Trial Design Considerations for Acute Pain in Neonates and Infants: Industry Perspective

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Current newborn/infant pain interventional trials on www.clinicatrials.gov

- Not yet recruiting; recruiting; active, not recruiting
- 22 trials
  - 18 studies were non-pharmacological interventions (touch/comfort glucose)
  - 4 pharmacological studies, all independent universities

Terms and Synonyms Searched:

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<th>Terms</th>
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Trial Design Considerations for Acute Pain in Neonates and Infants: Industry Perspective: current situation

Lack of studies/clinical data and labeling for analgesics in infants/neonates; most drugs used are off label; before BPCA/PREA

• As of June 2021:
  • 671 pediatric label changes due to BPCA/PREA
  • 9 label changes in 3 therapeutic categories - (Pain, Non-opioid; Pain, Opioid and Pain, Topical)
  • Included two products for ages birth – 2 years
    • Caldolor (ibuprofen injection) expanded label down to 6 months
    • Ofirmev (acetaminophen injection) – studied for treatment of pain and fever in patients birth – 2 years
      • Label did not expand use below 2 years of age for treatment of pain due to lack of efficacy shown in study of infants and neonates.
Industry must start a neonatal/infant pain study: so many questions; where do you start???
Trial Design Considerations for Acute Pain in Neonates and Infants:

Industry Perspective: challenges clinically/trial design

Trial Design Challenges

- Neonatal trials are often combined with infants and children
- Study design must accommodate different age groups, premature neonate; neonate; infant; child; adolescent
- ADME differences in this wide age span

- Placebo-controlled trials used in adults – ethical issues in children

- Differences in labeling and Standard of Care between regions (but only a few analgesics labeled for neonates – makes it difficult to design studies with SOC)

- Formulation, palatability and acceptability considerations – some take years to develop

- Limited blood volume for sampling – need to use microsampling techniques when possible
Trial Design Considerations for Acute Pain in Neonates and Infants: Industry Perspective: challenges clinically/trial design

- Over 40 different validated pain assessment tools for neonates and infants.

- What pain model do you use?
  - Not consistent across ages (neonate, heel lance/circumcision; Infant/toddler, tonsillectomy, herniorrhaphy)

- Sample size – must consider many pediatric populations may be difficult to enroll
  - Study design almost impossible to enroll if long term opioid use required
  - How can we minimize exposure?

- Endpoints
  - Immediate Rescue/opioid sparing
  - Time to first rescue
  - Assessment of pain
  - Adverse events
Trial Design Considerations for Acute Pain in Neonates and Infants:
Industry Perspective: operational challenges

**Operational Challenges**

- Parents generally not interested in enrolling infants/neonate in study
  - limited benefit to patient
  - chance of suffering additional pain
  - extra blood draws, already sick infant/neonate, other invasive procedures

- Pain studies in children (PI—anesthesiologist, hospitalist, gen peds, intensivist);
  - Pain study in Neonates (PI—neonatologist)

- Number of eligible patients to fit study design are low

- Informed consent

- Opioids – opioid crisis, no interest in enrolling in these studies
Example of site identification and initiation for a pediatric opioid trial

• Just under 2000 potential investigators contacted (3 rounds) – in US
  • Feasibility started in 2013
  • 560 investigators declined
  • 2017 - 36 sites selected/ 20 sites had a Site Initiation Visit – 14 active sites
There are some answers of where to start:

Tools and References for Infant and Neonatal Trial Design
FDA Guidance Document for Neonatal studies

neonatal subgroup classifications

Pharmacokinetic, dynamics and genomics differences

Study design considerations – dose selection; formulation, sample size, blood vol limits;

Data analysis: modeling and simulation; pop pk; PBPK modeling
Other regulatory guidance to support pediatric studies

- European Medicines Agency
  - Scientific guidelines: paediatrics | European Medicines Agency (europa.eu)

- ICH E11
  - GUIDELINE FOR GOOD CLINICAL PRACTICE (ich.org)
Guidance/Literature: neonatal and infant pain study design and considerations:

- FDA workshop – Dec 2009
- Publication Jan 2012
  - [Pediatric analgesic clinical trial designs, measures, and extrapolation: report of an FDA scientific workshop - PubMed (nih.gov)](PubMed (nih.gov))
- This is a consensus developed during the workshop on pediatric analgesic clinical trial design
  - immediate-rescue designs using opioid-sparing, rather than pain scores, as a primary outcome measure
Guidance/Literature: neonatal and infant pain study design and considerations:

