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Review: Therapeutic Drug Monitoring in Pediatrics

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Therapeutic drug monitoring (TDM) can be defined as the measurement of drug concentrations in biologic fluids to assess whether they correlate with the patient's clinical condition and whether the dosage or dosage intervals need to be changed. This is done to optimize the management of patients receiving drug therapy for the alleviation or prevention of disease. Therapeutic drug monitoring is a relatively new service in the clinical pharmacology and toxicology laboratory and has evolved from being a luxury to a necessity. The principles of TDM were developed in the 1960s. Advances in research and knowledge and increasingly sophisticated laboratory methods led to an expansion of TDM (1–3).

A drug must meet the following criteria to be eligible for monitoring:

1. There should be a clinically interpretable correlation between the serum drug concentration and its pharmacologic effect. This usually implies a clinically significant correlation between the serum drug concentration and its concentration in the target tissue (1). There should be a better correlation between the plasma drug concentration and the pharmacologic effect than between the drug dosage and the pharmacologic effect.
2. A narrow margin should exist between serum concentrations that cause toxic effects and concentrations that produce therapeutic effects.
3. The serum concentration resulting from a given drug dose is unpredictable as a result of inter- and intraindividual differences in drug absorption, distribution, and elimination. Such poor correlation between serum concentration and drug dosage has been shown with clomipramine used in treatment of enuresis (2).
4. The pharmacologic effects of drugs are not readily measurable (e.g., suppression of seizure activity is difficult to monitor clinically when administering anticonvulsant drugs).
5. There must be a rapid and reliable method for the analysis of the drug.

The criteria for monitoring drugs in children are the same as those for adults (6), but several additional factors must be considered. Neonates, infants, and children undergo major and rapid age-related physiologic and biochemical changes, especially during the first year of life, resulting in different clinical pharmacokinetic and pharmacodynamic parameters from adults (Table 1). Recent indications are that approximately 12% of all drugs prescribed in the United States are for children age 9 years and younger (4). Further, review of drug-

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dosing habits in neonatal intensive care units has shown that the average number of drugs administered to premature infants weighing less than 1,000 g varies from institution to institution but is usually in the range of 15 to 20 drugs; infants weighing more than 2,500 g usually receive 4 to 10 drugs during their hospital stay. Obviously, drug concentrations in many of these patients need to be monitored by the laboratory, and the possibility of drug interactions needs to be considered. Thus, it is important to have a clear understanding of not only the principles of TDM but also the additional factors inherent in and specific to pediatric clinical pharmacology.

When administering drugs to children, age-related differences in drug absorption, distribution, metabolism, and clearance should be taken into account to optimize drug efficacy and to avoid toxicity. There are major differences not only between adults and children but also between neonates and pre- and postpubertal children.

The following are some important differences between adults and children:

1. Changes in gastric pH and gastric emptying time during the neonatal period lead to variation in the absorption of many drugs.
2. Differences in body composition (neonates are composed of less body fat and more water) lead to differences in the apparent volume of distribution between neonates, children, and adults (Table 2).
3. Slow total drug clearance in premature infants and neonates is due to immature hepatic and renal function.
4. Immaturity of the hepatic microsomal enzyme system produces slow biotransformation of many drugs in premature infants and neonates, requiring a lower mg/kg dosage to achieve therapeutic concentrations.
5. Greater microsomal enzyme activity in prepubertal children than in postpubertal children and adults necessitates a higher mg/kg dosage to achieve similar serum concentrations of some drugs.

DRUG ABSORPTION

Drug absorption is affected by numerous factors, including the route of administration, drug formulation, age of recipient, and concomitant administration of other drugs or food (3). Administration by the intravenous route provides immediate systemic bioavailability. In contrast, absorption of some drugs, such as phenytoin or diazepam, after intramuscular administration is slower and less complete. Being dependent on blood supply and flow to the injected muscle, intramuscular dosing of such drugs should be avoided whenever possible.

