The Opioid Crisis, Neonatal Analgesia, and Neonatal Opioid Withdrawal Syndrome

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FDA

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Disclaimer

• The views expressed in this presentation are mine and do not necessarily represent the policies of the Food and Drug Administration or the Department of Health and Human Services.

• I have no financial conflicts of interest or relevant financial relationships to disclose.
Topics for Today

• Scope and sources of opioid crisis of abuse and overdose
• FDA response
• Implications for neonates
Big Picture

• The ‘Opioid Crisis’ is not one crisis, but multiple challenges to prescribers, patients, and the healthcare system.

• FDA is working in a prioritized way in multiple areas to confront opioid overdoses while working to ensure patients receive appropriate treatment for pain, addiction, and withdrawal.

• Effects of the crisis have permeated through all areas of pain management and drug development for analgesics, medication assisted treatment for addiction, and medications to manage opioid withdrawal.
Misuse and Abuse of Prescription Opioid Analgesics Remains an Important Public Health Problem

- In 2017, prescription opioids were the largest category of pharmaceutical products misused and abused in US
  - 11.1 million people estimated to have past-year misuse/abuse
  - 1.7 million people estimated with DSM IV criteria for substance use disorder involving prescription opioid analgesics
- In comparison, 886,000 estimated to have past-year heroin use

Crisis Ongoing Despite Falling # of Prescriptions for Opioid Analgesics

*Immediate-Release formulations include oral solids, oral liquids, rectal, nasal, and transmucosal
**Extended-Release/Long-Acting formulations include oral solids and transdermal patches
Note: Include opioid analgesics only, excluding injectable formulations as well as opioid-containing cough-cold products and opioid-containing medication-assisted treatment (MAT) products
Consequences: Prescription Opioids and Overdose Death in the US

Source: CDC, NCHS/NVSS, 2019
Sources of the Opioid Crisis

• Prescribed opioids pose a risk beyond the patient who receives the prescription

• Among people who abuse prescription opioids, most get them
  – From a friend or relative for free (55%)
  – Prescribed by a physician (20%)
  – Bought from a friend or relative (11%)

• Among new heroin users, about three out of four report abusing prescription opioids before using heroin.

https://www.cdc.gov/drugoverdose/data/prescribing.html
The Opioid Crisis: FDA’s Priorities & Actions

1. Help prevent new addiction, reduce excess opioid analgesics in the community by reduction of unnecessary exposure to opioid analgesics
2. Support the treatment of those with opioid use disorder
3. Facilitate development of nonopioid analgesic medications, novel devices
4. Improving enforcement
1. Help prevent new addiction, reduce excess opioid analgesics in the community by reduction of unnecessary exposure to opioid analgesics

- Labeling appropriate dose/duration, indications
  - Scientific framework for developing evidence-based prescribing guidelines
  - Labeling: Indications, new tapering language
- Appropriate packaging, storage, and disposal
  - Considering unit-of-use packaging for outpatient dispensing
  - Jan 2018: Requested packaging in limited amounts OTC loperamide to curb intentional misuse and abuse.
  - FDA updated the disposal webpage on April 23, 2018
- Health care provider education - Opioid Analgesic REMS
  - Expanded to all outpatient opioid analgesics.
  - Content of education broadened to include pregnancy, postpartum period, breastfeeding, and neonatal opioid withdrawal syndrome
2. Support the treatment of those with opioid use disorder

• Naloxone
  – Facilitate development of new naloxone products, OTC naloxone
    • Drug Facts Labeling for OTC naloxone developed by FDA,
    • First generic naloxone nasal spray approved
  – Co-prescribing - FDA Advisory Committee on December 2018
    • Concerns about costs, diversion of resources (both money and naloxone) away from underserved areas,
    • Focus should be on educating prescribers/patients and supporting harm reduction efforts
• Improve/increase options for Medication Assisted Treatment (MAT)
  • Approval of novel buprenorphine products
    – Monthly depot formulation, Low dose 6-month implant
  • Two new guidances for industry:
    – final guidance: developing depot buprenorphine products
    – draft guidance: clinical endpoints for new MAT
3. Facilitate development of novel treatments

• Partnerships with other agencies, e.g., NIH HEAL Initiative
• Public-private-partnerships to develop better study designs, endpoints for clinical trials
• Use of FDA’s expedited pathways
• New guidances under development
4. Improving enforcement

• Expand information sharing with U.S. Customs and Border Protection (CBP), maximize each agency’s inspection and detection capabilities at the border
• Secure the legitimate supply chain by doing more to hold distributors responsible, closing illegal portals on the internet.
FDA Priorities Align with Recently Passed SUPPORT Act

• Substance Use-Disorder Prevention that Promotes Opioid Recovery and Treatment (SUPPORT) for Patients and Communities Act

• Provisions provide FDA with new tools to:
  – more efficiently stop illegal, illicit, unapproved, counterfeit and potentially dangerous drugs from entering the U.S. via International Mail Facilities (IMFs)
  – reduce exposure to opioids/ lower rate of new addiction
  – require certain packaging, such as unit dose blister packs, for opioids and other drugs that can be abused
  – require opioids be dispensed with safe disposal option

• Implementation ongoing

https://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm624268.htm
Pain in America

• From the Functioning and Disability Supplement of the 2012 National Health Interview Survey
  – 126.1 million adults reported some pain in the previous 3 months
  – 25.3 million adults (11.2%) suffering from daily (chronic) pain
  – 23.4 million (10.3%) reporting a lot of pain.
  – Based on the persistence and bothersomeness of their pain, 14.4 million adults (6.4%) were classified as having the highest level of pain, category 4, with an additional 25.4 million adults (11.3%) experiencing category 3 pain.

