CONSIDERATIONS ON METHODOLOGY, STUDY DESIGN AND STATISTICAL APPROACHES

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AGE CLASSES
(ICH E-11)

- NEONATES (0-28 DAYS)
  * PREMATURE (<37 w G.A.) OR TERM
  * 0-7 DAYS ; 8-28 JOURS

- INFANTS (29 DAYS-23 MONTHS)

- CHILDREN (2 YEARS – 11 ANS)

- ADOLESCENTS (12 YEARS - 16-18 YEARS)
NEONATES ARE DIFFERENT
AS COMPARED TO ADULTS
THEREFORE DATA OBTAINED IN ADULTS
CANNOT SIMPLY BE EXTRAPOLATED
TO NEONATES

using a proportionality rule
based upon body size
(weight or body surface area)
NEONATES ARE DIFFERENT
BECAUSE DRUGS BEHAVE DIFFERENTLY IN THEIR BODY

1/ the fate of drugs is different in the body of neonates

2/ the effect of drugs is different in neonates
   - the magnitude of the response may be different
   - the nature of the response may be different:
     some side effects only occur in neonates as their immature body undergoes growth and maturation
NEONATES ARE DIFFERENT

BECAUSE DISEASES MAY BE DIFFERENT IN NEONATES

1/ some diseases only exist in neonates

2/ other diseases differ from what is observed in adults

- infectious diseases:
  - different epidemiology of micro-organisms

- malignancies:
  - different histological types
  - different prognosis
  - different response to drug therapy
NEONATES ARE DIFFERENT

THEREFORE CLINICAL STUDIES HAVE TO BE PERFORMED SPECIFICALLY IN NEONATES

BUT THEY ...

1/ are more difficult to perform

2/ take longer

3) are more costly

... than in adults
NEONATES ARE DIFFERENT

AND CLINICAL STUDIES ARE MORE DIFFICULT TO PERFORM

WHY?

1/ invasiness is a limiting factor and has to be restricted as much as possible

2/ the recruitment is more difficult than in adults

3) appropriate tools have to be developed for the measurement of drug effect
ISSUES TO BE FACED

PROBLEM:
INVASIVENESS

- pain, stress
- blood deprivation
- irradiation
- exposure to clinical trials and to investigational new drugs … should be limited to the minimum required
INVASIVENESS HAS TO BE RESTRICTED

PROPOSED / USED CLUES

1- PREVENT PAIN AND STRESS

- **BLOOD SAMPLING**
  - local anesthesia (EMLA cream),
  - catheters

- **ASSESSMENT OF EFFICACY**
  - non invasive procedures
    (transcutaneous methods) (★)
ALTERNATIVES IN CLINICAL TRIALS / PD STUDIES

TO PREVENT PAIN AND ANXIETY

TRANSCUTANEOUS MEASUREMENTS:

- PO2, PCO2, SaO2, TEMPERATURE, BILIRUBINE

- ECHODOPPLER: CEREBRAL BLOOD FLOW, HEART, VESSELS

- NEURO-IMAGING
  - BUT ...

VALIDATION OF NON INVASIVE METHODS AND SURROGATE MARKERS (*)
NON INVASIVE METHODS IN CHILDREN

![Graph showing correlation between Glass Mercury and Aural temperatures with an R^2 value of 0.23.](image-url)
INVASIVENESS HAS TO BE RESTRICTED

2- RESTRICT BLOOD LOSS

- SMALL BLOOD VOLUMES

- micro-assays
THE PROBLEM
- 80 ml/kg (NN: 85-90 ml/kg)
- NN: 2 kg BV = 170 ml
  3 % BV = 5.1 ml
  1 % BV = 1.7 ml

THE SOLUTIONS:
- SENSITIVE ASSAYS
- SMALL NUMBER OF SAMPLES
INVASIVENESS HAS TO BE RESTRICTED

2- RESTRICT BLOOD LOSS

- SMALL BLOOD VOLUMES
  - micro-assays

- SMALL NUMBER OF SAMPLES
  - PK and PK/PD:
    population approaches (※)
1) POPULATION APPROACH (POP-PK)
   - few blood samples/patient
   - many patients

