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Helms Award Lecture

Optimum Use of Therapeutic Drug Monitoring and Pharmacokinetics-Pharmacodynamics in the NICU

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Therapeutic drug monitoring is increasingly giving way to dosing drugs based on population-based pharmacokinetic parameters, even when pharmacokinetic values vary quite a bit in individual patients. Further, drug concentrations are often considered appropriate if they are within a defined therapeutic range, even if the patient response is suboptimal. This lecture discusses the limitations of therapeutic ranges in neonates, and proposes greater emphasis on pharmacodynamic curves to individualize drug therapy. Examples are provided using methylxanthines, indomethacin, antiepileptic drugs and aminoglycosides. The potential to use pharmacokinetic findings to describe physiologic changes and occasionally assist with diagnosis is also discussed.

KEYWORDS neonate, pharmacodynamics, pharmacokinetics, therapeutic monitoring

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I am truly honored to receive the Helms Award for 2008, and fully appreciate how it recognizes individuals who have committed to contributions to pediatric pharmacy education and practice epitomized by Richard Helms. For my part, this must be considered a shared award by the health care team members from the neonatal ICU at Women's Hospital, Moses Cone Health System in Greensboro, North Carolina. The neonatologists, pharmacists, nurse practitioners, nurses, respiratory therapists, nutritionist, physical therapists, audiologist, social workers, and others have worked in a collaborative manner that has helped each team member to feel valued and maximize their potential. I would particularly like to recognize the key architect of this collaborative environment, J Laurence Ransom, MD, who was medical director of our Neonatal Intensive Care Unit (NICU) from 1983 to 2007, and remains a major collaborator in my clinical and research activities for the past 25 years. He is succeeded by John Wimmer, MD who has continued this collaborative approach. I would also like to recognize the first neonatologist to entice me into this wonderful area of medicine, Vildan Erkan, MD, who directed the NICU at Georgia Baptist Hospital in Atlanta, and was my first mentor in neonatal medicine. Thanks to the support and education from these physicians and other colleagues, I have been able to use therapeutic drug monitoring to individualize drug doses. It is my belief that such an individualized therapy strategy will result in better outcomes than using doses derived from population-based pharmacokinetic analyses to determine standard dosing guidelines.

ABBREVIATIONS FDA, Food and Drug Administration; NICU, Neonatal Intensive Care Unit; PDA, patent ductus arteriosus; PK-PD, pharmacokinetic and pharmacodynamic; VLBW, very low birth weight

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Table 1. Basis for therapeutic ranges in neonates

Drug	From Adults	Clinical Trials	Anecdotal Reports	Protein Binding
Aminoglycosides	●			
Caffeine		●	●	
Digoxin	●		●	
Indomethacin		●		
Phenobarbital	●	●	●	
Phenytoin	●			●
Theophylline	●	●*	●†	●*
Vancomycin	●		●	

**Apnea*
†Renal failure; ventilator wean; and apnea

INTRODUCTION

The focus of my Helms Award Lecture is to raise issues with the practice of using population-based pharmacokinetic data and reducing the role of individualized therapeutic drug monitoring, especially in the context of critically ill patients. Rather, I would like to make the case that therapeutic drug monitoring in the context of concentration-effect curves to describe pharmacodynamic profiles with individualized dosing to a target concentration is more desirable. Where possible, I will use our own work to support this argument.

The potential of pharmacodynamics has been recognized and promoted in numerous prior publications from at least the 1960s. I will use a chapter from a great pediatric pharmacist to exemplify this. In 1985 William Evans cautioned against the misunderstanding that drug concentrations in the therapeutic range imply that the desired response will occur.[1] Instead, he emphasized the need for appreciating that therapeutic ranges reflect a series of probabilities for drug effects and individual patients may respond best at different points along the concentration-response continuum. Gal and Reed made a similar argument and emphasized the lack of compelling data supporting therapeutic ranges for drugs in neonates.[2]

This review will highlight the limitations of drug dosing strategies based on population-based pharmacokinetic data, and stated therapeutic ranges used in NICU clinical practice, and highlight our efforts to promote individualized pharmacokinetic-based dosing which targets concentrations identified as specifically reflecting an optimum clinical response for an individual patient.

