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Safety in Small Populations, It's a Big Deal: Monitoring Safety in Pediatric Studies and Beyond

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Disclosures, Affiliations, and Acknowledgements

Disclosures

- I am an employee of Amgen Inc
- All data in this presentation is public

Overview

- Unique aspects of monitoring pediatric safety in studies
 - Randomized Clinical Trials
 - Variability in the pediatric population
 - “Windows” of development
 - Extrapolation
- Adverse events associated with development may not be immediately apparent
 - Longer term follow up may help with these events
- Potential solutions
 - Better event capture
 - Big data

Monitoring Safety During Clinical Trials

- Pediatric clinical trials difficult to power for efficacy, even harder to power for safety events
- Hard to sustain an adequate “N”
 - Potential duration between acute exposure and effect in the developing child
 - DES (diethylstilbestrol) and clear cell adenocarcinoma (CCA) (1)
 - Propensity of polypharmacy among the most vulnerable pediatric populations
 - Difficulty in separating out natural progression of disease from drug effect
 - Serious asthma-related events for pediatric patients relative to those attributable to LABAs (2)
 - Geographical and medical insurance mobility of pediatric population

Variability in the Pediatric Population

- Changes in drug burden (with age) over time
- Changes in metabolite burden (with age) over time
 - Tramadol is oxidized to an active metabolite O-desmethyltramadol (ODT) via CYP2D6, having a MU-opioid activity 200 times that of the parent drug.
 - Additionally, tramadol is inactivated to N-desmethyltramadol (NDT) by CYP3A4 and CYP2B6.
 - Secondary metabolism involves further oxidation and phase 2 conjugative reactions.
 - In early life, however, these primary metabolic pathways mature differently, and as a consequence, not only the absolute value of the clearance but also relative contributions of the different eliminating pathways may change over time. (3)

Additional Variability in Pediatrics

- Wide range of maturational stages of childhood with potential for discrete periods of susceptibility
 - Preterm newborn infants
 - Term newborn infants (0 to 27 days)
 - Infants and toddlers (28 days to 23 months)
 - Children (2 to 11 years)
 - Adolescents (12 to 16-18 years (dependent on region))

If the clearance pathways of a medicinal product are well established and the ontogeny of the pathways is understood, age categories for pharmacokinetic evaluation might be chosen based on any break point where clearance is likely to change significantly

The World According to Dianne Murphy

- Neonates are a physiologic environment unto themselves
- Childhood growth velocity not seen in any other period
- Bone and muscle changes are dramatic
- Enzymatic activation, immunologic development and physiologic changes develop during childhood and adolescence
- Neurological and cognitive development are most dynamic during first 18 years
- Puberty is hormonal and growth 'storm', not limited to changes in reproductive organ development

Safety and Transparency of Pediatric Drug Trials

Daniel K. Benjamin Jr, MD, PhD, MPH; P. Brian Smith, MD, MHS; M. Jessica M. Sun, MD;
M. Dianne Murphy, MD; Debbie Avant, RPh; Lisa Mathis, MD; William Rodriguez, MD;
Robert M. Califf, MD; Jennifer S. Li, MD, MHS

Arch Pediatr Adolesc Med. 2009;163(12):1080-1086

Conclusions: Medication adverse events in children often differ from those in adults, particularly those that are neuropsychiatric in nature. Labeling changes for pediatric use demonstrate that pediatric drug studies provide valuable and unique safety data that can guide the use of these drugs in children. Unfortunately, most of these articles are not published, and almost half of the published articles focus their attention away from the crucial safety data.