When administering drugs orally in neonates and infants, one must remember that they have diminished gastrointestinal motility, resulting in a relatively slower rate for the drug to reach therapeutic systemic levels compared with older children (4). In addition, neonates and infants have different gastrointestinal flora. Other factors that influence the amount and rate of a drug absorbed from the gastrointestinal tract include drug formulation, drug solubility and pK, concomitant administration of other drugs, and simultaneous ingestion of food.

Major determinants of oral drug bioavailability include the activity of cytochrome P-450 3A4 in intestinal phase 1 metabolism and active extrusion of absorbed drug by P-glycoprotein (well known for its role in multiple drug resistance). Both these proteins are present in high concentrations on the villus enterocytes of the small intestine. Inhibition of the function of either can greatly affect the oral bioavailability of the drug of interest (5,6). Food or any other factor that delays gastric emptying will delay drug absorption. Gastric

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emptying time is considerably prolonged in the neonate and approaches adult values only after age 6 months (7). Gastric pH affects the state of ionization of some drugs and hence their absorption across lipid membranes. Erythromycin and ampicillin are acid-labile, and extended retention in the stomach results in decreased absorption. Gastric pH is close to neutral at birth and decreases to approximately pH 2 within several hours; it does, however, return to neutrality by 24 hours and remains neutral for 1 to 2 weeks. Adult values for gastric acidity are reached only after age 2 (8).

Some drugs are absorbed better after rectal administration. For example, the bioavailability of diazepam has been shown to be higher after rectal administration of diazepam solutions versus oral administration. This is because blood supplies to the anus and lower rectum drain directly into the inferior vena cava. Other drugs, such as midazolam and atropine, are also clinically more effective when administered rectally than by intramuscular administration (4).

DRUG METABOLISM

Drug metabolism is influenced by genetic and dietary factors, by age, and by the activity of drug-metabolizing enzymes. In addition, altered hepatic, renal, and cardiac function can markedly affect biotransformation and may lead to serious drug accumulation if dosage regimens are not tailored accordingly. Most drugs are metabolized by the hepatic microsomal enzyme system. This system is under genetic control and is subject to many factors that influence its activity (9).

Age is of major influence. In the neonate, the hepatic microsomal enzyme system is immature; therefore, a much smaller dose per kilogram must be administered to attain the same therapeutic concentration of a drug. During the first 6 months of life, infants must be followed closely because their enzyme activity is increasing, causing major changes in drug dosage requirements. In children from about 6 months of age to puberty, the hepatic microsomal enzyme system has approximately double the activity of the adult, requiring about double the dose per kilogram to achieve the same therapeutic concentration as an adult. For most drugs, the elimination process follows exponential first-order kinetics (i.e., a constant fraction of the drug present in the body is eliminated per unit of time).

One can predict the effect of age on drug disposition. Hepatic microsomal enzymes are involved in two basic classes of reaction, phase I and II. Phase I reactions typically involve oxidation, reduction, or methylation, and they reach maturity around 6 months of age (4). Phase II reactions involve glucuronidation, sulfation, and acetylation and reach maturity only during the third and fourth year of life (4). As the youth goes through puberty, the activity of the system begins decreasing, and eventually the individual has essentially the same hepatic microsomal enzyme activity as an adult (10). Children going through puberty who are receiving drug therapy must be monitored closely because the activity of their enzyme system is changing rapidly over that period. If one is not aware of this phenomenon, therapeutic misadventures can occur. For example, phenytoin dosing regimens that are appropriate for a preteen can, if not lowered during puberty, cause ataxia, lethargy, and even seizures (11). We see a few cases of phenytoin toxicity every year when pediatricians fail to take into account this slowing down of drug metabolism. Phenytoin protects against seizures at concentrations ranging from 40 to 79 μmol/L (10–20 mg/L) but can cause seizures at concentrations of more than 115 μmol/L (29 mg/L) (11). The theophylline half-life in premature infants has been quoted as 14.4 to 57.7 hours, whereas the half-life in children between ages 1 and 4 years has been reported as 1.9 to 5.5 hours (12). In contrast, the theophylline half-life in adults is 3.0 to 9.5 hours (13) (see Table 1).

