$ patients, $N = 199$ time points

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<tr>
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</thead>
<tbody>
<tr>
<td>Mean 1-OH Midazolam Concentration (ng/ml)</td>
<td>42</td>
<td>6.6</td>
</tr>
<tr>
<td>Range 1-OH Midazolam Concentration (ng/ml)</td>
<td>5 - 211</td>
<td>5 - 8</td>
</tr>
</tbody>
</table>
Relationship between (a) Midazolam and (b) 1-OH Midazolam concentrations determined from wet blood samples and dry samples

$N = 56$ patients, $N = 199$ time points
Preliminary Findings

- Collecting blood samples for PK studies onto VAMS tips is simple
- Training to collect blood onto VAMS tips can be achieved in a relatively short period of time
- Management and storage of VAMS tips is easier than for wet samples
- Spoilt VAMS tips were uncommon (unlike dried blood spots)
- There is a strong correlation in blood midazolam and metabolite concentrations comparing VAMS samples and wet samples
Conclusion

• VAMS tips are superior to dry blood spots in relation to spoilt samples

• Our initial analysis suggest that VAMS tips provide equivalent concentration data to wet samples
The ‘4Ms’ Study: Key Collaborators

**Sponsor**: University of Leicester  
**Funder**: Neoteryx Limited  
GSK

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**Spooner Bio Solutions**
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Thank You

Any Questions?