U.S. FOOD & DRUG ADMINISTRATION

Pediatric Pain and the Approach to Studying Opioid Analgesics in Pediatric Populations

Joshua Lloyd, MD

Clinical Team Leader

Division of Anesthesia, Analgesia, and Addiction Products (DAAAP)

Joint Meeting of the Pediatric Advisory Committee (PAC) and the Drug Safety and Risk Management Advisory Committee (DSaRM)

September 26, 2019

Pediatric Drug Development

Pediatric Drug Development
General Principles

- Children should have access to products that have been appropriately evaluated
- Thoughtful drug development and inclusion of children in trials is critical to pediatric health

Current Pediatric Drug Legislation

- Best Pharmaceuticals for Children Act (BPCA) (2002)
- Pediatric Research Equity Act (PREA) (2003)

Best Pharmaceuticals for Children Act (BPCA)

- Provides for **voluntary** pediatric drug assessments via a Written Request (WR), including clinical and non-clinical studies
- Authorizes FDA to request studies for the drug moiety, for approved and/or unapproved pediatric indications including orphan indications
- Reflects a public health need for pediatric studies
- Provides a process for studying off-patent drugs
- Six months of marketing exclusivity granted if the terms of the WR are met

Pediatric Research Equity Act (PREA)

- Triggered by an application for a new indication, new dosage form, new dosing regimen, new route of administration or new active ingredient
- Authorizes FDA to **require** a pediatric assessment of certain drug/biologic products at the time the application is submitted
- Provides criteria for FDA to waive or defer pediatric studies and requires a plan for deferred studies
- Establishes the Pediatric Review Committee (PeRC) to review pediatric plans & assessments and waiver & deferral requests

U.S. FOOD & DRUG ADMINISTRATION

Pediatric Analgesic Drug Development

Pediatric Analgesic Drug Development

- Unmet needs in pediatric pain management
- Very few analgesics with pediatric indications or labeling, including opioids
- Although pediatric studies have been required by law since 2003, few analgesic studies have been completed
- Most infants and children are healthy and experience brief pain episodes, but some have severely painful conditions (e.g., epidermolysis bullosa, osteogenesis imperfecta, cancer, metabolic/neurologic disease, sickle cell disease)
- Most analgesic use in pediatric patients is off-label

Prior Pediatric Study Requirements for Opioid Analgesics

- For many years, efficacy, safety and pharmacokinetic (PK) studies were required for all age groups for all indications
- Few studies were conducted, few were completed
- Therefore, obtaining useful data in a more efficient manner was necessary
  - For example, extrapolation of efficacy from adult studies

Legislation allows for Extrapolation of Efficacy in Pediatric Patients

If the course of the disease and the effects of the drug are sufficiently similar in adults and pediatric patients, [FDA] may conclude that pediatric effectiveness can be extrapolated from adequate and well-controlled studies in adults, usually supplemented with other information obtained in pediatric patients, such as pharmacokinetic studies.

*21CFR §355c

Importance of Extrapolation

- Children are a vulnerable population and require additional safeguards in studies (e.g., inability to consent or communicate symptoms as well as adults, developing organ systems)
- Extrapolating efficacy when possible is important because there are a limited number of pediatric patients available to enroll
  - Extrapolating efficacy allows studies to be smaller and enroll fewer patients

Limitations to Extrapolation

- Novel mechanism of action for the drug
- Inconsistent systemic exposures between adults and children
  - For example, if exposures are lower in children when compared to adults, then it is unclear if extrapolation of efficacy from adults is appropriate
  - We recommend that sponsors collect pain scores and rescue medication usage in PK/safety studies to provide context

Scientific Basis for Extrapolation in Pain

- December 2009, FDA convened a workshop of leaders in pediatric pain, pediatric clinical studies, pediatric ethics and pediatric drug development
  - Discussed the development of the central nervous system, maturation of metabolic pathways, physiology of opioid receptors
  - Discussed different approaches for acute and chronic pain studies in children that do not increase risk of pain or delayed treatment to patients
  - Discussed available science to support extrapolation for analgesic drug classes