Nahin RL, J.Pain, 2015 Aug;16(8):769-80
Pain in America (cont)

- Optimal patient outcomes: comprehensive multidisciplinary care that integrates pharmacologic and nonpharmacologic therapies including physical medicine, behavioral medicine, neuromodulation, and interventional approaches
  - Multidisciplinary Pain Programs for Chronic Noncancer Pain, Technical brief Number 8, AHRQ Publication No. 11-EHC064-EF, September 2011

- Patients experience ongoing barriers to adequate pain management
  - “many related to non-existent or insufficient insurance coverage and reimbursement for evidence- and consensus-based therapies”

- Consequence: treatments have largely focused on prescription drugs, mainly opioids, and not multidisciplinary care
Unintended Consequences of Addressing the Opioid Crisis

• Pressure on Prescribers
  – Limited time to see patients, counseling proper use of opioid analgesics time consuming, not well reimbursed
  – May not have access to pain or addiction medicine specialists for guidance with challenging patients
  – Concern about liability, licensure

• Pressure to do something
  – Legislative and policy decisions resulting from the misinterpretation of gaps in data as negative data result in patient harms
    • Mandated maxima for opioid prescriptions, forced tapers
  – Insurance companies, pharmacies limiting opioid prescriptions without alternatives
Unintended Consequences of Addressing the Opioid Crisis

• Patients
  – Chronic pain patients requiring opioids confused with patients with opioid use disorder
  – Reduced access to clinicians willing to prescribe opioids, even for stable/compliant patients
  – Forced opioid tapers, risk of seeking alternative/ illicit opioids when prescriptions discontinued, associated with risk of suicide
  – Implications for pregnant women and infants
CDC Advises Against Misapplication of the Guideline for Prescribing Opioids for Chronic Pain

CDC commends efforts to improve opioid prescribing and reduce opioid misuse and overdose.

- some policies and practices that cite the Guideline are inconsistent with, and go beyond, its recommendations

- Misapplication to populations outside of the Guideline’s scope, e.g. acute sickle cell crises, post-surgical pain

- Misapplication of dosage recommendation, resulting in hard limits or “cutting off” opioids.
  
  - “When opioids are started, clinicians should prescribe the lowest effective dosage. ... avoid increasing dosage to ≥90 MME/day or carefully justify a decision to titrate dosage to ≥90 MME/day.”
  
  - Does not suggest discontinuation of opioids already prescribed at higher dosages.

- The Guideline does not support abrupt tapering or sudden discontinuation of opioids.

- Misapplication of dosage recommendation to patients receiving or starting medication-assisted treatment for opioid use disorder.

Implications for Neonates and Their Mothers

Admissions for Newborn Withdrawal Syndromes
(Number per 1000 Admissions)

Tolia VN, Patrick SW, et al. NEJM 2015;372:2118-2126
Implications for Neonates and Their Mothers

• Increased intrauterine exposure to opioids → Increased incidence of NOWS
  – Pain management during pregnancy
    • Focus on prescription opioids, lack of safe alternatives with comparable efficacy for many patients
    • Limited access to nonpharmacologic treatments
    • Forced tapers may expose fetus to opioid withdrawal
  – Increase in opioid abuse and addiction
    • Increased use of medication assisted treatment with opioid agonists
      – Mistaken belief that MAT should be avoided in pregnancy
      – Mother and fetus face risks from illicit drug use
    • Criminalization of mothers whose babies have symptoms of NOWS may reduce prenatal/postnatal care
Neonatal Analgesic Development

• Analgesic development in this patient group already extremely challenging, more complicated by emotional reactions to studies of opioids in children?
  – August 2015: OxyContin approved for use in children 11 years of age and older with stricter indication than adults
    • OxyContin had already been in use in children without labeling data for PK, dosing recommendations, requirement of prior opioid use
    • “Ever since the Food and Drug Administration approved the use of the narcotic painkiller OxyContin for certain children in August, it has faced unabated criticism from lawmakers and public officials who are wrestling with devastating rates of prescription opioid abuse in their communities. Last week, Hillary Rodham Clinton brought the issue to the presidential race, calling the agency’s action “absolutely incomprehensible”.

Conclusions

• FDA’s response to issues raised by opioids reflect unique challenges of how they are used, misused and abused

• Opioids are challenging on many fronts, and FDA is seeking to balance the appropriate need for them by patients with the crisis of opioid abuse and overdose

• Need to consider the full implications from actions to address the crisis, including the additional challenges for neonates and their mothers
Thank You
Endpoints for Evaluating Pain Treatments for Neonates

John Van den Anker and Lily Mulugeta – Co-Chairs

May 2, 2019
Endpoints for Evaluating Pain Treatments Session

8:00 a.m. – 8:15 a.m. Challenges with Developing Drugs to Treat Pain in Children
SHARON HERTZ, DIRECTOR OF ANESTHESIA, ANALGESIA, AND ADDICTION PRODUCTS (CDER/FDA)

8:15 a.m. – 10:00 a.m. Endpoints for Evaluating Pain Treatments for Neonates
JOHN VAN DEN ANKER (CHILDREN’S NATIONAL HOSPITAL) AND LILY MULUGETA (CDER/FDA), co-chairs
  Challenges in Neonatal Pain Trials – A Regulatory Perspective - Lisa Wiltrout (CDER/FDA)
  Alternative Measures of Pain– Rebeccah Slater (U-Oxford)
  Dose selection and PK Assessment in Neonatal Pain Trials – Dick Tibboel (Erasmus MC-Sophia Children’s H.)
Panelists:
• LYNNE YAO (CDER/FDA)
• RALPH BAX (EMA), by Webex
• GARY WALCO (U-Washington)
• EDRESS DARSEY (Pfizer)
Goals and objectives:

- Discuss unique scientific, ethical, and practical considerations for designing neonatal analgesic trials including best methods for assessing outcomes
- Propose a demonstration project for validating the proposed method using an old drug which will provide a framework for evaluation of new products in neonates
- Develop a multi-stakeholder INC statement/publication on the evaluation of both opioid and non-opioid analgesics in neonates
Challenges in Neonatal Pain Trials – A Regulatory Perspective

Lisa Wiltrout, MD
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Center for Drug Evaluation and Research
US Food and Drug Administration (FDA)
May 2, 2019
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Overview

• Evidentiary standards for efficacy in clinical trials
• Evidentiary standards for efficacy with analgesic drug products
• Ethical considerations for pediatric trials
• Enrollment difficulties in pediatric trials
• Challenges with neonatal and infant pain assessment
• Recommended study design for neonatal pain trials
• Example: Ofirmev® (IV acetaminophen)
Evidentiary Standards for Approval

• Pediatric product development is held to the same evidentiary standards as adult product development.
• A product approved for children must:
  – Demonstrate substantial evidence of effectiveness
  – Provide a clinical benefit
Definition of Substantial Evidence of Effectiveness

• Evidence of effectiveness
  – Consists of adequate and well-controlled investigations from which one could conclude that the drug will have the effect it purports to have under the conditions of use prescribed, recommended, or suggested in labeling.