INDIVIDUALIZED PHARMACOKINETICS AND PHARMACODYNAMICS

Drug doses for newborns are generally derived from a combination of extrapolated estimates of pharmacokinetic changes compared to adult values or population-based pharmacokinetic research.[2] In a similar manner, therapeutic ranges for neonates are often a reflection of what has been defined in the adult population; some correction factor of adult therapeutic ranges, often adjusted for protein binding; and occasionally clinical trials in neonates (Table 1). These approaches have multiple flaws including: assumption that receptor responses in neonates will be similar to those of adults at the same unbound plasma concentrations; assumption that a drug with a relatively wide therapeutic index does not require therapeutic drug monitoring to individualize dosing to a targeted response; assumption that the same pharmacologic actions are sought for neonates as adults, even if the pharmacologic action sought is for different indications in the neonate; ignoring the wide variability in pharmacokinetic values in neonates for the sake of simplicity by using averaged population data; failure to achieve optimum drug concentrations rapidly in critically ill patients; and failure to fully utilize

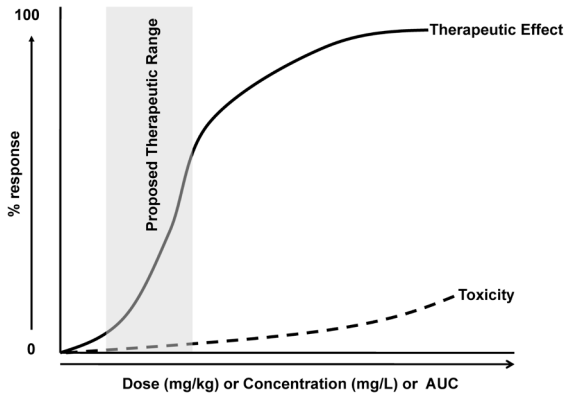

Figure 1. Theoretical pharmacodynamic curve for concentration vs response, or dose vs response relationships.

The proposed therapeutic range often misses many potential responders and equates responders at the lower therapeutic range with those at the higher end of the therapeutic range, as all are considered to have "therapeutic concentrations".

the physiologic value of individualized pharmacokinetic parameters. The reluctance to draw blood for drug concentrations has a reasonable basis, in that blood volume in a neonate reflects about 8% of body weight (i.e., 80 mL in a 1000 gram patient) and, consequently, blood transfusions in neonates are often a result of all the blood drawn for laboratory tests. However, the critical nature of this population makes it essential that optimum treatment must be provided rapidly, and failure to do so can actually result in more blood work for additional diagnostic purposes to rule out alternative diagnoses. This discussion will provide specific examples to make the case that identifying individualized drug concentration and response relationships provide better care for patients, and require more exact dosing calculations from pharmacists. This is conceptually explained by Figure 1. I will use a variety of specific examples to make the point that when we limit application of individualized and specific pharmacokinetic and pharmacodynamic approaches, we may compromise patient care.

