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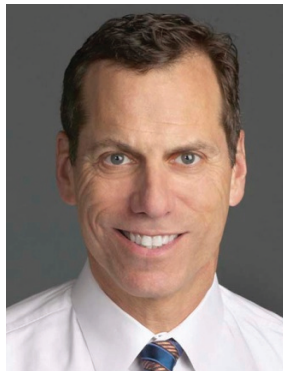

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Analgesic trials in children: safety, efficacy and innovation

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A premature newborn infant is being treated in a neonatal intensive care unit, quite ill and subject to an array of invasive procedures. We wish to do all we can to minimize that individual's suffering. Which analgesics may be effective? Are they safe? Are they metabolized by the youngest of human beings in a predictable way? Clearly, to answer these questions it is necessary to conduct clinical trials on children within this population. But is it ethical? Is it feasible? That is the tension experienced by pediatric practitioners who wish to invoke evidence to ease children's pain in a safe and effective manner.

The magnitude of the problem may be appreciated when one examines the epidemiology of pain in children. A prospective study conducted in neonatal intensive care settings showed that over the first 14 days of admission, each premature infant experienced a median of 75 (range: 3–364) painful procedures and ten (range: 0–51) painful procedures per day of hospitalization. Among the total of 42,413 painful procedures observed, newborns were provided with pharmacologic therapy specifically targeting the procedural pain only 2.1% of the time [1]. This study, and others in the field, tells us little about other, more ongoing pain in neonates, such as disease-related and postoperative pain. Of course, beyond the neonatal period, infants and children commonly experience acute pain due to surgery or injuries. In addition to acute pain, 5–23% of school-age children experience significant recurrent pain, such as headache, chest pain, abdominal pain and limb pain [2–4]. Children also endure chronic daily pain from headache disorders, neurodegenerative diseases, inflammatory and autoimmune disease, post-traumatic neuropathic pain conditions including complex regional pain syndrome, small fiber neuropathies and pain due to malignancies and other life-limiting diseases.

Key words: analgesics • clinical trials • ethics • extrapolation • pediatrics

With this as background, it is evident that there is a need for analgesic medications that have been shown to be safe and effective for use in young children. Historically, however, only a few drugs have been evaluated in children as part of the premarketing, preapproval investigational drug testing and most drugs are therefore commonly used off-label, and by extrapolation from adult practice by clinicians who treat children. Due to the fact that many pain conditions parallel those found in adults, often the same medications validated in adult samples are used with younger patients, merely correcting for dosage by scaling dosage based on body mass (e.g., mg/kg). However, this extrapolation from adult practice is not evidence-based and ignores obvious pharmacokinetic and pharmacodynamic differences between children and adults.

Various legislative remedies have provided the US FDA with 'carrots and sticks' to either encourage or require pharmaceutical companies to perform pediatric clinical trials, including the Food and Drug Modernization Act (FDAMA, 1997), the Best Pharmaceuticals for Children Act (BPCA, 2002) and the Pediatric Research

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Equity Act (PREA, 2007), reviews of which are beyond the scope of this editorial (see [5] for details). As reported by the FDA in January 2012, since these acts have been in place, there have been 426 labeling changes, with 388 new pediatric trials [101]. However, the impact of these initiatives on analgesic drug trials has been disappointing and it is striking to realize that, with the exception of local and/or topical anesthetics, very few analgesic drugs are labeled for use in children.

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Specifically, in children under 6 months of age, there are no such medications. For children between 6 and 24 months, only ibuprofen has been approved for analgesia and for those older than 2 years, the list expands to include oral acetaminophen, aspirin, meperidine, hydrocodone, tolmetin, the combination product of acetaminophen and codeine (for age >3 years); intravenous acetaminophen, buprenorphine, meperidine, fentanyl citrate, epidural chloroprocaine, lidocaine and mepivacaine, continuous epidural clonidine (for intractable cancer pain) and transdermal fentanyl. A handful of other NSAIDs are approved for the treatment of arthritis and have analgesic effects, including celecoxib, naproxen for children over 2 years and etodolac and oxaprozin for those over 6 years of age [5]. It should be noted that of these, aspirin is not used due to concerns over Reye syndrome, meperidine due to concern over normeperidine induced CNS excitation and seizures, and codeine due to its variable metabolism.