• Section 505(d) of the Food, Drug & Cosmetic Act
  “Congress generally intended to require at least two adequate and well-controlled studies, each convincing on its own, to establish effectiveness.”
Definition of Clinical Benefit

- Impacts how a patient feels, functions, or survives.
- Improves or delays the progression of clinically meaningful aspects of the disease.
Evidentiary Standards for Efficacy with Analgesic Drug Products

• In adults, replicated evidence of effectiveness
• In children ages 2 to 16 years, may be able to extrapolate efficacy from adults
  – If able to extrapolate efficacy, then need PK and safety data.
  – If unable to extrapolate efficacy, then need efficacy, PK, and safety data.
• In children ages birth to 2 years, cannot extrapolate findings of efficacy from adults
  – Since unable to extrapolate efficacy, then need efficacy, PK, and safety data.
• One adequate and well-controlled trial confirming efficacy may be acceptable if the product’s efficacy is well-demonstrated in adults.
Ethical Considerations for Pediatric Trials

• Children are vulnerable research participants:
  – They cannot represent their own views or self-interests.
  – They are unable to provide informed consent.

• Participation in research with more than minimal risk must be justified by potential direct benefit to the individual child.

• A placebo-controlled trial may be ethically problematic if exposure to more than minor pain occurs and there are effective treatments for the disease or condition being studied.
Enrollment Challenges in Pediatric Trials

• Ethical dilemmas
• Parental reluctance
  – Fear of harm to children
  – Exposure to extra procedures/painful procedures
• Investigator, study site and IRB reluctance
• Small patient populations
# Neonatal and Infant Pain Scales

<table>
<thead>
<tr>
<th>Pain scale</th>
<th>What variables are included</th>
<th>Type of pain</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>PIPP (premature infant pain profile)</td>
<td>Heart rate, oxygen saturation, facial actions</td>
<td>Procedural, postoperative</td>
<td>Reliable, valid, clinical utility is well established</td>
</tr>
<tr>
<td>NIPS (neonatal infant pain score)</td>
<td>Facial expression, crying, breathing patterns, arm and leg movements, arousal</td>
<td>Procedural</td>
<td>Reliable, valid</td>
</tr>
<tr>
<td>NFCS (neonatal facial coding system)</td>
<td>Facial actions</td>
<td>Procedural</td>
<td>Reliable, valid, clinical utility is well established, high degree of sensitivity to analgesia</td>
</tr>
<tr>
<td>N-PASS (neonatal pain, agitation and sedation scale)</td>
<td>Crying, irritability, facial expression, extremity tone, vital signs</td>
<td>Procedural, postoperative, mechanically ventilated patients</td>
<td>Reliable, valid. Includes sedation end of scale, does not distinguish pain from agitation</td>
</tr>
<tr>
<td>CRIES (cry, requires oxygen, increased vital signs, expression, sleeplessness)</td>
<td>Crying, facial expression, sleeplessness, requires oxygen to stay at &gt;95 % saturation, increased vital signs</td>
<td>Postoperative</td>
<td>reliable, valid</td>
</tr>
<tr>
<td>COMFORT scale</td>
<td>Movement, calmness, facial tension, alertness, respiration rate, muscle tone, heart rate, blood pressure</td>
<td>Postoperative, critical care</td>
<td>Reliable, valid, clinical utility well established</td>
</tr>
<tr>
<td>DAN (Douleur Aiguë du Nouveau-né)</td>
<td>Facial expression, limb movements, vocal expression</td>
<td>Procedural</td>
<td>Reliable, valid</td>
</tr>
</tbody>
</table>

Challenges with Pain Assessment in Neonates and Infants

- No objective measure of pain currently exists.
- Neonates and infants cannot rate their pain.
- Current pain scales use physiological and behavioral indicators.
- Physiological and behavioral indicators of pain show poor specificity.
  - Processes unrelated to pain can cause sympathetic stimulation and arousal.
  - Neural maturation in newborns affects the behavioral and autonomic responses to pain.
  - In extremely low birth weight infants, pain responses may be dampened or modified by contextual factors.
- Difficult to distinguish pain from other states using physiological and behavioral indicators alone.
Recommended Study Design for Efficacy Evaluation in Neonatal Pain Trials

- Add-on with immediate rescue paradigm
- Randomized, DB, PC study design
- Standard of care (opioid) provided to all enrolled
  - One arm receives study drug and one arm receives placebo in addition to SOC
- Primary endpoint is a measure of opioid use.
- Secondary endpoint is pain score.
- Post-operative pain is managed using nurse-controlled analgesia.
Ofirmev® (IV Acetaminophen) Regulatory History

11/2010 Ofirmev® NDA approved for use in adults and pediatric patients ≥ 2 years old with the following indication:

- Management of mild to moderate pain
- Management of moderate to severe pain with adjunctive opioid analgesics
- Reduction of fever

11/2010 Under the Pediatric Research Equity Act (PREA), Applicant required to conduct an efficacy, PK/PD, and safety study of IV APAP for the treatment of acute pain in pediatric patients ages birth to 2 years.
Ofirmev® (IV Acetaminophen)
Regulatory History

8/2012 – 8/2015  Applicant conducted the Ofirmev® pediatric pain trial at 18 sites in the US.

4/2016  The final study report (included in NDA 022450 Supplement 10) was submitted to the FDA for review.

1/2017  FDA approved NDA 022450 Supplement 10 with the following labeling changes to the indication:
– Reduction of fever in adult and pediatric patients
Ofirmev® Pediatric Pain Trial – Protocol Summary

Study Design:
R, DB, PC, parallel-group, multiple-dose, multiple-center study

Objectives:
To study the efficacy and safety of IV acetaminophen
To characterize the concentration-effect (PK/PD) relationship of IV acetaminophen
To determine the PK profile of IV acetaminophen

Study Population:
Hospitalized pediatric patients who were ≥ 28 weeks to ≤ 40 weeks gestational age at birth and < 2 years old at randomization
Acute post-surgical or post-traumatic injury pain
Expected to have moderate to severe pain requiring IV analgesia for 24 hours
PI score ≥ 4 on Leuven Neonatal Pain Scale (LNPS) for ages < 6 months
PI score ≥ 4 on Face, Legs, Activity, Cry, and Consolability (FLACC) for ages 6 to < 24 months
Needed at least one dose of IV opioid within 6 hours prior to randomization
Anticipated to require at least one dose of rescue IV opioid during the 24-hr treatment period
Have reliable vascular access for study drug infusion and PK sampling
Ofirmev® Pediatric Pain Trial – Protocol Summary

Treatment:
IV APAP groups – received Ofirmev IV every 6 hours x 4 doses plus SOC
Control groups – received normal saline placebo IV plus SOC

Opioid use:
Types of opioid – morphine, fentanyl, or hydromorphone
PRN before randomization and during the 24-hour treatment period
Loading dose 30 minutes before study drug infusion
Dosing and frequency at investigator’s discretion; goal pain score ≤ 3
Opioid rescue medication mandatory for pain score ≥ 6

