

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?



BMJ Parachute use to prevent death and major trauma related to gravitational challenge: systematic review of randomised controlled trials

Gordon C S Smith and Jill P Pell

BMJ 2003;327;1459-1461

doi:10.1136/bmj.327.7429.1459

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.



BMJ

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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

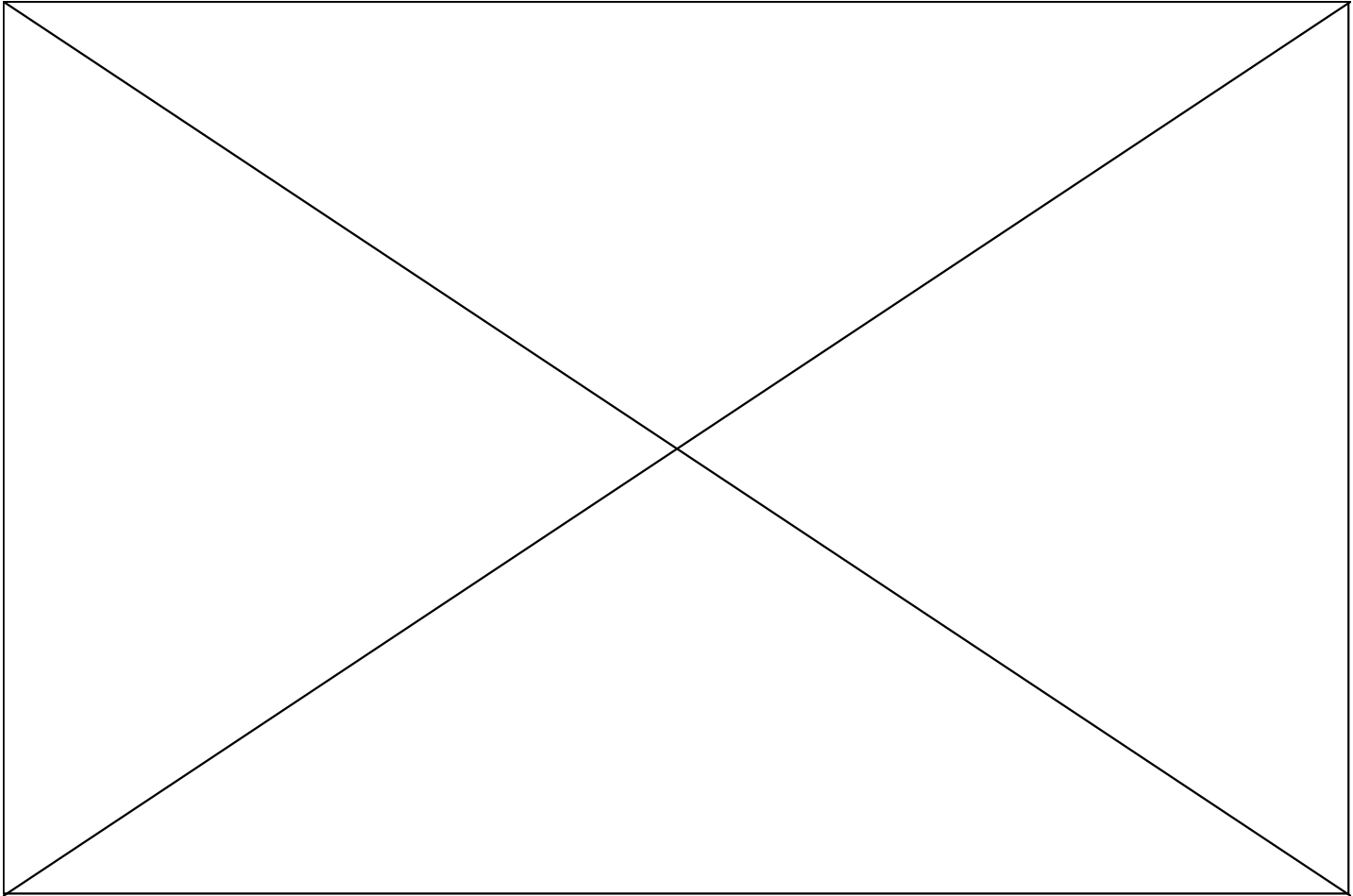
Malone et al 2008

Which one is a seizure?