2) RICH DATA INDIVIDUAL APPROACH
   - many blood samples
   - few patients

INVASIVENESS HAS TO BE RESTRICTED

ALTERNATIVES FOR PK STUDIES
INVASIVENESS HAS TO BE RESTRICTED

2- RESTRICT BLOOD LOSS

- SMALL BLOOD VOLUMES
  - micro-assays

- SMALL NUMBER OF SAMPLES
  - PK and PK/PD:
    population approaches

- ALTERNATIVE APPROACHES?: saliva?..
ALTERNATIVES FOR PK / METABOLIC STUDIES

. SALIVA
. CO2 BREATH TEST
. URINES
. HAIR, MECONIUM

BUT ...

VALIDATION OF NON INVASIVE METHODS
Group II - Citric acid salivette

![Graph showing the correlation between plasma and saliva theophylline levels.](image)
INVASIVENESS HAS TO BE RESTRICTED

3 - RESTRICT EXPOSURE TO CLINICAL STUDIES AND INVESTIGATIONAL NEW DRUGS whenever possible

- AVOID UNECESSARY STUDIES
  - extrapolation from adult data to the lowest possible age limit
  - use of the already available pediatric data (literature, data on file ...)

- ALTERNATIVE APPROACHES
AVOID UNNECESSARY STUDIES

1- EXTRAPOLATION FROM ADULT DATA

- adjust the dose for a similar drug systemic « exposure » (plasma concentration, AUC) using data on the maturational profiles on:

- **PK**: dose-concentration relationship
  - renal elimination
  - metabolic pathways

- **PK-PD**: plasma-concentration relationship
b) THE KNOWLEDGE OF THE ONTOGENY OF THE PROCESSES INVOLVED IN DRUG ELIMINATION (RENAL, HEPATIC, METABOLIC PATHWAYS) determine the **lower age limit for extrapolation**

- **PLANNING PEDIATRIC PK STUDIES** (OPTIMISATION OF AGE DISTRIBUTION IN RECRUITMENT OF PATIENTS)

- **MODELING OF THE INFLUENCE OF MATURATION (★)** (SIMULATION (★)– VALIDATION) Ex: SIMCYP
AVOID UNNECESSARY STUDIES

2- USE OF AVAILABLE DATA

- bio-availability studies
- population PK on published data
- meta-analysis (*)
INVASIVENESS OF PK STUDIES

3- APPROPRIATE DRUG DEVELOPMENT PLAN

- BIOAVAILABILITY OF NEONATAL FORMULATIONS IN HEALTHY ADULT VOLUNTEERS
Odds ratio of responders in STP group compared to placebo
- META-ANALYSIS (Kassaï B. et al., 2006)

Responders

Odds ratio, fixed model (sub-groups graph)
Bilateral CI, 95% for trials, 95% for MA

Calculated from:

<table>
<thead>
<tr>
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<th>T+</th>
<th>T-</th>
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</thead>
<tbody>
<tr>
<td>STICLO Italie 1</td>
<td>8/12</td>
<td>1/11</td>
</tr>
<tr>
<td>STICLO Italie 2</td>
<td>15/21</td>
<td>1/20</td>
</tr>
<tr>
<td>Total</td>
<td>23/33</td>
<td>2/31</td>
</tr>
</tbody>
</table>

Cochran Q het. p=0.60
INVASIVENESS HAS TO BE RESTRICTED

3- AVOID **IRRADIATION**

**THE PROBLEM**
- IRRADIATION FROM RADIO-ACTIVE ISOTOPEs

**THE SOLUTIONS :**
- USE OF STABLE ISOTOPEs (*)&
  - BIOAVAILABILITY STUDIES
  - PK REPEATED DOSES
  - METABOLIC STUDIES
  - CO₂ BREATH TEST
  - COMPLIANCE
NEONATES ARE DIFFERENT

AND CLINICAL STUDIES ARE
MORE DIFFICULT TO PERFORM

1/ invasiveness is a limiting factor and has to be restricted as much as possible

2/ the recruitment is more difficult than in adults
RECRUITMENT HAS TO BE FACILITATED

