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Determination of Appropriate Dosing of Influenza Drugs in Pediatric Patients

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Abstract

Dose-finding studies of influenza antiviral drugs are challenging because it is difficult to enroll subjects in pediatric interventional studies and also because of the lack of concentration (or toxicity)–response relationships, the short duration of antiviral therapy, and the continually developing metabolic profiles of infants and young children. The evaluation of influenza antiviral agents in premature infants adds even more complexity. Recent advances in exposure-targeted study designs and modeling and simulations have aided in addressing some of these challenges.

ABSORPTION AND DISPOSITION OF DEVELOPMENTAL DRUGS

Children who are <2 years of age are at high risk for adverse outcomes if they develop influenza. Mortality rates in this age group are highest among infants <6 months of age, followed by infants 6–23 months of age.^{1–5} Nearly half of young children who die from influenza have no underlying risk factors, other than age, to predispose them to poor outcomes.¹ Despite this degree of disease burden, there is still a paucity of data on influenza antiviral dosing in the pediatric age group.

There are a number of challenges that have an impact on the ability to evaluate antiviral therapeutics in young children. Developmental changes are fairly well established, and an excellent review on the ontogeny of drug absorption and disposition has been published.⁶ In brief, the spectrum of absorption, distribution, metabolism, and excretion can vary profoundly in infants and young children as they mature. The rate of absorption of many drugs is slower in infants than in older children, thereby prolonging the time required to reach maximum drug concentrations.⁷ An increase in total body water and altered plasma protein concentrations may affect the distribution volume. Metabolically, the expressions of phase I (e.g., cytochrome P450) and phase II (e.g., glucuronosyltransferase) enzymes also undergo developmental changes. Developmental changes in renal function significantly affect renal clearance and will therefore have to be taken into consideration in dosing decisions for drugs cleared by this pathway. Collectively, the ontogeny of absorption, distribution, metabolism, and excretion illustrates the dynamic nature of the developing infant and child and demonstrates the need for clinical trials of antivirals to define its impact

on this population. Table 1 lists pediatric anti-influenza dosing recommendations for currently approved agents and those under investigation.

GENERAL DOSE-FINDING ISSUES

For many antiviral drugs, there is a discordance between *in vitro* susceptibility test results and *in vivo* concentration–response (pharmacodynamic) data. For example, efavirenz is an antiretroviral commonly used as first-line therapy for HIV infection. The concentration of efavirenz that can inhibit replication of wild-type laboratory adapted strains and clinical isolates in cell culture by 90–95% (IC₉₀–IC₉₅) ranges from 1.7 to 25 nmol/l (0.5–7.9 ng/ml).⁸ Even after adjusting these susceptibilities for a high degree of *in vivo* protein binding, the IC₉₅ remains <100 ng/ml.⁹ In contrast, *in vivo* pharmacodynamic data suggest that the therapeutic range of efavirenz is 1,000–4,000 ng/ml.¹⁰ This discordance between *in vitro* and *in vivo* results is not uncommon for antivirals. It highlights the need for establishing concentration–response relationships in adults and makes it much more difficult to estimate appropriate exposure targets in babies and young children.

Wide-ranging dose-finding studies are needed to identify associations between concentration–response (or toxicity) and pharmacokinetic determinants of response. For many antiretrovirals, especially protease inhibitors, the primary pharmacokinetic determinant of response is the trough concentration. None of the currently available anti-influenza drugs has demonstrated *in vivo* concentration–response relationships, primarily because such a relationship has not been appropriately sought. Oseltamivir, for example, was dosed at either 75 or 150 mg twice daily for 5 days in studies WV15670 and WV15671 (ref. 11). There was no observed difference in clinical efficacy between the two doses. However, lower doses that created incrementally smaller effects were not studied; therefore, an attempt to define a concentration–response relationship was not possible because the net dosing effect was a fixed response (i.e., all subjects exhibited similar responses).

Complicating the anti-influenza dose-finding issue further are a wide range of influenza viral strains and highly variable susceptibility patterns. With each influenza season, antigenic drift (genetic mutations) or, less frequently, antigenic shift (recombinant virus) results in new strains, and these may or may not be susceptible to existing drugs. Therefore, previously established concentration–response relationships may not hold during a given influenza season. There does not seem to be a single “best” biological marker of virologic efficacy (e.g., plasma polymerase chain reaction and quantitative sputum viral load) for influenza, and therefore phase II and III clinical trials must rely on clinical end points such as duration of symptoms or other subjective criteria. This is challenging enough in adult subjects, but it is nearly impossible in young children, who may not even recognize the presence of such symptoms or may lack the ability to articulate degrees of symptom resolution.