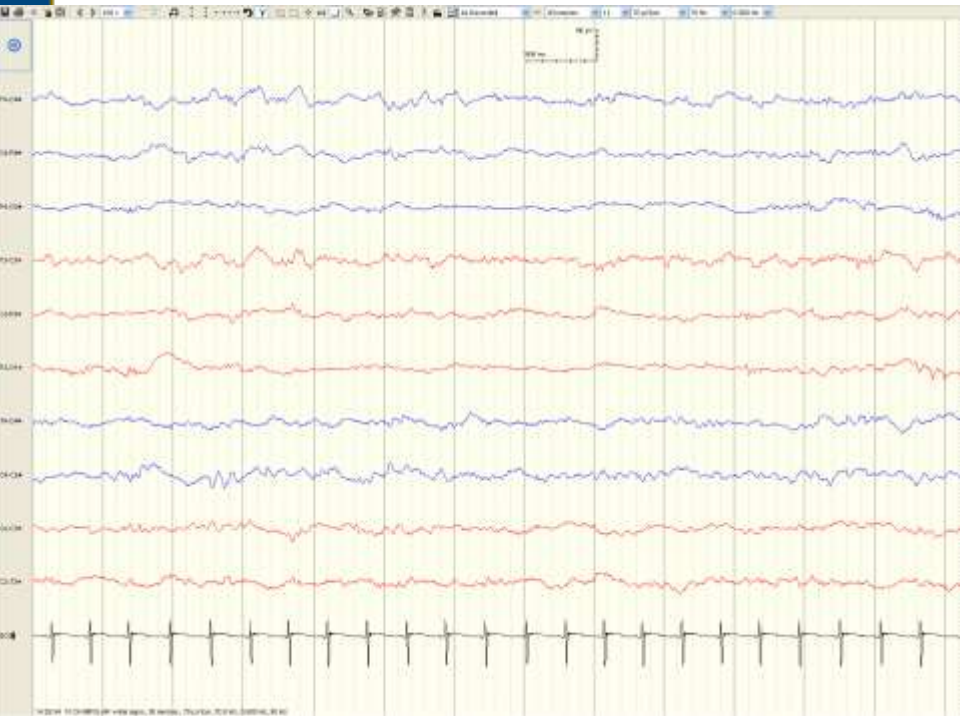
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Video B = 323352

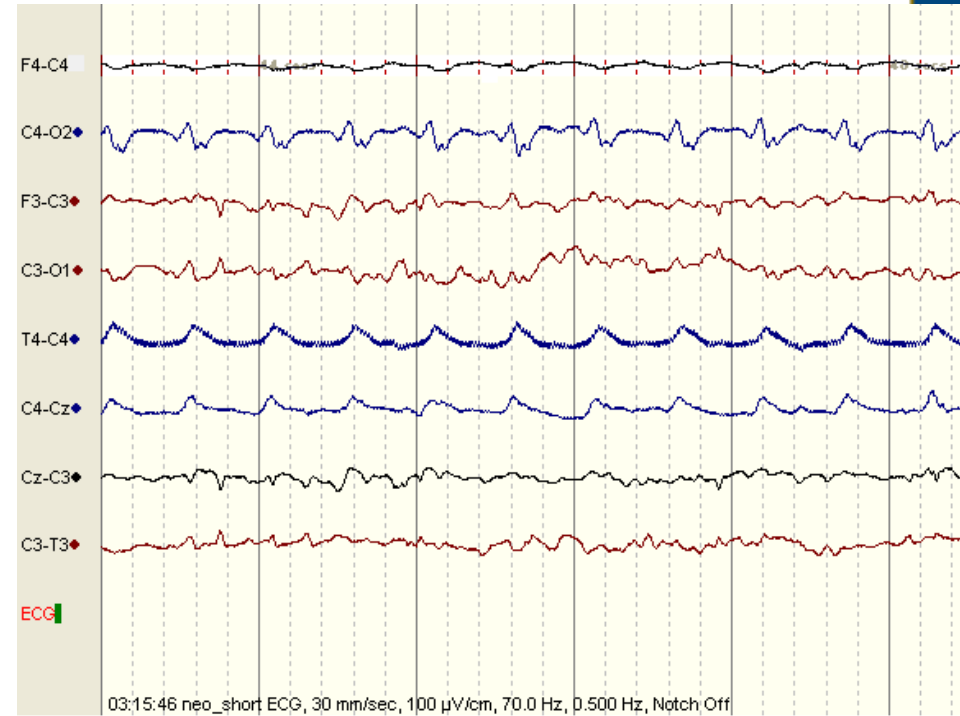
Text code to 22333



Which one is a seizure?