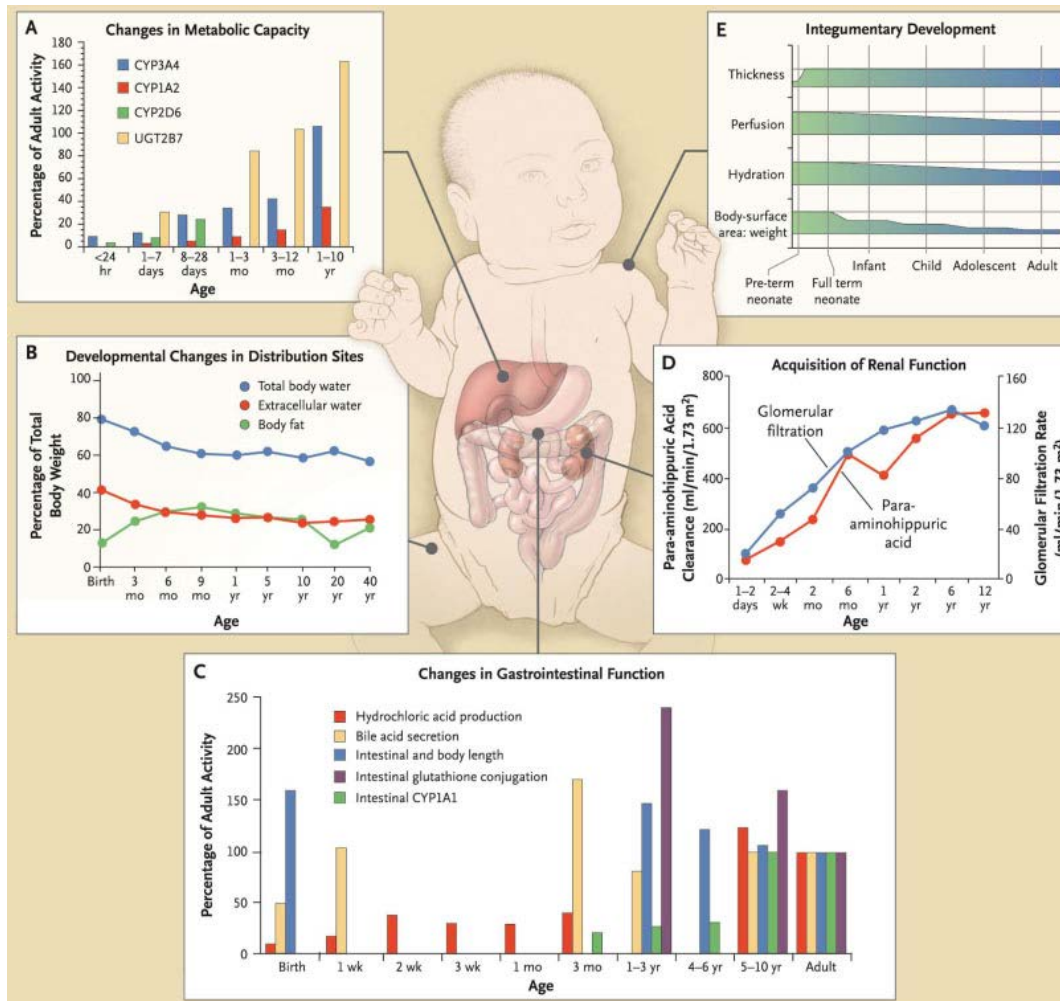
Unique Pediatric Adverse Events During Clinical Trials in Pediatrics

- For all SSRIs, antidepressants increased the risk of suicidal thoughts and behaviors in pediatric and young adult patients. Closely monitor for clinical worsening and emergence of suicidal thoughts and behaviors.(4)
- This signal was detected by a meta-analysis of pediatric studies
 - increased risk for suicidality and suicidal behavior in under 25 years population approaches that seen in children and adolescents
 - effect neutral on suicidal behavior but possibly protective for suicidal ideation in adults aged 25-64 and
 - Protective of both suicidality and suicidal behavior in those aged ≥ 65 .

Monitoring Safety During Neonatal Clinical Trials

- Often even more difficult as:
 - Absorption, distribution, metabolism and elimination affected by immature systems
 - For some measures, especially in premature neonates, the standard value may be variable (blood pressure)
 - Infants in clinical trials frequently have comorbidities, multiple medications, thus attribution is difficult
 - Enrollment even to contribute to overall pediatric efficacy difficult, for safety endpoint even more difficult
 - Long term outcomes could be multifactorial e.g.:
 - prematurity,
 - anoxia,
 - sepsis

Neonates/Infants



Extrapolation

- “Pediatric Extrapolation” is defined as an approach to providing evidence in support of effective and safe use of drugs in the pediatric population when it can be assumed that the course of the disease and the potential effects of the drug are sufficiently similar in the pediatric and reference (adult or other pediatric) population. (5)
- Pediatric populations can benefit from the utilization of prior knowledge as it may spare children from unnecessary clinical studies where appropriate.