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PROTEIN BINDING AND FREE DRUG CONCENTRATION

The extent of protein binding can significantly affect drug elimination. Usually it is the free (unbound) drug that is thought to be pharmacologically active. In disease states characterized by hypoalbuminemia (e.g., hepatic or renal failure, nephrotic syndrome, protein-losing enteropathy), the free fraction and the concentration of free, active drug will be higher at any given total drug concentration. This may give rise to toxicity in patients who nonetheless have a total serum concentration of the drug within the therapeutic range.

In addition to albumin, various blood constituents such as red blood cells and α-1-acid glycoprotein are capable of binding drugs. The concentration in plasma of α-1-acid glycoprotein, a protein that binds many basic drugs, increases with infectious, inflammatory, and malignant diseases and after surgery (14). The binding of drugs such as propranolol and chlorpromazine to α-1-acid glycoprotein is dependent on the concentration of this protein in serum (14). The concentration of α-1-acid glycoprotein in serum is low in the neonate, and consequently several drugs show reduced binding in neonatal serum. In a study by Piafsky and Mpamugo (15), the binding of both lidocaine and propranolol was reduced significantly in cord serum compared with binding in serum obtained from 14 healthy adult controls.

Drug distribution and protein binding in neonates and children are also affected by changes in body composition that occur with development. Total body water and extracellular water as a percentage of body weight are much higher than in adults and are clinically relevant, especially when the drugs in question are water-soluble (e.g., aminoglycosides) (see Table 2). When the drugs are lipid-soluble, they accumulate in lesser amounts in immature infants and neonates than in adults because the percentage of body fat as a percentage of total body weight is much lower.

Because measuring total drug concentration (the sum of free drug plus protein-bound drug) is far easier than measuring free drug concentration, the laboratory generally measures only the total drug concentration. Changes in the extent of protein binding on the free, pharmacologically active fraction are clinically significant only for highly bound drugs (greater than 80% bound) (10, 16,17). For example, if the binding of a drug changes from 98% to 96%, the total drug concentration is unaltered, but the concentration of the free fraction increases greatly (17). Any disease such as protein-losing enteropathy, nephrotic syndrome, or severe malnutrition that decreases total plasma protein causes a decrease in serum protein binding of drugs and is associated with a large increase in free drug concentration, which may lead to drug toxicity.

Although the routine measurement of free drug concentrations may be desirable, this is still an unrealized ideal. Equilibrium dialysis is time-consuming, and the various membranes available commercially that allow the free drug concentration to be measured after generation of protein-free ultrafiltrate are costly. Both of the above procedures demand large sample volumes, and this requirement is always a problem in a pediatric population. Nevertheless, in many situations measurement of the non-protein–bound drug allows a more meaningful evaluation of dosage requirements and probably will slowly replace the now-accepted correlation of total serum drug concentration with clinical effect.

Knowledge of the free drug concentration is most important when the drug is strongly protein-bound (e.g., phenytoin, valproic acid, and the tricyclic antidepressants). For many drugs with a high pKa value (e.g., phenytoin, primidone, ethosuximide, carbamazepine), the concentration in saliva has been shown to approximate the free serum drug concentration. This has led to the suggestion that in many instances saliva should be substituted for the plasma sample. Because saliva is collected by noninvasive techniques (18), there is a further

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advantage in this approach; it is, however, impractical in neonates and infants but can be useful in older children.

In our experience, the clinician's request for a free drug measurement occurs most frequently with phenytoin, which is strongly (90%) protein-bound. Any disease causing a decrease in serum protein binding of phenytoin can be associated with a large increase in the free phenytoin concentration, leading to phenytoin toxicity. This is known to occur in children with renal failure who may have signs of phenytoin toxicity at serum concentrations in the therapeutic range of 40 to 79 μmol/L (10–20 mg/L). In these instances the free phenytoin concentration should be adjusted to provide a free phenytoin concentration between 4.0 and 7.9 μmol/L (1–2 mg/L) (11,17). The protein binding of valproic acid is variable and dependent on many factors, including the concentration of valproic acid in serum; for example, at 69 to 416 μmol/L (10–60 mg/L) there is approximately 5% free drug, whereas at 1,005 μmol/L (145 mg/L) there is approximately 20% free drug. Therefore, measurement of the free valproic acid concentration is occasionally requested (17,19). The measurement of free tricyclic antidepressant concentrations is a goal for the future.