Video A



Video B

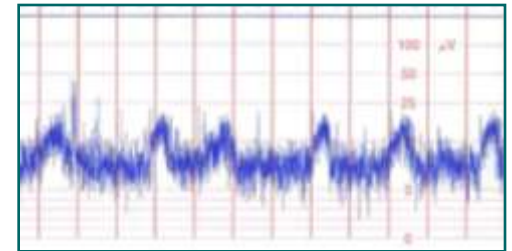
Seizures not a clinical diagnosis!

- 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 burden¹⁻²
 - High risk of under and over diagnosis¹
- aEEG vs cEEG
 - Sensitivity 20-60%³⁻⁵
 - Multiple channels better than 1



¹Murray D et al 2009; ²Nash KB et al 2011; ³Bourez-Swart MD et al 2009;
⁴Shellhaas ra ET AL 2007, ⁵Rennie et al 2004

Electroclinical dissociation or uncoupling

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



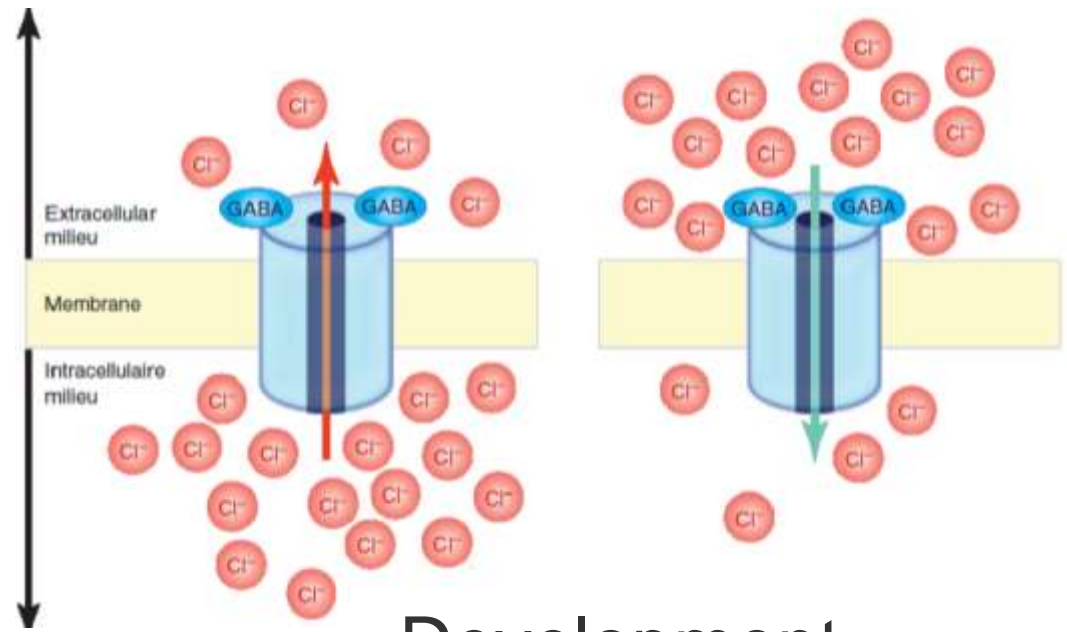
Weiner et al Ped Neurol 1991; Boylan et al Arch Dis Child 2002;
Scher et al Pediatr Neurol 2003; Glyks J et al Neuron 2009

