Breakout Session #1: Neonatal Brain Injury

Heike Rabe and Ronit Pressler, Moderators

International Neonatal Consortium

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

CRITICAL PATH INSTITUTE
a decade of excellence

10 YEARS

Participants of Neonatal Brain Injury Breakout

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PRIORITY AREA NEONATAL SEIZURES

- CRITERIA
- High incidence
- Burden of disease
- Clinical relevance
- Burden to parents
- Validated biomarkers for short and long term outcome
- Scientific needs

DETAILED RESPONSES - NS #1

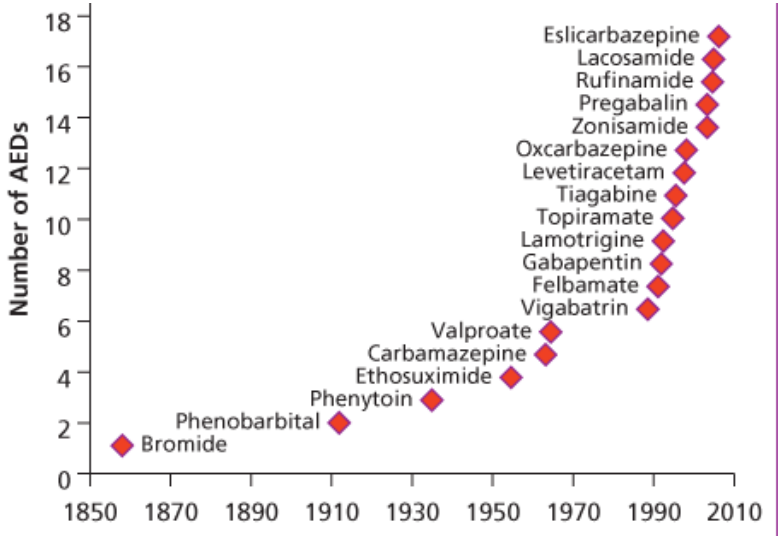
- Neonatal seizures
  - Most common neurological emergency in neonatal period
  - Incidence in term babies: 2-3/1000 live births, more frequent in preterm
  - Most common cause: HIE at term, IVH & PVL in preterm
  - Associated with poor neurodevelopmental outcome and epilepsy later in life. Evidence that seizures increase hypoxic brain damage in HIE.
  - 1st line treatment not changed over last 50 years, despite fact that phenobarbitone effective in only 50% of babies
  - Urgent need to develop new anti-seizure drugs for babies

Response to Breakout Question #2

- For indication X, what non-clinical studies?
  - Neonatal seizures
    - Some models exist, need to be used (in past inadequate models were used)
    - Juvenile animal studies needed for
      - new drugs for toxicity;
      - for prevention of seizures
      - long term effect for all AED
    - Dose finding and PK studies needed: new AED, eg brivaracetam

Neonatal seizures

- Diagnosis is made clinically or aEEG, not adequate for drug development (Boylan et al 2013)
- No evidence base for current management of neonatal seizures (Boots and Evans, 2004; WHO, 2011)
- No new AED developed (1st line PB)
- Risk due to frequent off -label use of antiepileptic drugs (Pressler, et al 2015)
- Outcomes poor (Uria-Avellanal et al 2013)



NEMO: Treatment of NEonatal seizures with Medication Off-patent

- European funded program (FP7)
- 14 partners in 8 countries:

  University College London, University College Cork, Uppsala University Hospital, University Medical Centre Utrecht, Karolinska University Hospital, University of Leeds, Erasmus Universitair MC Rotterdam, Great Ormond Street Hospital.

NEMO

Treatment of **NE**onatal seizures with **M**edication **O**ff-patent: evaluation of efficacy and safety of bumetanide