Over the years the overwhelming majority of Phase III clinical trials for analgesic medications excluded participants under 16 years of age, largely due to reluctance by the pharmaceutical companies based on concerns over ethics, finances, product liability and the challenges of adequate study design [5]. For example, the modal methodology in efficacy trials typically involved a comparison of an active analgesic drug with a placebo. To address these concerns, the FDA convened a consensus panel of experts to explore the reasons for the current state of affairs and possible solutions, a summary of which may be found in *Pediatrics* [6].

Due to the fact that child research participants are a vulnerable population and cannot provide their own informed consent, the standard of risk–benefit analysis shifts: children may not be disadvantaged by research participation and must derive some immediate personal benefit by that participation [7]. Experiencing any additional pain as a function of participation in an analgesic trial, such as being given a placebo and denied active analgesic medication, is ethically unjustifiable. Furthermore, even if there were some ethical justification, parents would be unlikely to consent to such a trial and few providers would enroll the children under their care.

Pediatric trials are further complicated by three unique but inter-related factors: limitations in pain assessment (and the use of surrogate pain measures); lack of expert consensus regarding pediatric analgesic study designs and measures; and limits on extrapolation of efficacy and risks from one developmental age to another, due to differences in metabolism, excretion, drug efficacy, receptor subtypes, receptor induction, signal transduction and cellular regulatory pathways. In general, the younger the child, the greater the difficulties posed by these concerns, which are most salient for premature newborns. Each of these issues is presented in more detail in the consensus paper [6].

Meeting the challenge of analgesic trials in young children

Understanding the nuances of pain assessment in very young and sick children requires unique expertise. Applying known developmental phenomena and how they might affect drug metabolism and related safety and efficacy likewise requires knowledge rarely possessed by those outside of pediatric settings. Finally, flexibility in methodology to accommodate the ethical and pragmatic demands of potential participants who are young and sick is uncommon among most researchers. It is, therefore, not surprising that a small cadre of experts were frequently called upon both by the pharmaceutical companies and the officials within the FDA to consult on these aspects of study design and implementation.

High-quality studies of the safety and efficacy of analgesic agents are needed to assure safe and evidence-based practice in treating pain in children. It became clear during the discussions at the consensus meeting that it might be in everybody's best interest for there to be a research collaborative focusing on analgesic trials in children. In so doing, the FDA would be assured of optimal research methodologies and clear guidance on the limits of extrapolation from adult studies versus conducting unique pediatric trials on issues of safety and efficacy. The pharmaceutical companies might welcome such an endeavor, as drug trials could be done more expeditiously and effectively. In order to obtain adequate sample size, multisite collaboration is essential, as even the largest pediatric centers do not have a sufficient volume of patients to conduct comprehensive clinical trials independently. Finally, the clinical researchers might be pleased that their work would have a greater effect upon the entire process, leading to better studies with greater clinical relevance. Ultimately, of course, pediatric patients

benefit, as the most relevant and valid data would guide clinical practice.

As a result of this work, we founded the Pediatric Research Network for Pain. With grants from the Mayday Fund, the National Institute of Child Health and Human Development and the Bungie Foundation, an initial investigators' meeting was held at which the structure of the organization was defined and by-laws drafted. There are 26 member institutions, 22 in the USA and four in Canada. The group is already working with a number of pharmaceutical firms in a consultative role and it is anticipated that direct involvement in clinical trials will begin in the near future. It seems clear that an independent collaborative research group, working closely with industry and regulatory bodies, will undoubtedly facilitate more optimal clinical trials in this vulnerable population.

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