Methylxanthines

The first example will be the use of methylxanthines in preterm infants. Theophylline has numerous uses in neonates (Table 2). These include bronchodilation for chronic lung disease, [3] prevention of intubation or assistance with extubation from mechanical ventilation,[4,5,6] treatment of apnea of prematurity,[7-9] and treatment of renal dysfunction.[10] The stated therapeutic range for theophylline is 6-10 mg/L[7] or 6-13 mg/L,[8] and is based on creating comparable unbound theophylline concentrations to adult values used for bronchodilation. The problem is that different pharmacological actions are needed for the different indications. Thus while concentrations between 4 and 16 mg/L may actually benefit neonates treated for apnea, most patients actually need concentrations between 10 and 16 mg/L for complete control. [9] When a different target action is sought, treatment of renal failure, theophylline concentrations below 5 mg/L are optimal.[10] Ignoring these data-based concepts can be potentially harmful. To exemplify this concern, I will use the guidelines by the Food and Drug Administration (FDA) for theophylline dosing and monitoring. The early experience with theophylline resulted in the FDA releasing dosing recommendations stated to achieve a target serum theophylline concentration range of 6-10 mg/L. However, the aminophylline doses recommended by the FDA ignored published pharmacokinetic information at that time for 229 neonates. These guidelines would result in underdosing in 82% of patients to even achieve theophylline concentrations of 6 mg/L;[7] thereby placing these neonates at increased risk of intubation to manage their apnea. The FDA recommendation is even more unfortunate given the concentration-response study by Muttitt et al.[9] which showed that most neonates needed theophylline concentrations above 10 mg/L to fully control apnea. Our experience has found that serum theophylline concentrations between 10 and 20 mg/L are rarely associated with toxicity (usually tachycardia), which is rapidly reversible. Failure to properly treat apnea could result in mechanical ventilation and extensive work up for other etiologies, both of which pose considerable and serious morbidity consequences.

Caffeine has also been used to treat apnea of prematurity, [11,12] assist with extubation from mechanical ventilation, [12-14] and reduce the risk of chronic lung disease.[14,15] The therapeutic range is widely reported to be 5-20 mg/L even though no clinical trials prove this to be the optimal range, and toxicity is relatively rare and typically reversible at serum caffeine concentrations below 50 mg/L. Our anecdotal experience suggests that the therapeutic range is truly between 10 and

Table 2. Pharmacologic actions and therapeutic ranges for theophylline in neonates based on clinical indication

Indication	Pharmacologic action	Therapeutic serum concentration range
Apnea of prematurity	CNS stimulation	4-20 mg/L
Chronic lung disease	Bronchodilation	5-10 mg/L
Renal failure	Adenosine inhibition	<5 mg/L
Ventilator prevention	Diaphragm and intercostal muscle contractility	5-20 mg/L
Ventilator weaning	Diaphragm and intercostal muscle contractility	5-20 mg/L

50 mg/L with likelihood of response and toxicity occurring along a continuum and specific to each individual.[16] Our experience would suggest that patients weighing over 1000 grams who are treated with caffeine for apnea often do well at concentrations below 30 mg/L, while very low birth weight (VLBW) infants and those neonates treated to prevent intubation or facilitate extubation often need serum caffeine concentrations above 30 mg/L. Some clinical trials also support the need for higher concentrations to facilitate extubation when compared to those needed for the treatment of apnea.[14] Despite this general experience, the potential for improving responses at higher caffeine concentrations can be easily addressed through the administration of extra caffeine boluses that are designed to incrementally increase caffeine concentrations by 5-10 mg/L until concentrations of at least 40 mg/L or signs of toxicity (usually mild tachycardia) are observed.

A recent article suggested that monitoring serum caffeine concentrations is not necessary because concentrations are predictably within the therapeutic range when standard doses are given.[11] This conclusion ignores the concepts that: ideal response to caffeine occurs along a continuum, part of which includes the therapeutic range; that caffeine concentration changes are not predictable within a narrow range of concentrations; and that directional change of caffeine concentrations over time are not consistent. A new onset of increasing apneas in a patient who initially responded to caffeine with no toxicity, can lead to a workup for possible causes (e.g., sepsis). This may result in additional blood collection and unnecessary antibiotic exposure, when the increasing apneas could be attributed to a decrease in caffeine concentration from a value that was safe and effective. Alternatively, the appearance of tachycardia may be incorrectly attributed to caffeine, which may result in withholding caffeine doses. This despite the fact that the same concentration was well tolerated previously and the real cause of tachycardia is fluid overload that resolves with diuresis. Although caffeine may have a wide therapeutic index, it does not necessarily have a wide concentration-effect relationship in an individual patient. There is a tendency is to ascribe apnea to a cause other than inadequate caffeine concentrations, just because the purported "therapeutic range" is achieved, or attribute toxicity, (e.g., tachycardia), to caffeine simply because the concentration is above "therapeutic". Both of these are inappropriate assumptions that have been frequently disproven in the clinical arena. Such findings can only be accomplished with appropriate monitoring of biomarkers of caffeine effects and correlation with prior caffeine concentrations in the individual patient.

