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Pediatric Antifungal Drug Development: Lessons Learned and Recommendations for the Future

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Invasive fungal infections in very or extremely premature neonates and older immuno-compromised children are common and often fatal. Successful treatment of these infections relies on optimal dosing of antifungal drugs, yet optimal dosing in children is still poorly defined for many antifungals.

The study of therapeutics in children has been dramatically advanced through legislative mandate (e.g., Pediatric Research Equity Act and the Best Pharmaceuticals for Children Act), and studies stimulated by these programs have taught us several important lessons. Foremost among these are: 1) antifungal pharmacokinetics (PK) and dosing differ, often dramatically, between children and adults; 2) inter-individual PK variability increases with decreasing developmental age; and 3) antifungal drug exposure targets vary between young infants, children, and adults. These lessons have implications for patient care, clinical trial design, and public policy for pediatric drug development.

PK changes from infants to adolescents

Historically, pediatric drug dosing has been extrapolated from adults by use of a linear model dividing the adult dose by an average adult weight (i.e., 70kg), allometrically ($\text{dose}_{\text{adult}} * [\text{child weight}/70]^{0.75}$) or by body surface area/ 1.73 m^2 . These strategies, although sometimes successful, do not always describe accurately the drug disposition differences among infants, children, and adults. A premature infant born at 27 weeks gestation is different from a healthy 10-year-old not only in size, but also in physiologic functions. Maturation changes in renal function and drug-metabolizing enzymes and changes in body composition as children age can each significantly alter drug pharmacokinetics. Yet for many drugs the same dose per kilogram of body weight is used in both of these hypothetical individuals. Without drug and population-specific evidence, there is significant risk that children will be under- or overdosed. Undre et al. in this issue of the journal show that children <5 years of age receiving micafungin had lower peak concentrations and lower overall exposure than older children.¹ Younger children had much higher concentrations of the M5 metabolite and increased drug clearance compared with older children, suggesting drug metabolism is different in younger individuals. This is consistent with past studies that showed children aged 2–8 years require doses 1.5 times higher than those used for adults on a per kilogram basis to achieve similar exposure.² Infants demonstrate an even higher micafungin clearance, as well as a larger volume of distribution requiring doses of 5–7 mg/kg to achieve adult exposures.³ These studies

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highlight the fallacy that weight-based dosing can be extrapolated linearly from adults to children. This would result in subtherapeutic exposure of micafungin that puts the patient at greater risk of death, morbidity, and development of resistance.

Prediction of pediatric drug dosing, safety, or efficacy from adult studies has consistently been challenging. When thought-leaders from industry, the Food and Drug Administration, the National Institutes of Health, academia, and practicing clinicians agree on a likely best dose for children prior to the conduct of the study, we are incorrect more than one third of the time. We have consistently failed to estimate exposure accurately across age groups and across therapeutic areas, conclusively proving that studies simply must be done in children. Unfortunately, the requirement that therapeutics be studied in children will disappear in the United States unless Congress renews pediatric legislation in 2012.

PK variability in children

Inter-individual PK variability is also influenced by age, with increased variability frequently seen in younger cohorts. Micafungin dosing has been well-studied in all age groups, from premature neonates to adults. These studies showed increased micafungin clearance with decreasing age. The precision of the estimate of clearance (coefficient of variation) is similar between adults (17%)⁴ and children (14%),² but that precision decreases substantially in neonates who have a much larger coefficient of variation (34%) than older patients.^{3,5,6} Multiple factors can affect observed variability; however, the increased inter-individual variability seen in neonates likely reflects developmental changes in drug disposition and metabolism, along with the impact of disease and other medication exposure on the pathways involved in micafungin clearance.

Voriconazole, on the other hand, exhibits wide variability in all ages. In adults, its variability is due primarily to non-linear PK.⁷ In children, voriconazole exhibits linear PK, yet significant inter-subject variability still exists.⁸ Voriconazole PK data in infants and toddlers are scarce. In this issue of the journal, Doby et al. report voriconazole serum concentrations in 10 children <3 years of age who had voriconazole trough concentrations measured per routine medical care.⁹ Trough concentrations did not correlate with amount of dose after administration of doses ranging from 3.4 mg/kg to 15 mg/kg. These findings suggest that therapeutic drug monitoring should be routine to guide accurate dosage adjustments in young children treated with voriconazole.

