Clinical trials in neonates - challenges for all stakeholders?

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Pediatrics does not deal with miniature men and women, with reduced doses the same class of disease in smaller bodies, but ..... has its own independent range and horizon

Abraham Jacobi more than 100 years ago
Neonate: 0 – 27 days

Term baby: age 1 day

Baby born at 26th week; 14 days old
Neonatal categories

0 – 27 days

0 to 7 days

8 – 28 days

Preterm babies <37 weeks

Term babies >37 weeks

VLBW <1500g

ELBW <1000g

SGA – small of gestational age; PMA – postmenstrual age; PNA – postnatal age; GA – gestational age
Unlicenced (UL) and off-label (OL) medicines are used in 90% cases in NICU

<table>
<thead>
<tr>
<th>Country</th>
<th>UL (%)</th>
<th>OL (%)</th>
<th>Most common UL</th>
<th>Most common OL (reason)</th>
</tr>
</thead>
<tbody>
<tr>
<td>UK, 1999</td>
<td>10</td>
<td>55</td>
<td>caffeine</td>
<td>Penicillin G (dose)</td>
</tr>
<tr>
<td>France, 2000</td>
<td>7</td>
<td>63</td>
<td>caffeine</td>
<td>Midazolam (age)</td>
</tr>
<tr>
<td>Israel, 2000</td>
<td>16</td>
<td>63</td>
<td>theophellin</td>
<td>Gentamicin (dose)</td>
</tr>
<tr>
<td>Netherlands, 2001</td>
<td>62</td>
<td>15</td>
<td>caffeine</td>
<td>Tobramicin (dosing)</td>
</tr>
<tr>
<td>Australia, 2002</td>
<td>11</td>
<td>47</td>
<td>NaCl 6% oral liquid</td>
<td>Morphine (indication)</td>
</tr>
</tbody>
</table>

Seminars in fetal and neonatal medicine 2005; 10: 115-122
Stakeholders in neonatal trials

- Neonate and his/her family
- Neonatologists and academic medicine
- Learned societies of neonatal medicine
- Governments & Regulatory agencies
- Patients organisations
- Pharmaceutical industry
Ethics and feasibility

- Is it ethical to conduct trials in neonates?
- Is it ethical not to conduct trials in neonates?
- How do obtain informed consent?
  - Intervention trials for critical conditions
  - Does parental consent protect a child
- The number of patients is limited
Five scenarios and degree of consent

**TABLE 1** Comparison of Mothers for the 5 Scenarios on their Degree of Consent

<table>
<thead>
<tr>
<th>Scenario</th>
<th>Psychological</th>
<th>Physiologic</th>
<th>Blood</th>
<th>Sleep</th>
<th>Vaccine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Term, mean ± SD</td>
<td>2.92 ± 0.69</td>
<td>2.85 ± 0.71</td>
<td>2.48 ± 0.79</td>
<td>2.67 ± 0.73</td>
<td>2.04 ± 0.72</td>
</tr>
<tr>
<td>Preterm, mean ± SD</td>
<td>3.06 ± 0.76</td>
<td>2.89 ± 0.81</td>
<td>2.64 ± 0.92</td>
<td>2.76 ± 0.70</td>
<td>1.95 ± 0.87</td>
</tr>
<tr>
<td>All mothers, mean ± SD</td>
<td>2.98 ± 0.72</td>
<td>2.86 ± 0.74</td>
<td>2.54 ± 0.84</td>
<td>2.71 ± 0.72</td>
<td>2.01 ± 0.78</td>
</tr>
<tr>
<td><strong>Percentage of consent</strong></td>
<td><strong>80.00</strong></td>
<td><strong>74.12</strong></td>
<td><strong>54.71</strong></td>
<td><strong>65.88</strong></td>
<td><strong>24.71</strong></td>
</tr>
</tbody>
</table>

For the answer categories, 1 indicates I am sure I would not consent; 2, I think I would not consent; 3, I think I would consent; 4, I am sure I would consent.

