Why reinforcing clinical developmental transnational process and organisation?

Experience reporting

...with the FP7 TINN projects
EU Projets since 2005
ESDPP group of Paediatric Pharmacologists

FP6 - Penta : C. Giaquinto
FP6 – Penta Labnet : C. Giaquinto
FP7 - TINN : E. Jacqz-Aigrain
FP7 - TINN2 : E. Jacqz-Aigrain
FP7 – GRIP : C. Giaquinto
FP7 – NeoVanc : M Sharland
# Context of the TINN project

## Drug evaluation in neonates

<table>
<thead>
<tr>
<th>Total number of birth in 2010</th>
<th>14.9 million babies</th>
</tr>
</thead>
<tbody>
<tr>
<td>Preterm &lt; 37W</td>
<td>1.0%</td>
</tr>
<tr>
<td>&lt;28 W</td>
<td>5.2%</td>
</tr>
<tr>
<td>28 – 32 W</td>
<td>10.4</td>
</tr>
<tr>
<td>33 - &lt;37 w</td>
<td>84.3</td>
</tr>
</tbody>
</table>

The neonatal population changes...

1. **Unique neonatal diseases**
   - Respiratory distress syndrome
   - Patent ductus arteriosus
   - Primary pulmonary hypertension
   - Infections...

2. **Unique susceptibilities particularly if premature**
   - Necrotizing enterocolitis
   - Retinopathy of prematurity
   - Intraventricular hemorrhage
   - Neuro-developmental impact - toxicity
High risk of neonatal death

Daily risk of death during first month of life
based on analysis of 47 DHS datasets (1995-2003) with 10 048 neonatal deaths

Estimated distribution of direct causes of neonatal deaths for the year 2000
Based on vital registration data for 45 countries and modelled estimates for 147 countries.
A high number of drugs prescribed in neonates are used off-labelled.

Treluyer JM Arch Fr Ped 2000
Understand developmental pharmacology – pharmacokinetics

Immaturity

Changes in body composition hepatic and renal functions…with

AGE

Drug Disposition

Pharmacogenetics relation between phenotype and genotype

Kearns G

NEnglJMed 2000
And the **same dose** and the **same drug formulation**?

Do you think that the **same drug** may be suitable for adults, children and neonates?

Adapted from Van den Anker - Manzoni
Drug evaluation in neonates
Why a transnational FP7 project?

There are many major **scientific, practical and ethical issues** in relation to studying medicines in the vulnerable group of preterm and term neonates

- limited number of neonates with comparable diseases.
- Need for adapted **formulations**
- Need for suitable **methodological approaches** for clinical trials
- Need **trained investigators** with expertise in neonatal clinical trials (inadequate **critical mass of investigators** in any single European country)
- Lack of **adequate drug monitoring programs** in this population
- Major **ethical issues**
1999 - 2012

130 928 trials
29 420 pediatric trials
264 neonatal trials: 0.2%

Panseri 2013 (submitted)
Challenges to....Concile very different objectives

- Scientific Progresses
- Regulatory Requirements
- Costs
- Ethics
The TINN project aims at validate PIPs for two anti-infective drugs in the « EMEA priority list » and apply for a PUMA:

**Evaluation of the pharmacokinetics, efficacy and safety:**

- **Ciprofloxacin** administered to treat neonates with sepsis caused by multiple resistant organisms, against which only ciprofloxacin is effective.
- **Fluconazole** administered to prevent and or treat neonates with invasive candidiasis.

**Treat Infections in NeoNates**
The Governing Council
Formed by all partners.
**Decision-making body.**
1 vote per Beneficiary.

The Executive Council
**Decision-drafting body. Operational**

**Coordinator** (Evelyne, WP6)
WP leaders:
Imti (Co-ordinator, WP5), Jerome (WP1),
Berhouz (WP2), Mark (WP3), Paolo (WP4),
John (WP7),

WP teams
Partners contributing to a WP.
WP leader coordinates.

The Coordinator
The sole contact point with the EC
Inserm and Inserm-Transfert
Reports to the Commission.
Signs all consortium’s letters.
Receives & distributes funding

Independent Advisory Boards
SAB, EAB and ISMB
3 independent experts each.
Confidentiality agreements signed
*Irja Lutsar, Gregory Kearns, Stephanie Laer, Neil Morton, David Field, Trevor Johnson*
The original TINN investigation project

PIP: Paediatric Investigation Plan
PUMA: Paediatric Use Marketing Authorisation

2007

Tinn
Ciprofloxacin

- Potent, bactericidal antimicrobial (Gram -/+)
- Tissue penetration +
- Active against 90% of Gram (-) community strains
- Limited use in pediatrics: joint toxicity
- Hypothesis: in neonates: benefits >> risks