Age dependant mechanisms

GABA

excitatory

inhibitory



Development

Baby

Adult

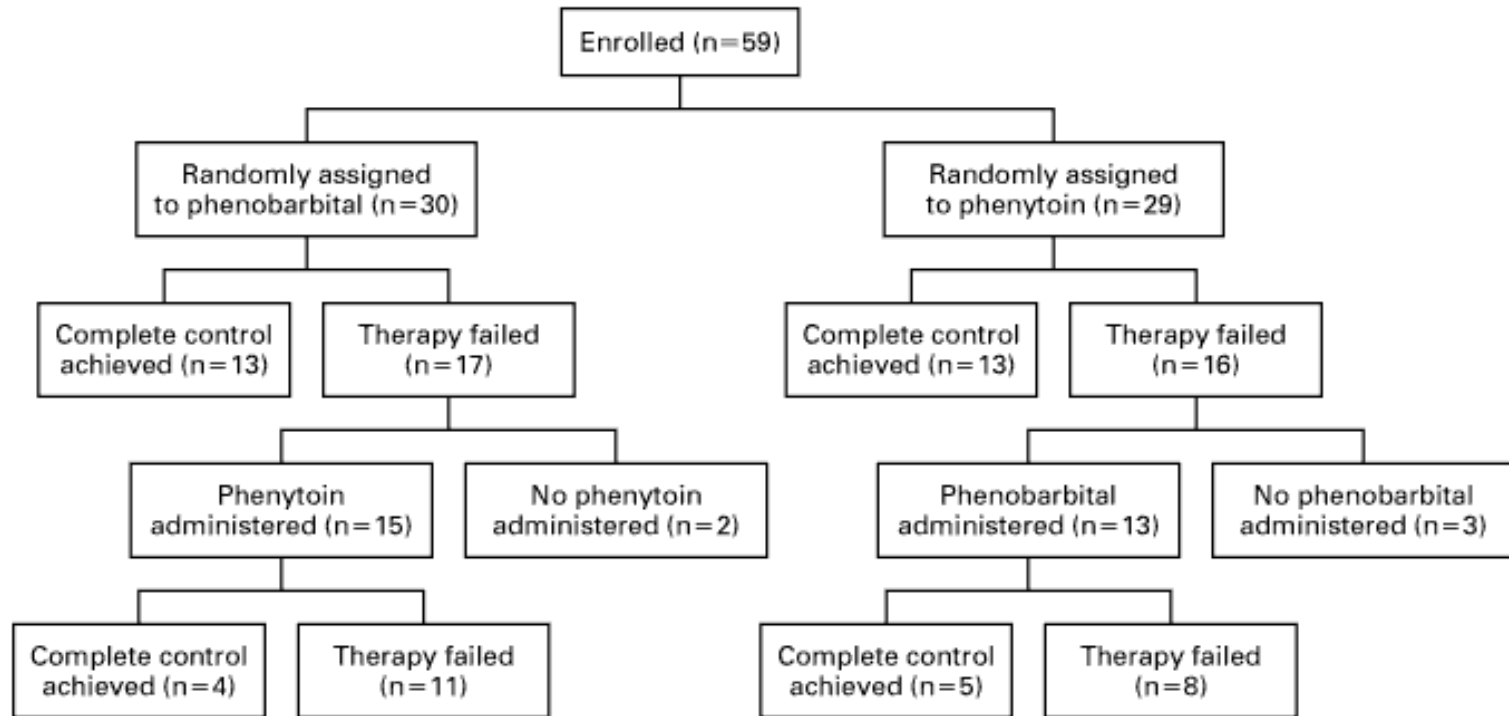
High NKCC1, low KCC2 Low NKCC1, high KCC2
Co-transporter