Efficacy Data:
Frequent pain intensity (PI) scores using LNPS and FLACC
Frequent sedation scores using University of Michigan Sedation Scale
Global Evaluation of Satisfaction with study treatment

Safety Data:
AEs; Vital signs/PE; Clinical laboratory tests
Ofirmev® Pediatric Pain Trial – Endpoints

Primary Endpoint:
Total amount of rescue opioid over 24 hours (µg/kg IV morphine or morphine equivalent)

Secondary and Other Endpoints:
PD/PK correlation between APAP concentration and pain scores at 1 hour
PD/PK correlation between APAP concentration and total rescue opioid use in first 12 hours
Standard PK parameters (using sparse blood sampling and pop PK analyses)
Weighted SPID3
Total amount of rescue opioid over first 12 hours and over the 6 hours for each dosing interval
Time to first rescue medication
Percentage of patients requiring rescue opioids at 12 and 24 hours
Mean PI scores adjusted for corresponding quantity of rescue opioids
Sedation score in first 12 hours
Global evaluation by assessor and caregiver
Ofirmev® Pediatric Pain Trial – Results

Demographics
198 pediatric patients received at least one dose of study drug
128 received IV APAP and 70 received normal saline placebo
   38 neonates (ages < 29 days)
   54 younger infants (ages 29 days to < 6 months)
   55 intermediate infants (ages 6 months to < 12 months)
   51 older infants/children (ages 12 months to < 24 months)
2/3 male and 1/3 female
69% Caucasian, 15% African-American, 7% Asian, 7% other races,
   <1% American Indian or Alaska Native

Disposition
80% of 198 patients completed the study

Exposure
85% of IV APAP group received all four doses
79% of placebo group received all four doses
Ofirmev® Pediatric Pain Trial – Results

Primary Efficacy Endpoint Results
• No statistically significant differences in 24-hour total rescue opioid use between the IV APAP groups and the combined placebo groups.
• Average amount of 24-hour rescue opioid use for each treatment group was relatively small and similar between the IV APAP groups and the placebo groups.

Secondary and Other Efficacy Endpoint Results
• Very small treatment differences for amount of rescue opioid used over different time intervals, number of rescue opioid doses, percentage of patients requiring rescue opioids at different timepoints, and time to first rescue medication.
• Treatment differences in sedation score and global evaluation were minimal.
• Pain scores were much reduced in response to the opioid loading dose and were in the range of 0.6 to 2.2 at baseline before first dose of study drug.
• Pain scores after study drug infusion showed no clear trend to suggest a treatment effect from IV APAP.
Why did the Ofirmev® Pediatric Pain Trial Fail?

Possible reasons include:

– Use of pain scales that are unable to adequately differentiate pain from other states that may look like pain
– Opioids are used to treat more than just pain in neonates and infants
– Analgesic properties of IV APAP may not be strong enough to demonstrate a treatment effect when used in conjunction with SOC opioids
Summary

- Exposure to acute pain is common in neonates and infants
- Well-designed pediatric pain trials are needed
- Ethical considerations are critical
- Enrollment challenges exist
- Pain assessment in neonates and infants is complicated
- Current pain scales demonstrate poor specificity for pain
- FDA recommends an add-on with immediate rescue study design:
  - Subjects randomized to receive either study drug or placebo in addition to SOC
  - Primary endpoint is measure of opioid use
  - Secondary endpoint is pain score
- FDA is open to discussing alternative study designs and endpoints with industry
Thank you!
Alternative Measures of Pain

Dr Rebeccah Slater
Professor of Paediatric Neuroscience, University of Oxford
How do we measure infant pain?

- Facial expression
- Heart rate
- Oxygen saturation
- Respiratory rate
- Metabolic responses
- Blood pressure
- Motor activity
- Palmar sweating
- Skin blood flow
- Crying
The development of pain-related behaviour

Green et al., (2018) *Pain*
A multi-modal approach to the measurement of infant pain

Moultrie et al., (2017) Current Opinions in supportive and palliative care
Nociceptive input elicits activity across all levels of the nervous system

Slater et al. (2007) *Seminars in Perinatology*
A mechanistic look at infant pain

*Sci Trans Med 2017; Lancet 2010, 2018*  
*eLife 2015; Mag Res Med 2016*  
*Current Biology 2011; 2016*
A blinded randomised placebo-controlled trial investigating the efficacy of morphine for procedural pain in infants

Hartley & Moultrie et al., Lancet (2018)
Retinopathy of prematurity

ROP is an eye condition, which affects premature or low birthweight infants.

The blood vessel supply to the retina is not fully developed at birth.

There is a tendency for disorganised blood vessels growth, which can lead to problems with vision.

Stages of Retinopathy of prematurity
Retinopathy of prematurity screening

- 30% increase in new onset apnoea in the 48 hours post ROP screening (Mitchell et al., 2011)
- Current analgesic treatment options are considered inadequate (Cochrane Review)
Retinopathy of prematurity screening is painful

- Current analgesic treatment options are considered inadequate (Disher et al., 2018 *Paediatrics*)

Trial design

Clinical Intervention

Heel lance

ROP screening

Population

156 premature infants
<32 weeks or <1501g at birth
>34 weeks at study

Treatment

Morphine 100µg/kg

Placebo

Why morphine? Which dose?

- Effective analgesic in adults and children
- Commonly used sedative in neonatal care
- Insufficient evidence to support use for procedural pain

**For pain BNFc (and other international formularies) recommends:**
- For neonate (subcutaneous injection): 100 ug/kg every 6 hours
- For neonate (intravenous injection): 50 ug/kg every 6 hours
- For Child 1–2 months (mouth): 50–100 ug/kg every 4 hours

- Our local practice is to give 100 ug/kg of oral morphine for laser eye surgery

- Previous pilot study used 200 ug/kg for ROP screening (with no report of adverse effects)

- Assumed bioavailability is 50% of IV dose.
Outcome measures: analgesic efficacy and drug safety
Recruitment flow chart

276 patients assessed for eligibility

181 ineligible:
• 120 discharged prior to approach
• 1 discharged from requiring ROP screen before approach
• 31 died
• 29 inclusion criteria not met

95 patients approached for inclusion

36 enrolled

59 not consented:
• 45 declined consent
• 10 discharged after initial approach
• 4 discharged from requiring ROP screen after approach

31 randomised

15 assigned to receive morphine
16 assigned to receive placebo

15 received morphine
15 received placebo

15 included in per protocol analysis
15 included in per protocol analysis

0 withdrawals

5 not randomised:
• 2 became ineligible
• 3 discharged

1 did not receive placebo:
• Withdrawn due to parental request before study commenced due to imminent discharge.

