An open label exploratory dose finding and pharmacokinetic clinical trial of bumetanide for the treatment of NEonatal seizure using Medication Off-patent (NEMO).

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The aim of the trial is to obtain data on the optimal dose, feasibility and pharmacokinetics of bumetanide when given as an add-on treatment for seizures in full term babies with hypoxic ischemic encephalopathy (HIE). Bumetanide will be given in a...

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Congenital and peripartum neurological conditions
Study type	Interventional

Summary

ID

NL-OMON36769

Source
ToetsingOnline

Brief title
Neonatal seizures using medication off patent (NEMO).

Condition

- Congenital and peripartum neurological conditions
- Neonatal and perinatal conditions

Synonym
epilepsy, seizures

Research involving
Human

Sponsors and support

Primary sponsor: Only For Children Pharmaceuticals
Source(s) of monetary or material Support: EU

Intervention

Keyword: anticonvulsant, newborn, seizures

Outcome measures

Primary outcome

Primary Endpoint

• The optimal dose is defined as achieving effective seizure

reduction:

o Reduction of electrographic seizure burden by >= 80% during

the 3rd and 4th hour after the first bumetanide administration

compared to a 2 hour epoch prior to Bumetanide

administration.

o No need for rescue AED within 48 hours

• An acceptable safety profile at any time within 48 hours

after the first dose is defined as

o Absence of Suspected Unexpected Serious Adverse Reactions

(SUSARs)

o Serious Adverse Reactions (SAR) which are at least probably

related in <10%

o Clinically acceptable frequency of adverse reactions

* Severe hypokalaemia (<2.8mmol/l) and / or ECG

changes in <10%

* Severe dehydration (dehydration with hypotension

(mean BP< 35mmHg persistent > 1 hour) which requires inotropic support)

in <10%

Stage 2

• PK measurements (bumetanide at the optimal dose)

Secondary outcome

Stage 1

• PK measurements

• Overall seizure control within the first 24 hr after bumetanide

administration evaluated after the end of trial

Stage 2

• Safety of bumetanide in babies with HIE

• Overall seizure control within the first 24 hr after bumetanide

administration evaluated after the end of trial

Study description

Background summary

Perinatal asphyxia occurs in approximately 20 per 1,000 live births. A proportion of these babies develop an early neonatal encephalopathy, or hypoxic ischaemic encephalopathy (HIE) which is a major cause of perinatal mortality (60% of perinatal mortality), and long-term severe neuro-disability (Volpe, 2008). The incidence of HIE is around 2-3/1000 births in the developed world, but much higher in the developing world. The prognosis varies greatly, and depends on the severity of the clinical encephalopathy, varying from mild irritability to deep coma. Seizures are the hallmark of HIE, and EEG studies have shown that many asphyxiated babies often have seizures that go unnoticed and which is not reduced by current antiepileptic drug therapy.
Data from both human and animal studies suggest that seizures amplify neonatal hypoxic-ischemic brain damage. In a recent study of term newborns with HIE brain injury was independently associated with the severity of seizures (Miller et al., 2002). Prolonged seizures cause progressive cerebral hypoxia and changes in cerebral blood flow (Boylan et al., 1999). These findings support the hypothesis based on data from animal models, that neonatal seizures are not only a manifestation of acute ischemic brain injury, but also exacerbate tissue damage (Wirrell et al., 2001) and provide evidence for the conjecture that effective treatment of neonatal seizures could attenuate acute brain injury in this setting.
Phenobarbitone remains the first line antiepileptic drug (AED) for seizures in infants or babies world-wide despite the fact that it has limited efficacy. The prognosis for neurodevelopmental outcome is poor in babies with seizures. Furthermore, there is evidence that phenobarbitone may itself impair neurodevelopmental outcome and may cause additional brain damage by increasing neuronal death (apoptosis).
Better treatments for neonatal seizures have been identified as a high priority for research worldwide. We propose to evaluate the use of bumetanide in babies whose seizures are resistant to the standard first-line AED regimen (phenobarbitone). We know that for these babies the outlook is poor. Hence a trial of novel treatments, based on current knowledge gained in basic research, is justified. Our research consortium has extensive experience in the study of neonatal seizures as well as in clinical management and basic neuronal mechanisms. This will enable us to use continuous EEG monitoring to measure treatment responses in all infants.
The results of this trial should translate into better care for babies with seizures and improved neurological outcomes.

