Drug Monitoring in the Neonate

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ABSTRACT

Drug monitoring has recently been extended into the neonatal population largely owing to improvements in analytical techniques. This important area of study represents a wide diversity of patients,—from mature infants to low-birth weight infants owing either to premature birth or intrauterine growth retardation. Neonates provide a highly variable population base which undergoes rapid changes in rate of absorption, metabolism, and elimination of drugs during the first weeks of life. Rational drug administration at this time can be very difficult. Drug monitoring in conjunction with effective therapeutic ranges can be of great assistance to the physician.

Introduction

Over the past decade the monitoring of drug concentrations to assess therapeutic management and avoid toxic side effects has increased dramatically. It is now well established that for most drugs, knowledge of serum drug concentrations enables the physician to establish optimal drug therapy for individual patients. The wide usage of therapeutic drug monitoring has provided a data base to establish general guidelines for an individual drug's half-life, therapeutic range, and toxic level in most patients.

This information has also pointed out wide individual variations in response to a given dose of drug in the adult population. In the past, large sample requirements precluded similar investigations in neonates, infants, and very young children. Recent improvements in analytical techniques have provided the capability of measuring drug concentrations in small sample volumes and have extended such investigations into the pediatric population. This population has a more dramatic variation when one considers the drastic changes of drug elimination pathways in the neonate and infant.

It is the purpose of this paper to present some of the basic principles of pharmacokinetics with particular emphasis on the unique features of drug disposition in the neonate and to help provide guidelines in the interpretation of the information derived from the clinical toxicology laboratory.

Analytical Methods

During the past few years, several novel technologies have been developed. The analytical technique employing nephe-
lometric inhibition immunoassay (NIIA)\textsuperscript{7} has recently been applied to the therapeutic drug monitoring of several antiepileptic drugs and theophylline.\textsuperscript{26} This technique, as well as fluorescence polarization immunoassays (FPIA)\textsuperscript{13} and the substrate-linked fluorescent immunoassays (SLFIA's) are quite sensitive and specific but presently suffer from the limited number of drugs for which commercial reagents are available.\textsuperscript{6,10,41} At this time enzyme multiplied immunoassay (EMIT) techniques\textsuperscript{40} continue to be the most prevalent analytical technique in therapeutic drug monitoring. The broad spectrum of drugs which can be assayed in small (0.05 ml) sample volumes allows the use of capillary blood samples which is ideal in premature infants.

Advanced technology in high pressure liquid chromatography (HPLC) has made this technique a relatively simple analytical tool which is capable of great versatility and sensitivity. High pressure liquid chromatography is well suited to micro-determination of frequently requested drugs such as caffeine\textsuperscript{28} and chloramphenicol.\textsuperscript{8}

Because of increasingly smaller sample requirements, the half-lives of a number of drugs can be determined readily, thus allowing individual drug regimens to be optimized in this extremely variable patient population. In the future these new methodologies will undoubtedly have an increasing role in therapeutic drug monitoring.

**Drug Metabolism and Disposition in the Neonate**

This presentation will not provide complete and detailed information on all aspects of pediatric clinical pharmacology; however, the subject of pediatric clinical pharmacology has been treated in depth in several recent monographs.\textsuperscript{21,24} The principles of pharmacology and pharmacokinetics, covered in medical pharmacology texts, form the foundation upon which modern drug therapy is based. In the neonate, generally, all the pharmacokinetic variables are altered or somewhat modified. However, with modern neonatal intensive care, there is a rapidly improving survival rate in very low birth weight premature infants, such that the neonate itself represents a diverse group having various degrees of physiological maturation. Clinically, the neonate is classified as a normal or low-birth-weight infant. The low-birth-weight infant is then sub-classified into premature birth and those who are small secondary to intrauterine growth retardation. These classifications help the physician anticipate clinical problems and even the pharmacokinetic profiles of certain drugs. The difference in the maturity of the neonate based on gestational age, the lack of development owing to intrauterine growth retardation and complications secondary to delivery may cause tremendous variation in the organ systems involved in the absorption, metabolism, and excretion of drugs. In this regard, the neonate is a very unique patient for whom drug therapy must be rationalized in the context of the individual clinical setting.

