No Pain during infancy by adapting off-patent medicines

Project information

NEOOPIOID
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Project website

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Coordinated by:
KAROLINSKA INSTITUTET
Sweden

Final Report Summary - NEOOPIOID (No Pain during infancy by adapting off-patent medicines)

Executive Summary:

The main objectives of this project were to study the current clinical practices regarding these drugs in the EU and develop more personalized sedative/analgetic (S/A) drug therapy of neonates considering individual pharmacogenetic and kinetic properties. The ultimate aim was to develop more personalized S/A drug therapy considering individual pharmacogenetic and kinetic properties.

Main Results

Assessment of pain and the use of S/A drugs for infants cared at neonatal intensive care units (NICU) were studied using special web-based questionnaires. About 6700 patients from 18 EU countries were included. Most centres use either morphine or fentanyl. However, there is a trend to use more fentanyl. Paracetamol is also very often used either alone or in combination with the other drugs. More than half of the NICUs did not practice any kind of pain assessment of ventilated neonates. Most ventilated infants were treated with continuous and bolus administration of S/A drugs. Only 12 % of the non-ventilated babies received S/A treatment.

For the clinical trial a lot of effort has been spent to develop a protocol and optimize the scoring of pain in preterm infants. These scores are studied in relation to the PK/PG properties of the analgetic drugs. This part of the project has been delayed due to considerable changes in neonatal intensive care during the last years. Newly updated European consensus guidelines emphasize a minimum handling of the preterm infant, ventilatory treatment with CPAP and with very limited use of opioids and fentanyl. This explains to some extent the slow recruitment of infants.

The methods to analyse opioids and their metabolites have been improved with special regard to the small blood samples from neonates. Of particular interest is the active morphine-6-glucuronide metabolite, which was detected in some infants.

The relation between polymorphisms in candidate genes (COMT and KCNJ6 genes) have been studied in relation to the pain relieving effect.

Child friendly formulations of fentanyl have been developed and used for the clinical trial.
A number of ad hoc studies on the preterm brain have been performed. Of particularly interest are the studies of the spontaneous resting activity of both preterm and term infants. These studies are of particular importance to understand the effect of the analgesic drugs.

Expected final results and potential impact:

The results of the survey may lead to the development of uniform recommendations how to assess and treat neonatal pain with S/A drugs.

The results of the PK/PG studies are of importance to develop a more personalized treatment with S/A drugs.

More child friendly drugs may be developed.

The most important impact is the increase of knowledge how to assess and alleviate pain in newborn infants. This knowledge will hopefully be disseminated among pediatricians and nurses in the entire EU and also worldwide. We will then be able to treat infants in the same individualized way as adult patients and fulfil the Hippocratic oath to alleviate without damage. Furthermore reducing procedural pain as well as chronic distress is essential for normal brain development.

Project website: [www.neopioid.eu](http://www.neopioid.eu)

Project Context and Objectives:

It is now well established that newborn infants not only show physiological and behaviour responses to pain but also reach pain to conscious level. Newborn infants seem to be even more sensitive to pain, since some of the modulating neurosystems are not developed (Fitzgerald et al, 2000). Newborns admitted to neonatal intensive care units (NICU) may experience prolonged pain and repeated painful procedures as part of their medical treatment. Several hundreds of invasive procedures may be performed in extremely preterm infants during neonatal intensive care, particularly during the first weeks after birth. The most frequent procedures include heel sticks for blood sampling, endotracheal suctioning during mechanical ventilation, and intravenous line insertion (Baker DP et al, 1995, Simons SH et al, 2003).

The current management of neonatal pain is not optimal in spite of an increased awareness among clinicians to reduce the burden of pain in ill newborn infants. Several aspects of pain management need to be improved, which includes treatment and prevention of continuous pain and stress, as well as intermittent procedural pain. Data from a French prospective multicentre study, The French EPIPAIN Study showed that 30,018 painful procedures and 30,951 mainly stressful procedures were recorded during the first 14 days after NICU-admission in 430 newborn infants. Analgesic treatment was given only during 27.4% of painful procedures (Carbajal R et al, 2008).

The experimental evidence for adverse neurodevelopmental outcome follow painful stimuli is strong. Human studies also show evidence of adverse long-term effects of repeated or prolonged pain in the newborn period, which includes cognitive outcomes, adverse behavioural and neuro-endocrine responses and alterations in somatosensory perception (both hypo- and hyper-sensitivity). Pain may also lead to increased blood pressure and fluctuations in cerebral blood flow, which in the preterm infants can be deleterious with development of intracranial haemorrhages. It was recently shown that painful experiences are processed at a cortical level also in preterm infants, and that there are clear gender effects with increased responses in male infants (Bartocci et al, 2006, Slater et al, 2006).