While extrapolation helps us with efficacy, it does not extend to safety. Adult safety only alerts us to safety items that should be monitored in pediatrics as well

Pediatric Adverse Events in the Context of Adult Adverse Events

- Unique pediatric adverse events may be diluted in a large number of adult adverse events and overlooked (6)
 - Imiquimod off label use in pediatric patients resulted in genital swelling and urethral occlusion. Because the use was so high in adults and the cases were few in pediatrics, the percentage of events being reported was too low to attract attention. Now, included in labeling.

Aldara USPI: “Severe local inflammatory reactions of the female external genitalia can lead to severe vulvar swelling. Severe vulvar swelling can lead to urinary retention; dosing should be interrupted or discontinued.”

Safety and Randomized Clinical Trials

- RCT's are designed for pre-specified efficacy endpoints and rarely for anticipated or unanticipated safety outcomes
- RCT's are usually underpowered for safety outcomes and therefore need other studies or integrated summaries of other studies for enough data
- Examining many (multiple) safety outcomes that have low events rates, may lead to complexities in interpreting true from false positive findings

Most RCTs in pediatrics are not powered even for efficacy much less safety across all pediatric age groups

Monitoring Safety During Clinical Trials

- Routine safety assessments must be collected at baseline and appropriate follow-up times, e.g.,
 - vital signs (pulse rate and blood pressure), weight, height (as measured by stadiometer), clinical laboratory measures (chemistry, including liver function tests and bilirubin; hematology; serum lipids; glucose; and urinalysis), ECGs
 - Must be adjusted for age
 - Any signals from adult studies and nonclinical studies
 - May need nonclinical studies of juvenile animals to assess signal

Latuda (lurasidone hydrochloride) tablets, atypical antipsychotic for the treatment of:

- Schizophrenia
- Depressive Episodes associated with Bipolar I Disorder (bipolar depression), as monotherapy and as adjunctive therapy with lithium or valproate

Written Request dated 4/20/2012 required juvenile animal studies

LATUDA (lurasidone hydrochloride) USPI

- Safety and effectiveness in pediatric patients have not been established.
- Antidepressants increased the risk of suicidal thoughts and behaviors in pediatric and young adult patients. Closely monitor for clinical worsening and emergence of suicidal thoughts and behaviors.
- Section 8.4 PEDIATRICS:
 - The safety and effectiveness of LATUDA 40-mg/day and 80-mg/day for the treatment of schizophrenia in adolescents (13 to 17 years) was established in a 6-week, placebo-controlled clinical study in 326 adolescent patients
 - The safety and effectiveness of LATUDA have not been established in pediatric patients with depression.
 - The effectiveness of LATUDA in pediatric patients for the treatment of irritability associated with autistic disorder has not been established.
 - Nonclinical Data: Adverse effects were seen on growth, physical and neurobehavioral development at doses as low as 0.2 times the MRHD based on mg/m². Lurasidone was orally administered to rats from postnatal days 21 through 91 (this period corresponds to childhood, adolescence, and young adulthood in humans) at doses of 3, 30, and 150 (males) or 300 (females) mg/kg/day which are 0.2 to 10 times (males) and 20 times (females) the maximum recommended adult human dose (MRHD) of 160 mg/day based on mg/m². The adverse effects included dose-dependent decreases in femoral length, bone mineral content, body and brain weights at 2 times the MRHD in both sexes, and motor hyperactivity at 0.2 and 2 times the MRHD in both sexes based on mg/m². In females, there was a delay in attainment of sexual maturity at 2 times the MRHD, associated with decreased serum estradiol.

Ascertaining Adverse Events

- Events of interest must be actively ascertained
- May need testing focused on event of interest
 - Eg – visual testing if nonclinical/clinical testing demonstrates optic signs/symptoms
- For reported events, may need to have parents/guardian reported adverse events for patients less than 7-9 years of age
 - Parent/guardians should be provided list of things to monitor and how to monitor

Zolpidem studied for “Insomnia associated with ADHD” psychiatric and nervous system disorders comprised > 5% of treatment emergent adverse events, including dizziness (23.5%) headache (12.5%) and hallucinations (7.4%)

Longer Term Safety Data

Long Term Studies

Types of Studies –

- Controlled – Placebo or active controlled
- Uncontrolled – Open label extension study
- Observational – Registry
 - Retrospective data
- Other Options?