- Overview for considerations when designing protocol
- Pain Models
- Recommendation for trial design

Clinical trial designs and models for analgesic medications for acute pain in neonates, infants, toddlers, children, and adolescents: ACTTION recommendations - PubMed (nih.gov)
Abstract: It is broadly accepted that children of all age groups including (preterm) neonates and young infants can perceive pain and that there is an absolute need to treat their pain safely and effectively. The approved treatment options for children, particularly (preterm) neonates and young infants, are very limited with only a few medications specifically labelled for this population. This article presents the challenges of developing pain medications for children. A short overview gives information on pain in children, including pain perception, prevalence of pain and the long-term consequences of leaving pain untreated in this vulnerable population. Current pain management practices are briefly discussed. The challenges of conducting pediatric clinical trials in general and trials involving analgesic medications in particular within the regulatory framework available to develop these medications for children are presented. Emphasis is given to the operational hurdles faced in conducting a pediatric clinical trial program. Some suggestions to overcome these hurdles are provided based on our experience during the pediatric trial program for the strong analgesic tapentadol used for the treatment of moderate to severe acute pain.

Keywords: pediatric patients, Pediatric Investigation Plan, pain relief, acute pain, tapentadol
Outcomes of the Pediatric Development Plan of Tapentadol

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Abstract: The opioid analgesic tapentadol was the first pain medication to be developed for the treatment of pain in children under a formal process established by the regulatory authorities. This article summarizes the outcomes of the pediatric development program for tapentadol across the entire age range from birth (including neonates) to adolescents <18 years of age. In addition, the challenges experienced when designing and conducting the pediatric tapentadol clinical trials as well as the interactions with the regulatory authorities are discussed. As a first outcome, the oral solution of tapentadol was authorized in the EU in 2018 as a new treatment option in the hospital setting for moderate to severe acute pain in children from 2 to <18 years of age.

Keywords: pain, pediatric, regulations, tapentadol, review

Background: Pharmacokinetics (PK), efficacy, and safety of the opioid analgesic tapentadol in the treatment of moderate-to-severe acute pain have so far not been investigated in pediatric patients <2 years of age.

Patients and Methods: Two multicenter, open-label trials assessed the pharmacokinetic profiles, safety, tolerability, and efficacy of single doses of tapentadol oral solution (OS; NCT02221674; n=19) or intravenous infusion (IV; NCT01438229; n=28) in children from birth to <2 years of age. Of these, 8 patients neonates were included in the IV trial. A third randomized, double-blind, placebo-controlled trial (NCT03081391) investigated the efficacy and safety of multiple tapentadol OS doses in patients from birth to <2 years (placebo n=4, tapentadol n=11) using an immediate rescue trial design. Patients in all three trials underwent surgery, but in the investigator’s opinion, reliably produced moderate-to-severe pain requiring opioid treatment.

Results: Administration of single tapentadol doses resulted in tapentadol serum concentrations within the targeted range known to be safe and efficacious in adults and compared well to the range observed for children aged 2 to <18 years. Pain intensity almost improved 13 min after administration. In the multiple dose trial, amounts of supplemental opioid analgesics within the first 24 h after start of trial medication were low (placebo 0.92 mg/kg, tapentadol 0.65 mg/kg). All patients stopped treatment with the trial medication because opioid analgesics were no longer required. Treatment-emergent adverse events occurred in 42.1% (tapentadol OS single dose), 28.9% (tapentadol IV), and 12% (placebo and 54.5% of tapentadol patients (tapentadol OS multiple doses), some of them serious.

Conclusion: Tapentadol showed a favorable PK and safety profile in children <2 years of age. Multiple tapentadol OS doses are efficacious and generally well tolerated in children ≥2 years and might also be a useful treatment option for children <2 years in need of strong analgesics.

Keywords: infants, intravenous formulation, neonates, oral formulation, pain management, tapentadol
From an industry standpoint, what would help infant and neonatal acute pain clinical trial success?

- Workshops like this to share new ideas and collaborate

- Collaborative working groups (industry, academia, regulatory, parents)
  - Sharing info
  - Patient/parent insights

- Additional opportunities for open dialog and feedback with the regulatory agencies, including the review division and pediatric division to accommodate challenges regarding neonatal pain study design