PEDIATRICS®

OFFICIAL JOURNAL OF THE AMERICAN ACADEMY OF PEDIATRICS

Pediatric Analgesic Clinical Trial Designs, Measures, and Extrapolation: Report of an FDA Scientific Workshop

Charles B. Berde, Gary A. Walco, Elliot J. Krane, K. J. S. Anand, Jacob V. Aranda, Kenneth D. Craig, Carlton D. Dampier, Julia C. Finkel, Martin Grabois, Celeste Johnston, John Lantos, Alyssa Lebel, Lynne G. Maxwell, Patrick McGrath, Timothy F. Oberlander, Laura E. Schanberg, Bonnie Stevens, Anna Taddio, Carl L. von Baeyer, Myron Yaster and William T. Zempsky

Pediatrics; originally published online January 16, 2012;
DOI: 10.1542/peds.2010-3591

Current Approach for Pediatric Opioid Studies

- Immediate-release (IR) opioid analgesic products
  - Ages 0 to < 2 years of age: Efficacy, safety and pharmacokinetics
  - Ages 2 to < 17 years of age: Safety and pharmacokinetics with extrapolation of efficacy from adult studies

- Extended-release (ER) opioid analgesic products
  - Ages 0 to < 7 years of age: Waived due to low prevalence of subjects with relevant conditions in this age range (i.e., chronic pain)
  - Ages 7 to < 17 years of age: Safety and pharmacokinetics with extrapolation of efficacy from adult studies

(More) Recently Approved Pediatric Labeling for OxyContin

OxyContin

- The purpose of the pediatric study was to describe the PK and safety of OxyContin in pediatric patients requiring treatment with an extended-release opioid analgesic

- Pediatric indication approved August 2015
- **Approval did not create novel uses for OxyContin in pediatric patients-but provided data in patients who require this treatment**
- http://www.fda.gov/Drugs/NewsEvents/ucm456973.htm

----------INDICATIONS AND USAGE----------

OXYCONTIN is an opioid agonist indicated for the management of pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate in:

- Adults; and
- Opioid-tolerant pediatric patients 11 years of age and older who are already receiving and tolerate a minimum daily opioid dose of at least 20 mg oxycodone orally or its equivalent.

Limitations of Use

- Because of the risks of addiction, abuse and misuse with opioids, even at recommended doses, and because of the greater risks of overdose and death with extended-release opioid formulations, reserve OXYCONTIN for use in patients for whom alternative treatment options (e.g. non-opioid analgesics or immediate-release opioids) are ineffective, not tolerated, or would be otherwise inadequate to provide sufficient management of pain. (1)
- OXYCONTIN is not indicated as an as-needed (prn) analgesic. (1)

OxyContin Post-Marketing Requirements

- Novel PMRs were put in place to further understand the impact of pediatric indication for OxyContin
- The Sponsor is required to assess the safety and use of OxyContin in pediatric patients in two postmarketing studies:
  - Study 1:
    - Assess risks of respiratory depression, overdose, misuse, accidental exposure and med errors in opioid tolerant patients aged 11-17 and children younger than approved age range or do not meet criteria for opioid tolerance
    - Analysis of post-market adverse events described above on all pediatric ages
  - Study 2:
    - National drug utilization study to characterize use of OxyContin in pediatrics
    - Data from study will provide denominator for study 1 to assess risk

Conclusions

- FDA has worked (and continues to work) to develop a rational approach to inform prescribers about the safe and effective use of opioids for the treatment of pain in children
- FDA's approach to studying opioids in pediatrics has evolved over time to address the need for pediatric data, particularly given that these products are already used off-label in this population
- FDA encourages Sponsors to collect data as efficiently as possible to add knowledge about this population to benefit pediatric public health

Acknowledgements

- Sharon Hertz, MD
  - Director, DAAAP
- Ellen Fields, MD, MPH
  - Associate Director, DAAAP


FDA
U.S. FOOD & DRUG
ADMINISTRATION