Microdosing:
An opportunity for safer drug development in children?

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Pediatric Intensivist-Clinical Pharmacologist
Magnitude of the problem

Fatalities in children

1959

2007
Drug failure – HIV example

Blood levels

- Too low
- Adequate

Van Rossum, Fraaij, de Groot Lancet ID, 2002
Microdosing: smart solution?

- Microdose
  - 1/100 of therapeutic dose
  - or max 100 µg
  - ± Radioactive label: $^{14}\text{C}$

- Drug levels with LC-MS or AMS

- FDA/EMA supported
Dose linearity important

**Figure 4** Time profiles of AAP and its metabolites in the pooled plasma of six subjects after oral administration of $^{14}$C-AAP. Pooled plasma specimens collected at 0.25, 0.5, 1, 2, and 8 h were subjected to LC-AMS analysis. 3-O-Sul, AAP-3-hydroxysulfate; 4-O-Sul, AAP-4-hydroxysulfate; AAP, acetaminophen; Glu, AAP-glucuronide; LC-AMS, liquid chromatography–accelerator mass spectrometry.
Radioactivity in kids?
Radiation comparison

- Microdose neonate
- Chest X-ray
- Environment (year)
- Flight in Europe
- Flight to USA

Units: microSv
Paracetamol as probe for UGT and ST

Paracetamol (AAP)

- Glucuronidation
- Sulphation
- CYP + GSH conjugation

Neonate
Birth – 10 days

Neonate
11 days – 1 mth

Infant
1 – 6 mth

Toddler
6 mth – 2 yr

Child
2 – 6 yr
Study aim and design

**Aim:** To study the **impact of age** on intestinal and hepatic **CYP3A** or **UGT** activity using the oral and IV clearance of **midazolam** or **paracetamol**, respectively.

**Design:** PK microtracer study, 0-6 yrs of age, n=60, each drug
TNO the Netherlands - AMS facility
$^{14}$C-Paracetamol microtracer study

- Eligible (n = 232)
  - No informed consent (n = 64)
  - Logistics / other study (n = 118)

- Enrolled (n = 50)
Detectable $[^{14}\text{C}]$paracetamol and metabolites

**Patient 1** age 3.6 months  
**Patient 2** age 10.6 months

![Graph showing concentration (ng/L) vs. time (h) for Patient 1 and Patient 2](image)

Time (h)  
Concentration (ng/L)

- [${}^{14}\text{C}]$AAP
- [${}^{14}\text{C}]$AAP-Glu
- [${}^{14}\text{C}]$AAP-4Sul

Mooij, Clin Pharmacokin, 2014  
Radboudumc
Dose linear?

**Patient 1** age 3.6 months

**Patient 2** age 10.6 months

Mooij et al, Clin Pharmacokin, 2014  
Radboudumc
Age affects paracetamol metabolism

\[ \text{Age affects paracetamol metabolism} \]

\[ \text{AUC}_{0-\text{inf}} \]

\[ \text{AAP- Glu} \]

\[ \text{AAP- Sul} \]

Age 0-6 years (log scale)

Mooij et al, Clin Pharmacokinetic, 2017
Oral bioavailability in children lower?
Challenges for microdosing studies

- Choice of probe drugs
- Dose linearity specific for pathway
- Manufacturing
- Costs
- Perceived radiation risk
- Recruitment
- Practical issues (sampling)
Future opportunities

- Other special populations
  - Pregnancy,
  - Dementia
  - Critically ill
- Metabolites In Safety Testing (MIST)
- Industry?
Acknowledgements

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Dr. S. Hartman
14C-Midazolam: Preliminary results

October 2015 – February 2017

n=227 midazolam IV and indwelling catheter

→ Exclusion criteria/logistic issues: n=180

→ No informed consent: n=22

Inclusion: n=25

→ Analyzed with accelerator mass spectrometry: n=9
## Dose linearity?

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<td><strong>Age</strong></td>
<td>Preterms</td>
<td>0 – 6 yr</td>
<td>6 mth – 16 yr</td>
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<td><strong>Cmax mida (ng/ml)</strong></td>
<td>161 (38-510)</td>
<td>99.8 (17.6 – 287.1)</td>
<td>55.6 ± 30.2</td>
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<td><strong>Cmax OHM (ng/ml)</strong></td>
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## Effect of age and disease?

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Midazolam preliminary results - example

Age 3.3 months

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<th>Time after microdose (hour)</th>
<th>Plasma concentration (ng/L)</th>
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<tbody>
<tr>
<td>0</td>
<td>10</td>
</tr>
<tr>
<td>5</td>
<td>5</td>
</tr>
<tr>
<td>10</td>
<td>2</td>
</tr>
<tr>
<td>15</td>
<td>1</td>
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- [1^4]C midazolam
- [1^4]C OH-midazolam