A prospective investigation into the role of therapeutic hypothermia on medication metabolism and excretion in newborns with perinatal resuscitation.

No registrations found.

Ethical review	Positive opinion
Status	Recruitment stopped
Health condition type	-
Study type	Observational non invasive

Summary

ID

NL-OMON28126

Source
NTR

Brief title
PharmaCool

Health condition

perinatal asphyxia, therapeutic hypothermia, pharmacokinetics, pharmacodynamics.

Dutch:
perinatale asfyxie, therapeutische hypothermie, farmacokinetiek/ farmacodynamiek.

Sponsors and support

Primary sponsor: performers:
Academic Medical Center / Emma Childrens Hospital (Amsterdam)
UMCU/ Wilhelmina Childrens Hospital (Utrecht)
Source(s) of monetary or material Support: ZonMw
Priority Medicines Programma
Laan van Nieuw oost Indie 334
2593 CE den Haag
dosiier nummer:40-41500-98-9002

Intervention

Outcome measures

Primary outcome

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

Secondary outcome

Assessment of possible correlations between medication use during neuroprotective hypothermia and long term neurodevelopmental outcome.

Study description

Background summary

Urgency of pharmacokinetic and pharmacodynamic (PK/PD) research in neonatal post asphyxia hypothermia.

In the Netherlands, perinatal asphyxia (severe perinatal oxygen shortage) necessitating newborn resuscitation occurs in 200 out of 185.000 newly born infants each year. Approximately 20% of these infants die during the first month, and at least 25% of the survivors suffer long term neurological sequelae e.g. cerebral palsy leading to long-term healthcare costs. International randomized controlled trials have demonstrated an improved neurological outcome with therapeutic hypothermia (ca. 33.5 degrees Celsius) during intensive care treatment, which is now the national standard of care.

Yet, a major unmet need is the unknown pharmacokinetics and pharmacodynamics (PK/PD) of life saving medications due to post resuscitation multi organ failure and to the metabolic effects of the cooling treatment itself. We estimate that each year 200 newborns treated for perinatal asphyxia are being exposed to possible unwanted side effects or possible sub therapeutic dosing. To fully benefit from the new hypothermia treatment i.e. to prevent toxicity and/or sub therapeutic drug therapy, we propose a population PK/PD study to establish safe and effective dosage regimens for the CNS drugs and antibiotics frequently used in the intensive care of encephalopathic neonates who undergo therapeutic hypothermia.

There is scarce literature on correct dosage regimens or possible toxic side effects of life-saving drugs commonly used in neonatal intensive care during hypothermia treatment. Unwanted prolonged clinical effects of sedative drugs as well as unpredictable or toxic drug levels during therapeutic hypothermia have been noted in these patients in daily clinical care.

Evidence based pharmacotherapy cannot be applied at this time as basic knowledge on uptake, distribution and clearance of drugs during hypothermia is lacking. Sub therapeutic dosing poses serious threats to recovery, survival and neurological outcome of these critically ill neonatal patients. There is no evidence base for effective and safe therapeutic dosage regimens during hypothermia in neonates. Current medication protocols for hypothermic neonatal patients are largely based on personal experience or experience in normothermic cases. However, there is evidence from animal and human studies that hypothermia influences essential enzyme systems responsible for drug elimination. Therefore, normothermic PK data can not simply be extrapolated to critically ill neonates in the hypothermic state.

There is clearly an urgent need to critically evaluate drug dosing during newborn hypothermia. Finding the right dose will limit the number of patients exposed to hazardous drug regimens. Well designed trials will provide timely and adequate PK/PD data to develop correct drug dosing schedules and rational therapeutic drug monitoring during hypothermia. Because of the relatively small numbers of patients per centre, only multicenter studies will provide these data in a relatively short time span.

This multi-centre study will provide a serum repository enabling simultaneous PK and PD investigations of multiple drugs reducing study costs and increasing efficiency.

Methods:

All term neonates treated with hypothermia for Hypoxic Ischemic Encephalopathy (HIE) resulting from perinatal asphyxia in one of the 10 Dutch Neonatal Intensive Care Units (NICUs) will be eligible for this cohort study. During the first 3-5 days of life blood samples will be taken from indwelling catheters to investigate blood levels of frequently used drug types, i.e. antibiotics, analgesics, sedatives and anti-epileptic drugs (AED). Pharmacokinetic population parameters of volume of distribution (Vd) and
clearance (Cl) during cooling will be modelled using NONMEM. Pharmacokinetic models will be developed for each individual agent. Allometry and maturation will be implemented in the models. The association with pharmacodynamic population parameters such as EEG, blood pressure, pain assessment and infection clearance will be investigated by multivariable repeated measures regression analysis.

Study output and impact:

Data resulting from this multicenter study will be the foundation for establishing an evidence based national guideline on drug dosing during neonatal hypothermia treatment. This guideline will be published on the Dutch Paediatric Association (NVK) website for peer review before implementation. As all Neonatal Intensive Care Units will participate in this study, results will lead to a uniform treatment of hypothermic neonatal patients. Results will also inform the web based evidence based paediatric
formulary and other national and international paediatric drug references.

Study objective

Therapeutic hypothermia is the standard of care in perinatal asphyxia. Current medication protocols for hypothermic neonatal patients are largely based on personal experience or experience in normothermic patients. Evidence based dosing schedules do not exist. However, there is evidence from animal and human studies that therapeutic hypothermia, used as a neuroprotective treatment modality, influences essential enzyme systems responsible for drug elimination.

The hypothesis is that adaptation of drugdosing in newborns will be needed for optimal and safe treatment under hypothermic conditions.

Study design

1. Start inclusion: 01-01-2011;

2. Interim analysis of available data: When half of the targeted incusion number is reached (estimated at: 01-06-2012;

3. End inclusion: 01-01-2014;

4. End follow up for neurodevelopment: 01-01-2016.

Intervention

N/A

Contacts

Public
Meibergdreef 9
T.R. Haan, de
Amsterdam 1100 DD
The Netherlands

+31 (0)20 5663477
Scientific
Meibergdreef 9
T.R. Haan, de
Amsterdam 1100 DD
The Netherlands
+31 (0)20 5663477

Eligibility criteria

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 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 and arterial bloodstream access for blood sampling;

3. Without written parental consent to participate following informed consent interview.

Study design

Design

Study type:	Observational non invasive
Intervention model:	Parallel
Allocation:	Non controlled trial
Masking:	Open (masking not used)
Control:	N/A , unknown

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	01-01-2011
Enrollment:	270
Type:	Actual

Ethics review

Positive opinion

Date:	22-09-2010
Application type:	First submission

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
NTR-new	NL2421

Register	ID
NTR-old	NTR2529
Other	ZonMW : 40-41500-98-9002
ISRCTN	ISRCTN wordt niet meer aangevraagd.

Study results

Summary results
N/A