

Obtaining Clinical Safety and Efficacy Data in Neonatal Infections

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Anti-Infective Drug Development in Neonates
FDA Workshop

September 15, 2016

Disclosure

- I am a full-time employee of Johnson & Johnson
- The opinions and positions shared in this presentation are mine and not those of my employer or of my J&J colleagues

Topics to Consider

- Obtaining data supporting conclusions
 - of safety and tolerability of new antibiotics in newborns
 - of efficacy of new antibiotics as treatment for infections in the newborn
- Thoughts on obtaining data that holds the greatest promise for understanding the appropriate use of new antibiotics in newborns

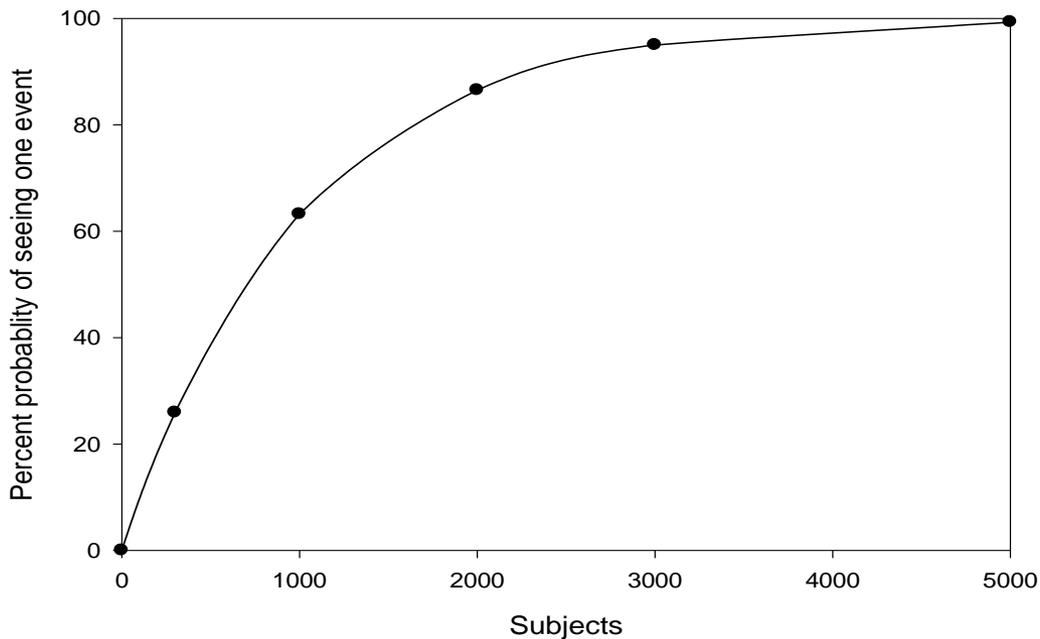
Safety and tolerability

- Goal → inform physician's choice by understanding potential risks of using an antibiotic to treat a patient with an infectious disease
 - Most appropriate data obtained from patients with the target disease
- Construct of a profile for newborns needs to consider
 - Observations made in older children and adults
 - Heterogeneity of the newborn population (eg prematurity, timing of onset of infection, chronological age)
 - Co-morbid conditions
 - Concomitant medications
 - Sample size

Sample size

- A sample size of 3000 patients would be required to have a > 90% probability of observing an event that occurs in 1/1000 patients.
- There is > 90% probability of correctly concluding an event is occurring in <1/100 patients, if the event is not observed in a sample of 300 patients.

Probability of detecting event in subject population
assuming an incidence of 1/1000



Safety and tolerability

- Recognize strengths and limitations of conclusions based on analyses of data collected in clinical studies
- Consider profiles initially derived from clinical trials as estimates that require continued rigorous assessments of clinical practice experience, especially in the critically ill newborn

Efficacy

- Goal → inform physician's choice by understanding the potential benefit of using an antibiotic to treat a patient with an infectious disease
- Conclusions of efficacy
 - should be influenced by observations made in older children and adults
 - need to consider the uniqueness of infectious diseases occurring in the newborn
 - Microbiology of disease
 - Host defense/responses
 - will seldom, if ever, be based solely on data from RCTs sufficiently sized to test clinical outcomes as a primary endpoint

Efficacy (continued)

- Given our current understanding of bacterial infection in the newborn, the most compelling data supporting efficacy of new antibiotics in newborns will
 - build on observations made outside the NICU in patients with infections that have comparable pathophysiology (eg vascular catheter associated infection)
 - define pharmacokinetics/dynamics of a new antibiotic in newborns that permit extrapolation of efficacy based on drug exposure

All things considered...

Challenges of obtaining the data needed to define safety/tolerability and efficacy in newborns are only, in part, driven by the medical considerations

1. Obtaining these data depends on
 - designing trials with objectives that can be clearly communicated and are acceptable to all stakeholders (parents, ethics committees, practitioners, investigators, sponsors)
 - being able to establish trust with parents and providing informed consent amidst the chaos of an acute illness and in circumstances of extreme stress
2. Complications associated with empiricism → **Because most newborns treated with an antibiotic will not have a bacterial infection, there is considerable risk that trials designed to align with current practice will involve collection of data from newborns whose outcome and clinical course are not related to antibiotic therapy**
 - Enormous variability in antibiotic use across NICUs is independent of proven infection (Pediat 2015; 135:826)
 - Suspected, not documented, bacterial infection is the major reason for treating newborns with antibiotics

Obtaining the best data: the future

- There is still much to learn that could have great importance in enabling collection of the best data to assess new antibiotics in the newborn
 - The role of host response in disease caused by bacteria in the newborn
 - Incorporating host response in new methods aimed at accurate diagnosis of bacterial infection
 - Selection of drugs complementing host response
 - Defining comparability of pathogenesis of specific infectious diseases (esp bacterial sepsis) between older children/adults and newborns
 - Understanding this comparability is required for accepting use of extrapolation to support conclusions of efficacy for new therapies
 - Developing rapid molecular diagnostic methods that establish bacteriologic diagnoses in the newborn
 - Reducing unnecessary use of antibacterials
 - Focused development of narrow spectrum agents
 - Effects of antibiotics on the developing microbiome
 - Including potential effects in considerations of benefit-risk
 - Guiding the need and rational design for long-term assessments of antibiotic

Summary

- Understanding the safety and efficacy of new antibiotics for use in newborns is essential for providing the best intensive care for these vulnerable patients
- Limitations in obtaining the best data for supporting conclusions of safety and efficacy in the newborn need to be recognized
- Improving our understanding of bacterial infectious diseases in the newborn can help address these limitations and should be considered an integral part of development of antibiotics for use in newborns