PROBLEMS

1- NUMBER OF PATIENTS OFTEN LIMITED

2- INFORMED CONSENT MORE DIFFICULT TO OBTAIN

- clinical trials takes longer
- clinical trials may cost more
RECRRUITMENT HAS TO BE FACILITATED

PROBLEMS

3- EXPOSURE TO CLINICAL TRIALS AND TO INVESTIGATIONAL NEW DRUGS SHOULD BE LIMITED TO THE MINIMUM REQUIRED

⇒ Ethical issue: smallest possible numbers

⇒ Validity of scientific data / acceptance by regulatory bodies: numbers not too small
RECRUITMENT HAS TO BE FACILITATED

INNOVATIVE METHODOLOGICAL APPROACHES

→ limit the number of patients

PROPOSALS:

- **Sequential approaches** (*)
  - dose-finding studies (phase II)
  - comparative trials (phase III)
- **Enrichment methods** (*)
- **Clinical trial modeling and in silico simulation**
  avenue to explore (*)
  a relatively new effort to devise *in silico* simulations of human physiology and genetic variation.
a) **DOSE FINDING PARALLEL GROUP STUDIES ARE DIFFICULT TO PERFORM IN CHILDREN**

- RELATIVELY NARROW DOSE RANGE AND SMALL INTERVAL BETWEEN TESTED DOSES

- IMPORTANT INTERINDIVIDUAL VARIABILITY OF THE PARAMETERS MEASURED

- LARGE NUMBER OF PATIENTS REQUIRED
1 - DOSE-FINDING STUDIES IN NEONATES (PHASE II)

NEW PROMISING METHOD:

- BAYESIAN SEQUENTIAL ANALYSIS
There are new promising methods like Bayesian Sequential Analysis.
### BAYESIAN SEQUENTIAL APPROACH

A posteriori estimated probabilities of success of the six tested doses, updated after each included patient

<table>
<thead>
<tr>
<th>Subject</th>
<th>Administered dose (n°)</th>
<th>Clinical response</th>
<th>Dose-range studied</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>1     2     3     4     5     6</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>A priori probabilities of success (%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>35  50  70  90  95  100</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>A posteriori estimated probabilities of success (%)</td>
</tr>
<tr>
<td>1</td>
<td>3</td>
<td>Failure</td>
<td>3     4     6     9     12  21</td>
</tr>
<tr>
<td>2</td>
<td>6</td>
<td>Success</td>
<td>9     12    19    35    64  70</td>
</tr>
<tr>
<td>3</td>
<td>6</td>
<td>Success</td>
<td>12    18    28    59    62  84</td>
</tr>
<tr>
<td>9</td>
<td>6</td>
<td>Success</td>
<td>23    33    51    77    86  96</td>
</tr>
<tr>
<td>10</td>
<td>5</td>
<td>Success</td>
<td>25    37    56    81    89  97</td>
</tr>
<tr>
<td>13</td>
<td>5</td>
<td>Success</td>
<td>31    45    65    87    93  99</td>
</tr>
<tr>
<td>14</td>
<td>4</td>
<td>Success</td>
<td>33    47    67    88    94  99</td>
</tr>
</tbody>
</table>
BAYESIAN SEQUENTIAL APPROACH

A posteriori probabilities

Dose (mg/kg)

A priori
Patient 1
Patient 2
Patient 3
Patient 9
BAYESIAN SEQUENTIAL ANALYSIS

A posteriori estimated probabilities of success of the six tested doses, updated after each included patient

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<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>1</td>
</tr>
<tr>
<td>15</td>
<td>4</td>
<td>Success</td>
<td>35</td>
</tr>
<tr>
<td>16</td>
<td>4</td>
<td>Failure</td>
<td>26</td>
</tr>
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<td>17</td>
<td>5</td>
<td>Success</td>
<td>27</td>
</tr>
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<td>5</td>
<td>Success</td>
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<td>23</td>
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<td>24</td>
<td>4</td>
<td>Success</td>
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</tr>
<tr>
<td>25</td>
<td>4</td>
<td>Success</td>
<td>33</td>
</tr>
</tbody>
</table>
BAYESIAN SEQUENTIAL APPROACH