During the last decade major efforts have been made to improve standards of care for pain management in sick newborn infants. Two large multicentres randomised clinical trials (RCTs) evaluated morphine versus placebo during mechanical ventilation, with slightly different doses of morphine. One of the studies was conducted in the Netherlands and included 150 infants born 2000 to 2002 (Simons et al, 2003). The other study included 898 very preterm neonates (gestational age <33 weeks) in 16 centres in Europe and USA during the time-period 1999 to 2001 (Anand et al, 2004). Pain and stress responses (plasma catecholamines) were reduced in infants receiving morphine. However, one of the studies showed a small, but significant, increase in intraventricular haemorrhages (IVH) in infants at 27-29 gestational weeks and in those who receive additional boluses of open-label morphine. A Finnish RCT compared effects from morphine and fentanyl during mechanical ventilation in 163 infants born 1994-1996. Both drugs were equally effective in
reducing pain and stress responses, although fentanyl was associated with fewer gastrointestinal side effects (Saarenmaa et al, 1999).

Although treatment with morphine and fentanyl analgesia is associated with reduced pain and stress responses, the current knowledge about long-term safety from newborn treatment with these drugs, as compared to placebo, is limited. The problem is significant since around 100,000 infants are born very preterm in Europe, with increasing survival rate, a large number of infants are exposed to opioid or suboptimal pain relief.

The alleviation of pain is a basic and human right regardless of age – also newborn and preterm infants feel pain and require analgesics. We present a comprehensive study designed to investigate the clinical efficacy and safety effects of opioid therapy in newborns. The NeoOpioid project will advance the science of neonatal pain and stress, the clinical practice of analgesia, its pharmacokinetic determinants, while documenting current therapies and guidelines and developing a new European standard of care for pain relief in its most vulnerable population.

- To provide new standards of care regarding the use of opioids in neonatal intensive care.
- To evaluate acute effects of pain, and treatment with opioids, in relation to pharmacokinetics.
- To develop a pharmacokinetic (PK) model for morphine and fentanyl dosing in newborn infants that takes into account developmental stage.
- To compare safety and effects on pain and stress responses in relation to pharmacokinetic predisposition in a new cohort of newborn infants who will receive morphine or fentanyl, which will be administered as judged by pain scoring.
- To develop new drug formulations for safe administration of opioids to newborn infants.
- To implement and disseminate new knowledge on effects of neonatal pain and treatment with opioids in the newborn period.
- To submit and get approvals for two Paediatric Use Marketing Authorisation (PUMA) with application to the EMEA (European Medicines Agency).

References


Project Results:

Please see attachment - NeoOpioid Final Report

Potential Impact:

This study has shown that although 82% of ventilated neonates in European NICUs receive some form of sedation/analgesia (S/A), important variations in the rates of S/A occur among countries. Moreover, different drugs are used to among countries and in most countries S/A is performed without a formal pain assessment.

We believe that some of the implications of these results are:

- The creation of a well motivated network of NICUs across Europe capable of making important improvements in the management of neonatal pain
- The development of a benchmarking process by units to improve their S/A practices in view of the results of other units.
- The need to develop European up-to-date recommendations to serve as a guide to S/A practices in ventilated and non ventilated neonates admitted to NICUs across Europe.
- The need to promote the use of validated pain scales in NICUs whenever a S/A is used or deemed necessary
- The need to continue the improvement of pain assessment tools for ventilated and non ventilated neonates
- The need to study the long term effects of S/A used in neonates admitted to NICUs

Dissemination activities and the exploitation of results

The aim of this project has been to provide evidence for a better use of analgesics in newborn infants, and to improve care of newborn infants. Dissemination, implementation, exploration and knowledge transfer and education to develop child analgesic friendly formulation are important parts of the project.

A website: www.neoopioid.eu is in the air since the beginning of the project and this website has been updated throughout the progress of the project. In addition, a website for the EUROPAIN survey has been created www.europainsurvey.eu

Neonatal intensive care units all over Europe have been encouraged to participate in the EUROPAIN survey. A total of 243 units in 18 countries all over Europe have registered data from 6680 newborn infants. Our hope is that this has laid the ground for a fruitful network that facilitate other collaborations in the future.

The investigators involved in the NeoOpioid project have arranged workshops and held oral presentations at scientific and medical conferences. Several reviews and scientific articles have been written.

The clinical and pharmacokinetic analyses have not been finalized. However, based on our pilot studies we propose provisional guidelines using Fentanyl for procedural pain and Morphine for chronic pain. We recommend intermittent bolus administration based on the scoring of pain. Continuous administration is not recommended. Results from the method development studies and pilot studies have been presented in scientific publications and reports.

The main studies within the project have been registered in publically accessible databases (clinicaltrials.gov and/or...
Preliminary results from the Europain survey have been presented at scientific conferences in some of the participating countries. The final results will be presented in scientific peer review journals and at scientific conferences. We also aim to communicate the final result in press releases and on the project websites.

List of Websites:

www.neoopioid.eu

www.europainsurvey.eu

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