Study objective

The aim of the trial is to obtain data on the optimal dose, feasibility and pharmacokinetics of bumetanide when given as an add-on treatment for seizures in full term babies with hypoxic ischemic encephalopathy (HIE). Bumetanide will be given in a range of doses from 0.05 to 0.3 mg/kg as an adjunct to the standard treatment (phenobarbitone). The trial will consist of two stages: Stage 1: a dose-finding and confirmatory stage and Stage 2: a pharmacokinetic (PK) stage at the optimal dose. Overall this trial will also evaluate the

feasibility of a subsequent larger randomised controlled trial (NEMO2).

Primary Objectives

Stage 1
• To estimate the optimal dose of bumetanide for use as an adjuvant therapy to phenobarbitone in neonatal seizures. This optimum dose will be that which achieves the maximum seizure reduction with an acceptable safety profile when used in addition to standard therapy (second dose of phenobarbitone) in > 50% of patients
.
Stage 2
• To determine the pharmacokinetics of bumetanide when given at the optimal dose as an add-on to phenobarbitone for neonatal seizures not responding to the first dose phenobarbitone

Secondary Objectives
• To assess the feasibility of neonatal seizure treatment with bumetanide in babies with HIE and seizures that are not responding to a first dose of phenobarbitone alone.
• To assess whether bumetanide reduces the need for rescue medication.
• To assess bumetanide as a diuretic in babies with HIE.

Study design

This multicentre clinical trial will consist of two stages: Stage 1: a dose-finding and confirmatory stage and Stage 2: a PK stage, at the optimal dose.
The dose-finding and confirmatory stage will be conducted using the continual reassessment method requiring a Bayesian sequential design. Four different dosage regimens will be tested: dosages of 0.05, 0.1, 0.2, 0.3 mg/kg followed by three further doses at the same dosage at 12-h intervals. Efficacy will be evaluated with continuous EEG monitoring.

If seizure burden is not reduced by >80% after the firts dose of bumetanide, the rescue medication can be given according to the preferences of each participating recruitment centre. There should be however a delay of at least two hours before the rescue medication is given, to allow time to see a potential effect of bumetanide. Only when a status epilepticus is present, a rescue medication may be given earlier. However it is recommended to use either midazolam or lignocaine (see section 9.12 Rescue Medication for dose recommendations).
Due to a relatively low incidence of hypoxic encephalopathy and seizure it is necessary to recruit form several trial sites, hence this will be a multicentre clinical trial.

Sample Size Determination

Infants will be studied in nine centres in Europe (Utrecht, Rotterdam, Cork, Uppsala, Stockholm, Paris, London, Leeds, Helsinki)
• Stage 1 (Dose-finding and confirmatory stage): 24 patients
• Stage 2 (PK stage): Minimum 25 patients

In the dose-finding and confirmatory stage, cohorts of two consecutive patients will receive the same dose regimen, as determined by the statistician on the basis of the preceding cohort results. The primary efficacy endpoint will be the reduction of seizure burden of >=80% on EEG after phenobarbitone and bumetanide treatment defined as >= 80% reduction of seizure burden within hours 3 and 4 after the first bumetanide administration, compared to the baseline; a 2 hour epoch immediately prior to the first Bumetanide administration.
A decision rule will be set up before initiating the trial in order to avoid further exposure to side effects in subsequent patients and consisting in situations where the calculation would lead to increase the dose either to maintain the previous dose or to decrease it according to a pre-established intensity simple 3-steps ranking of the side effect of interest.
In the PK stage, patients will receive bumetanide at the optimal dose established in the dose-finding and confirmatory stage

