Therapeutic Drug Monitoring—the Appropriate Use of Drug Level Measurement in the Care of the Neonate

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• Therapeutic drug monitoring • Aminoglycosides • Vancomycin
• Caffeine • Digoxin • Hypothermia

The goal of therapeutic drug monitoring (TDM) is to tailor drug dosage to maximize therapeutic benefits while minimizing toxicity. Traditionally, this approach has been performed by measuring serum drug concentrations, applying pharmacokinetic and pharmacodynamic principles, and then adjusting the dose to keep the drug concentration in the therapeutic range. By its very nature, TDM is primarily applicable for medications that possess narrow therapeutic indices (ie, the drug concentration required for therapeutic effect is close to the toxic concentration) and for agents that demonstrate a good correlation between serum concentrations and pharmacologic effect. In clinical situations with a wide therapeutic index for the medication in question, it is less important for the clinician to closely follow drug levels.

NEONATAL PHARMACOKINETIC CONSIDERATIONS

Neonates and young infants are in a unique and dynamic pharmacokinetic (PK) state, where they undergo relatively rapid maturational changes in drug absorption, distribution, metabolism, and excretion. These PK variables are strongly influenced both by gestational age, being most pronounced in the extremely premature infants, and postnatal age, when the changes are greatest in the first few weeks after birth. Body composition also significantly affects the distribution of drugs in the body. Neonates,
especially premature infants, have a relatively high proportion of total body water and a low proportion of fat; this increases the apparent volume of distribution (Vd) for water-soluble compounds, and decreases the Vd for fat-soluble compounds. In addition, because the brain-to-body mass ratio is high, and body fat content is low, lipid-soluble drugs tend to concentrate in the central nervous system. Protein binding in neonates is diminished, so that free drug concentrations are higher even if total serum drug concentrations are the same as in older patients. Clearance of drugs is prolonged, due to both immature hepatic metabolism and immature renal excretion. This physiology leads to both higher drug concentrations and higher metabolite concentrations. Clearance is even more prolonged in infants with intrauterine growth restriction because of altered renal morphogenesis.\(^2\) In addition to these maturational factors, most drug PK studies in neonates show wide interindividual variability despite similar gestational and postnatal ages. In some neonates, a portion of this variability may be explained by the presence of a patent ductus arteriosus or its treatment with indomethacin or ibuprofen. For most infants, however, this variability remains unexplained; hence TDM is a necessary tool in the neonatal intensive care unit (NICU).

**SPECIFIC MEDICATIONS**

* Aminoglycosides

The bactericidal effect of aminoglycosides (gentamicin, tobramycin, amikacin) is strongly associated with the peak serum concentration (C\(_{\text{max}}\)) drawn 30 minutes after a 30-minute infusion. Studies in adults have demonstrated that a C\(_{\text{max}}\) /minimum inhibitory concentration (MIC) ratio of at least 8 to 10 is associated with improved outcomes.\(^3\) Studies in neonates have been underpowered to assess clinical outcomes because of the infrequency of documented neonatal infections.\(^4\) Nonetheless, current recommendations suggest that when treating serious infections with gentamicin, where the bacterial MIC = 0.5 \(\mu\)g/mL, the target C\(_{\text{max}}\) is at least 4 to 5 mg/dL; if MIC = 1, the target C\(_{\text{max}}\) is at least 8–10 \(\mu\)g/mL.

Ototoxicity and nephrotoxicity are the most concerning adverse effects of aminoglycosides. Neonates may be less susceptible to these toxicities than adults.\(^5\) Nonetheless, measuring trough serum concentrations continues to be recommended, both to minimize the risk of toxicity, and as a surrogate assessment of renal function. In the past, the target trough concentration to lessen the risk of toxicity was less than 2 \(\mu\)g/mL. With the recognition of the postantibiotic effect of aminoglycosides, the in vitro demonstration of adaptive resistance with high trough levels, and the efficacy of prolonged (>24 hours) dosing intervals, the target trough concentration has been revised and is now considered to be less than 1 \(\mu\)g/mL.

Aminoglycosides are small hydrophilic molecules with a volume of distribution similar to extracellular fluid volume and clearance directly proportional to glomerular filtration rate. During the first week of life, Vd is higher and clearance prolonged, especially in the most premature neonates. Neonatal dosage nomograms with extended dosing intervals take these factors into account. Interindividual variability is wide, however, and the large number of dosing schedules reported in the literature indicates that the optimal schedule has yet to be determined.\(^6\)

Most neonates treated for suspected sepsis have antibiotic therapy discontinued within 48 hours of initiation, negating the need to measure serum drug concentrations in these patients. For those being treated for more than 5 days due to positive blood cultures or clinical suspicion of true sepsis, or for those with disease states or therapies discussed in the sections that follow, TDM is indicated. For treating mild-to-moderate infections in clinically stable patients in whom the
aminoglycoside is being used primarily for its synergistic effect, measuring peak concentrations is usually not necessary, and trough concentrations would be sufficient.