A posteriori probabilities vs. Dose (mg/kg) for different patients:
- A priori
- Patient 1
- Patient 2
- Patient 3
- Patient 9
## BAYESIAN SEQUENTIAL ANALYSIS

A posteriori estimated probabilities of success
Curative IV NSAID in patent ductus arteriosus

<table>
<thead>
<tr>
<th>Patients</th>
<th>Dose</th>
<th>A priori estimated probabilities of success (%)</th>
<th>A posteriori estimated probabilities of success (%)</th>
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</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>0.6</td>
<td>0.8</td>
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<tr>
<td>1</td>
<td>10</td>
<td>0.481</td>
<td>0.683</td>
</tr>
<tr>
<td>2</td>
<td>5</td>
<td>0.370</td>
<td>0.544</td>
</tr>
<tr>
<td>3</td>
<td>15</td>
<td>0.539</td>
<td>0.744</td>
</tr>
<tr>
<td>4</td>
<td>10</td>
<td>0.512</td>
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<td>5</td>
<td>15</td>
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<td>0.500</td>
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<tr>
<td>7</td>
<td>10</td>
<td>0.519</td>
<td>0.723</td>
</tr>
<tr>
<td>8</td>
<td>15</td>
<td>0.553</td>
<td>0.757</td>
</tr>
<tr>
<td>9</td>
<td>10</td>
<td>0.567</td>
<td>0.771</td>
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</tbody>
</table>
BAYESIAN SEQUENTIAL ANALYSIS
A posteriori estimated probability of success of the minimal efficient dose (95 % credibility interval)
BAYESIAN SEQUENTIAL ANALYSIS

● ADVANTAGES
  - NO PLACEBO GROUP REQUIRED
  - ETHICS
  - LIMITED NUMBER OF PATIENTS

● FLAWS
  - QUALITATIVE PARAMETER
  - RAPID EVALUATION OF RESPONSE
  - ORGANISATION
2 - EFFICACY STUDIES IN NEONATES (PHASE III)

POTENTIAL INTEREST IN METHODS THAT MAY LIMIT THE NUMBER OF PATIENTS TO BE RECRUITED

1- POTENTIAL INTEREST OF SEQUENTIAL METHODS (TRIANGULAR TEST)

2- RESPONDER PATIENT POPULATION ENRICHMENT - WITHDRAWAL
METOCLOPRAMIDE IN GASTROESOPHAGEAL REFLUX

Z = 5.495 + 0.2726 V

Z = -5.495 + 0.8177 V

(V = 20.16 ; Z = 10.99)

TRIANGULAR TEST AND SAMPLE PATH

RECRUITMENT HAS TO BE FACILITATED

INNOVATIVE METHODOLOGICAL APPROACHES

→ limit the number of patients

- **Sequential approaches**
  - dose-finding studies (phase II)
  - comparative trials (phase III)

- **Enrichment methods** (☆)(.getIncrease variability, get stat power)
  - enrichment in responders
  - withdrawal in the placebo group
RESPONDER POPULATION ENRICHMENT - WITHDRAWAL PLACEBO CONTROLLED TRIAL

Stiripentol in partial epilepsy in children

Baseline  | Open period | Double-blind | Open follow-up
---|---|---|---
1 mth | 4 mths | 6 mths

Pre-inclusion | Open add-on STP | Randomization of responders | End

Blood Samples: 1 2 | 3 4 | 5
Neonates are different and clinical studies are more difficult to perform.

1/ Invasiness is a limiting factor and has to be restricted as much as possible.

2/ The recruitment is more difficult than in adults.