Intervention

Trial design

Dose-finding and confirmatory design

The primary aim of the trial is to determine the efficacy and toxicity of four dose levels of bumetanide (0.05 -0.3 mg/kg).
A dose-finding combined phase I/IIa open sequential trial will be performed. Patient response and tolerance will be jointly modelled as dual binary endpoints. The recommended dose levels for future experimentation will the one satisfying both efficacy criteria and toxicity restriction.
The trial will consist of the sequential treatment of groups of two patients until a total number of at least 24 patients had been reached. The first group will be treated at the first dose level (i.e. 0.05 mg/kg), whereas the doses levels for the subsequent groups will be determined according to the model estimates of the dose-efficacy and dose-toxicity relationships.
At each dose level, data will be recorded in a computer program that performed an analysis of both efficacy and safety. The trial is planned to end before the fixed maximal number of patients, if all the dose levels had an efficacy lower than the defined target, and/or if all the dose levels had toxicity higher than the target (Figure 1). An underlying mathematical model expressed the probabilities of response and tolerance as independent functions of dose (O*Quigley et al. 2001, Zohar and O*Quigley 2006).
The treatment allocation will be performed by the eCRF following this

methodology base on safety and efficacy outcomes from previous patients. This means that it is crucial to enter efficacy and safety criteria for all babies in real time. To secure the process, an e-mail will be automatically sent by the server (ClinInfo) specifying the current treatment allocation and the next treatment allocation depending on the various simulated hypothesis.

Study burden and risks

All infants recruited for the study will be admitted to a neonatal intensive care unit and will be monitored continuously for most vital signs, such as respiratory rate, heart rate and bloodpressure. EEG will be used to monitor brain activity continuously as well. Compared to care given before the study period, no additional monitoring will be used and no invasive tests will be performed. Blood samples will be taken, but as all children will have an arterial line inserted while being in the NICU, this will be not an invasive/painful procedure. The bloodsamples will be small (4 x 0.5 mL) and as the infants will be full term, the amount sampled is not likely to lead to additional blood transfusions.
The drug that will be used, has been used in neonates as a diuretic, especially in the United States. Side effects that can occur in adults are • Muscle cramps (seen in 1.1% of treated patients)
• Dizziness (1.1%)
• Hypotension (0.8%)
• Headache (0.6%)
• Nausea (0.6%)
• Encephalopathy in patients with pre-existing liver disease (0.6%)
• Dehydration
• Tachycardia

Note: assessment of the symptoms and signs listed above will be limited to quantifiable signs in the neonatal patient; i.e. dehydration and secondary hypotension and tachycardia.
The benefit of particpation in the study is that infants will be monitored carefully for neonatal seizures and these will be treated. In our unit this is not really different from the care at present and the benefit may be that bumetanide will be more effective than drugs used at present in this group of infants.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Children (2-11 years)

Inclusion criteria

* Male or female term baby with gestational age of 37-43 weeks and postnatal age < 48 hours
* One or more of the following:
- APGAR score < 5 at 5 minutes
- Umbilical cord or first arterial blood sample pH < 7.1 or base deficit > 16 mmol/L
- Postnatal resuscitation still required 10 minutes after birth
* Clinical evolving encephalopathy
* Received one dose of standard anticonvulsive therapy (phenobarbitone, 20 mg/kg) for clinical or electrographic seizures
* EEG: equal to or more than 3 minutes cumulative seizures, or 2 or more seizures of > 30 sec duration over 2 hr period within first 48 hr of life
* Written informed consent of parent or guardian
* EEG monitoring has commenced within the first 48 hours of birth

Exclusion criteria

•Suspected or confirmed brain malformation, inborn error of metabolism, genetic syndrome, or major congenial malformation

•Congenital (in utero) infection (TORCH).
•Babies who have received diuretics such as furosemide or bumetanide within the past 24 hours in routine clinical management
•Total serum bilirubin > 15 mg/dl (255 micro mol/ll) at inclusion
•On any other anticonvulsive medication other than phenobarbitone or single doses(s) of midazolam for intubation.
•Anuria/renal failure defined as serum creatinine > 200 micro mol/l.
•Severe electrolyte depletion (Na <120mmol/l, K <3.0mmol/l)

Study design

Design

Study phase:	2
Study type:	Interventional
Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	29-10-2011
Enrollment:	20
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Bumetanide 0.2 mg/mL sterile solution for IV administration
Generic name:	bumetanide

Ethics review

Approved WMO

Date:	20-01-2011

Application type:	First submission
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	14-03-2011
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	19-08-2011
Application type:	First submission
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	01-02-2012
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	03-04-2012
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	12-04-2012
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	17-04-2012
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	18-04-2012
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	25-07-2012
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	22-10-2012

Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
EudraCT	EUCTR2010-020797-41-NL
CCMO	NL31194.041.11