Treatment of Neonatal Seizures –
The Evidence Base
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Disclosure

- EU funding (FP7 program, GA 241479)
- No other disclosures
Learning Objectives

By the end of this session you should

- Understand the evidence of current practice in the management of neonatal seizures
- Appreciate the ethical predicament and logistic difficulties of clinical trials in this age group
- Recognize ways how to overcome these
Neonatal seizures

- Incidence of seizures:
  - 0.5-3 per 1,000 term live births
  - 10-130 per 1,000 preterm live births

- Seizure classification
  - Volpe (1989, 2008)
  - Mizrahi (1998)
  - ILAE (NS currently not included)

- Nearly all acute seizures
  - birth asphyxia (HIE)
  - vascular
  - Infections

Current practice in management of neonatal seizures

Diagnosis:

- clinically
- amplitude integrated EEG (aEEG)

First line drug: phenobarbitone

Evidence to justify this practice?
Abstract

Objectives To determine whether parachutes are effective in preventing major trauma related to gravitational challenge.

Design Systematic review of randomised controlled trials.

Data sources: Medline, Web of Science, Embase, and the Cochrane Library databases; appropriate internet sites and citation lists.

Study selection: Studies showing the effects of using a parachute during free fall.

Main outcome measure Death or major trauma, defined as an injury severity score > 15.

Results We were unable to identify any randomised controlled trials of parachute intervention.

Conclusions As with many interventions intended to prevent ill health, the effectiveness of parachutes has not been subjected to rigorous evaluation by using randomised controlled trials. Advocates of evidence based medicine have criticised the adoption of interventions evaluated by using only observational data. We think that everyone might benefit if the most radical protagonists of evidence based medicine organised and participated in a double blind, randomised, placebo controlled, crossover trial of the parachute.
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Seizures a clinical diagnosis?

- 20 video clips of 11 seizures and 9 other events
- Evaluated by 137 health professionals (US, Ire, UK)
  - 91 doctors (consultants, fellows, residents)
  - 46 NICU nurses / midwives
- Asked to identify seizures vs non-seizures

Malone et al 2008
Which one is a seizure?

Video A = 323351

Video B = 323352

Text code to 22333
Which one is a seizure?

Video A

Video B
Seizures not a clinical diagnosis!

- Correctly identified events: 10/20 in average
  - Clonic seizures most frequently identified
  - Others poorly
- Poor agreement with correct diagnosis (0.09/-0.02)
- Poor inter-observer agreement (0.21/0.29)

Malone et al 2008
Seizure detection on neonatal ITU

- Clinical vs cEEG
  - Clinical seizures activity in 20-50% of total EEG seizure burden\(^1\)\(^-\)\(^2\)
  - High risk of under and over diagnosis\(^1\)

- aEEG vs cEEG
  - Sensitivity 20-60%\(^3\)-\(^5\)
  - Multiple channels better than 1

\(^1\)Murray D et al 2009; \(^2\)Nash KB et al 2011; \(^3\)Bourez-Swart MD et al 2009; \(^4\)Shellhaas ra ET AL 2007, \(^5\)Rennie et al 2004
Electroclinical dissociation or uncoupling

Occurs in at least 50% of babies after PB or phenytoin
Related to excitatory function of GABA

Weiner et al Ped Neurol 1991; Boylan et al Arch Dis Child 2002;
Age dependant mechanisms

I am not just a little adult!

Ben-Ari 2002

Development

Baby
High NKCC1, low KCC2

Adult
Low NKCC1, high KCC2

Co-transporter
Evidence base for treatment of neonatal seizures (Cochrane Report)

Database search 1966-2004

- **Objective**: seizure frequency, reduced mortality/disability
- **Only 2 adequate trials (RCT with EEG monitoring)**
  - Painter et al 1999 and Boylan et al 2004

Booth D and Evans DJ Cochrane Database Syst Rev. 2004
Phenobarbital compared with phenytoin for neonatal seizures

Seizure control achieved in 59% of babies

Second line AED treatment

- 27 electrographic and electroclinical
  - 5 protocol violations
- 22 phenobarbitone
  - 11 responders
  - 3 midazolam
    - 0 responders
  - 5 lignocaine
    - 3 responders
  - 3 clonazepam
    - 0 responders

Seizure control achieved in 52% of babies

Boylan G et al Neurology 2004
Evidence base for treatment of neonatal seizures (Cochrane Report)

Database search 1966-2004

- **Objective**: seizure frequency, reduced mortality/disability
- **Only 2 adequate trials** (RCT with EEG monitoring)
  - Painter et al 1999 and Boylan et al 2004
  - Phenobarbitone / phenytoin successful in 40-50%
- **Conclusion:**
  Little evidence from RCT to support use of any AED in neonatal period