**Vancomycin**

Vancomycin is a glycopeptide used primarily to treat infections caused by methicillin-resistant *Staphylococcus aureus* and *S. epidermidis*. Unlike aminoglycosides, vancomycin activity against staphylococci is primarily a time-dependent process. Pharmacodynamic efficacy, on the basis of in vitro, animal, and limited human data, is best predicted by the 24-hour area under the concentration curve (AUC) divided by the MIC (AUC/MIC). Vancomycin dosing and monitoring remain sources of controversy. Recent Infectious Diseases Society of America (IDSA) recommendations suggest a target AUC/MIC value of 400 to adequately treat serious staphylococcal infections (bacteremia, infective endocarditis, osteomyelitis, meningitis, pneumonia, and necrotizing fasciitis) if the MIC is no more than 1 μg/mL; if the MIC is 2 μg/mL or greater, an alternative drug should be used.7 For adults with normal renal function, a serum trough concentration of 15 to 20 μg/mL reliably predicts that the AUC/MIC will be greater than 400 and has been shown to modestly improve patient outcomes.8 Whether these PK targets are associated with an increased risk of nephrotoxicity or ototoxicity remains a point of controversy, although toxicity appears to be related more to the underlying disease state and concurrent use of medications such as furosemide and gentamicin. If these PK targets are desired when treating serious infections in neonates, then higher and more frequent dosing than most current nomograms will be required. There are no studies of outcomes in neonates treated using these recommendations. Monitoring of peak serum concentrations is not recommended, as they do not correlate with efficacy or toxicity. The uncertainties mentioned have resulted in a wide range of practice methods, from very infrequent to excessive monitoring of concentrations.

**Caffeine**

Caffeine has been one of the most frequently prescribed drugs in the NICU for many years. Usage has increased recently since publication of the caffeine for apnea of prematurity (CAP) trial results showing improvement in both short- and long-term outcomes.9 The traditional therapeutic concentration range to treat apnea of prematurity is wide—5 to 20 μg/mL—and traditional standard dosages (20 mg/kg loading dose and 5 mg/kg/d maintenance) attain these concentrations independent of low gestational age, elevated liver enzymes, or renal dysfunction.10 In the CAP trial, which used these dosages and enrolled over 900 neonates in the treatment arm, serum concentrations were not measured, and no significant toxicity was observed.9 In studies using doses fourfold higher than standard doses, efficacy is improved in some patients without any increase in adverse events.11 Monitoring of plasma caffeine concentrations is therefore not necessary.12 The usual clinical sign of mild toxicity in neonates is tachycardia, which is treated by holding doses or stopping the drug without the need for measuring serum concentrations.

**Anticonvulsants**

The pharmacodynamic target of anticonvulsants is the cessation of seizures, but it remains controversial as to whether complete cessation of both clinical and electrographic seizures leads to improved outcomes in neonates with hypoxic–ischemic encephalopathy.13,14 Treating all electrical seizures may require higher dosages of anticonvulsants and potentially increase the risk of toxicity. Many clinicians now use
continuous electroencephalogram (EEG) monitoring to assess efficacy, yielding an individualized patient therapeutic level.

Phenobarbital remains the first-line drug for most neonatal seizures. The dosage predicts the serum concentration fairly well in the newborn period; a loading dose of 20 mg/kg yields a serum concentration of 17 to 23 μg/mL in the great majority of neonates. The serum concentration necessary to control clinical seizures in approximately 70% of neonates is 17 to 40 μg/mL, and additional loading doses of 5 to 10 mg/kg are often used.\textsuperscript{15,16} The success rate for cessation of all electrographic seizures is somewhat less. Somnolence is common if the serum concentration is greater than 50 μg/mL. The half-life of phenobarbital in the first few days of life is greater than 100 hours, and drug accumulation may occur. A trough concentration measured several days after the loading dose therefore does not assess steady state, which may not occur for 2 weeks.

Fosphenytoin has replaced phenytoin as a commonly used second drug in the treatment of neonatal seizures because of its improved water solubility and reduced infusion-related toxicity. It is completely and rapidly converted to phenytoin in neonates. Dosing is expressed in phenytoin equivalents, and TDM continues to be measurement of serum phenytoin concentrations. Pharmacokinetics are dose-dependent, nonlinear, and change significantly over the first few weeks of life, so TDM is especially important. Trough levels should be measured 48 hours after the loading dose, and obtained at least 2 hours after an intravenous dose and 4 hours after an intramuscular dose to avoid fosphenytoin interaction with immunoanalytic methods. The therapeutic range for total phenytoin concentrations in children and adults is 10 to 20 μg/mL\textsuperscript{17}; in neonates it is approximately 8 to 15 μg/mL due to less protein binding. Measuring free phenytoin concentrations may be preferred in neonates, and this is especially important in patients with hypoalbuminemia or hyperbilirubinemia.\textsuperscript{18} The therapeutic range for serum free phenytoin concentrations is 1 to 2 μg/mL.