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

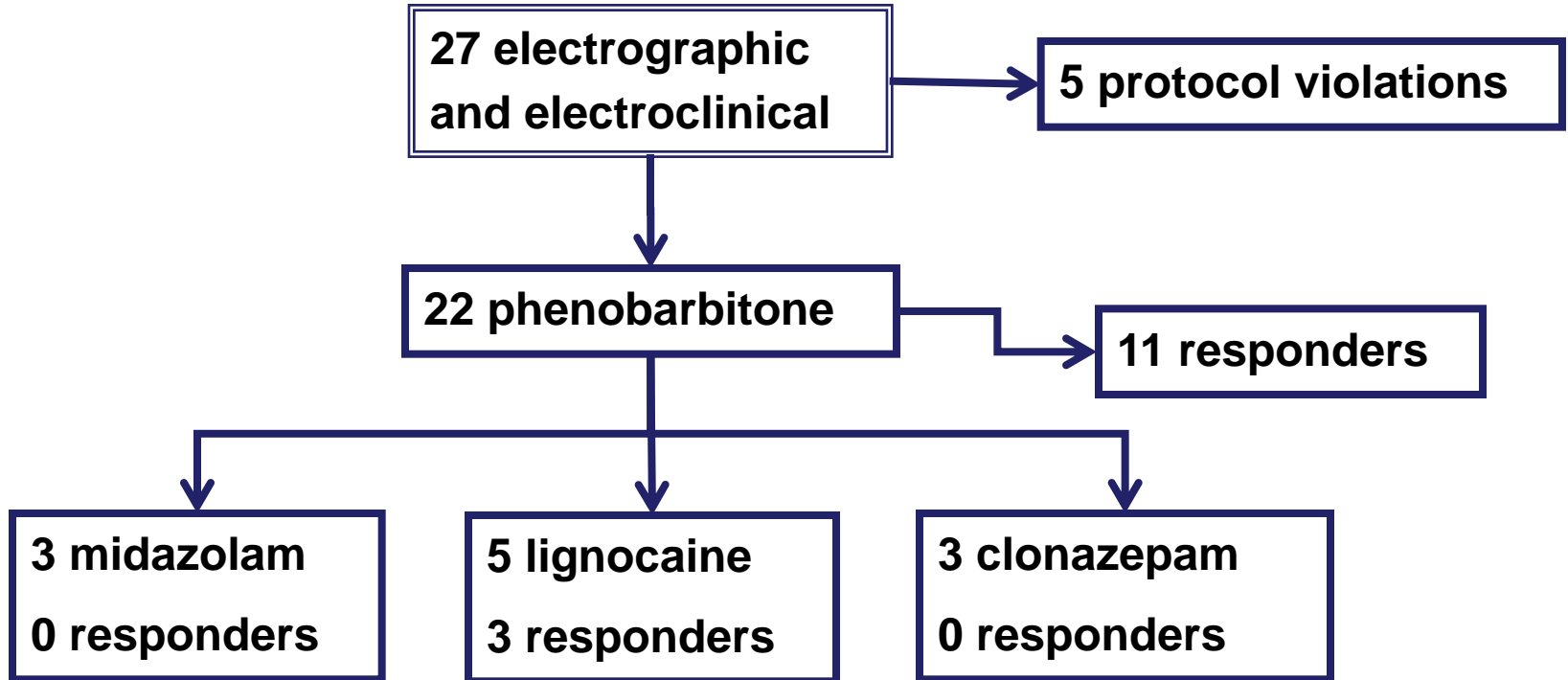
Phenobarbital compared with phenytoin for neonatal seizures



Seizure control achieved in 59% of babies

Painter MJ et al 1999 (NEJM:341:485-9):

