Pharmacokinetics and Pharmacodynamics of Medication in Asphyxiated Newborns During Controlled Hypothermia PharmaCool National Multicenter Study.

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This project aims to develop an evidence based effective and "safe" dosing regimen for commonly used life saving medicationsused in the treatment of asphyxiated, critically ill newborns, undergoing therapeutic hypothermia.To this aim the...

Ethical review	Approved WMO
Status	Pending
Health condition type	Congenital and peripartum neurological conditions
Study type	Observational invasive

Summary

ID

NL-OMON34433

Source
ToetsingOnline

Brief title
PharmaCool National Multicenter Study.

Condition

- Congenital and peripartum neurological conditions
- Neonatal and perinatal conditions

Synonym
medication metabolism during the intensive care treatment of resuscitated newborns

Research involving
Human

Sponsors and support

Primary sponsor: Academisch Medisch Centrum
Source(s) of monetary or material Support: ZonMw subsidie: Programma :Priority Medicines for Children

Intervention

Keyword: hypothermia, multicenter study, perinatal asfyxia, pharmacodynamics/ kinetics

Outcome measures

Primary outcome

Primary study outcomes:

1) PK properties of three groups of drugs in a prospective cohort of patients:

Group I: Antibiotic medications

Group II: Analgesic medications

Group III:Sedative and anti-epileptic drugs

2) PD parameters :

-anti-epileptic drugs: successful seizure control (anti-epileptics),

-sedative drugs: measuring newborn stress using the Comfort Scale.

-antibiotics: adequate treatment of perinatal infection shown by negative

repeat blood culture, normalisation of C-reactive protein and leukocyte counts

(antibiotics),

- determination of the MIC -value of cultured microorganisms to evaluate

antibiotic susceptibility -or resistance.

3) possible side effects:(e.g. gentamyxcin)

-(acute) drug effects on end organs such as liver, kidney, bone marrow,

-(long-term outcome) hearing screening at 3 months of age including the ALGO newborn hearing screening.

Secondary outcome

FOLLOW-UP

Long term follow-up in these asphyxiated neonates is part of the standard care protocol of the Dutch Working Group of Neonatal follow-up (L.N.F.). Data are collected outside the scope of this project. Long term outcome by neurodevelopmental testing at the ages of 6 months, 1 and 2 years will be related to neonatal pharmacological and clinical data.

Study description

Background summary

Perinatal asphyxia resulting in hypoxic ischemic encephalopathy (HIE) occurs in 1-2 infants per 1000 deliveries.. Term neonates experiencing a severe hypoxic-ischemic insult during birth may develop HIE within hours. There is a high risk for long term neurological sequelae as cerebral palsy, psychomotor retardation or visual or auditory handicaps
CONCEPT
Supportive treatment comprises mechanical ventilation, cardiovascular support, and treatment of infections and seizures. The most frequently used life-saving drugs in these cases are sedatives, analgesics, antibiotics, and antiepileptic drugs (AED).
CONTROLLED HYPOTHERMIA
The standard treatment for HIE is aimed at stabilisation of physiological vital parameters and detection and management of neonatal seizures. Recent large randomized controlled trials in human asphyxiated neonates demonstrated a statistically significant and clinically important improvement of long term outcome. Maximum benefit of hypothermia is attained when this

treatment is initiated within six hours following the perinatal hypoxic ischemic event. Since 2009, all 10 Neonatal Intensive Care Units (NICUs) in the Netherlands have adopted controlled hypothermia as the standard of care in neuroprotection for neonates with HIE.
PHARMACOTHERAPY AND THERAPEUTIC HYPOTHERMIA
PK/PD properties of commonly used drugs in neonatal intensive care are influenced by hypothermia. Unknown Pharmacokinetics may also result in subtherapeutic drug dosing. Since each year 200 newborns will be exposed to controlled hypothermia in the Netherlands, the development of evidence based guidelines concerning drug dosing (including loading dose and dose interval) and therapeutic drug monitoring are urgently needed.
This study has been prioritized by the NNRN and is featured in the top 5 of the Research Agenda 2009-2011 of the MCRN.

Study objective

This project aims to develop an evidence based effective and "safe" dosing regimen for commonly used life saving medicationsused in the treatment of asphyxiated, critically ill newborns, undergoing therapeutic hypothermia.

To this aim the PK/PD properties of three groups of drugs will be investigated in a prospective cohort of patients:

Group I: Antibiotic medications: Penicillin; Amoxycillin; Gentamycin; Amikacin; Vancomycin; Ceftazidim
Group II: Analgesic medications: Morphine
Group III:Sedative and anti-epileptic drugs: Midazolam; Phenobarbitone; Lidocaine

After the translation of results into dosing regimens tailored to this patient group these regimens will be implemented in all Dutch NICUs.

Study design

Multicenter nationwide prospective cohort study in 10 NICUs treating asphyxiated newborns with controlled hypothermia in which plasma levels of antiepileptic, sedative and antibiotic drugs will be measured and used for PK analysis to develop rational and safe
dosage regimens. As a secondary outcome measure the association of possible toxic drug levels with long term clinical outcome will be investigated.

Study burden and risks

The patient burden consists of additional bloodsampling for PKPD research. In total maximally 7 ml will be taken from the bloodstream by indwelling arterial line catheters that are in place in all patients. No extra

venapunctures will be performed for this research.

As the average birth weight of a term newborn is 3.5 kg and the circulating blood volume is 80 ml/ kg (total blood volume: 280 ml), 7 ml will comprise only 2.5% of the total circulating volume for this whole study. A mean volume of only 0.7% of the total circulating blood volume will thus be taken each day for PK/PD research. This is clinically entirely acceptable in terms of circulatory compromise or risk for anemia.
Blood samples for PKPD research will be taken together with clinically indicated blood sampling. Central (arterial) lines will provide bloodstream access for blood sampling. If these lines are not functioning or cannot be placed, infants can not participate in this study.

Contacts

Public
Academisch Medisch Centrum

meibergdreef 9
1100DD Amsterdam
NL
Scientific
Academisch Medisch Centrum

meibergdreef 9
1100DD Amsterdam
NL

Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Children (2-11 years)

Inclusion criteria

Any newborn :;1) with a gestational age > 36 weeks and a birth weight > 3 kg;
2) with Apgar Score at 5 minutes postnatal < 5;
3) with continued resuscitation at 10 minutes postnatally;
4) with 1 hour postnatal bloodgas analysis with pH < 7.0 or base deficit > 16
5) with clinical signs of moderate to severe encephalopathy (defined as a Thomson score of >7 or a Sarnat score of >1)
6) who is undergoing neuroprotective treatment by controlled hypothermia < 6 hours postnatally.

Exclusion criteria

1) congenital hepatic or renal pathology (as this makes interpretation of PKPD results impossible);
2) without central venous line or arterial bloodstream access for blood sampling;
3) without written parental consent to participate following informed consent interview.

Study design

Design

Study type: Observational invasive

Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Pending
Start date (anticipated):	01-01-2011
Enrollment:	270
Type:	Anticipated

Ethics review

Approved WMO

Application type:	First submission
Review commission:	METC Amsterdam UMC

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
CCMO	NL32724.018.10