Optimizing Pain Treatment in Pre-Term Neonates

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To evaluate the relationship of developmental stage (defined by both gestational and postnatal age) to UGT2B7 activity (as determined by CLf,M3G and CLf,M6G).To evaluate the relationship of UGT2B7 genetic variability to UGT2B7 activity (as...

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Other condition
Study type	Interventional

Summary

ID

NL-OMON38405

Source
ToetsingOnline

Brief title
Morphine study

Condition

- Other condition

Synonym
criticall illness prematurity, pain

Health condition

prematuur geboren kinderen

Research involving
Human

Sponsors and support

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

Intervention

Keyword: Critically ill, Morphine, Pain, Preterm Neonates

Outcome measures

Primary outcome

Safety: Infants will have continuous monitoring of vital signs, oxygen saturation, movements and adverse events to determine the safety of morphine.

Pharmacodynamics: The Neonatal Infant Pain (NIP) and Premature Infant Pain Profile (PIPP) will be performed at baseline, (prior to drug administration)and at pre-determined time intervals after the dose to assess pain for the efficacy of morphine.

Pharmacokinetics: The concentrations of morphine and its metabolites will be measured in plasma and urine at pre-determined time points and will be used to calculate the formation and elimination clearances of morphine and its metabolites.

Pharmacogenetics: Impact of genetic variation in the UGT2B7 gene on the formation clearances of the morphine metabolites will be studied as well as the genetic variation in the μ-opioid receptor, COMT, and β-arrestin 2 genes on the PD of morphine use.

Secondary outcome

nvt

Study description

Background summary

The recognition that significant pain is experienced by neonates has led to the more common use of morphine in neonatal intensive care units . There are data demonstrating a developmental pattern in the metabolism and pharmacokinetics (PK) of morphine that needs to be considered when it is used. This information, however, has yet to be applied to the morphine dosage schedule for neonates so that differences in both drug disposition and action are recognized. A recent NIH study (NEOPAIN) has, in fact, demonstrated a high incidence of serious adverse drug events (ADEs), including hypotension, associated with extremely high morphine plasma concentrations (500 ng/ml vs. therapeutic concentrations, 20-40 ng/ml) (personal communication Dr. Anand). This resulted from the use of *customary* mg/kg therapeutic doses of the drug rather than considering the specific requirements of neonates.

There is far less information concerning developmental aspects of the exposure-response relationship of morphine in preterm neonates as compared to full-term infants. Morphine is a substrate for UDP-glucuronosyltransferase 2B7 (UGT2B7); and the activity of this isoenzyme is markedly reduced (i.e., 20% of adult activity) in the first months of life . Glomerular filtration rate (GFR) is reduced as well (i.e. 10% of adults) during the neonatal period. This limited capacity for morphine biotransformation and renal clearance of its metabolites morphine-3-glucuronide (M3G) and morphine-6-glucuronide (M6G) in newborns may, in part, explain the high incidence of ADEs using current neonatal dosing guidelines. Available information regarding the impact of ontogeny on both UGT2B7 activity and renal function could predict morphine (and metabolite) PK during the first month of life. This would enhance our ability to use a physiology-based (i.e., considering the impact of development on hepatic metabolism and renal drug clearance) model to better individualize morphine therapy for neonates and improve its safety and efficacy.

In addition, inter-individual variation in PK may arise from differences in enzyme expression and/or from the presence of allelic variants (single nucleotide polymorphisms or SNPs) encoding enzymes with a compromised catalytic ability. Clinically important genetic variants of the UGT2B7 gene could be discovered and incorporated into the kinetic model. Moreover the translation of drug dosage to clinical response is not solely dependent on plasma concentrations of morphine and its metabolites. Genetic variability in the *-

opioid receptor and catechol-O-methyltransferase (COMT) gene might play a role in the dynamic portion of the PK/PD (pharmacokinetic/ pharmacodynamic) model. In order to further improve the physiology-based model of morphine dosing, we will explore the potential contribution of genetic variants in the UGT2B7, COMT, and *-opioid receptor genes to the observed variability in PK and PD of morphine in newborn infants.