PEDIATRIC DOSE FINDING

Area-under-the-curve-targeted designs

In the absence of concentration–response data for anti-influenza drugs, an alternative approach to pediatric dose-finding is an area-under-the-curve (AUC)-targeted study design based on previous pharmacokinetic data from the adult population. The general concept behind this design is to target an AUC in pediatric patients using an adult dose approved by the US Food and Drug Administration. Assumptions underlying the use of this design are that an optimal adult dose has already been determined and that the influenza strain remains susceptible at that particular drug exposure. Depending on the drug being studied, this

design typically requires real-time drug quantitation and pharmacokinetic analyses for rapid turnaround and dosing decisions.

The AUC-targeted design has been successfully applied in two recent studies. The first was a neonatal dose-finding trial of a new oral valganciclovir suspension formulation for symptomatic congenital cytomegalovirus disease.^{12,13} The AUC target was based on intravenous dosing in the same population, and the final dose produced nearly identical average AUC results after oral or intravenous administration. A more recent AUC-targeted study examined oseltamivir dosing in babies and children from birth through 23 months of age.¹⁴ The prodrug oseltamivir phosphate is converted to its active metabolite, oseltamivir carboxylate, which is cleared unchanged by the kidney. Interim results of this AUC-targeted study suggest that the appropriate oseltamivir dose is 3.0 mg/kg/dose from birth through 8 months and 3.5 mg/kg/dose from 9 months through 11 months, administered twice daily. In children 12 through 23 months, the Food and Drug Administration-registered dosage of 30 mg twice daily provided carboxylate exposures lower than the targets based on protocol criteria; a dosage of 3.5 mg/kg/dose twice daily is being evaluated.

Topical anti-influenza drugs, such as zanamivir, present additional challenges to identifying appropriate pediatric doses with alternative formulations. Because the drug is inhaled, no more than 17% is systemically available.¹⁵ With no available concentration-response data, converting the adult Food and Drug Administration-approved inhaled dose to an intravenous pediatric dose is problematic. One solution is to develop a safe and effective adult intravenous dose and then utilize an AUC-targeted approach to define the pediatric dose. Unfortunately, in a pandemic situation, there may not be time to take these additional steps. This situation emphasizes the need to have reliable adult-related antiviral concentration-response data available, so that application in a pediatric setting can be swifter and more accurate.

Dose finding in premature infants

Premature neonates are one of the most challenging populations in which to establish optimal dosing, especially for anti-influenza drugs. Therapy for influenza is generally short term in nature, making real-time drug measurement and pharmacokinetic analyses for dose adjustment impractical for an individual patient. With premature neonates, ethical issues prevent study designs involving healthy subjects, sparse sampling is nearly always the norm, and the volume of the blood sample for concentration determination is restricted. Advances in mass spectrometry and the ability to quantify drug concentrations from dried blood spots (from heel or finger sticks) have alleviated some of these problems, but significant difficulties remain. The vast majority of (more likely all) premature babies would be in a neonatal intensive care unit setting. The only approach to assessing the pharmacokinetics of influenza drugs in such a setting is either to have a standing protocol open across multiple neonatal intensive care units during the influenza season or to rapidly employ a protocol in a particular neonatal intensive care unit when an exposure actually occurs and therapy is administered. This situation arose shortly after the 2009 H1N1 outbreak.¹⁶ For the study discussed in this paper, we collected a single blood sample from each child for oseltamivir and oseltamivir carboxylate measurements, using time windows throughout the dosing interval. The raw concentration-time data and best model fit from the population pharmacokinetic assessment are presented in Figure 1. Although this design and subsequent analysis yielded important dosing information, it would appear, in retrospect, that if we had collected at least two samples after the dose from each neonate, we would have had more robust data, and it would have been possible to derive individual *post hoc* parameter estimates. However, this would probably have impeded accrual of subjects for the study because parents are more reluctant to have their babies experience two needle sticks than

one. This illustrates the tensions that exist and the dynamic balance that must be struck between science and sensibilities in every interventional pediatric study.

Role of modeling and simulations

Pharmacokinetics-based dose-finding approaches (modeling and simulation based on developmental pharmacology) have become more common in determining initial pediatric dosing regimens for antivirals, especially when little or no pediatric pharmacokinetic data are available. The allometric 3/4 power model has been used extensively for scaling pediatric doses and provides relatively accurate initial dose estimates:¹⁷

$$\text{Dose}_{\text{child}} = \text{Dose}_{\text{adult}} \left(\frac{\text{Weight}_{\text{child (kg)}}}{70 \text{ (kg)}} \right)^{0.75},$$

where the 0.75 exponent on weight is used to scale drug clearance, based on the relationship between the log of basal metabolic rate and the log of body weight across species. More complex modeling and simulation exercises can also be employed:¹⁸

$$F_{\text{PMA}} = \frac{\text{PMA}^{\text{Hill}}}{\text{TM}_{50}^{\text{Hill}} + \text{PMA}^{\text{Hill}}},$$

where F_{PMA} is the factor for PMA (or maturation function), PMA is postmenstrual age, Hill is the Hill coefficient, and TM_{50} is the maturation half-life (time to reach 50% of adult clearance). This sigmoid E_{max} model allows continuing maturation of clearance from infancy through the adult period. These equations were initially used to develop dosing algorithms for hospitalized infants and young children requiring intravenous peramivir therapy during the 2009 H1N1 pandemic under the Emergency Use Authorization. These formulas provide starting points for conducting targeted pediatric dose-finding studies, as described above. Pharmacokinetic modeling and simulations are likely to play a much larger role in pediatric drug development in the future, and not only in the matter of antivirals.