Non-steroidal anti-inflammatory drugs

Another example of applying individualized pharmacokinetic and pharmacodynamic (PK-PD) dosing is treatment of patent ductus arteriosus (PDA) with indomethacin. We have demonstrated that such an individualized strategy will increase PDA closure rates from 40%-60% to above 90%.[17,18] This has pharmacoeconomic implications since the alternative treatment is surgical ligation, which can cost at least $15,000 per procedure.

We treat approximately 30 PDAs annually in our NICU. The cost of failed PDA closures would be at least $180,000, as individualized indomethacin dosing based on PK-PD modeling would close at least 12 additional PDA cases when compared to standard dosing. Once again, the concentration versus response relationship fits an Emax pharmacodynamic model, which requires each patient to be monitored using appropriate

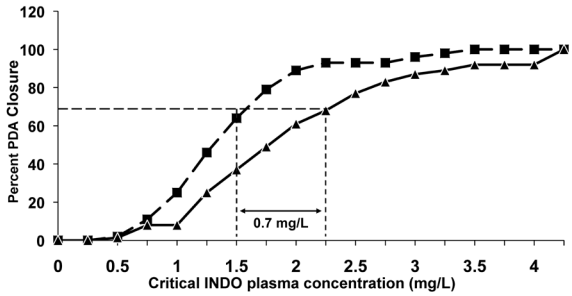

Figure 2. Concentration vs response for PDA closure with indomethacin and the effect of natural surfactant on indomethacin pharmacodynamics.

-■- = Control; -▲- = Surfactant
Figure demonstrates that to achieve the same 70% closure rate as before surfactant availability would require indomethacin concentration to be about 0.7 mg/L higher. (Gal et al. unpublished)

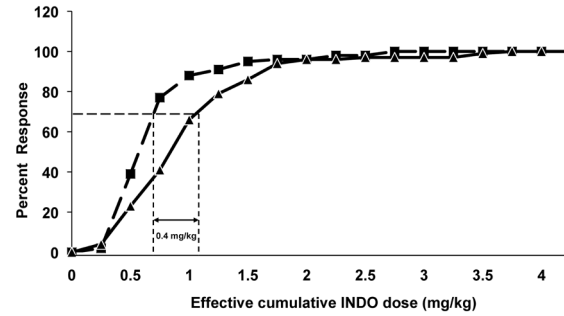

Figure 3. Dose vs response for PDA closure with indomethacin and the effect of natural surfactant on indomethacin pharmacodynamics.

-■- = Control (n = 96); -▲- = Surfactant (n = 365)
Figure demonstrates that to achieve the same 70% closure rate as before surfactant availability would require indomethacin total dose to be about 0.4 mg/kg higher. (Gal et al. unpublished)

biomarkers, and the dose to be individualized based on pharmacokinetic data and the desired indomethacin concentration.