3) Appropriate tools have to be developed for the measurement of drug effect.
APPROPRIATE TOOLS HAVE TO BE DEVELOPED FOR THE MEASUREMENT OF DRUG EFFECT

NEONATES DO NOT EXPRESS THEIR DISTRESS THE SAME WAY AS ADULTS
APPROPRIATE TOOLS HAVE TO BE USED / DEVELOPPED
FOR THE MEASUREMENT OF DRUG EFFECT

1/ DEVELOPMENT OF SCALES (＊)
   - PAIN
   - SEDATION

2/ DEVELOPMENT OF NEW END-POINTS AND SURROGATE MARKERS (＊)
   - CLINICAL
   - BIOLOGICAL
ASSESSMENT OF THE EFFECT OF DRUGS

I - END-POINTS ADAPTED TO PATIENT ’S AGE

- ASSESSMENT OF PAIN

I - SELF-EVALUATION (>6 YEARS)

1) VISUAL ANALOGUE SCALE
   4 - 6 YEARS

2) FACE SCALES
   4 - 6 YEARS

3) « POKER CHIP »
   4 - 6 YEARS
VISUAL ANALOGUE SCALES (VAS)

PAIN SCALES FPS-R

TOKENS
II- **HETERO-EVALUATION** (<6 YEARS)

**BEHAVIORAL MEASURES OF PAIN**  
**BIRTH – 6 YEARS**

1/ **POST-OPERATIVE PAIN:**

- **OBJECTIVE PAIN SCALE (OPS) > 2 MONTHS**
- **CHILDREN ’S HOSPITAL OF EASTERN ONTARIO PAIN SCALE (CHEOPS) : 1- 6 YEARS**
- **AMIEL-TISON SCALE : 1 MONTH - 3 YEARS**
II- HETERO-EVALUATION (<6 YEARS)

2/ OTHER ACUTE PAIN:
   - NEONATAL FACIAL CODING SYSTEM (NFCS) : 0-18 MONTHS
   - CHEOPS

3/ LONG-LASTING ACUTE PAIN:
   - DEGR SCALE : 2-6 YEARS
   - EDIN SCALE : PREMATURE NEONATES
APPROPRIATE TOOLS HAVE TO BE USED / DEVELOPPEED

FOR THE MEASUREMENT OF DRUG EFFECT

FOR UNPREDICTED LATE TOXICITY ON DEVELOPING ORGANS

POST MARKETING STUDIES ARE OF PARTICULAR INTEREST IN NEONATES
POST MARKETING STUDIES

THERAPEUTIC CATASTROPHIES OF THE PAST:
- PHOCOMELIA: THALIDOMIDE
- ADENOCARDINOMA OF THE VAGINA: DIETHYLSTILBOESTROL
- RETROLENTAL FIBROPLASIA: O2
- BRONCHOPULMONARY DYSPLASIA: MECHANICAL VENTILATION

MORE RECENT FINDINGS:
- DELAYED CARDIAC TOXICITY OF ANTHRACYCLINS
- DELAYED TESTICULAR TOXICITY OF HODGKIN-MOP CHEMOTHERAPY
- DELAYED OVARIAN TOXICITY OF HIGH DOSES BUSULFAN BEFORE BMT
POST MARKETING STUDIES

LONG TERM PROSPECTIVE FOLLOW UP STUDIES

- GROWTH AND MATURATION
- REPRODUCTIVE CAPACITY
- ABILITY TO LEARN ; COGNITIVE SKILLS
- EMOTIONALITY AND PSYCHOLOGICAL DEVELOPMENT

SIDE EFFECTS THAT OCCUR FAR BEYOND THE PERIOD OF DRUG EXPOSURE
APPROPRIATE METHODOLOGICAL APPROACHES HAVE TO BE USED / DEVELOPED FOR THE MEASUREMENT OF DRUG EFFECT FOR UNPREDICTED LATE TOXICITY ON DEVELOPING ORGANS

CASE-STUDIES NESTED IN COHORT STUDIES ARE OF PARTICULAR INTEREST IN NEONATES
CONCLUSION (I)

- Innovative methodologies are potential useful tools to facilitate drug evaluation in neonates whenever necessary.

- Are not expected to replace classical approaches.

- The limits of validity of these approaches are to evaluated for an appropriate level of proof of efficacy and safety.
CONCLUSION (II)

-DUE TO THE CONSTRAINTS OF DRUG EVALUATION IN NEONATES NEONATAL CLINICAL PHARMACOLOGY REPRESENTS A CHALLENGING AREA FOR METHODOLOGICAL CREATIVITY WHICH MAY ULTIMATELY BENEFIT TO OTHERS AREA OF CLINICAL PHARMACOLOGY INCLUDING ADULTS