Second line AED treatment



Seizure control achieved in 52% of babies

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

Evidence base for the treatment of Neonatal Seizures

NEUROLOGY 2005;64:776-777

Editorial



Neonatal seizures

After all these years we still love what doesn't work

Raman Sankar, MD, PhD; and Michael J. Painter, MD

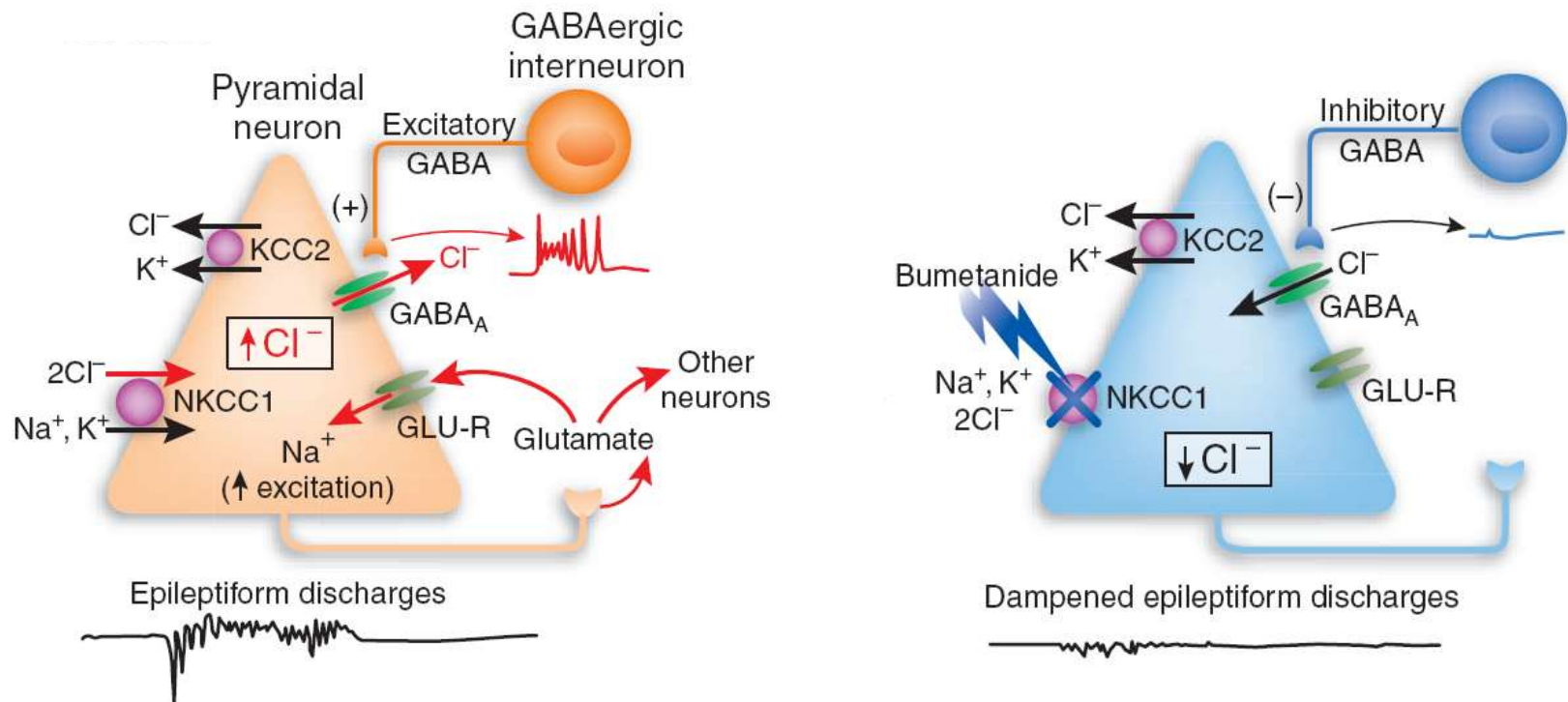
In the treatment of neonatal seizures, the chasm between what we know from the bench and what we do in routine bedside practice is wide. The two most commonly used medications, phenobarbital and phenytoin, were introduced as anticonvulsants in 1914 and 1938. Little was known then about the control of 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.⁹ There are numerous relevant molecular targets in the immature brain for anticonvulsants and neuroprotectants,⁹ 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**

Bumetanide inhibits epileptic activity in immature rats



Dzhala VJ et al Nature 2005, Ann Neurol 2008
Source: Fukuda 2005

Bumetanide

- Diuretic: blocks NKCC1 co-transporter
- PK/PD:
 - Studied in critically ill babies, incl preterm¹ (unclear during cooling)
- Safety:
 - Good safety profile as diuretic²⁻⁴
 - Ototoxicity?⁵⁻⁶
- Other issues:
 - Penetration of BBB unclear



¹Lopez-Samblas et al 1997, ²Marshall et al 1998, ³Sullivan et al 1996;
⁴Brown 1981, ⁵Rybak 1993, ⁶Rais-Bahrami et al 2004

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; Lawrence, 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 **NE**onatal seizures with **M**edication **O**ff-patent

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



NEMO

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



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- European funded program (FP7)
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- 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
 - Randomised controlled trial (NEMO2)
 - Drug development (PUMA)