Study objective

To evaluate the relationship of developmental stage (defined by both gestational and postnatal age) to UGT2B7 activity (as determined by CLf,M3G and CLf,M6G).
To evaluate the relationship of UGT2B7 genetic variability to UGT2B7 activity (as determined by CLf,M3G and CLf,M6G).
To evaluate the relationship of glomerular filtration rate to the elimination clearances of morphine, M3G and M6G (CLother, CLM3G, and CLM6G) and morphine concentrations in both blood and urine.
To evaluate the relationship of μ-opioid receptor and COMT genetic variability to clinical response following administration of morphine.
To develop a population PK/PD model of morphine dosing based on gestational age, postnatal age, glomerular filtration rate, and variability in UGT2B7, μ-opioid receptor and COMT genes.

Study design

Allocation: Non-Randomized
Endpoint Classification: Pharmacokinetics/Dynamics Study
Intervention Model: Single Group Assignment
Masking: Open Label
Primary Purpose: Treatment

Intervention

Morphine:
0.05 mg/kg loading dose of morphine will be given by an intravenous infusion over 30-minutes in preterm neonates with a GA of less than 29 weeks, followed by a continuous infusion of 0.005 mg/kg/h. A loading dose of 0.1 mg/kg will be given by an intravenous infusion over 30-minutes in preterm neonates with a GA of 29 weeks or more followed by a continuous infusion of 0.01 mg/kg/h. These measures will minimize the risks of severe adverse events such as hypotension in this vulnerable population. The decision to administer extra morphine or to discontinue the morphine infusion will be made by the attending neonatologist and will be documented. To increase the morphine exposure to the neonate, a bolus infusion of 50 microgram/kg given by a 30-minute infusion.
Inulin will be administered as a glucose 10%-inulin solution containing 25 gr. inulin/L, at an infusion rate of 0.6 mL/kg/h. After 24 h, the inulin clearance

will be calculated from the infusion rate, the inulin concentration in the infused solution, and the serum inulin concentration.

Study burden and risks

There are small additional risks to the subjects as compared to the current routine clinical care of these infants. To reduce the need for venipuncture or heel prick, only blood samples from an arterial line will be collected. Arterial lines will already be in place for clinical purposes (i.e, adequately monitoring the blood pressure, blood gas analysis, etc.). The measurement of pain with the use of validated pain measure instruments, NIPS (Neonatal Infant Pain Scale) and PIPP (Premature Infant Pain Profile) is non-invasive (observational techniques), but potentially might influence the social interaction of the preterm neonate with his/her caregivers. The investigators will try to minimize any social interruptions. Spontaneously voided urine will be collected in the diaper as is standard in the Neonatal Intensive Care and does not carry any risk. The infusion of inulin for the measurement of the glomerular filtration rate (GFR) carries a potential risk comparable with every other intravenous infusion. It is important to mention that inulin has been used in preterm newborns for over 20 years to measure GFR and is viewed as the gold standard because serum creatinine cannot be reliably used to monitor renal function during the first weeks of life. Adverse events related to inulin infusion have never been reported. Inulin will only be infused if the infant already has an intravenous line for clinical purposes.

All preterm neonates who will be participants in this study will be admitted in the NICU, and therefore continuous professional intervention will be available in case of an adverse drug reaction.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Children (2-11 years)

Inclusion criteria

Preterm neonates of both genders and all races between 23 and 32 weeks
postnatal age less than 30 days
an indwelling (peripheral or umbilical) arterial line, and
a clinical indication for intravenous morphine administration

Exclusion criteria

Neonates with severe asphyxia, grade III or IV intraventricular hemorrhage, major congenital malformations/facial malformations, neurological disorders, and those receiving continuous or intermittent neuromuscular blockers.
clinical or biochemical evidence of hepatic and renal compromise (including systemic hypoperfusion) or
received drugs that are UGT2B7 substrates (including Lorazepam, ibuprofen, valproic acid, naloxone and other morphine derivatives or propanolol)

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):	01-04-2012
Enrollment:	30
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Morphine
Generic name:	Morphine
Registration:	Yes - NL intended use

Ethics review

Approved WMO

Date:	29-12-2011
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)

Approved WMO

Date:	11-07-2012
Application type:	First submission
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

ID: 24146
Source: NTR
Title:

In other registers

Register	ID
EudraCT	EUCTR2011-001783-21-NL
ClinicalTrials.gov	NCT00494429
CCMO	NL36524.078.11
OMON	NL-OMON24146