Such an approach has enabled us to create pharmacodynamic curves, which have been modified over time, for response and renal toxicity. Although the concurrence of respiratory distress syndrome and PDA is well known, and most neonates with PDA also have received surfactant, the dosing recommendations for indomethacin were created before the availability of surfactant. We know that the indomethacin pharmacodynamic curve has shifted as a result of surfactant exposure, and the dosing guidelines created before surfactant will result in much lower PDA closure rates. Surfactant exposure requires both higher indomethacin concentrations (Figure 2) and larger doses (Figure 3). These curves reflect our initial experience with about 150 treatment courses, and we are in the process of refining these data with a much larger population. The dose-response curve is also affected by postnatal age, with neonates over 10 days old requiring much larger indomethacin doses to achieve comparable serum concentrations. PDA reopens in 20%-25% of patients treated with indomethacin.[19] One additional value of indomethacin therapeutic monitoring is the ability to predict permanent closure. A reduction in volume of distribution predicts permanent closure in nearly all patients, and sustained effective concentrations for at least 24 hours provides similar predictive value of permanent closure.[20,21] We refer to this application as pharmacophysiology, since we are using pharmacokinetic information to provide physiologic information. Finally, the pharmacodynamic curves for response and toxicity allow discussions of risk and benefit when deciding how high a dose or concentration should be before risk outweighs benefit. This is a discussion worth having, especially at the higher ranges of the concentration-response curve, to allow a more aggressive dosing strategy.

Phenobarbital

The importance of having the correct biomarkers for endpoints is exemplified by the use of phenobarbital to treat neonatal seizures. We defined the pharmacodynamic concentration-response curves for phenobarbital based on cessation of clinical seizure activity.[22,23] However, half the patients who stop having clinical seizures, have electro-clinical dissociation, so they are actually continuing to have electrical seizures.[24,25] Many NICUs do not confirm cessation of seizures on continuous EEG monitoring. Although it is important to recognize that half the clinically controlled patients may still be having electrical seizures,[26,27] the pharmacodynamic curve we established is appropriate for units that use clinical seizure activity endpoints. Alternatively, a dose-response curve that assumes each 1 mg/kg dose increases phenobarbital serum concentration by 1 mg/L, would yield a different pharmacodynamic curve that is consistent with the one likely seen if continuous EEG monitoring of seizure endpoints were used.[26] While the need to suppress

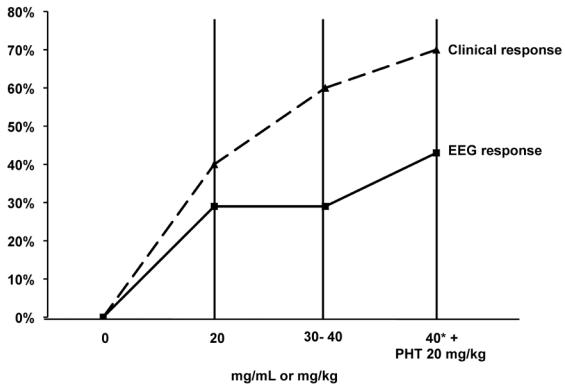

Figure 4. Phenobarbital pharmacodynamics for seizure control.

Based on assumption that phenobarbital 20 mg/kg = 20 mg/L, 30 mg/kg = 30 mg/L, and 40 mg/kg = 40 mg/L. The 50% lower response with EEG is consistent with the 50% electro-clinical dissociation rate. Clinical response rates are from Gilman et al.[23] and EEG response rates from Boylan et al.[27]

all seizure activity noted on EEG is presumed to be optimal, compelling evidence for this is lacking.[26-29] The pharmacodynamic curves for clinical and EEG seizure control with phenobarbital are demonstrated in Figure 4.

Gentamicin

Gentamicin is commonly used in neonates. A frequent practice is to follow guidelines from dosing handbooks, which often recommend measuring gentamicin peak and trough serum concentrations immediately before and after the third dose of gentamicin. An alternative approach would be to individualize gentamicin dosing by obtaining serum concentrations from the initial loading dose. This method assures that appropriate (i.e., therapeutic) concentrations are achieved early in the course of treatment. Additionally, the strategy of individualizing gentamicin doses using concentrations obtained from the initial loading dose has been shown to result in fewer drug concentrations collected when compared to obtaining gentamicin concentrations after dosing strategies based on concentrations from subsequent doses.[30]

However there are several more compelling reasons to obtain serum concentrations after the loading dose and individualizing dosing.