Serum concentrations for the other anticonvulsants frequently used in neonates—levetiracetam, lorazepam, and lidocaine—are not routinely monitored, as there is no clear relationship between serum concentration and either effect or toxicity.

**Digoxin**

The pharmacologic mechanisms of action of digoxin are complex and beyond the scope of this article. The pharmacodynamic target in neonates is resolution of supraventricular tachycardia or improvement in congestive heart failure. Digoxin is an example where TDM consists of a combination of measuring serum drug concentrations and monitoring other clinical parameters—in this case serial electrocardiograms (EKGs)—to assess for both therapeutic and toxic effects on heart rate and rhythm.\textsuperscript{19} In addition, it is important to maintain normal serum potassium, calcium, and magnesium levels.

Pharmacokinetic studies indicate that infants require a larger weight-adjusted dose of digoxin than adults to attain comparable serum levels, principally because of higher body clearance and larger volume of distribution. Yet, with similar serum levels in infants and adults, the myocardium of infants and children contains more digoxin than adult myocardium. Therapeutic serum levels are approximately 1 to 2 ng/mL, with the lower end of the range more desirable. Serum levels obtained during digitalization and for the first few days of therapy are usually higher than when the steady state is reached. Serum digoxin levels must be interpreted in the context of the total clinical picture, including EKG changes and serum electrolyte values.
Serum digoxin levels may bear a relationship to digoxin content in the myocardium, but digitalis toxicity is a manifestation of dysfunction at the pacemaker site or in the conduction tissue. EKG changes reflective of therapeutic effect (shortening of QT interval, sagging of ST segment, diminished T wave amplitude, lower heart rate) are related to ventricular repolarization, whereas signs of toxicity (prolongation of PR interval, sinus bradycardia, atrial or ectopic beats, ventricular arrhythmias) reflect disturbances in the formation and conduction of the impulse. Electrolyte disturbances such as hypokalemia and hypercalcemia can predispose to digitalis toxicity, even in the presence of low serum digoxin levels.

SPECIAL CIRCUMSTANCES THAT MAY REQUIRE TDM

Therapeutic Hypothermia

The effects of hypothermia on pharmacodynamics and PK in neonates are incompletely understood due to limited data. Most research has been done in animals and in adults, without the effects of perinatal asphyxia. Some of these studies were done under conditions of severe hypothermia (28°C), rather than moderate hypothermia (33–34°C) as used to treat neonatal asphyxia.

Hypothermia causes redistribution of regional blood flow, which may significantly alter drug distribution and clearance. Volume of distribution is increased for phenobarbital and midazolam, while Vd is decreased for gentamicin, fentanyl, morphine, and pancuronium. The drug metabolizing activity of hepatic enzymes is impaired at lower temperatures. This phenomenon likely explains the prolonged clearance of morphine and phenobarbital observed in asphyxiated neonates treated with hypothermia compared with a normothermic control group. Decreased drug clearance may also occur due to diminished renal blood flow. A recent study in neonates, however, showed that the effects of asphyxia on renal function overwhelm any changes in gentamicin clearance related to hypothermia.

Extracorporeal Membrane Oxygenation

The apparent volume of distribution is increased during extracorporeal membrane oxygenation (ECMO) due to increased circulating blood volume. There is also drug lost in the ECMO circuit, the amount depending on the type of circuit used, the age of the circuit, and the characteristics of the drug. The largest number of PK studies has been conducted with gentamicin and vancomycin. Both drugs have been found to have an increased Vd and prolonged elimination half-lives during ECMO, with several studies demonstrating a return to expected values after decannulation.

SUMMARY

The known wide variability in neonatal PK makes the concept of therapeutic drug monitoring very attractive. The value of routine TDM for most drugs used in neonates remains uncertain, however, due to the paucity of neonatal-specific outcome data. Prevention of toxicity continues to be a primary goal of TDM, as neonatal drug clearance is often unpredictable, and drug accumulation may occur.

Therapeutic drug monitoring is evolving toward a new era of personalized therapeutics. There is increasing recognition that many adverse drug reactions or treatment failures, initially characterized as idiosyncratic, find their origin in genetic or genomic variation. As more is learned about pharmacogenomics, it is likely that the overall approach to TDM and PK testing will evolve into more than just measuring serum drug concentrations.
REFERENCES