~ 40 % recruitment success rate
No suggestion that morphine provided effective analgesia
Morphine causes physiological instability

Apnoeas

8/15 morphine-treated infants had new-onset apnoeas or increased apnoeas in 24 hours post-procedure

3/15 placebo-treated infants (risk ratio 2.7, 95% CI 0.9–8.2, p=0.085).

Respiratory Support

5/15 morphine-treated infants needed increased respiratory support in 24 hours post-procedure

0/15 placebo-treated infants (risk difference 0.3, 95% CI 0.1–0.6, p=0.006).
Administration of oral morphine (100μg/kg) to non-ventilated premature infants has the potential for harm without analgesic efficacy.

**We do not recommend** oral morphine in non-ventilated premature infants for ROP screening.
✓ **We do not recommend** oral morphine in non-ventilated premature infants for ROP screening.

✓ **We advise caution** if considering morphine for other acute painful procedures.

✓ Morphine produces cardiorespiratory effects that last ~ 6–8 hours. Infants may need respiratory support or resuscitation.

✓ **Unknown** if higher doses of morphine, administered to ventilated infants, are analgesic. Clinical trials are urgently needed.

✓ Importance of including dose finding studies highlighted

✓ Methodology used in Poppi sets new standards for the conduct of clinical trials of analgesics in infants.
Oxford

John Radcliffe Hospital
Dose selection and PK assessment in neonatal pain trials

Dick Tibboel
Dose selection and PK assessment in neonatal pain trials

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No disclosures
Dose selection and PK assessment in neonatal pain trials

The truth

the whole truth

and nothing but the truth
Dose selection and PK assessment in neonatal pain trials

- The morphine dosages used in the world are based on adequate dose finding studies and RCT’s
- Pain assessment instruments measure pain
- Opioids are always needed in case of severe pain
- Plasma concentrations are the Gold Standard for pharmacokinetic studies as they reflect therapeutic targets
- Every individual is born with the same pain threshold
- The distribution of the opioid receptor in the central nervous system in humans is known
Sedation and analgesia practices in neonatal intensive care units (EUROPAIN): results from a prospective cohort study


Summary
Background Neonates who are in pain or are stressed during care in the intensive care unit (ICU) are often given sedation or analgesia. We investigated the current use of sedation or analgesia in neonatal ICUs (NICUs) in European countries.

Methods EUROPAIN (EUROpean Pain Audit In Neonates) was a prospective cohort study of the management of sedation and analgesia in patients in NICUs. All neonates admitted to NICUs during 1 month were included in this study. Data on demographics, methods of respiration, use of continuous or intermittent sedation, analgesia, or neuromuscular blockers, pain assessments, and drug withdrawal syndromes were gathered during the first 28 days of admission to NICUs. Multivariable linear regression models and propensity scores were used to assess the association between duration of tracheal ventilation (TV) and exposure to opioids, sedatives-hypnotics, or general anaesthetics in neonates (O-SH-GA). This study is registered with ClinicalTrials.gov, number NCT01694745.

Findings From Oct 1, 2012, to June 30, 2013, 6680 neonates were enrolled in 243 NICUs in 18 European countries. Mean gestational age of these neonates was 35.0 weeks (SD 4.6) and birthweight was 2384 g (1007). 2142 (32%) neonates were given TV, 1496 (22%) non-invasive ventilation (NIV), and 3042 (46%) were kept on spontaneous ventilation (SV). 1746 (82%), 266 (18%), and 282 (9%) neonates in the TV, NIV, and SV groups, respectively, were given sedation or analgesia as a continuous infusion, intermittent doses, or both (p<0.0001). In the participating NICUs, the median use of sedation or analgesia was 89.3% (70–0–100) for neonates in the TV group, Opioids were given to 1764 (26%) of 6680 neonates and to 1589 (74%) of 2142 neonates in the TV group. Midazolam was given to 576 (9%) of 6680 neonates and 536 (25%) of 2142 neonates in the TV group. 342 (25%) neonates in the TV group were given neuromuscular blockers, which were administered as continuous infusions to 146 (7%) of these neonates. Pain assessments were recorded in 1250 (58%) of 2135, 672 (45%) of 1493, and 916 (30%) of 3017 neonates in the TV, NIV, and SV groups, respectively (p<0.0001). In the univariate analysis, neonates given O-SH-GA in the TV group needed a longer duration of TV than did those who were not given O-SH-GA (mean 136.2 h [SD 173.1] vs 39.8 h [94–7] h; p<0.0001). Multivariable and propensity score analyses confirmed this association (p<0.0001).

Interpretation Wide variations in sedation and analgesia practices occur between NICUs and countries. Widespread use of O-SH-GA in intubated neonates might prolong their need for mechanical ventilation, but further research is needed to investigate the therapeutic and adverse effects of O-SH-GA in neonates, and to develop new and safe approaches for sedation and analgesia.
Morphine requirements and plasma concentrations in term neonates and infants after non-cardiac surgery:
the truth for 30 years

<table>
<thead>
<tr>
<th>Age</th>
<th>( n )</th>
<th>Loading dose or single dose (µg/kg)</th>
<th>Dosage M infusion (µg/kg/h)</th>
<th>Plasma concentration morphine (ng/ml)</th>
<th>Time</th>
</tr>
</thead>
<tbody>
<tr>
<td>1-7 days</td>
<td>4</td>
<td>50 (L)</td>
<td>7-11</td>
<td>18.9 (15.0-29.0) median (range)</td>
<td>Steady state</td>
</tr>
<tr>
<td>31-90 days</td>
<td>6</td>
<td>50 (L)</td>
<td>13-19</td>
<td>9.1 (6.5-14.5) median (range)</td>
<td>Steady state</td>
</tr>
<tr>
<td>91-180 days</td>
<td>6</td>
<td>50 (L)</td>
<td>17-25</td>
<td>10.5 (7.0-22.0) median (range)</td>
<td>Steady state</td>
</tr>
<tr>
<td>180-380 days</td>
<td>10</td>
<td>50 (L)</td>
<td>25-35</td>
<td>10.0 (6.0-17.0) median (range)</td>
<td>Steady state</td>
</tr>
<tr>
<td>1-18 days</td>
<td>20</td>
<td>50 (L)</td>
<td>15</td>
<td>39.0 (23.0) mean (SD)</td>
<td>Steady state</td>
</tr>
<tr>
<td>0-6 months</td>
<td>5</td>
<td>150 (S)</td>
<td></td>
<td>26.2 (22.5) mean (SD)</td>
<td>129 min after M</td>
</tr>
<tr>
<td>2-4 years</td>
<td>5</td>
<td>150 (S)</td>
<td></td>
<td>3.8 (2.3) mean (SD)</td>
<td>189 min after M</td>
</tr>
</tbody>
</table>