Although digoxin is only slightly protein bound (20–40%), measurement of free digoxin is being increasingly requested in neonates who commonly have circulating digoxin-like immunoreactive factors (DLIFS) (17), which are strongly protein-bound. Measurement of digoxin in the ultrafiltrate provides the free digoxin concentration and separates it from the cross-reactive DLIFS. DLIFS can give rise to digoxin readings as high as 2.5 nmol/L (2.0 ng/mL), and measurement of free digoxin in neonates is strongly recommended to evaluate the neonate's digoxin status even in the presence of DLIFS. By multiplying the conventional therapeutic range of 1.0 to 2.5 nmol/L (0.8–2.0 ng/mL) by 0.8, one arrives at a therapeutic range for free digoxin of 0.8 to 2.0 nmol/L (0.6–1.6 ng/mL). Finally, children receiving Digibind for treatment of digoxin toxicity will have very high plasma or serum concentrations of digoxin when measured by most methods. This is because the Fab antibody Digibind draws digoxin out of skeletal muscle and heart tissue. This Fab-bound digoxin is not pharmacologically active digoxin, and for this reason measurement of free digoxin in the ultrafiltrate is again strongly recommended (17,20). In-depth reviews of free drug measurement have recently been published (16,17,21).

RENAL CLEARANCE AND ELIMINATION HALF-LIFE

In addition to reduced metabolism, the clearance rate of drugs is often low in premature infants and neonates as a result of immature renal function. Plasma creatinine and creatinine clearance are low at birth and increase gradually to adult values, which are achieved only after puberty (22). Table 1 lists some factors affecting drug distribution and disposition and how they differ with age (10).

CHRONOPHARMACOLOGY

Chronopharmacology is an important issue that is frequently not addressed (23). Drug metabolism and clearance can be affected significantly by the time of drug administration. Rivard et al (24) showed that the outcome in children with acute lymphoblastic leukemia (ALL) who received their maintenance 6-mercaptopurine (6MP) dose at night was significantly better than in those who received their dose in the morning. Subsequently, Langevin et al (25) showed that the area under the serum concentration versus time curve was 1.5 times greater in children with ALL if they received their 6MP dosage at night rather than in the morning. A recent publication emphasizes the clinical implications and importance of chronopharmacology for amikacin, suggesting that standard morning sampling times may lead to an overestimate of serum concentrations for the 24 hours (26).

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NEONATAL APNEA

In the United States and Canada, caffeine (intravenous or oral) is preferred over theophylline for the treatment of neonatal apnea. Approximately 30% to 50% of premature infants suffer from apnea, generally defined as cessation of respiration for more than 20 seconds, with or without bradycardia, cyanosis, or both. For infants younger than 29 weeks gestational age, the incidence increases to more than 90%. Reasons for preferring caffeine to theophylline include its wider therapeutic index, slower excretion, and reduced toxicity, and the fact that in the neonate, substantial amounts of theophylline are metabolized to caffeine, giving rise to the need to monitor both drugs. The therapeutic range for caffeine is 25 to 150 μmol/L (5–30 mg/L). Although most cases of neonatal apnea respond to caffeine concentrations between 51 and 103 μmol/L (10–20 mg/L), it has been our experience that some patients may need caffeine concentrations closer to 155 to 180 μmol/L (30–35 mg/L). In contrast, theophylline cannot be used at concentrations greater than 111 μmol/L (20 mg/L) because of toxicity. Nevertheless, it is still used for the treatment of neonatal apnea in some countries.

