New drugs for neonatal seizures

Dr Ronit Pressler and Professor Geraldine Boylan are leading the first ever international effort to evaluate antiepileptic drugs and management protocols specifically designed for newborn babies.

Could you explain how you both became involved in the project ‘Treatment of NEonatal seizures with Medication Off-patent’ (NEMO)?

We met at King’s College Hospital in London while undertaking our PhDs and soon realised that we had many shared research interests. We have worked together ever since, developing our interest in neonatal seizures and electroencephalography (EEG). In 2008, we applied for European Union Seventh Framework Programme (FP7) funding to build a European research consortium to study treatments for neonatal seizures.

What are the key aims and objectives of NEMO?

The goal is to develop new effective antiepileptic drugs (AEDs) suitable for the treatment of neonatal seizures using innovative methods and novel diagnostic technologies. At the same time, we aim to evaluate other aspects of neonatal seizure management, such as indications for treatment, choice of first- and second-line drugs, duration of treatment, and pharmacokinetics and pharmacodynamics specific to the neonatal age group.

Why is the traditional method for measuring seizure burden not applicable for neonatal seizures?

Seizures in the newborn period are difficult to diagnose. Reliable differentiation between a clinical seizure and a non-seizure-related movement in this age group is almost impossible, which results both in over- and under-diagnosis.

In many cases, clinical signs cannot be identified; therefore, continuous monitoring of the brain’s electrical activity with EEG is necessary to reliably detect seizures and monitor treatment. However, performing and analysing continuous EEG monitoring is not a trivial task in the neonatal intensive care unit.

How does neonatal hypoxic ischaemic encephalopathy (HIE) affect newborn babies?

A small number of babies show signs of stress at delivery – and sometimes this indicates that the baby suffered a lack of oxygen or blood supply around the time of its birth. Most of these babies do well once they are resuscitated; however, in some the brain may have been significantly compromised, resulting in HIE, the most common aetiology of seizures in the neonatal period.

There is a high risk that HIE complicated by seizures will cause permanent neurological injury leading to lifelong disability such as cerebral palsy, epilepsy and learning difficulties. The quality of life of the child with profound neurological handicap is very poor, and the amount of care they require has implications for parents, siblings and the health service.

Why is this particular area of research a high priority for Europe?

Neonatal seizures can be difficult to control using currently available AEDs. However, very few studies have addressed issues relating to the use of these drugs in neonates.

Phenobarbital (PB) is the most widely used first-line AED for neonatal seizures, but there is considerable variation in the choice of second-line AEDs for treating seizures that do not respond to PB. With lack of evidence, effective treatments are potentially being withheld from this young age group of patients.

Should seizures in babies be treated differently from seizures in adults?

Only a few years ago, preclinical researchers found out why the drugs we use in children and adults do not work in babies. One of the main differences is that an important neurotransmitter called gamma-aminobutyric acid (GABA) has opposite effects in babies compared with older children and adults. In mature neurons, GABA reduces and stops seizure activity, whereas in newborn babies it may increase and worsen it. Furthermore, some of the drugs we are currently using can cause additional brain damage by increasing apoptosis.

Can you summarise the findings from NEMO’s first second-line drug trial using bumetanide?

Bumetanide, a loop diuretic, specifically blocks the age-dependent mechanism responsible for seizure development in the newborn brain. It has been safely used in babies as a diuretic for many years.

The trial used EEG monitoring to evaluate bumetanide initially in an open feasibility and dose-finding study, where newborn babies received bumetanide in addition to PB. Due to safety concerns and a lack of recruitment efficacy, the trial was prematurely terminated in November 2012. The results have recently been published in Lancet Neurology.

Are there any other treatments you are planning on testing?

We are now planning to evaluate the efficacy and safety of lidocaine in an international, multicentre randomised controlled trial. Lidocaine is the only drug currently on the priority list for research in neonatal seizures by the European Medicines Agency. The aim of this study is to evaluate the safety and efficacy of a new formulation of lidocaine as second-line treatment in cases of seizures not responding to first-line PB.
Protecting newborn potential

Coordinated by University College Cork, Ireland, and University College London, UK, the NEMO expert consortium is focusing on neonatal seizures to provide evidence-based improvements in neonatal care. The goal is to reduce the burden of motor or cognitive disability resulting from neurological damage.

ABNORMAL ELECTRICAL ACTIVITY in the brain that gives rise to seizures is a relatively common occurrence in newborn babies admitted to intensive care, and even more prevalent in premature babies. One of the most common causes of seizures in newborns is encephalopathy due to a lack of oxygen supply to the brain often caused by complications during or just before birth. There is a risk that babies experiencing seizure events will have lasting brain injury that will predispose the child to neurodevelopmental impairment later in life.

It is therefore important to treat and monitor episodes in a timely and efficacious manner. The current standard first-line treatment for seizures in babies is phenobarbital (PB), a barbiturate (ie. sleep-inducing) anti-epileptic drug (AED) originally developed in the early 1900s. However, according to Dr Ronit Pressler, a consultant in clinical neurophysiology at Great Ormond Street Hospital for children, only 40 to 60 per cent of babies respond to PB treatment. Over the past 20 years, there have been a variety of new AEDs developed and licensed for treating adult and child epilepsy. Yet, within the past five decades, there have been no new drugs developed that specifically treat seizures in newborn babies.

