Novel approaches to clinical trials: How smart design can improve yield

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Presentation overview

- Microdosing
- Model-based dosing
- Sequential trial design
- Umbrella/basket design
- European Pediatric Trial Network
  - Innovation in Scientific Advice
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Oral bioavailability— information gap

- \( F = \frac{\text{AUCoral}}{\text{AUCiv}} \)

- Limitation cross-over design:
  - Drug 2 times, days apart
  - Non-therapeutic drug dosing

- Unethical in children?
Microdosing - Definition

- **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
Radioactivity in kids?
Radiation comparison

- Microdose neonate: 0 microSv
- Chest X-ray: 0 microSv
- Environment (year): 1 microSv
- Flight in Europe: 2 microSv
- Flight to USA: 44 microSv
Paracetamol oral bioavailability study

Paracetamol IV, 15 mg/kg, q6h

$[^{14}C]$ Paracetamol 2ng/kg enteral

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Arterial of central venous catheter
Age affects paracetamol metabolism

Age 0-6 years (log scale)

AUC_{0-inf}  

AAP- Glu  

AAP- Sul  

Mooij et al, Clin Pharmacokinnet 2017
Paracetamol oral bioavailability

Kleiber, Mooij et al., manuscript in preparation
Metabolite in Safety Testing: Midazolam

![Graph showing activity per fraction (µBq) over time (min) for Pool X.](image-url)
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Effect of Intravenous Paracetamol on Postoperative Morphine Requirements in Neonates and Infants Undergoing Major Noncardiac Surgery: A Randomized Controlled Trial

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Tom G. de Leeuw, MD
Ron Mathôt, PharmD, PhD
Catherine A. J. Knibbe, PharmD, PhD
Dick Tibboel, MD, PhD

Importance Continuous morphine infusion as standard postoperative analgesia in young infants is associated with unwanted adverse effects such as respiratory depression.

Objective To determine whether intravenous paracetamol (acetaminophen) significantly (>30%) reduce morphine requirements in neonates and infants undergoing surgery.

Design, Setting, and Patients Single-center, randomized, double-blind study conducted in a level 3 pediatric intensive care unit in Rotterdam, the Netherlands. Pati 71 neonates or infants younger than 1 year undergoing major thoracic (noncardiac) abdominal surgery between March 2008 and July 2010, with follow-up of 48 hours.

Interventions All patients received a loading dose of morphine 30 minutes before the end of surgery, followed by continuous morphine or intermittent intravenous paracetamol up to 48 hours postsurgery. Infants in both study groups received morphine (boluses and/or continuous infusion) as rescue medication on the basis of pain.
Morphine pharmacokinetics infants

Traditional dosing:
100 mcg/kg followed by
10mcg/kg/u

Model-based dosing
100 mcg/kg followed by :
>10 dagen: 10 mcg/kg^{1.5}/h
<10 dagen: \frac{1}{2}(10mcg/kg^{1.5}/h)

Knibbe et al 2009, clin pharmacokinet
Paracetamol group 66% less morphine

[Box plot showing cumulative morphine amount in mcg/kg for Paracetamol and Morphine, with a P<0.05 significance level.]
Morphine concentrations versus age

Steady-state concentration vs. age in days.
Age-related PK changes and use modeling & simulation for pediatric dose selection

• 2 clinical trials gabapentin for neuropathic pain

• Which dose to use?

• PK data in children (Ouellet et al): On a weight basis, 33% larger doses would be required in younger children (<5 years) to achieve the same exposure as older children
Gabapentin PK Modelling

Observed PK data

Visual predictive check

Pediatric Patients

Gabbapentin Concentration (μg/mL)

Time Post-Dose (hr)

Gabbapentin Concentration (mg/L)

Time (h)

This project has received funding from the European Union’s Seventh Framework Programme for research, technological development and demonstration under Grant Agreement n° 602962.
Predicted gabapentin exposure

Weight groups: Left >15 kg, right 5-15 kg Adults

3 doses
Proposed gabapentin dosing

2 weight groups and titration
Day 1 starting dose in mg/kg/day;
Day 3 2 times the starting dose;
Day 5 3 times the starting dose;
Day 14 2 times the dose of Day 5;
Day 21 3 times the dose of Day 5.