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- Uppsala University Hospital, Lena Hellstrom-Westas, Johan
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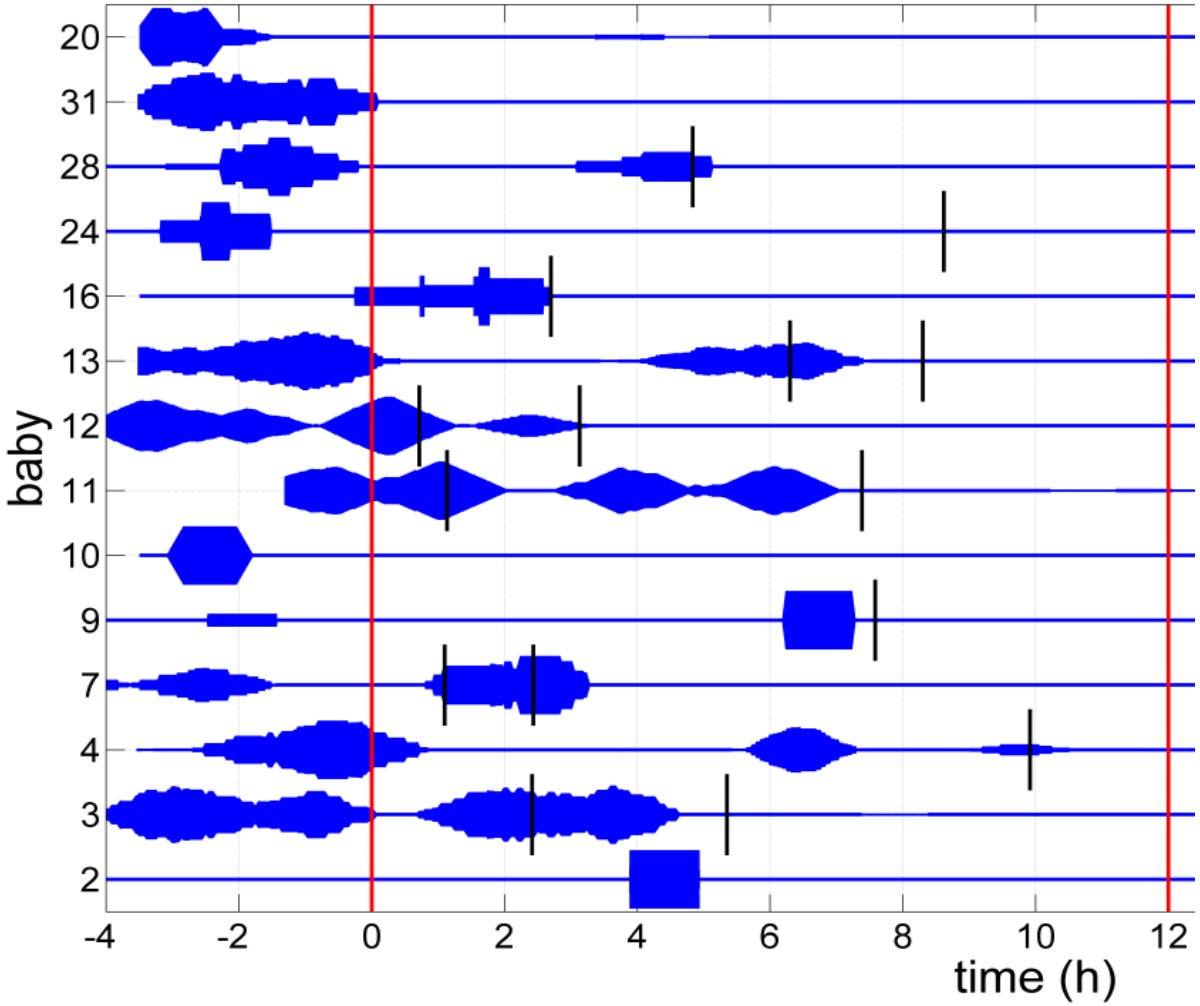
- Erasmus Universitair MC Rotterdam, Renate Swarte
- INMED, INSERM U29, Yehezkel Ben-Ari,
- Duke Clinical Research Institute, Barry Mangum
- Great Ormond Street Hospital: Vanshree Patel
- Only for Children Pharmaceuticals, Vincent Grek
- Scientific advisory board: Eli Mizrahi, Paul Coldiz

Evolution of seizures



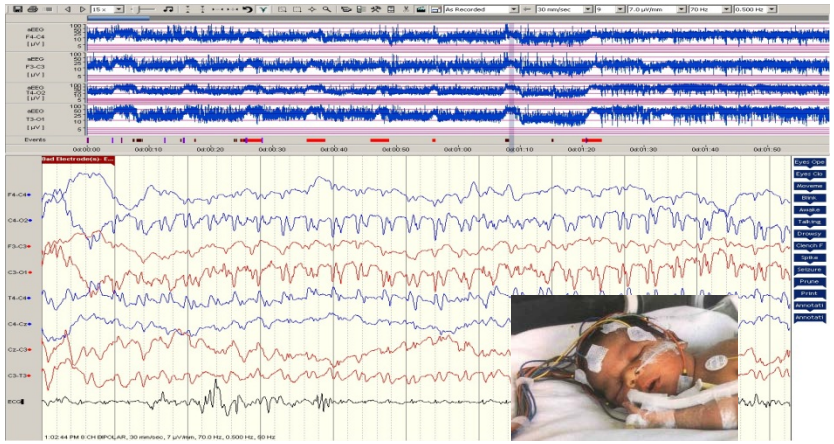
DETAILED RESPONSES – NS #3

- Extrapolated form adults to neonates limited,
- no RCT for most drugs, 1 for phenobarbitone
- Master protocol very helpful and achievable in this setting
- Drug classes alter inclusion/exclusion criteria only in exceptions
- Parameters for modelling & simulation tool depend on drug