Doxapram is an effective drug in the treatment of idiopathic apnea of prematurity that is refractory to xanthine (theophylline, caffeine) therapy. In general, infants respond to doxapram at serum concentrations of 4.0 to 10.6 μmol/L (1.5–4.0 mg/L). Concentrations of more than 13.2 μmol/L (5 mg/L) are associated with toxicity (8). Caffeine and doxapram can be measured by high-performance liquid chromatography (HPLC) (27,28). Caffeine can also be measured by immunoassay (29).

OPTIMAL SAMPLING TIME

As in adults, the interpretation of drug concentration measurements depends not only on the dosage regimen but also on the time of the last dose relative to the time of blood sampling. For accurate and intelligent interpretation of drug concentrations, one must know the time of drug administration and the time of sampling. The optimal sampling time is the steady-state trough sample. For drugs with a short half-life, such as the aminoglycosides, it may be important to measure both the expected peak and trough concentrations. Lack of knowledge of the time of drug delivery or random sampling will result in much less useful information. A good review of therapeutic drug monitoring in pediatrics can be found in “Biochemical Basis of Pediatric Disease” (10). The initiation of a TDM program at two pediatric hospitals led to a significant reduction of toxic events and to a far more rapid achievement of drug concentrations in the therapeutic range (30–32).

Although TDM is very useful overall, studies suggest that it could be improved and thus reduce the overall costs of care. Many strategies, too, have been developed to improve physician education in this important area of patient care (33). Two examples of the impact of the introduction of a TDM program in pediatrics are shown in Table 3 and Table 4. In Table 3 it is clear that the frequency of drug concentrations in the toxic range has been greatly reduced (32); Table 4 shows that a TDM program in the neonatal intensive care unit resulted far more quickly in aminoglycoside concentrations within the therapeutic range than before the introduction of this program (31).

For a drug administered orally at intervals equal to its half-life, it takes four to five times the half-life to achieve steady-state plateau concentrations. For most drugs, there is an excellent correlation between the dose and the steady-state serum concentration (e.g., doubling the dose will also double the steady-state concentration). Exceptions to the rule include drugs undergoing saturation kinetics (e.g., phenytoin, ethanol, and salicylate). Therefore, specimens for analysis should not be drawn until sufficient time has elapsed to enable steady-state concentrations to be achieved (unless, of course, toxicity is suspected at an earlier stage).

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ADDITIONAL ASPECTS TO CONSIDER IN CHILDREN

For many drugs, information about the response in children is lacking. TDM is especially useful in a pediatric population, which is prone to under- or overrespond to the usual dosing regimens. In the very young, pharmacokinetic and pharmacodynamic behaviors differ greatly compared with the “normal” adult populations. Some drug interactions are still poorly understood. Pharmacodynamic differences are the result of changes in end-organ responsiveness, receptor function, protein binding, and agonist and antagonist concentration. Table 1 shows pharmacokinetic differences for commonly used drugs in various stages of childhood compared with adults.

Additional special circumstances exist with children, and especially with neonates. These include low blood volume; need for immediacy; inability or diminished ability to tolerate, recognize, or communicate drug effects; pain/fear; need for small blood samples; lack of suitable or approved formulations; and compliance. Patient noncompliance is a major problem, and in pediatrics this can be accentuated because often it involves parent compliance with administering the drugs at the appropriate time intervals. Problems in adherence to oral medication regimens by adolescents with cancer have been well documented (34,35). Misdosing may result from errors in drug measurement or refused, vomited, repeated, or forgotten drug doses. For example, dosing error is likelier when trying to measure 0.1 mg from a 50-g/L solution of a drug. In addition, weight can change dramatically in the pediatric population during a single course of therapy.

DRUG MEASUREMENT

A final TDM issue is the question of whether the assays being used are precise or accurate enough to be useful clinically. In the early years (1970s), Pippenger et al (36) proposed the concept of a performance index, with concentrations within 20% of the target being appropriate. The performance index includes the elements of both accuracy and precision. Since then, improvements have been made in both accuracy and precision of drug assays, so that today one could well expect laboratories to provide results within 10% of the target concentration (performance index <10%), and expect 2 coefficients of variance to be 10% or less. The College of American Pathologists provides a proficiency testing program for almost all drugs involved in TDM, and a similar proficiency testing scheme is available in Europe. These programs allow laboratories to assess their performance relative to their peers.

