FDA Public Workshop: 13th - 14th October 2021
Analgesic Clinical Trial Designs, Extrapolation, and Endpoints in Pediatric Patients from Birth to Less Than 2 Years of Age

Brain-derived approaches to assess neonatal & infant pain

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Challenges with current pain measurement approaches

- Neonatal pain measurement is primarily reliant on observing changes in behavioural and physiological activity (e.g. heart rate).

- These measures are subjective, lacking specificity and sensitivity
  - Non-noxious stimuli (e.g. diaper change) can evoke high pain scores
  - Noxious stimulation may not elicit behavioral change in high % of neonates leading to low pain scores

- Advances in understanding neonatal physiology have occurred in recent years that may help improve measures of neonatal pain

Green at al., (2019) Pain
Quantifying noxious-evoked activity in the neonate

1980
Transcutaneous partial pressure of O2 & CO2
Rawlings et al., Am J Dis Child

1984
Crying
Owens et al., Pain

1993
Body movements
Craig et al., Pain

1996
Multimodal measures
Stevens et al., Clin J Pain

2010
EEG: Noxious-evoked potentials
Slater et al., EJP

1984
Increased heart rate
Owens et al., Pain

1987
Facial expressions
Grunau et al., Pain

1994
Reflex withdrawal
Andrews et al., Pain

2006
NIRS: total haemoglobin conc.
Bartocci et al., Pain

2015
fMRI: BOLD
Goksan et al., eLife

O2: oxygen; CO2: carbon dioxide; NIRS: near-infrared spectroscopy; EEG: electroencephalography; fMRI: functional MRI
Quantifying noxious-evoked activity in the neonate

Moultrie at al., (2017) Current Opinions in supportive and palliative care
Advances in brain-derived approaches to better understand neonatal pain

2006
J Neuro, Pain
Recording noxious-evoked haemodynamic activity (NIRS).

2008
EJP
Recording noxious-evoked electrical brain activity (EEG).

2011
Current Biology
Early development of noxious-evoked brain activity.

2017
Current Biology
Impact of stress on noxious-evoked brain activity

2006
Pain
Long-term consequences of early life pain.

2010 & 2018
Lancet
Using brain-derived endpoints in clinical trials.

2015, 2017
eLife, Acta Paed
Measuring noxious-evoked brain activity using fMRI.

2021
Nature Comms
Understanding individual variability in pain responses.
Measuring noxious-evoked brain activity in the infant brain
Measuring noxious-evoked brain activity

Near-infrared spectroscopy

Clinically required noxious procedure (heel lance for blood sampling)

Electroencephalography (EEG)

Pain-related brain activity

Background EEG

Non-noxious touch

Noxious heel lance

25µV

Noxious-evoked brain activity in adults compared with infants

Similar patterns of noxious-evoked brain activity are recorded in neonates and adults when the same intensity nociceptive input is applied to the body, and adults verbally report that the stimuli are mildly painful.

Goksan et al., (2015, 2017) eLife
Duff et al., Lancet Digital Health (2020) ... in collaboration with Tor Wager
Data reproducibility at independent sites: noxious-evoked brain activity

van der Vaart at al., ....... in collaboration with Fabrizi et al., at UCL (2021) Cerebral Cortex revision under review
Pilot data: paracetamol modulates neonatal noxious-evoked brain activity
Pilot data: paracetamol modulates neonatal responses to immunisation

Classifier correctly classified 85% of observations as noxious in neonates who did not receive paracetamol prior to the immunisation. The scores were significantly lower when the infants were treated with paracetamol (p = 0.025)
Using brain activity as a measure of analgesic efficacy in infants

Collaboration with regulators, industry, clinicians and academics

Preterm health: time to bridge the evidence gap

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Despite the development of revolutionary life-sustaining advances in neonatal medicine, medications are frequently administered in an ad-hoc and suboptimal way. Most drugs prescribed in neonatal care have not been submitted to the stringent regulatory processes of drug licensing that are standard in adult medicine. Although clinical research and licensing regulations differ between countries, the scarcity of licensed medications and inevitable use of off-label drugs is greater in neonatal medicine. This has resulted in repetitive underdosings. Doing research in preterm infants presents considerable ethical, logistical, and commercial challenges. Specific barriers include the challenging ethics of gaining consent from vulnerable parents of critically ill infants, high rates of morbidity and mortality, a greater risk of adverse drug events in this population, issues surrounding clinical equipoise with the widespread use of drugs without evidence, the acceptability of placebo use, and concerns over liability.
Brain-derived approaches can be used as end points in clinical trials.

Develop methods to improve treatments, through better understanding of the pharmacokinetic and pharmacodynamic properties of analgesics.

Advances in imaging and analytical methods provide an opportunity to test the efficacy of analgesics across a range of clinical procedures.
Thank you