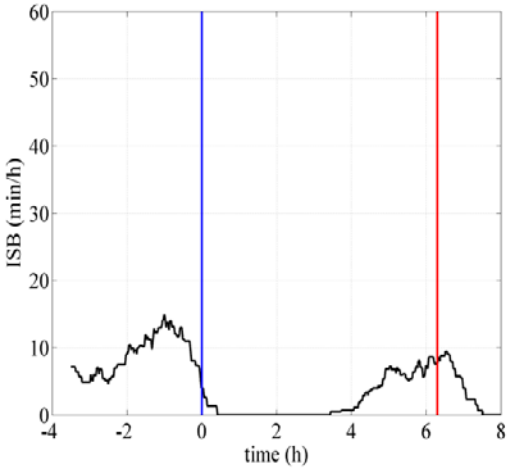
PROPOSED STARTER PROJECT NEONATAL BRAIN

- Develop and Write MASTER STUDY PROTOCOL for seizures in Neonatal Neuro-Critical Care
- Start with Term infants and seizures
- Biomarker: continuous EEG
  - Needs standardisation & validation (from existing standards)
- Short term outcome: reduce seizure burden in cEEG

EEG monitoring



Seizure burden



| Drug 1
| Drug 2

PROPOSED STARTER PROJECT NEONATAL BRAIN

- Develop and Write MASTER STUDY PROTOCOL for seizures in Neonatal Neuro-Critical Care
- Start with Term infants and seizures
- Biomarker: continuous EEG
  - Needs standardisation and validation (from existing published standards)
- Short term outcome: reduce seizure burden in cEEG
- Long term outcome: MRI imaging, neuro-developmental assessments

SHORT ACHIEVABLE GOALS

- MASTER STUDY PROTOCOL
- BRINGS INC TOGETHER ON ACHIEVABLE GOAL
- PUBLISH CONSENSUS STATEMENT IN PEER REVIEWED JOURNAL

- All of the above: measurable deliverables
- Time frame: 1 year

NEXT SLIDES FOR LONG PANEL SESSION

Response to Breakout Question #1

- For neonatal brain injury, what indication(s) are in most need of effective therapies?
- Neonatal seizures
  - Most common neurological emergency in neonatal period: at least 2-3/1000 term births, more common in VLBW
  - Common causes: HIE, IVH / PVL
  - Associated with poor neurodevelopmental outcome & epilepsy
- IVH in preterm
  - Incidence 1-12% in VLBW
  - Associated with poor neurodevelopmental outcome
- White (and gray) matter injury in preterm
  - Incidence 3-4% VLBW
  - Associated with poor neurodevelopmental outcome

Response to Breakout Question #2

- For indication X, what non-clinical studies?
  - Neonatal seizures
    - Some models exist, need to be used (in past inadequate models were used)
    - Juvenile animal studies needed for
      - new drugs for toxicity;
      - for prevention of seizures
      - long term effect for all AED
    - Dose finding and PK studies needed: new AED, eg brivaracetam
  - IVH
    - Some models exist, need to be used
    - Juvenile animal studies should assess drug efficacy for underlying pathophysiology
  - PVL
    - Some models exist, need to be used
    - Juvenile animal studies can mimic chorioamnionitis

DETAILED RESPONSES – NS #2 - I

- Non-clinical studies for neonatal seizures
  - Phenobarbitone for prevention of seizures
    - No juvenile animal toxicity studies needed
    - Dose finding and PK studies available for neonates
    - RCT to proof efficacy needed
  - Midazolam
    - Juvenile animal toxicity studies needed
    - Dose finding and PK studies available for neonates
    - RCT to proof efficacy needed
  - Lidocaine
    - No juvenile animal toxicity studies needed
    - Dose finding and PK studies available for neonates
    - RCT to proof efficacy needed

DETAILED RESPONSES – NS #2 - II

- Non-clinical studies for neonatal seizures
  - Levetiracetam
    - Juvenile animal toxicity studies needed
    - Dose finding and PK studies available for neonates
    - RCT on going
  - Brivaracetam
    - Juvenile animal toxicity studies needed
    - No dose finding and PK studies
    - RCT to proof efficacy needed
  - Topiramate
    - juvenile animal toxicity studies needed
    - Limited PK and dose finding studies available
    - non-clinical data be extrapolated to inform some but not all clinical development (concern: specific language impairment)