TINN WP

- Literature review
- Survey of the use of ciprofloxacin in NICUs in Europe
- Preclinical juvenile studies
- HPLC MS methods adapted to neonates to measure ciprofloxacin
- Population PK in neonates
Literature search
focus on Information relevant to prescribing PK, Efficacy, safety

- **Abstracts screened**: 1153
  - Excluded by reading abstract: 1056
  - Full text reports retrieved: 97
    - Relevant full text: 42
      - Studies included: 32
      - Excluded: 10

- Excluded by reading full text report: 55
  - 18 epidemiology + microbiology reports
  - 16 review reports
  - 9 letters + editorials + preliminary reports
  - 3 use of other fluoroquinolones or other antibiotics
  - 3 administrations of ciprofloxacin > 3 months of age
  - 2 infections starting > 28 days of life
  - 2 administrations of ciprofloxacin in adults
  - 2 no precision on age
32 included in the analysis

- No RCT
- 5 cohort studies
- 14 cases reports
- 13 series of 2 to 29 patients
- 1 PK study: 20 premature patients

Synthesis

Low methodological quality + level of evidence
Not sufficient PK data to establish optimal dosing schedule in neonatal sepsis
Efficacy + safety evaluation limited by
- Various drug combinations + neonatal critical health state
- Variability in patients’ follow-up
- Absence of validated method to assess joint toxicity
Survey

• 189 level II and III NICUs in 25 EU countries
• Wide intra- and inter-country variability in drug use and dosage in very-low-birth-weight
• 5 to 45 mg/kg/day

Main concerns
• Antibiotic resistance
• lack of safety and efficacy data
• Lack of PK, penetration in the cerebrospinal fluid and validated dose
**Challenge**: Develop and use animal models for neonatal evaluation of new treatments *in vivo*

- Animal models available for proof-of-concept studies in metabolic, neuromuscular and ophthalmological rare diseases (Enzyme replacement in Pompe disease, miglustat in Niemann-Pick disease or Gaucher’s disease)
- Some have enabled the development of much-needed therapies such as enzyme replacement therapy (Continuing need to develop more effective models to facilitate drug development and clinical trial design for rare diseases

*European Medicines Agency’s Committee for Orphan Medicinal Products 2013*
Challenge: Develop methodologies for neonatal evaluation of new treatments \textit{in vivo}

Non-invasive tools for the exploration of rare diseases in mouse models since birth (UMR Inserm 676)

Vital functions
- Breathing
- ECG
- Body temperature
- Vocalizations
- Movements
- $O_2$ consumption

Motor development

Learning and memory
Example: mouse model of Congenital Central Hypoventilation Syndrome (Ondine’s syndrome)

- Understanding of physiopathology
- Research on therapeutic strategies (Desogestrel): in progress

- Baseline ventilation is decreased on P2
- No ventilatory response to CO₂
Juvenile Animal Studies
Ciprofloxacin

- Mice (OF1)
- **Treatment duration**: 11 days (from 2 days to 12 days)
- Route: SC daily
- **Dose**: 0 / 10 / 30 / 100 mg/kg/day

**PK**

- PK single dose
  - *CFX-P1*
- PK chronic regimen
  - *CFX-P2*

**Safety**

- *in vivo* psychomotor tests
  - *CFX-M2*
- *in vivo* cognitive test
  - *CFX-M3*
- + Histology

**Timepoints**

- M12
- M18
- M30
- M36

B. Matrot, J. Gallego - Phenopups
Ciprofloxacin (three doses) had no impact on vital functions, physiological and neurological testing.
Ciprofloxacin arthrotoxicity
Safety study CFX-M1

Ciprofloxacin SC daily (PND 2 to PND 12)
-No lesions found except an inflammatory response in surrounded tissues for the highest dose in a few animals

Articulations collected at PND 14 and PND 60

Humero-ulnar joint
Tibio-tarsal joint

B. Matrot, J. Gallego - Phenopups
Fluconazole

Determination of fluconazole total clearance

Extrapolated neonatal PK parameters based on juvenile mice → Estimated PK parameters in neonates → 100 Simulated Clinical Trials → Simulated concentration-time profiles

Extrapolated neonatal PK parameters based on health volunteers

Extrapolated neonatal PK parameters based on in vitro dataset

Referenced V, CL and AUC in neonates based on neonatal PK parameters versus Extrapolated V, CL and AUC in neonates based on juvenile mice, adult volunteers and in vitro data
Challenge
Define which studies are needed in neonates…

Pediatric Study Decision Tree

Reasonable to assume (pediatrics vs adults)
✓ similar disease progression?
✓ similar response to intervention?

NO

YES TO BOTH

Reasonable to assume similar concentration-response (C-R) in pediatrics and adults?