Longer Term Studies

Clinical trials desirable for long-term pediatric safety monitoring when other data sources may be confounded:

- Outcome is a continuous variable that must be measured precisely
 - Cognitive function
 - Blood pressure
- Safety event is similar to events related to the disease being treated
 - Hospitalization
- Long-term control (i.e., placebo) group is desirable
 - Growth
 - Cognitive development

Prospective Registry Study - Darbepoetin Alfa (7)

- Prospective, observational registry in children ≤ 16 years of age with CKD anemia and receiving DA were observed for ≤ 2 years.
- Adverse events (AEs), DA dosing, hemoglobin (Hb) concentrations, and transfusions were recorded.
- Inclusion Criteria: children and adolescents age 0–16 years with anemia attributed to CKD receiving dialysis or have an eGFR of < 60 ml/min \times 1.73 m² for at least 3 months, and receiving DA at the time of study enrollment.
- Patients were followed up for a maximum of 2 years, or until study withdrawal if this occurred earlier.
- Protocol-specified reasons for premature study withdrawal included permanent cessation of DA treatment, renal transplantation, enrollment into an interventional study, or withdrawal of informed consent.

Follow Up

- Of the 321 patients who entered the study, 145 (45.2 %) patients completed the study, and 176 (54.8 %) withdrew prematurely
 - Ineligible, 4 (1.2%)
 - Adverse event, 2 (0.6%)
 - Consent withdrawn, 3 (0.9%)
 - Required alternative therapy, 2 (0.6%)
 - Administrative reasons, 4 (1.2%)
 - Lost to follow-up, 11 (3.4%)
 - Death, 6 (1.9%)
- Protocol-specified criteria:
 - Renal transplant, 121 (37.7%)
 - Permanently discontinued DA, 20 (6.2%)
 - Enrolled into interventional study, 1 (0.3%)

Long-term Safety and Efficacy of Etanercept (8)

- 5-year, open-label extension study enrolling 182 patients aged 4 to 17 years who had participated in a 48-week parent study.
- End points included:
 - Occurrence of adverse events (AEs) and serious AEs including infections, and
 - Rates of 75% and 90% improvement in Psoriasis Area and Severity Index score and clear/almost clear on static physician global assessment
- Of 182 patients enrolled, 181 received etanercept and 69 completed 264 weeks.
- Through week 264, 161 (89.0%) patients reported an AE, most commonly upper respiratory tract infection (37.6%), nasopharyngitis (26.0%), and headache (21.5%).
- Seven patients reported 8 serious AEs; only 1 (cellulitis) was considered treatment-related.
- No cases of opportunistic infections or malignancy were reported

Limitations of the OLE Etanercept Study

- Relatively small number of patients in the study overall and in the number of patients who remained on etanercept through the OLE study.
- Rare safety events that may only occur in children and adolescents would be unlikely to be observed with so few patient-years of exposure.
- In addition, as patients had strict eligibility requirements for entry into the parent study, these results are not generalizable to the overall population of pediatric patients with psoriasis.

Solutions

- Increase Adverse Event Recognition and Reporting
 - Integrative Drug Safety Service
 - An integrative approach consisting of computerized triggers, voluntary reporting, and a standardized electronic ADR questionnaire facilitated this process and allowed for improved detection and reporting (9)
- Use of large data sets
 - Meta analysis of multiple studies
 - Medical records from treatment centers such as Davita
 - Sentinel
 - Signal Detection Algorithms

Sentinel

Develop a national electronic safety monitoring system

Leveraging multiple sources of currently available electronic data

Partnering with data holders (Healthcare systems, insurance companies) to:

- Enhance active post-market monitoring of medical product safety
- More effectively look at common outcomes (e.g. MI, fractures)
- Have denominators to calculate rates
- Increase sample size with improved access to population subgroups
- Use validated design and statistical methods
- Near real-time monitoring by using a common data model & “Library” of tools/resources
- Integrate active surveillance with current post-market safety monitoring systems

Summary

- Pharmacovigilance during clinical studies and afterwards are critical to assess benefit/risk of medications for pediatric populations
- Pediatric population is heterogeneous with different vulnerabilities
- While studies are complex, they are not impossible
- Extrapolation applies to efficacy, however, the ability to leverage data from sources other than randomized clinical trials allows for more data to make a benefit- risk analysis for medication use in pediatric populations
- While pharmacovigilance is a shared responsibility, the market application holder must take primary responsibility for defining the data sources to support safety in the pediatric population



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