Recently it has been shown that some immunoassays lack specificity and cross-react with drug metabolites, as well as other compounds. This is true, for example, for carbamazepine, where the active metabolite carbamazepine 10,11-epoxide cross-reacts in many of the immunoassays available (37). For drugs such as digoxin and the immunosuppressives that are extensively metabolized, immunoassays also often lack specificity (38,39). Examples include cyclosporine, tacrolimus, and sirolimus and other approaches such as HPLC and HPLC-tandem mass spectrometry or immunophilin binding assays may be preferable (40,41). In general, modern techniques allow the measurement of drug concentrations in small sample volumes, an important issue especially for neonates.

FUTURE CONSIDERATIONS

Based on theoretical and practical knowledge, physicians attempt to choose the ideal drug for treatment of an identified disease or pathophysiologic process. This search for optimal pharmacotherapy is made more difficult by the growing awareness of the immense genetically, environmentally, and age-determined variations in drug response (42). Informed physicians must know about the risks, limitations, and use of drugs they prescribe. For

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certain drugs, this necessitates their measurement in plasma or serum, followed by appropriate dosage adjustments if required. All these issues are complicated by additional factors in children. An emerging and exciting area is the TDM of drugs used to treat patients with AIDS. Use of tandem mass spectrometry has permitted the simultaneous measurement of any combination of AIDS drugs. This allows assessment of both patient compliance and the ready optimization of dosage regimens (43–46).

In the future, it may be helpful to identify genotypes as an aid to TDM (47). However, even knowledge of metabolizer status will not allow prediction of exact serum concentrations, and measurement of drug concentrations in the blood will remain a clinical necessity.

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Table 1

Pharmacokinetic parameters of drugs commonly used in children

Drug	% Oral dose absorbed	Route of administration	% Protein bound	Maintenance doses (mg/kg/d)			
				Neonates	Infants	Children	Adults
Acetaminophen	100	oral/PR	20–30			20–40	17–34
Acetylsalicylic acid	80–100	oral/PR	50–80			14–25	30–70
Amikacin	not absorbed orally	IM/IV	10	10–15		10–15	10–15
Carbamazepine	70–80	oral	65–83			15–20	7–15
Chloramphenicol	75–90	oral/IV	60–80	25		50	50–100
Digoxin	50–93	IV/oral	20–40	0.010	0.015	0.01	0.008–0.012
Disopyramide	80	oral/IV	10–80				8.6
Ethosuximide	100	oral	0			15–40	15–30
Gentamicin	not absorbed orally	IM/IV	0–30			6–7.5	3–5
Imipramine	29–77	oral/IM					0.7–1.4
Lidocaine		IM/IV	60–80			0.02–0.05 (per min)	1–3 (per min)
Methotrexate	variable	IV/oral	50–70			variable	variable
Phenobarbital	80–100	IV/IM/Oral/PR	45–60			3–8	2–4
Phenytoin	90	IV/IM/Oral	87–93	3–5	3–5	5–15	5–10
Primidone	80–90	oral/IM	0–20			10–25	10–20
Procainamide	70–95	IV/oral	15				2.8–3 (per h)
Propranolol	90	oral/IV	85–96				1.1–9
Quinidine	40–98		80–90			5–30	10–30
Theophylline	95–100	PR/oral/IV	55–65			16–24	13–18
Tobramycin		IM/IV	0–10	3		3–5	3–5
Valproic acid	85–100	oral	90–95			15–100	15–45