The primary reason that we have such limited data for voriconazole is that the company that makes the product was able to obtain from the Food and Drug Administration a waiver from studying the molecule in children younger than 24 months. To our knowledge, the company has not supported a study of this molecule in children <24 months and did not provide support to the teams at the University of Utah and Duke for the work conducted by Doby et al. While there are certainly compelling reasons to have only limited study of this molecule in toddlers and infants, the variability documented by Doby et al. shows that, when companies receive a waiver from the study of a molecule in a pediatric patient population,² outcomes are likely: 1) the company will not support such a study; and 2) we are at risk of giving an ineffective or toxic dose of a potentially life-saving molecule for a prolonged period of time. In our view, the public policy “lesson learned” from the work by Doby et al. is that waivers should be granted rarely and much less frequently than they are given today.

Therapeutic targets for antifungal agents differ in young infants

The natural history of systemic candidiasis in older children is similar to that observed in adults. Therefore, the current therapeutic approach in this age group is to mirror adult exposure for molecules that have proven successful in the treatment of invasive fungal

infection.^{10–17} However, infants are at much greater risk for hematogenous *Candida* meningoencephalitis (HCME); below 3 months of age, HCME should be assumed in all infants with systemic candidiasis. Consequently, antifungal agents in young infants should be dosed to target appropriate exposure in the brain parenchyma. This compartment is inaccessible to PK sampling in human clinical trials, and therefore bridging studies combining animal and human data with computer simulations have been used successfully to estimate antifungal exposures at this critical target site.

These bridging studies are best conducted in animals large enough that sampling of the various compartments of the central nervous system can be completed. Investigators have conducted a series of laboratory and subsequent clinical studies to validate this approach. Hope and colleagues assessed the PK and pharmacodynamics (PD) of micafungin in an experimental model of HCME in rabbits; an area under the concentration–time curve from 0 to 24 hours (AUC_{0-24}) 166.5 $\mu\text{g}\cdot\text{h}/\text{ml}$ was considered necessary to penetrate the central nervous system and treat HCME.¹⁸ The authors evaluated the translation of these findings to humans through a bridging study that demonstrated that a dose of 9–15 mg/kg should induce near-maximal effect in a majority of neonates with HCME. To verify these observations, this study was followed by a clinical trial in neonates with suspected invasive candidiasis that showed doses of 10mg/kg achieved concentrations necessary to treat central nervous system infection.⁵

Parallel to these laboratory and clinical PK/PD studies, investigators from the Neonatal Research Network were able to complete 2 cohort studies that linked previous animal model work and human autopsy studies to infant development.^{19,20} Animal models and prior case series had shown that *Candida* species frequently invade the central nervous system of the young infant.^{18,21–24} The Neonatal Research Network investigators confirmed that central nervous involvement should be assumed in young infants with invasive candidiasis.^{19,20} To date, of the 3 echinocandins commercially available, only micafungin has been thoroughly studied in the larger animal model-bridging pathway that we believe is essential for guiding antifungal dosing in the young infant.

The considerable data generated for micafungin and the extremely limited data that we have for voriconazole provide an ideal contrast demonstrating the importance of incorporating development, natural history studies, and protection of the central nervous system in pediatric studies. These studies also show the considerable investigation that should be undertaken before extrapolating adult dosing data to infants. Without adequate study, antifungal treatment of other infections with significant morbidity and mortality will proceed empirically at the expense of pediatric patients.

Summary

Hospitalized children of all ages are at risk of invasive fungal disease and deserve studies that can describe optimal dosing for their unique physiology. Linear weight-based extrapolation from adult data is inadequate and too often results in drug under- or overexposure. This places children at risk for unacceptable therapeutic failure or toxicity. New legislation in the last 15 years has made it advantageous, and in some cases mandatory, for drug companies to include pediatric trials in new drug development. We recommend that the study of antifungal therapeutics routinely include PK and dosing in children of all ages, especially those <2 years of age where variability and maturational changes are highest. In drugs with high variability and a narrow therapeutic window, therapeutic drug monitoring should be considered. Finally, when recommending a dose, the therapeutic target must reflect the natural history of the disease in the target population. Incorporating these

recommendations in the development of new antifungals will lead to safer and more effective antifungal therapy in children.

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