As recently appointed Chair of the taskforce on neonatal seizures for the International League Against Epilepsy, Pressler is seeking to address the dearth of reliable treatments for seizures in newborn babies. With her long-term collaborator Geraldine Boylan, Professor of Neonatal Physiology at University College Cork, Pressler has instigated and is coordinating a large European project that brings together a consortium of experts in the field to improve the outcomes of babies who have seizures by using novel AEDs.

‘Treatment of NEonatal seizures with Medication Off-patent’ (NEMO) is a five-year project funded through the European Union Seventh Framework Programme (FP7). It endeavours to meet calls from bodies such as the European Medicines Agency for better treatments for neonatal seizures, particularly in babies with hypoxic ischaemic encephalopathy (HIE).

THE NEMO CONSORTIUM

The World Health Organization (WHO) Guidelines issued in 2011 state that there is a clear need for evidence of effectiveness when it comes to management of neonatal seizures. The NEMO consortium aims to gather such evidence: it comprises 14 partners from universities and hospitals in eight countries across Europe and the US, representing pure scientific and practical clinical expertise in neonatology, paediatrics, neurophysiology, pharmacology, neurobiology and epileptology. This multidisciplinary group will be conducting the largest multicentre international clinical trial specifically devised for treating seizures in very young babies.

It is extremely difficult to clinically detect seizures in a young baby. For this reason, the researchers are employing continuous electroencephalography (EEG): “Babies cannot tell us how they feel and many seizures are missed,” explains Boylan. “It is imperative that we use EEG monitoring and interpretation in the neonatal population for seizure detection and treatment monitoring.”

The term ‘off-patent medicines’ describes those that have been in use for many years and are no longer under license by a pharmaceutical company. Two such drugs have been considered by NEMO as second-line options where a baby’s response to PB is inadequate. Over the project’s first four years, a loop diuretic called bumetanide was trialled; now, a protocol is being developed to test the safety and efficacy of lidocaine, which can act as both an anaesthetic and AED and is already used in many centres across Europe to treat seizures in newborns.

SPECIAL CONSIDERATIONS

The question of ethics and legal implications in trials involving vulnerable babies is naturally a concern for the NEMO consortium – in addition to such practical issues as obtaining consent from appropriately informed parents during a very difficult period, the project is ensuring compliance with all the relevant codes, guidelines, conventions and declarations, including conformance to data protection rules, as well as the national regulations of the countries in which the drug trials are conducted: Ireland, the UK, France, Sweden, Finland and the Netherlands. The project is also being run according to the rules for Good Clinical Practice and Good Manufacturing Practice as they apply to European studies. A consequence of this is that, though the second-line drug under evaluation may be replaced with a placebo for some of the participants in the trials, the first-line drug, PB, will always be administered.

So far, nearly 20 papers have been published by the NEMO consortium, with an additional 10 papers to follow soon. The results of the main study have been published in Lancet Neurology (Pressler et al, 2015, Lancet Neurol, [Epub ahead of print]), and can be viewed here: www.thelancet.com/journals/laneur/article/PIIS1474-4422(14)70303-5/abstract
A key issue for the project is that a newborn baby’s brain responds differently to certain drugs compared with children of more than a few months old and adults: “The brain of a baby is immature; it is not just a small adult brain, it works differently,” observes Pressler. One of the most important differences lies in the mechanisms of the gamma-aminobutyric acid (GABA) neurotransmitter, which many AEDs target. In fact, most AEDs increase GABA activity, which can have deleterious consequences: “Certain ion pumps, which are overexpressed in immature neurons, cause GABA to act in an excitatory way in babies, which can exacerbate seizures,” Pressler explains. After the first few months of life, however, this mechanism reverses, hence the need to test any new AEDs in newborn babies and conduct research in this vulnerable group.

LESSONS LEARNED
A widening of the use of hypothermia for HIE, in which a lower body temperature is induced under controlled conditions to prevent further brain damage, meant that fewer candidate patients than anticipated were presented for possible inclusion in the bumetanide trial. Of the 14 patients eventually recruited, hearing loss was found in three. Though the sample size was small and hearing loss is also associated with HIE, the NEMO consortium agreed that the bumetanide trial should be stopped. The project is now embarking on the next planned trial, using a new formulation of lidocaine as a potential second-line drug.

A notable achievement of the project so far is its successful establishment of the NEMO consortium, a unique assembly of renowned research centres dedicated to improving management of neonatal seizures. Pressler and Boylan are keen to share some valuable insights from developing this taskforce, such as the importance of choosing the right outcome measures – given that gauging seizure burden is unreliable when it comes to neonatal patients – and the fact that conducting a trial in neonatal intensive care units inherently involves logistical challenges that only highly skilled and collaborative teams can overcome. Above all is the value of continuous EEG monitoring where neonates are concerned – though Boylan emphasises that this currently requires specialised equipment and specific expertise for both recording and interpreting the results: “We have a vision for 21st Century management of babies with seizures. Early technology-aided diagnosis and timely treatment should ensure improved outcomes. Automated real-time analysis of the EEG at the cot-side may prove to be the best solution”.

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