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<th>Weight group</th>
<th>Day 1</th>
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<td>5-15 kg</td>
<td>7</td>
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<td>&gt;15 kg</td>
<td>5</td>
<td>10</td>
<td>15</td>
<td>30</td>
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Population PK of clonidine in pediatric ECMO
Target attainment with model-based vancomycin dosing guidelines?

Aim 1. Assess incidence of target attainment with new dosing guideline
Aim 2. Identify risk factors for non-therapeutic concentrations
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RCT with sequential analysis

**Effect of early low-dose hydrocortisone on survival without bronchopulmonary dysplasia in extremely preterm infants (PREMILOC): a double-blind, placebo-controlled, multicentre, randomised trial**

- Sequential analytical design, based on intention to treat
- Planned sample size $n=786$, analyses at every 100 included patients
- Stopped prematurely for financial and technical support limitations
- Final sample size $N=523$
- OR $1.48$ (CI $1.02$-$2.16$, $p=0.04$) for BPD-free survival treatment vs control
Sequential analysis example

Accrued difference in outcome between groups at each interim data inspection

Upper boundary stopping rule (significant difference)

Lower boundary stopping rule (no significant difference)
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MAMS: multi-arm, multi-stage design

Several agents or combinations of agents versus a single control group in a randomised controlled trial (RCT)

Arm with insufficient promise: discontinue
Promising arms: continue
Control arm: continue

UNTIL: sufficient patients to assess impact related to primary outcome
Randomisation arms: example

- **A**: Hormone therapy alone
  - **B**: Hormone therapy + zoledronic acid
  - **C**: Hormone therapy + docetaxel
  - **D**: Hormone therapy + celecoxib
  - **E**: Hormone therapy + zoledronic acid + docetaxel
  - **F**: Hormone therapy + zoledronic acid + celecoxib

- Eligible patient
  - RANDOMISE
  - Control arm
Genomic/biomarker trial design

(a) Basket Trial

(b) Umbrella Trial

Radboudumc
Example of umbrella trials

Heart Failure with preserved ejection fraction
Models for umbrella trials
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Pediatric Drug Development: EU outlook

3. Pediatric label / more data for off-label use

2. **PEDCRIN**
   Paediatric Clinical Research Infrastructure

**IMI2**
European Pediatric Clinical Trial Network
PEDMED-NL

1. **EPTRI**
   European Paediatric Translational Research Infrastructure
Innovative Medicines Initiative

- IMI2 funding
  - 50% European Commission
  - 50% EFPIA European Federation of Pharmaceutical Industry Association

- Call 2017: European Pediatric Clinical Trial Network

- 130 million euros

- 6 years
Network Mission

• Improve availability of information about medicines used by children

• Promote the delivery of high quality trials of medicines for children by supporting:
  • Trial implementation using resources shared between studies
  • Trial design through a combination of information about natural history, feasibility and expert opinion
  • Public- and industry-funded studies
Time-line of studies

- National network
- Network hub
- Expert advice
  - Feasibility
  - Study Site identification
  - Site Set-up
  - Recruitment

Scientific advice
Scientific innovative advice

Strategic feasibility groups

Requests

Advice
- Single drug
- Single/multiple PIP development
- Clinical
- Methodology
- Feasibility assessment
Strategic feasibility groups

- Innovative methodology experts 4.2
  - Study design
  - Statistics
  - E-Health
  - Modelling

- Clinical experts 4.3
  - Oncology
  - Neurology
  - Immunology
  - Intensive care

- Patient participation groups 4.4
  - Patients
  - Parents
  - YPAG
  - CYP
Added value for network goals

- Innovative methodology experts 4.2
- Clinical experts 4.3
- Patient participation groups 4.4

White papers
- Multistakeholder meetings
- Tools for patient involvement
Pediatric Drug Development: EU outlook

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IMI2
European Pediatric Clinical Trial Network PEDMED-NL

1. EPTRI
European Paediatric Translational Research Infrastructure

‘Best evidence’ dose

Improve

Clinical studies

Translational Research
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Funding
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Pediatrics: enough room for innovation

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