Booth D and Evans DJ Cochrane Database Syst Rev. 2004
In the treatment of neonatal seizures, the chasm between what we know from the bench and what we do in routine bedside practice is wide. The two most commonly used medications, phenobarbital and phenytoin, were introduced as anticonvulsants in 1914 and 1938. Little was known then about the control of cellular and network excitability or how the developing brain is physiologically distinct from the mature insult. In the same setting, topiramate (and possibly, AMPA antagonists as a group) are safe. There are numerous relevant molecular targets in the immature brain for anticonvulsants and neuroprotectants, although no agents designed to act at these sites are undergoing clinical trials at this time. The development of a parenteral form of topiramate has been halted for business reasons.
Age dependent mechanisms of seizures in the immature brain

- Enhanced excitatory neurotransmission
  - GABA excitatory
  - GluR-mediated excitation
- Neuropeptides increase hyperexcitability
- Ion channel configuration favours depolarization
- Reduced inhibitory neurotransmission

Ben-Ari Y & Holmes GL 2006; Jensen F 2010
Bumetanide inhibits epileptic activity in immature rats

Source: Fukuda 2005
Bumetanide

- Diuretic: blocks NKCC1 co-transporter
- PK/PD:
  - Studied in critically ill babies, incl preterm\(^1\) (unclear during cooling)
- Safety:
  - Good safety profile as diuretic \(^2\)\(^-\)\(^4\)
  - Ototoxicity? \(^5\)\(^-\)\(^6\)
- Other issues:
  - Penetration of BBB unclear

Challenges of clinical trials and drug development in neonatal seizure

• Ethical predicament
  • Vulnerable age group
  • Acute seizures, critically ill, co-morbidity

• Logistical difficulties
  • Diagnosis and monitoring
  • Recruitment
  • Regulatory requirements (EMA/FDA, GCP)

• Expensive, but low return

Chiron C et al Drugs 2008; Lawrencea, R et al , J Ped Neurol 2009
Small patients – big challenges
Small patients – big challenges

Need for collaboration within and between specialities and countries
How to overcome the challenges of clinical trials in neonatal seizure

- Multicenter, collaborative trials
- Innovative methods (statistics, pharmacokinetics)
- cEEG for diagnosis and efficacy
- High ethical standards
- High standards of trials (GMP, GCP)
- Central funding necessary
**NEMO**: Treatment of NEonatal seizures with Medication Off-patent

- European funded program (FP7)
- Evaluation of efficacy & safety of bumetanide for treatment of NS
- 14 partners in 8 countries

**Plan**:
- Phase I/II (NEMO1)
  - Dose-finding and PK evaluation
  - Open label exploratory study
  - Continuous EEG monitoring
  - Bayesian approach
  - PK population approach

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    - Open label exploratory study
    - Continuous EEG monitoring
    - Bayesian approach
    - PK population approach
  - Randomised controlled trial (NEMO2)
  - Drug development (PUMA)
Attention to detail

• Multicenter, multidisciplinary collaborative trial
• Innovative methods
  • Bayesian statistics,
  • PK population approach
  • Standardising iv lines

¹Allmark P & Mason D J Med Ethics 2006
Attention to detail

• Multicenter, multidisciplinary collaborative trial
• Innovative methods
  • Bayesian statistics,
  • PK population approach
  • Standardising iv lines
• cEEG for diagnosis and efficacy
• High ethical standards: continuous consenting
• High standards of trials (GMP, GCP)

¹Allmark P & Mason D J Med Ethics 2006
Clinical Trials Directive 2001/20/EC

- Went into effect 01/05/04
- deals primarily with implementation of GCP
- defines minimum organizational requirements
- Commencement, conduct and conclusion.
Impact on Clinical Care and Practice

Take home messages:

• No evidence for the current practice in the management of neonatal seizures

• Clinical trials in this age group provide many logistical and ethical difficulties

• Obligation of causing no harm but at the same time to improve treatment

• High standards of trials are necessary, making central funding necessary
NEMO Partners

- University College London, Ronit Pressler, Helen Cross, Neil Marlow
- University College Cork, Geraldine Boylan, B Murphy, D Murray
- INSERM U663, Catherine Chiron, Stèphane Auvin, Perrine Plouin
- Assistance Publique – Hopitaux de Paris, Gerard Pons, Vincent Jullian
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- Helsinki University Central Hospital, Sampsa Vanhatalo, M Metsaranta
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- University Medical Centre Utrecht, Lena Hellstrom-Westas
- Karolinska University Hospital, Mats Blennow, Boubou Hallberg
- Duke Clinical Research Institute, Barry Mangum
- University of Leeds, Malcolm Levene, Sharon England
- Erasmus Universitair MC Rotterdam, Renate Schwarz,
- Great Ormond Street Hospital: Biren Patel, Havinder Hara
- Only for Children Pharmaceuticals, Vincent Grek
- ClinInfo S.A, Patrick Chevarier
- GABO:mi, Brigitte Fuchs

http://www.nemo-europe.com/