CONCLUSIONS

Anti-influenza therapy in premature babies, infants, and young children presents unique and challenging circumstances for dose-finding strategies. In influenza, the situation is compounded by the short duration of therapy, variable susceptibilities, lack of concentration–response relationships, and a population that, by definition, necessitates limited study designs. Efforts to address some of these problems have been undertaken, such as utilizing an AUC-targeted study design, rapidly implementing studies for premature neonatal exposures, and applying pharmacokinetic modeling and simulations to predict initial pediatric doses. Through these approaches, it is possible to answer clinically important questions in a relatively timely fashion, especially during an influenza outbreak.

It is critical that, at the least, an attempt be made to define concentration–response relationships for antiviral drugs. If phase I single- and multiple-ascending-dose studies in adults indicate little or no toxicity concerns, and a good biomarker of efficacy exists, phase II studies in patients should incorporate a wide dose-finding algorithm encompassing at least a 10-fold range of doses in order to populate the concentration–response curve. Understanding the pharmacokinetics and establishing pharmacodynamic relationships with

respect to anti-influenza compounds is clinically vital in order to (i) ensure proper dose selection during early-phase development and possibly make go or no-go decisions, (ii) evaluate the clinical significance of real or potential drug–drug interactions, (iii) explore alternative dosing schedules (e.g., once daily vs. twice daily), (iv) introduce new formulations with different pharmacokinetic characteristics, and (v) make a drug available for the first time for the treatment of a pediatric population. Defining these metrics in adults will help to ensure prompt dosing translation into the pediatric population when the next influenza pandemic occurs.

The evaluation of oseltamivir dosing in infants and young children in support of the global response to pandemic 2009 H1N1 was a direct result of preparedness by the National Institute of Allergy and Infectious Diseases, which instructed an existing network—the Collaborative Antiviral Study Group—to undertake this trial years prior to the actual pandemic. Without this clinical research network in place, it is highly unlikely that our response to the pandemic in the pediatric population would have been as timely or informative. It would have been unfortunate if the pandemic strain had been severe, and it is clear that there is a need for continued support of networks of clinical sites and research infrastructure to ensure that critical pediatric drug-dosing data are available when the need arises.

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Figure 1. Oseltamivir and oseltamivir carboxylate concentrations in premature neonates. **(a)** Oseltamivir and **(b)** oseltamivir carboxylate concentrations (triangles) and modeled curve fit (solid line) in premature neonates. Each observation is from a separate subject. The study was designed to collect one sample from each subject within different postdose interval windows (0–3, 4–6, 7–9, and 10–12 h). Data were analyzed as though a single subject received the average dose at steady state using the average of all available concentrations at each time point. A combined structural model incorporating parent (two compartment) and metabolite (one compartment) was implemented, using ADAPT 5.0 with MLEM parameter estimation.¹⁹ MLEM, maximum-likelihood expectation maximization.

Table 1

Pediatric dosing of approved and investigational anti-influenza drugs

Osetamivir ^a	Zanamivir ^b	Peramivir ^c	Rimantadine/amantadine ^{d,20}
9–23 Months	3.5 mg/kg/dose p.o. twice daily	Two 5-mg inhalations (10 mg) twice daily	6 mg/kg i.v. once daily
0–8 Months	3.0 mg/kg/dose p.o. twice daily	1–3 Months	8 mg/kg i.v. once daily
Premature neonates	1.0 mg/kg/dose p.o. twice daily	3–6 Months	10 mg/kg i.v. once daily
		6 Months–5 years	12 mg/kg i.v. once daily
		6–17 Years	10 mg/kg i.v. once daily
i.v. Dosing under investigation	i.v. Dosing under investigation	Confirmation of i.v. dosing is under way	

FDA, US Food and Drug Administration; i.v., intravenous; p.o., oral.

^aDoses listed are based on refs. 14 and 16. The FDA-registered pediatric oseltamivir doses are 30 (15 kg), 45 (15–23 kg), 60 (23–40 kg), and 75 mg twice daily (>40 kg).²¹

^bFor children 7 years of age.

^cEmergency Use Authorization intravenous doses for 2009 H1N1 based on pharmacokinetic modeling and simulations.²² No pediatric dosing information is available in the United States. Dose is adjusted for creatinine clearance. Approved in Japan for adults at 600 mg i.v. once daily and for children at 10 mg/kg i.v. once daily. The peramivir Emergency Use Authorization expired 23 June 2010. After that date, access will be available only through clinical trials.

^dNot active against influenza B viruses.