Pharmacokinetic and pharmacodynamic modelling of routinely used off label drugs in premature neonates

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Recently, population PK/PD modeling and simulation studies have enabled the development of evidence-based individualized dosing schemes for children with a limited number of subjects, thus improving drug safety and efficacy. The application of PK/PD…

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Other condition
Study type	Observational non invasive

Summary

ID

NL-OMON44214

Source
ToetsingOnline

Brief title
DINO study

Condition

- Other condition
- Seizures (incl subtypes)
- Neonatal respiratory disorders

Synonym
Prematurity

Health condition

Pijn en sedatie

Research involving

Human

Sponsors and support

Primary sponsor: Erasmus MC, Universitair Medisch Centrum Rotterdam
Source(s) of monetary or material Support: ZonMw

Intervention

Keyword: drug, pharmacodynamics, pharmacokinetics, premature

Outcome measures

Primary outcome

1) Pharmacokinetic endpoints are clearance en volume of distribution.

Secondary outcome

Pharmacodynamics of all drugs used will be explored in all included preterm neonates. Drug specific effects of drugs (e.g. pain scores for morphine, blood pressure for dopamine) as well as side effects and short term effects on morbidity and outcome will be analyzed. Additional pharmacodynamic endpoints for 8 of the 9 study drugs is the Drug target concentration for each drug that is related to the desired effect. Fluconazole will only be studied for the PK.

The parameters to measure the effect of the drugs:

a) Fentanyl and paracetamol, used as analgetics; clinical endpoint is pain relief, as routinely measured by the validated COMFORTneo scale and the NRS scale.

b) Midazolam, phenobarbital and levetiracetam, used as anticonvulsive drugs; clinical endpoint is control of convulsions, measured by Cerebral Function Monitoring using amplitude-integrated EEG (aEEG).

c) Midazolam and fentanyl, used as a sedative drug during endotracheal

intubation; clinical endpoint is the intubation readiness score (IRS) and a qualitative intubation score and sedation score.

d) Midazolam and fentanyl, used as a sedative drug during nursing care is measured by the COMFORTneo scale.

e) Doxapram, used as treatment for neonatal apnea; clinical endpoint is control of neonatal apnea and endotracheal intubation in case of failure. The first endpoint can be measured by modern monitoring technology, in which central post-monitoring data stored after initiation of treatment will reveal the effect of doxapram on the reduction or elimination of apneas.

f) Sildenafil, a treatment for PPHN; clinical endpoints are level of ventilatory support, oxygen need (repetitive oxygenation index analyses) and BPD development.

g) Ibuprofen, a treatment for PDA; clinical endpoint is closure of the ductus arteriosus. Echocardiographic imaging allows the measurement of the diameter of the ductus and to calculate the LA/AO ratio (left atrial to aortic root ratio).

Inter- and intra-patient variability of the PD and PK parameters of the drugs to be investigated. Parameters with effect on this variability will be identified.

Tertiary outcome:

a) Development of a minimally invasive Dried Blood Spot analysis method to perform future pharmacokinetic studies in neonates. The measured concentration of the drugs in the dried blood spot samples will be compared with the concentration of the blood samples in the vial, which is the current validated standard method. The validity of the DBS method will be the endpoint.

b) Influence of specific polymorphisms involved in the metabolism of the

investigated drugs.

Study description

Background summary

Approximately 60% of drugs are used off-label in critically ill neonates in the Neonatal Intensive Care Units (NICU). This is even more true for pre-term born neonates in whom pharmacokinetics of these agents may be different due to immature elimination pathways. The lack of sufficient data about efficacy and safety of many of these drugs makes it difficult to have evidence based dosing guidelines for these agents. Therefore the urge for drug research in this population is of great importance.