Low patient numbers; not model based
Loeser's concept

Pain behaviour

Pain modulation

Pain sensation

Nociception

PK/PD

Central nervous system

Pain assessment

Loeser’s concept
Pharmacokinetics - Pharmacodynamics
Fig. 1: Overlap of behavioural cues in pain, sedation, withdrawal syndrome and delirium
From No-scoring to One size fits All

- Important methodological shortcomings (neuropathic; chronic etc)

- The quality of the studies using pain scores and it’s relative significance is variable

- In many institutions appropriate training and subsequent implementation is not well established

- The real pharmacodynamic parameter for the use of analgesic drugs is:
  - the change in pain score and the sensitivity to change
Paracetamol and morphine for infant and neonatal pain; still a long way to go?

Manuel A. Baarslag, Karel Allegaert, John N. Van Den Anker, Cathrijne A.J. Knibbe, Monique Van Dijk, Sinno H.P. Simons and Dick Tibboel
Table 2. Potential pharmacodynamic markers in neonates and infants.

<table>
<thead>
<tr>
<th>Potential outcome measures</th>
<th>Advantages</th>
<th>Limitations</th>
</tr>
</thead>
<tbody>
<tr>
<td>NIRS [27,28]</td>
<td>Noninvasive, continuously monitoring</td>
<td>Measures only cortical response</td>
</tr>
<tr>
<td>aEEG [29]</td>
<td>Continuous monitoring</td>
<td>Not validated for pain in children &lt;2 years</td>
</tr>
<tr>
<td>Skin conductance [30–33]</td>
<td>Noninvasive, continuously monitoring</td>
<td>Sympathetic activity may be caused by anxiety and/or distress as well</td>
</tr>
<tr>
<td>SSEP [34,35]</td>
<td>Noninvasive, continuously monitoring (when repetitive stimuli are being given)</td>
<td>Only reflects sensory response, not validated in infants</td>
</tr>
<tr>
<td>Pupillary reflex dilatation [36,37]</td>
<td>Promising bedside application in older children</td>
<td>Sympathetic activity may be caused by anxiety and/or distress, practical difficulties in infants</td>
</tr>
<tr>
<td>HRV (including ANI) [38–50]</td>
<td>Noninvasive, continuously monitoring</td>
<td>Sympathetic activity may be caused by anxiety and/or distress</td>
</tr>
<tr>
<td>fMRI [51,52]</td>
<td>Good overlap between findings in infants and adults, insight in pain beyond the sensory cortex</td>
<td>Not suitable for clinical application</td>
</tr>
<tr>
<td>Salivary cortisol levels</td>
<td>Noninvasive collection of sample</td>
<td>Delay in laboratory results</td>
</tr>
<tr>
<td>Plasma cortisol levels [53–55]</td>
<td>Suitable for both short- and long-term pain</td>
<td>Delay in laboratory results, sampling restricted in neonates</td>
</tr>
<tr>
<td>Plasma adrenalin levels [53,56]</td>
<td></td>
<td>Delay in laboratory results, less sensitive than noradrenalin</td>
</tr>
<tr>
<td>Plasma noradrenalin levels [53,56]</td>
<td>Significantly reduced by analgesics</td>
<td>Delay in laboratory results, sampling restricted in neonates</td>
</tr>
</tbody>
</table>

aEEG: amplitude-integrated electroencephalography; ANI: Analgesia Nociception Index; fMRI: functional magnetic resonance imaging; HRV: heart rate variability; NIRS: near-infrared spectroscopy; SSEP: somatosensory evoked potentials.
Figure 2. Schematic diagram of clinical research with morphine and paracetamol (white boxes) in practice. Black boxes represent new drugs to be studied. Dose finding and population PK/PD modelling with both ion into clinical practice will be possible. RCT: randomized controlled trial; pop PK/PD: population pharmacokinetics/pharmacodynamics; PCM: paracetamol.
PK-based dosing regimens are lacking for routinely used analgetics in specific groups of (preterm) neonates, infants or children in specific subgroups, like e.g. HT, ECMO, or cardiac surgery.

PK parameters depend not only on maturational, but also on non-maturational changes. These covariates, combined with intra-patient variability throughout the disease process further add to the variability in PK/PD of analgesics and the choice of the drug throughout childhood.

PD assessment is necessary but difficult given the diversity of the patient population and their disease characteristics. Its variability further adds to the intra- and interpatient variability observed in the PK/PD relationship.

New techniques in modelling, such as (semi-)physiologic models and PK/PD-based models, may better describe the clinical situation and estimate the extent of differences between specific subpopulations.
The role of population PK–PD modelling in paediatric clinical research

Roosmarijn F. W. De Cock • Chiara Piana • Elke H. J. Krekels • Meindert Danhof • Karel Allegaert • Catherijne A. J. Knibbe

**Fig. 1** Schematic representation of the relationship between dose and concentration (pharmacokinetics, PK) and between concentration and a pharmacological (side) effect (pharmacodynamics, PD). Important covariates that may affect both the PK and/or PD are body weight, age, disease status (e.g. critically ill versus healthy children) and genetics.
Simultaneous analysis of all available data:
PK and/or PD parameters are simultaneously estimated taking into account differences between patients

De Cock R et al, Eur J Clin Pharmacol 2010
Simultaneous analysis of all available data: PK and/or PD parameters are simultaneously estimated taking into account differences between patients.