Response to Breakout Question #3

- What information needed before starting clinical trial?
  - Neonatal seizures
    - Neonatal models need to be tested form beginning as extrapolated form adults to neonates very limited.
    - Master protocol very helpful and achievable in this setting
    - Inclusion/exclusion criteria need to be adapted to drug classes
    - Parameters for modelling & simulation tool depend on drug
  - IVH
    - Establish pathophysiological pathways to be studied in animal modes
    - Investigate protective effects of placetal transfusion
  - PVL
    - Animal models to establish pathophysiological pathways

Response to Breakout Question #4

- Are there impediments to establishing a master protocol (do multiple approaches exist – comparative effectiveness studies)? Is there equipoise?
  - Neonatal seizures
    - Master protocol urgently needed to aid new drugs licenced
    - Need for input from industry, academia and regulators
  - IVH
    - Defined inclusion criteria & outcomes needed to aid new drugs licenced
    - Need for input from industry, academia and regulators
  - PVL
    - As above

Response to Breakout Question #5

- What potential biomarkers and clinical trial endpoints could be used?
  - Are any prognostic, predictive, pharmacodynamic, and safety biomarkers available? Are any regulatory ready?
  - Neonatal seizures
    - Validated biomarker: continuous EEG (seizure burden) = primary outcome measure
    - Sec outcome measures: rescue drugs, short and long-term neurological (MRI score) outcome
  - IVH
    - Primary outcome measure: prevention IVH (biomarker US / MRI)
    - Secondary outcome measure: severity / hydrocephalus
  - PVL
    - Primary outcome measure: prevention PVL (biomarker US / MRI)
    - Secondary outcome: progression

Response to Breakout Question #6

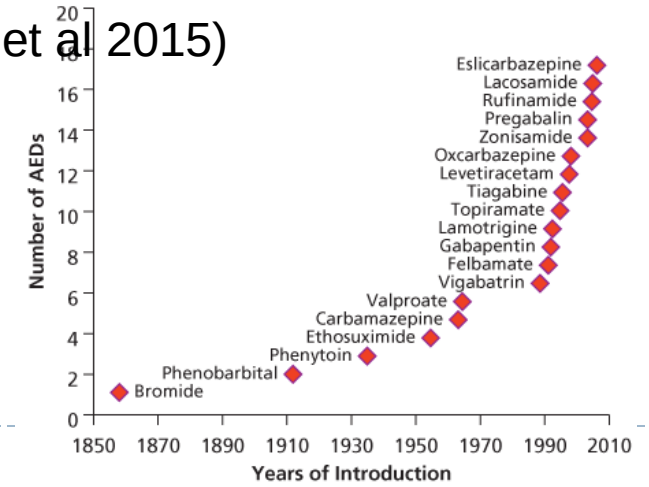
- What long-term outcome measures are available to assess the safety and efficacy of the therapy?
- Neonatal seizures
  - Short term efficacy of seizure burden (contin. EEG)
  - Short term outcome incl MRI score & neuro status
  - Validate neurostatus
  - Long term outcome ages/stages questionnaire or similar
  - Long term outcome at 24 months (Bayley Scales III).
  - Socioeconomic effect & impact on careers of intervention needed
- IVH
  - Short term outcome incl Sono/MRI score & neuro status
  - Long term outcome ages/stages questionnaire or similar
  - Long term outcome at 24 months (Bayley Scales III).
  - Socioeconomic effect & impact on careers of intervention needed
- PVL
  - As above

Response to Breakout Question #7

- In light of your responses to Questions 1-6, where are the gaps in knowledge and how would you prioritize the studies needed to approach the neonatal brain injury indication?
- Neonatal seizures:
  - No RCT available for most drugs, need for new anti-seizure drugs
  - Master protocol incl meaningful outcome measures needed to aid development and efficacy testing of anti-seizure drugs
- IVH
  - Indomethacin for prevention
  - Definition of common inclusion criteria and outcome measures
- PVL
  - Animal models for pathophysiology
  - Definition of common inclusion criteria and outcome measures

DETAILED RESPONSES – NS #1

- Diagnosis clinically or aEEG - not adequate for drug development (Boylan et al 2013)
- No evidence base for current management of neonatal seizures (Boots and Evans, 2004; WHO, 2011)
- No new Anti-Epileptic Drug developed for neonatal seizures
- Risk due to frequent off-label use of antiepileptic drugs (Silverstein et al 2008; Pressler et al 2015)



AED: antiepileptic drug.