NO

• Conduct PK studies
• Conduct safety/efficacy trials

NO

Is there a PD measurement that can be used to predict efficacy?

YES

• Conduct PK/PD studies to get C-R for PD measurement
• Conduct PK studies to achieve target concentrations based on C-R

NO

• Conduct PK studies to achieve levels similar to adults
• Conduct safety trials

YES
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NO
Population Pharmacokinetics of ciprofloxacin

- 62 preterm and term neonates
  - Gestational age: 30.4 (5.8) weeks
  - Post-menstrual age: 35.8 (6.6) weeks
  - Birth weight: 1532 (902) g

- Limited number of samples per patient
- Ciprofloxacin 10mg/kg either twice (preterm) or three times daily (term and young infants)
- AUC24/MIC target: 125 for MIC value of 0.5 mg/L
  (Standard EUCAST MIC susceptibility breakpoint)

Tinn Consortium: H. Hill, M. Turner (Liverpool)
Z. Wei, E. Jacqz-Aigrain (Paris)
POPULATION APPROACH – PK MODEL

Non linear mixed effects model

Single-stage approach (population analysis)

From Steiner (1992): « Population models and methods, with emphasis on pharmacokinetics », in M. Rowland and L. Aarons (eds), New strategies in drug development and clinical evaluationm the population approach
Ciprofloxacin concentrations versus time

Graphs showing Ciprofloxacin concentrations over time for PK1 and PK2.
Population pharmacokinetics of ciprofloxacin

Target attainment rates

- 7.5 mg/kg for preterm neonates
- 12.5 mg/kg for term neonates and young infants
- when given twice daily, allow 77%, and 79% patients respectively to achieve the AUC/MIC target

Tinn Consortium: H.Hill, M.Turner (Liverpool)
Z.Wei, E. Jacqz-Aigrain (Paris).
There will be no marketing authorization for ciprofloxacin in neonates, in the absence of PIP (no adapted formulation, no RCT for efficacy)

- Ciprofloxacin is used as a salvage therapy in neonates with multiresistant Gram- infection ....
- Literature review and survey confirmed that neonatal data were required

**TINN**

- Efficacy is based on a PK/PD parameter
- The dose should be adapted to individual factors including gestational age, weight...to reach a defined target AUC / MIC
- Safety from juvenile animal data was demonstrated
- Neonatal safety (short and longterm follow up) remains to be finalized
HOW reinforcing clinical developmental transnational process and organisation?

Experience reporting

...with the FP7 TINN projects
Unique Goal of all partners: Deliver high quality data allowing safe drug prescription in children

• Validate the scientific project and trial design
• Conduct the trial
• Optimize recruitment
• Respect high ethical standards
• Avoid trial failure
Challenges of the FP7 TINN project
Concile different objectives

- Scientific Progresses
- Regulatory Requirements
- Costs
- Ethics
Keys for success?
Detailed feasibility assessments

Validated data sources - Survey

Assess if investigators have sufficient time to support studies

“NO” may be the best answer
The sponsor has a central role in organizing and following the trial

Experienced team
Dedicated trial manager

Reactivity to reduce delays
Scientific / Regulatory Evaluation

TINN2
1. Scientific Advice - EMA
2. FP7 Project evaluation
3. PIP evaluation - EMA
4. PedCo Scientific meeting
5. Sponsor evaluation – Inserm (Cossec)
6. ECRIN Scientific board
7. VHP

DUPLICATION?
Ethics

1. FP7 Project evaluation
2. TINN Ethic board
3. Parents associations
4. Sponsor review
5. National Ethic Committees (not included in the VHP..)

DUPLICATION?
Professionals

Clinicians are clinicians
Trial managers are trial managers
Regulators are regulators
Ethicists are ethicists

“should be questionned and should express (limit ?) opinions, comments or interventions in their area of expertise”
Parents

Parents can contribute a great deal to all stages of trial development

But
Need to be questioned (when?)
Need sensitive support (and feedback)

Parents are even busier than clinicians
Recruitment

Recruitment to randomised trials: strategies for trial enrolment and participation study. The STEPS study Campbell et al. 2007 [http://www.hta.ac.uk/execsumm/summ1148.htm](http://www.hta.ac.uk/execsumm/summ1148.htm)

Less than one-third of trials recruited their original target within the time originally specified, and around one-third had extensions.
Everyone thinks he is important

Good things can happen by accident, but consistency requires hard work

Managing personalities is important
   Recognize strengths
   Negotiate around weaknesses
Clinical expertise and a good protocol will succeed one third of times

To increase the chances of success
- Professional sponsorship
- Professional trial management
- Risk assessment
- Performance management
- Good relationships

Thank you