The relationship of peak gentamicin concentration/minimum inhibitory concentration ratio in the first few days of treatment to clinical response is well known to influence the efficacy of gentamicin. Kashuba, et al.[31] elegantly demonstrated that a Cmax/MIC ratio of 10 is optimal for infection resolution. Since many Gram-negative organisms have MIC values of 1 µg/mL, it is prudent to target peak concentrations ≥ 10 µg/mL. The relatively large volume of distribution in neonates and consequent need for initial gentamicin loading doses of 5 mg/kg was demonstrated in 1990.[32,33]

Others have also reported success with calculation of gentamicin doses following the initial loading dose.[34] However, lower doses continued to be used in many neonatal ICUs, based on recommendations from standard dosing handbooks. The consequences of under dosing were not considered, even though these are factors leading to therapeutic failure and bacterial resistance.[35,36]

There are additional issues with using the dosing approaches recommended by handbooks. The use of combined trough gentamicin concentration, followed by peak concentration after the next dose, likely results in inaccurate pharmacokinetic calculations[37] and this issue is rarely discussed. Furthermore, collecting the trough-then dose-then peak places considerable burden on nursing and laboratory personnel for precise timing in medication administration and sample collection. The approach is likely to breakdown at some point, placing pharmacists at odds with the nursing and laboratory personnel. This sequence of administration and sampling frequently requires extra sample collection. When two samples are drawn after an initial loading dose, the only concern is that the exact times of dosing administration and sample collection are correctly noted. Because there is a wide range of peak concentrations achieved after the same loading dose, a rapid and appropriate adjustment in dose can be made in those patients who have "subtherapeutic" concentrations. A delay in achievingtherapeutic concentrations has been associated with poor response.[32,38]

Pharmacophysiology opportunities are also missed when initial gentamicin pharmacokinetics are not determined. For example, a gentamicin volume of distribution above 0.7 L/kg suggests the presence of a PDA in over 90 percent of cases.[39] Gentamicin clearance can also be used as a surrogate marker for glomerular filtration rate.[40] Indomethacin volume of distribution sharply decreases when PDA closes[20,21] and can guide when

repeat echocardiography to confirm PDA closure is warranted, which may be particularly useful in the 50% of PDAs that are silent. Recurrence of clinical problems or occurrence of symptoms that are consistent with toxicity can be classified as being from other physiologic causes if drug concentrations are the same as those previously proven to be therapeutic and nontoxic. The emphasis on accurate biomarkers for drug effect is obviously key to this approach and enhances the role of the clinical pharmacist.

SUMMARY

In summary, the use of individualized therapy correlating each patient's personal response to specific drug concentrations, rather than assuming a drug is therapeutic within a desired range, can improve clinical outcomes if the correct biomarkers are selected for response. This has been a particular focus of clinical and research activities in our NICU because we feel it has produced beneficial results with improved patient responses, reduced consequences of therapeutic failure, reduced drug toxicity, and additional insight into diagnostic and physiologic processes. The early therapeutic monitoring has also allowed us to identify drug administration problems, including intravenous administration problems that justify rebolusing drugs in critically ill patients and limitations to pump technology that must be overcome in administration protocols. This is an under-appreciated problem in many NICUs.

I would like to thank PPAG for selecting me for this wonderful honor and providing a platform to advocate for my particular style of clinical service and therapeutic interventions. I have been blessed with a wonderful clinical environment and extraordinary and supportive professional colleagues in multiple disciplines. At Women's Hospital in Greensboro, this multidisciplinary approach allows all team members to excel, including our team of pharmacists. We have a rich pharmacy educational environment with a pharmacotherapy fellow or resident, and pharmacy students as learners present most of the time. The successes of our interventions highlighted above, and the honor of this award must be shared by the clinical and administrative personnel who make such an environment possible.

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