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

Gepubliceerd: 22-09-2010 Laatst bijgewerkt: 18-08-2022

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...

Ethische beoordeling	Positief advies
Status	Werving gestopt
Type aandoening	-
Onderzoekstype	Observationeel onderzoek, zonder invasieve metingen

Samenvatting

ID

NL-OMON28126

Bron
NTR

Verkorte titel
PharmaCool

Aandoening

perinatal asphyxia, therapeutic hypothermia, pharmacokinetics, pharmacodynamics.

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

Ondersteuning

Primaire sponsor: performers:
Academic Medical Center / Emma Childrens Hospital (Amsterdam)
UMCU/ Wilhelmina Childrens Hospital (Utrecht)
Overige ondersteuning: ZonMw
Priority Medicines Programma

Laan van Nieuw oost Indie 334
2593 CE den Haag
dosiier nummer:40-41500-98-9002

Onderzoeksproduct en/of interventie

Uitkomstmaten

Primaire uitkomstmaten

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.

Toelichting onderzoek

Achtergrond van het onderzoek

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.

Doel van het onderzoek

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.

Onderzoeksopzet

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.

Onderzoeksproduct en/of interventie

N/A

Contactpersonen

Publiek

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Deelname eisen

Belangrijkste voorwaarden om deel te mogen nemen (Inclusiecriteria)

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.

Belangrijkste redenen om niet deel te kunnen nemen (Exclusiecriteria)

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.

Onderzoeksopzet

Opzet

Type:	Observationeel onderzoek, zonder invasieve metingen
Onderzoeksmodel:	Parallel
Toewijzing:	N.v.t. / één studie arm
Blindering:	Open / niet geblindeerd
Controle:	N.v.t. / onbekend

Deelname

Nederland

Status:	Werving gestopt
(Verwachte) startdatum:	01-01-2011
Aantal proefpersonen:	270
Type:	Werkelijke startdatum

Ethische beoordeling

Positief advies

Datum:	22-09-2010
Soort:	Eerste indiening

Registraties

Opgevolgd door onderstaande (mogelijk meer actuele) registratie

Geen registraties gevonden.

Andere (mogelijk minder actuele) registraties in dit register

Geen registraties gevonden.

In overige registers

Register	ID
NTR-new	NL2421
NTR-old	NTR2529
Ander register	ZonMW : 40-41500-98-9002
ISRCTN	ISRCTN wordt niet meer aangevraagd.

Resultaten

Samenvatting resultaten
N/A