Drug	Effective plasma concentration (mg/L)	Toxic plasma Concentration (mg/L)	Half-life (h) of parent drug				Time (h) to peak plasma concentration	Apparent volume of distribution (L/kg)
			Neonates	Infants	Children	Adults		
Acetaminophen	n/a	>25			2–4	2–4	0.5–1.0	0.8–1.0
Acetylsalicylic acid	antipyretic 20–100	>300			0.25–0.35	0.25–0.35	1.0–2.0	

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Drug	Effective plasma concentration (mg/L)	Toxic plasma Concentration (mg/L)	Half-life (h) of parent drug				Time (h) to peak plasma concentration	Apparent volume of distribution (L/kg)
			Neonates	Infants	Children	Adults		
	anti-inflammatory 100–250							
Amikacin	15–25	>30 peak, >5 trough	variable			2–3	0.5–1	0.05–0.7
Carbamazepine	4–12	>12	8–28		5–30	5–30	3	0.8–1.9
Chloramphenicol	10–25	>25	8–15	15–22	2.4–3.4	1.5–5.0	2	0.6
Digoxin	0.8–2.0 μg/L	>2.4 μg/L	20–76	36–180	12–42	33–51	0.5–5.0	5.0–10.0
Disopyramide	2–5	>5				5–6	0.5–3.0	0.8
Ethosuximide	40–100	>100			30–50	40–60	2–4 capsule, 1–2 syrup	0.7–0.9
Gentamicin	5–10	>12 peak, >2 trough			2–3	2–3	0.5–1	0.15–0.25 (adults) 0.07–0.7 (children)
Imipramine	0.150–0.250	>0.5				9–24	0.5–2	10–20
Lidocaine	1.5–5.0	>5.0				1–2	0.25–0.5	1.7
Methotrexate	Depends on therapeutic regimen	24 h, $>10^{-5}$ molar			variable	variable	1–2	0.75
		48 h, $>10^{-6}$ molar						
		72 h, $>10^{-7}$ molar						
Phenobarbital	15–40	>40	67–99	40–70	40–70	50–120	6–18	0.7–1 (adults)
Phenytoin	10–20 (adults) 5–20 (children)	>20	17–60 *	75 +/−64.5	12–22 *	18–30 *	4–8	0.5–0.8
Primidone	5–12	>12			10–12	10–12	2–4	0.6–1.0
Procainamide	4–10	>10				2–4	1–2 oral, 0.5 IM	1.7–2.4
Propranolol	0.05–0.10	variable				2–6	1–4	2.0–6.4
Quinidine	2–5	>5				4–7	1–2 sulfate	3 +/−0.25
Theophylline	10–20	>20	24–30	14.4–57.7		3.6–12.0	2–3 oral	0.3–0.7
Tobramycin	5–10	>12 peak, >2 trough			1–10	2–3	1 IM	0.22
Valproic acid	50–150	>150			6–15	8–15	0.5–4.0	0.15–0.40

* Exhibits saturation kinetics. Half-life therefore dependent on serum concentration. (Modified from MacLeod SM, Raddle IC [3]. Reproduced with permission.)

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Table 2

Some factors affecting drug distribution and disposition

	% of total body weight		
Factor	**Preterm**	**Term**	**Adult**
Total body water	85	7–75	50–60
Extracellular water compartment		40	20
Total body fat	1	15	20

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Table 3

Percentage of toxic levels for six drugs before and after implementation of a TDM program

	June	July	Aug	Sept	Oct
Before TDM	—	6.4	3.5	4.6	3.1
After TDM	2.7	3.7	2.0	2.9	2.8

Hospital for Sick Children, Toronto, Canada.

TDM, therapeutic drug monitoring.

(Soldin SJ, Koren G. Optimization of a therapeutic drug monitoring program. *AACC* 1984;2:1–6.)

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Table 4

Therapeutic values for gentamicin and vancomycin

Drug	Number of tests ordered	Within therapeutic drug range after dosage adjustment	Out of therapeutic drug range
Gentamicin fore TDM	32	27	5
After TDM	28	28	0
Vancomycin before TDM	20	9	11
After TDM	16	16	0

Neonatal unit at Children's National Medical Center, Washington, DC. TDM, therapeutic drug monitoring.