A. Inter-individual variability

De Cock R et al, Eur J Clin Pharmacol 2010
Population PK-PD modelling

- Applicable to sparse and unbalanced data sets (neonates, children, critically ill patients etc)

- Co-variate analysis for identification of predictors of variability in PK and PD (genetics, body weight, age, interactions etc)

- Scientific basis for study/trial simulations, dose adjustment or labeling extensions in other populations (intra and interspecies extrapolations)
FDA’s pharmaceutical science and clinical pharmacology advisory committee (March 2012)

Modeling and simulation should be considered in all pediatric drug development programs.
Examples of PK-model based dosages advices

Morphine
Midazolam
Vancomycine
Renal clearance
FIGURE 1
Proposed multi-step approach for modeling and simulation using nonlinear mixed effects modeling for the optimization of drug dosing in children. The four steps that are proposed are (1) optimization of clinical trial designs based on simulations using preliminary data; (2) development and internal validation of population PK-PD models using sparse data; (3) external validation of the population PK-PD models using independent data; and (4) prospective clinical evaluation of the PK-PD model based dosing regimen. PK, pharmacokinetics; PD, pharmacodynamics.
Predictive Performance of a Recently Developed Population Pharmacokinetic Model for Morphine and its Metabolites in New Datasets of (Preterm) Neonates, Infants and Children

Elke H.J. Krekels,1,2 Joost DeJongh,1,3 Richard A. van Lingen,4 Caroline D. van der Marel,2 Inti Choonara,5 Anne M. Lynn,6 Meindert Danhof,1 Dick Tibboel2 and Catherine A.J. Knibbe1,2,7

Conclusion: The predictive value of the original morphine pharmacokinetic model is demonstrated in new datasets by the use of six different validation and evaluation tools. It is herewith justified to undertake a proof-of-principle approach in the development of rational dosing recommendations – namely, performing a prospective clinical trial in which the model-based dosing algorithm is clinically evaluated.
Fig. 7. (a, d) Morphine concentrations, (b, e) morphine-3-glucuronide (M3G) concentrations, and (c, f) morphine-6-glucuronide (M6G) concentrations predicted in model-based simulations in children weighing 0.5, 1, 2, 2.5 and 4 kg and a postnatal age of <10 days (dotted lines) and children weighing 0.5, 1, 2, 2.5, 4, 10 and 17 kg and a postnatal age of >10 days (solid lines) based on (a–c) a dosing regimen with a loading dose of 100 μg/kg and maintenance dose of 10 μg/kg/h and (d–f) a regimen with a loading dose of 100 μg/kg followed by an infusion of 10 μg/kg^{1.5}/h with a 50% reduction in the maintenance dose for children with a postnatal age <10 days.
Validation of the proposed dosing regimen in a prospective trial *(NTR Number NTR1438)*

Traditional dosing scheme in **µg/kg/h**

Proposed dosing scheme **µg/kg^{1.5}/h**
Validation of the proposed dosing regimen in a prospective trial *(NTR Number NTR1438)*

<table>
<thead>
<tr>
<th>BW kg</th>
<th>PNA &lt; 10</th>
<th>PNA &gt; 10</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>2.5 μg/kg^{1.5}/h</td>
<td>5 μg/kg^{1.5}/h</td>
</tr>
<tr>
<td>infusion rate</td>
<td>μg/h</td>
<td>μg/h</td>
</tr>
<tr>
<td>0.5</td>
<td>0.9</td>
<td>1.8</td>
</tr>
<tr>
<td>1</td>
<td>2.5</td>
<td>5.0</td>
</tr>
<tr>
<td>1.5</td>
<td>4.6</td>
<td>9.2</td>
</tr>
<tr>
<td>2</td>
<td>7.1</td>
<td>14.1</td>
</tr>
<tr>
<td>2.5</td>
<td>9.9</td>
<td>19.8</td>
</tr>
<tr>
<td>3</td>
<td>13.0</td>
<td>26.0</td>
</tr>
<tr>
<td>3.5</td>
<td>16.4</td>
<td>32.7</td>
</tr>
<tr>
<td>4</td>
<td>20.0</td>
<td>40.0</td>
</tr>
<tr>
<td>4.5</td>
<td>23.9</td>
<td>47.7</td>
</tr>
<tr>
<td>5</td>
<td>28.0</td>
<td>55.9</td>
</tr>
<tr>
<td>5.5</td>
<td>32.2</td>
<td>64.5</td>
</tr>
<tr>
<td>6</td>
<td>36.7</td>
<td>73.5</td>
</tr>
<tr>
<td>6.5</td>
<td>41.4</td>
<td>82.9</td>
</tr>
<tr>
<td>7</td>
<td>46.3</td>
<td>92.6</td>
</tr>
<tr>
<td>7.5</td>
<td>.</td>
<td>102.7</td>
</tr>
<tr>
<td>8</td>
<td>.</td>
<td>113.1</td>
</tr>
<tr>
<td>8.5</td>
<td>.</td>
<td>123.9</td>
</tr>
<tr>
<td>9</td>
<td>.</td>
<td>135.0</td>
</tr>
</tbody>
</table>

75% dose reduction in neonates
6 behaviour items

Alertness
Calmness/agitation
Respiratory response/crying
Physical movement
Facial tension
Muscle tone
Effect of Intravenous Paracetamol on Postoperative Morphine Requirements in Neonates and Infants Undergoing Major Noncardiac Surgery
A Randomized Controlled Trial

Ilse Geelie, MD, PhD
Saskia N. de Wildt, MD, PhD
Monique van Dijk, MSc, PhD
Margreeth M. J. van den Berg, MD
Gerbrich E. van den Bosch, MD
Hugo J. Duivenvoorden, PhD
Tom G. de Leeuw, MD
Ron Mathôt, PharmD, PhD
Catherijne A. J. Knibbe, PharmD, PhD
Dick Tibboel, MD, PhD

The treatment of pain in young children has improved after the publications by Anand et al. in 1987 that made clear that neonates have well-developed nociceptive pathways and therefore are capable of experiencing pain. Because untreated pain is both an unwanted experience and ultimately may lead to adverse consequences, opioids were introduced and have been used ever since. Opioid therapy, however, is associated with adverse effects, in particular respiratory depression.

Importance Continuous morphine infusion as standard postoperative analgesic therapy in young infants is associated with unwanted adverse effects such as respiratory depression.

Objective To determine whether intravenous paracetamol (acetaminophen) would significantly (>30%) reduce morphine requirements in neonates and infants after major surgery.

Design, Setting, and Patients Single-center, randomized, double-blind study conducted in a level 3 pediatric intensive care unit in Rotterdam, the Netherlands. Patients were 71 neonates or infants younger than 1 year undergoing major thoracic (noncardiac) or abdominal surgery between March 2008 and July 2010, with follow-up of 48 hours.

Interventions All patients received a loading dose of morphine 30 minutes before the end of surgery, followed by continuous morphine or intermittent intravenous paracetamol up to 48 hours postsurgery. Infants in both study groups received morphine (boluses and/or continuous infusion) as rescue medication on the guidance of the validated pain assessment instruments.

Main Outcome Measures Primary outcome was cumulative morphine dose (study and rescue dose). Secondary outcomes were pain scores and morphine-related adverse effects.