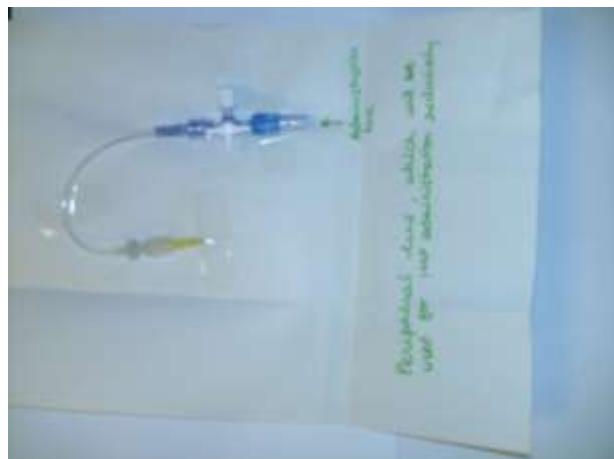
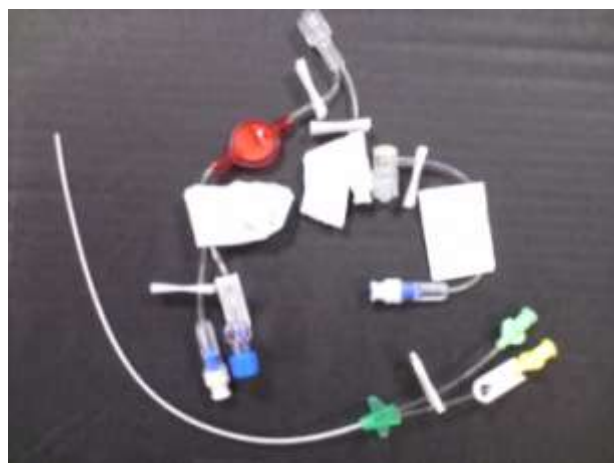
NEMO

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



Attention to detail

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



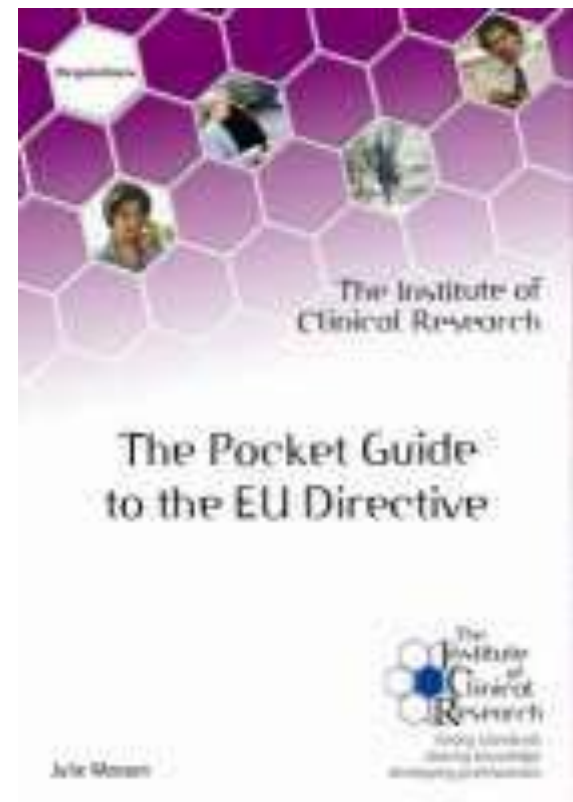
Attention to detail

- Multicenter, multidisciplinary collaborative trial
- Innovative methods
 - Bayesian statistics,
 - PK population approach
 - Standardising iv lines
- cEEG for diagnosis and efficacy
- High ethical standards: continuous consenting¹
- 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, Stéphane Auvin, Perrine Plouin
- Assistance Publique – Hopitaux de Paris, Gerard Pons, Vincent Jullian
- INMED, INSERM U29, Yehezkel Ben-Ari, R Khazipov, I Khalilov
- Helsinki University Central Hospital, Sampsa Vanhatalo, M Metsaranta
- Uppsala University Hospital, Linda De Vries, Mona Toet, Kees v Huffelen
- 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/>