*Data show the percentage of consent, based on answers (3 + 4).*

**Psychological/physiological** – monitoring child’s development, including hearing, visual function
**Blood** – one blood sample taken
**Sleep** – special monitor used
**Vaccine** – varicella vaccine at age of 1 mo with blood samples

*Pediatrics* 2008;121;e590-e596
### Conditions of the Research and Degree of Consent

<table>
<thead>
<tr>
<th>Conditions</th>
<th>Consent %</th>
<th>Mean</th>
<th>SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. If the study serves to solve a medical problem from which the infant suffers</td>
<td>91</td>
<td>3.16</td>
<td>0.65</td>
</tr>
<tr>
<td>2. If you become convinced that no harm is involved</td>
<td>71</td>
<td>2.82</td>
<td>0.80</td>
</tr>
<tr>
<td>3. If you would learn something about your infant</td>
<td>64</td>
<td>2.66</td>
<td>0.83</td>
</tr>
<tr>
<td>4. If you become convinced that the infant will not suffer</td>
<td>63</td>
<td>2.67</td>
<td>0.87</td>
</tr>
<tr>
<td>5. If the study is imperative to solve a severe medical problem of infants</td>
<td>63</td>
<td>2.65</td>
<td>0.73</td>
</tr>
<tr>
<td>6. If you become convinced that the study will contribute significantly to medical knowledge</td>
<td>58</td>
<td>2.52</td>
<td>0.78</td>
</tr>
<tr>
<td>7. If the infant will receive special attention from the medical staff</td>
<td>35</td>
<td>2.06</td>
<td>0.94</td>
</tr>
<tr>
<td>8. If you will be paid an appropriate sum of money</td>
<td>25</td>
<td>1.83</td>
<td>0.83</td>
</tr>
<tr>
<td>9. If the research requires several visits to the hospital over the year</td>
<td>19</td>
<td>1.78</td>
<td>0.73</td>
</tr>
</tbody>
</table>

For the answer categories, 1 indicates I am sure I would not consent; 2, I think I would not consent; 3, I think would consent; 4, I am sure I would consent. Percentage of consent is based on answers (3 + 4).
Type of studies needed

• Almost always
  – Pharmacokinetic studies
  – Safety studies

• Sometimes
  – Efficacy & PK/PD studies
    • In diseases that have different mechanisms
    • In diseases that are unique for neonates
  – Juvenile animal toxicity studies
Pharmacokinetics is different
Pharmacokinetics of penicillin G in ELBW neonates

<table>
<thead>
<tr>
<th></th>
<th>$T_{1/2}$</th>
<th>$C_{max}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Premature &lt; 1200 g</td>
<td></td>
<td></td>
</tr>
<tr>
<td>30 mg/kg</td>
<td>3.8 h</td>
<td>145.5 mcg/ml</td>
</tr>
<tr>
<td>15 mg/kg</td>
<td>4.6 h</td>
<td>58.9 mcg/ml</td>
</tr>
<tr>
<td>Full-term baby</td>
<td></td>
<td></td>
</tr>
<tr>
<td>15 mg/kg</td>
<td>3.4 h</td>
<td>22.0 mcg/ml</td>
</tr>
<tr>
<td>adult</td>
<td></td>
<td></td>
</tr>
<tr>
<td>600 mg/dosi</td>
<td>0.5 h</td>
<td>45 mcg/ml</td>
</tr>
</tbody>
</table>

Metsvaht et al. AAC 2007; 51: 1995-00
The need for efficacy studies if the disease is different

• Different pathomechanisms
  – Neonatal sepsis
  – Neonatal seizures

• Unique disease
  – ABO or Rhesus incompatibility
  – Persistent ductus arteriosus
  – Congenital CMV infection
  – Congenital HIV infection
Safety complicated to evaluate

• Patient does not have any complaints
  – Classical side effects (nausea & vomiting, headache, rash) extremely rare
  – Several symptoms (intraventricular haemorrhage, seizures, changes in laboratory parameters) common at that age

• Effect of a new agent on growth and development needs to be evaluated
  – Long-term studies – 5 to 10 years
  – Interference with bowel colonisation in antibiotics
  – Effect of drugs on learning
Issues

• Minimisation of pain & distress
• Blood loss via repeated sampling
  – How much blood could be taken?
• Formulations
  – Oral administration may not be feasible
  – IV formulations in large vials (dilution 1:1000)
• Low interest from industry
  – Small market
  – Vulnerable population
  – Studies difficult to conduct
How to get information to physicians?

- Off label use of gentamicin is common (Israel, 2000)
  - Dose not identified
- 03.08.2008 PubMed search
  - 180 titles on gentamicin & pharmacokinetics & neonates
  - Most have some recommendations on dosing
- SPC for gentamicin
  - Dose in children is 3.5 to 7 mg/kg once daily
  - No mentioning of different dosing regimen for neonates, especially of VLBW or ELBW
Future directions

- Not enough information to extrapolate PK, efficacy or safety from older age categories
- If there is a medical need studies in neonates should be encouraged
- Co-operation is a key
  - Between different countries and hospitals
  - Between academia – industry - regulators
- Overstudying & overrecruiting should be avoided
  - Available data should be analysed and made available
  - Innovative study design – less subjects and less pain & distress
- New data are awaited through WR and EU paediatric regulation