The pharmacokinetic (PK) and pharmacodynamic (PD) characteristics of drugs in premature infants are different from the characteristics found in term neonates, older children and adults. These differences are caused among others by a different body composition, by immaturity of the renal excretion systems, the metabolic pathways in the liver and other organ functions as well as immature drug receptors and transporters. After birth, there is a rapid development of many of these functions, necessitating frequent adaptation of dosage guidelines in the first few weeks of life. Besides age and size, co-morbidity, co-administration of drugs and genetic heterogeneity may further contribute to this extensive inter-individual variability in pharmacokinetics and pharmacodynamics of premature infants. There is a critical lack of evidence-based data of drug dosing in (extremely) preterm neonates.

Study objective

Recently, population PK/PD modeling and simulation studies have enabled the development of evidence-based individualized dosing schemes for children with a limited number of subjects, thus improving drug safety and efficacy. The application of PK/PD modeling in the most critically ill population of premature infants, with the highest variability in the pharmacokinetics of drugs, and the greatest lack of adequate data underscoring optimal dosage, can contribute to the development of rational, individualized and safe dosing regimens.

This study will provide information on the pharmacokinetics, safety and effectiveness of off-label drugs used in critically ill premature infants: doxapram, fentanyl, midazolam, paracetamol, phenobarbital, sildenafil, levetiracetam, ibuprofen and fluconazole. PK/PD analysis will result in

(adapted) dosage guidelines, thus contributing towards an improvement in the quality of care and cost efficiency. Furthermore the development of Dried Blood Spot (DBS) analysis is investigated for these drugs as a minimally invasive method for conventional patient care and to perform pharmacological studies in children. The adapted dosage guidelines will be implemented directly into clinical practice in collaboration with the NKFK. Therefore the study is designed as an observational multicenter study to be able to collect sufficient data for the drugs of interest.

Study design

This is a prospective observational multicenter study on the pharmacokinetics and pharmacodynamics of paracetamol, fentanyl, midazolam, phenobarbital, doxapram, levetiracetam, sildenafil and ibuprofen, and the pharmacokinetics of fluconazole routinely administered to preterm infants according to standard protocols. The treatment regimen is left to the discretion of the treating physician in accordance with current guidelines. During this study a limited number of additional blood samples will be drawn from the participants for pharmacokinetic analysis, never exceeding 3% of the total blood volume during any four-week period or 1% at any single time.
It is standard care in the Netherlands for all premature born infants under 32 weeks to get seen by the paediatrician at the age of two years for a check on growth and development. The visit to the day care clinic of the hospital of their admission on birth, enables us to collect qualitative data on growth and physiological development as well as from psychological and neurodevelopmental standardised tests.The collected data enables us to gain a better description of the subjects in our study and to further determine safety of the studied drugs.

Study burden and risks

The risk in this study is minimal though the only intervention is additional blood sampling. Blood will only be collected from indwelling arterial lines or during routine blood sampling. Blood will be sampled by experienced professionals according to unit policies, which include measures to minimize pain and distress. If study sampling requires an invasive procedure (i.e. heel prick method), this will only be performed when a blood sample is required for clinical reasons, so study participants will not experience any additional invasive procedures. Furthermore the samples will be obtained from remaining clinical blood samples available in the hospital laboratories (after all relevant routine analyses have been completed). In order to ensure the burden is negligible, the additional sampling is limited to a maximum of 3% of the total blood volume during any four-week period or 1% at any single time. This is in accordance with the EMA guideline on neonatal research. The investigator and attending physicians can decide to withdraw a subject from a scheduled blood sample for medical reasons; ie too low Hb level.

According to the guideline of the Netherlands Federation of University Medical Centres *Kwaliteitsborging mensgebonden onderzoek 2.0*, the risk of participation in this study is categorized as negligible.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Children (2-11 years)

Inclusion criteria

* Gestational age < 32 weeks
* Admitted to 1 of the participating NICUs
* Use of one of the studied drugs as standard of care
* Signed Informed Consent by both parents or guardians

Exclusion criteria

None

Study design

Design

Study type: Observational non invasive

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

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	10-09-2014
Enrollment:	600
Type:	Actual

Ethics review

Approved WMO Date:	21-05-2014
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	03-06-2015
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	08-12-2015
Application type:	Amendment

Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	15-12-2016
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)

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	NL47409.078.14