Results The cumulative median morphine dose in the first 48 hours postoperatively was 121 (interquartile range, 99-264) µg/kg in the paracetamol group (n=33) and 357 (interquartile range, 220-605) µg/kg in the morphine group (n=38), P < .001, with a between-group difference that was 66% (95% CI, 34%-109%) lower in the paracetamol group. Pain scores and adverse effects were not significantly different between groups.

Conclusion and Relevance Among infants undergoing major surgery, postoperative use of intermittent intravenous paracetamol compared with continuous morphine resulted in a lower cumulative morphine dose over 48 hours.

Trial Registration trialregister.nl Identifier: NTR1438

JAMA. 2013;309(2):149-154
Table 2. End Points in First 48 Postoperative Hours

<table>
<thead>
<tr>
<th>End Point</th>
<th>Paracetamol (n = 33)</th>
<th>Morphine (n = 38)</th>
<th>P Value</th>
<th>OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cumulative morphine dose, median (IQR), μg/kg</td>
<td>121 (99-264)</td>
<td>357 (220-605)</td>
<td>&lt;.001</td>
<td></td>
</tr>
<tr>
<td>Rescue morphine dose, median (IQR), μg/kg</td>
<td>25 (0-164)</td>
<td>20 (0-226)</td>
<td>.99</td>
<td></td>
</tr>
<tr>
<td>Rescue morphine doses and infusions, median (IQR), No.</td>
<td>2 (0-6)</td>
<td>2 (0-5)</td>
<td>.97</td>
<td></td>
</tr>
<tr>
<td>Patients receiving rescue morphine</td>
<td>22 (66.77)</td>
<td>23 (60.5)</td>
<td>.59</td>
<td></td>
</tr>
<tr>
<td>Comedication</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Midazolam</td>
<td>5 (15.2)</td>
<td>3 (7.9)</td>
<td>.34</td>
<td></td>
</tr>
<tr>
<td>Fentanyl</td>
<td>0</td>
<td>1 (2.6)</td>
<td>.35</td>
<td></td>
</tr>
<tr>
<td>Vecuronium</td>
<td>1 (3.0)</td>
<td>0</td>
<td>.28</td>
<td></td>
</tr>
<tr>
<td>Locoregional block</td>
<td>0</td>
<td>3 (7.9)</td>
<td>.10</td>
<td></td>
</tr>
<tr>
<td>Adverse events</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any adverse event</td>
<td>9 (27.3)</td>
<td>11 (28.9)</td>
<td>0.9 (0.3-2.6)</td>
<td></td>
</tr>
<tr>
<td>Reintubation</td>
<td>1 (3.0)</td>
<td>2 (5.3)</td>
<td>0.6 (0.1-6.5)</td>
<td></td>
</tr>
<tr>
<td>Apnea</td>
<td>4 (12.1)</td>
<td>10 (26.3)</td>
<td>0.5 (0.1-1.9)</td>
<td></td>
</tr>
<tr>
<td>Apnea with naloxone</td>
<td>0</td>
<td>3 (7.9)</td>
<td>0.5 (0.4-0.7)</td>
<td></td>
</tr>
<tr>
<td>Bradycardia</td>
<td>6 (18.2)</td>
<td>7 (18.4)</td>
<td>1.0 (0.3-3.3)</td>
<td></td>
</tr>
<tr>
<td>Urinary retentiona</td>
<td>1</td>
<td>0</td>
<td>0.5 (0.4-0.6)</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: IQR, interquartile range; OR, odds ratio.

a Twenty-six patients in the paracetamol group and 31 in the morphine group had a urinary catheter in place.
Do we really need morphine?

Morphine i.v. versus Paracetamol i.v. in neonates and young infants undergoing major non-cardiac surgery

Conclusion: Equipotency between paracetamol and morphine as the additional need for morphine showed no differences between the study groups
Implementation in daily clinical practice

- All patients < 1 year following major non-cardiac surgery in 2014
- Total number of patients 86
- No need for additional morphine 46
- Rescue bolus dosages of morphine 36
  - of which 25
- Needed continuous morphine infusions in the new model based dosage (66% less in the newborns!!)

Baarslag, M.A. et all. Arch Dis Child 2018 103 p.1168-1169
Figure 2. A Paracetamol plasma concentrations for the 3 treatment groups

After a single dose of 10, 15 and 20 mg/kg acetaminophen median plasma peak
Concentrations were 10.6 mg/l (IQR 2.1), 16.5 mg/l (IQR 5.0) and 21.3 mg/l (IQR 3.6)
(p < 0.001, Kruskal-Wallis test).
Figure 2. PIPP scores during CVC placement (n=10 in each box)
The mean PIPP score during and after the procedure was 4.3 (1.8) and 3.6 (1.5), respectively (scores <6 indicate no pain).

**CONCLUSION:** Intranasal fentanyl delivered as 150 microg/mL at a dose of 1.7 microg/kg was shown to be an effective analgesic in children aged 7 to 15 years presenting to an ED with an acute fracture when compared to intravenous morphine at 0.1 mg/kg.
Conclusions

- An increasing number of analgesic and sedative drugs have been subjected to population PK-PD modeling guiding dosages of future studies.

- Validated assessment instruments are the primary targets for therapeutic changes in children less than 3 years of age in the absence of self report as the Gold standard.

- Future RCT’s should be conducted as proof of principle studies following in vitro trials simulation and dose determination.
Challenges and solutions

- Easy access to training modules in different languages in a web-based way
- Structured collaboration between hospital pharmacists and treatment teams
- Application of population PK-PD approaches for future trial design and dosing
- Detailed psychometric analysis of the existing pain assessments instruments and prevent the use of 90 percent of the instruments
Acknowledgements:

- Monique van Dijk
- Karel Allegaert
- John van den Anker
- Sinno Simons
- Erwin Ista
- Matthijs de Hoog
- Enno Wildschut
Panel Questions

• What pain models are relevant in neonates (e.g. acute/procedural, post-operative, etc.)?

• Pain assessment tools: What are the barriers in getting these tools validated?

• What are the scientific, ethical and practical concerns around the use of the endpoints currently used in neonatal analgesic trials? What other innovative approaches could be used and what would be needed to take them to the next stage? What would be needed from a regulatory and industry standpoint?

• What lessons have been learnt from completed neonatal pain trials?

• Can we use existing drug safety and efficacy knowledge from adults and older children to guide dose selection for neonatal pain trials? Should neonatal pain trials include dose ranging studies?

• What challenges exist in conducting neonatal pain trials in light of the opioid epidemic? How do we overcome these challenges?

• How do we design studies for old drugs that are already in use versus new molecules?