For most reversible acting drugs the intensity of the pharmacological effect is proportional to the drug concentration at the receptor. Since the measurement of receptor drug concentration is generally impractical, the total drug levels in plasma usually are considered to be a reflection of the many equilibria effecting free drug available at its receptor site. While cognizance of a specific drug's dose effect curve is of importance, it has been well documented that there is a better correlation between therapeutic response and plasma drug concentrations than is observed between total drug dosage and therapeutic response.

The plasma steady state drug concentrations among patients receiving a fixed
daily dose is influenced by numerous factors affecting drug disposition, such as the rate of drug absorption, volume of distribution, the degree of protein binding, the rate of drug metabolism and the rate of renal excretion.

In the neonate these variables are markedly different from those in older children and adults, furthermore they undergo continual and often rapid changes due to maturational stage.24

**ABSORPTION**

Some of the common routes of drug administration may result in unexpectedly poor absorption. Gastric emptying time and gastric pH are two of the major factors affecting gastrointestinal (G.I.) tract absorption of drugs. At birth a mature infant's gastric pH is about 7, but it decreases to about pH 2 within a few hours. Since acid secretion is closely correlated to development of the gastric mucosa, premature infants are not able to maintain gastric acidity until after eight to ten days. Clinical observations have demonstrated that this decreased acidity condition allows a higher availability of the penicillin class of drugs, but delays or reduces absorption of drugs which are transported from the G.I. tract only in their ionized form at a low gastric pH such as acetaminophen, gentamicin, phenobarbital and phenytoin.23

The variability of the biliary function may be a factor both in the absorption of drugs as well as their disposition where interohepatic recycling is implicated. In the premature infant a primary disease in bile salt secretion or a secondary decrease owing to decreased reabsorption may result in steatorrhea. This inadequate solubilization of fat often results in decreased absorption of large lipid soluble molecules, e.g., digoxin.24 Another situation which will modify oral absorption is cardiac insufficiency with resultant decrease in perfusion of the splanchnic bed resulting in either decreased or prolonged absorption.

Intramuscular absorption is erratic, being highly efficient for some drugs such as phenobarbital and very poor for others such as phentoin and digoxin. Variable absorption of a particular drug in the newborn population has been attributed to relative changes in blood flow through an area owing either to hypoxia, cardiac insufficiency, or exposure to a cold environment. The resulting peripheral vasoconstriction may change the absorption of the drug.23

Rectal route of administration can often be quite effective for some drugs such as diazepam15 but the data are somewhat scarce.

Because of all these factors, it is understandable that most drugs are best administered intravenously by continuous infusion. This provides a method of obtaining an optimum plasma drug level, free of peaks and troughs.

**DEGREE OF PROTEIN BINDING**

The neonate exhibits reduced plasma protein binding of several drugs owing to a number of physiological factors such as reduced gammaglobulin and total protein concentrations, the presence of low drug affinity fetal albumin, elevated bilirubin, and free fatty acids as well as a relatively acid blood pH.24

This reduced binding capacity results in increased amounts of free drug in the circulation. For the individual neonate this presents few problems, once it is realized that dose schedules must undergo change with increasing maturity, and that the changes are only important for those drugs which are highly protein bound such as phentoin, sodium valproate, and diazepam. Not incidentally, these highly protein bound drugs displace bilirubin from plasma albumin and could lead to an exacerbation of kernicterus.
During the first postnatal week, the rate of drug disposition is slow compared to the adult. The slow rate of renal drug elimination is clearly related to renal functional immaturity where virtually all the physiological variables such as glomerular filtration rate, tubular secretion and reabsorption, and renal blood flow are reduced. For drugs eliminated largely unchanged in the urine, such as antibiotics, digoxin and several sulfonamides, this very slow clearance may increase the risk of toxic effects. The effects of certain pathophysiological states are less widely appreciated. Conditions such as malnutrition, hypoxia, asphyxia, and the presence of patent ductus arteriosus may lead to delays in maturation and further compromise an already functionally immature system.

As with renal excretion, functionally deficient hepatic metabolism contributes to a prolonged biological half-life for many drugs. During the first 15 days of life, the premature and full-term infant exhibit a considerably reduced drug catabolism. In addition to dramatic changes in hemodynamics, there is a reduced activity of a number of enzymes. The low activities of blood esterases in the newborn, along with the decreased activities of the hepatic microsomal mixed function oxidases (cytochrome P-450 dependent) contribute largely to prolongation of drug half-life. There is additionally a reduction in conjugative pathways owing to the immaturity of the glucuronyltransferase system. After more than a decade of use, chloramphenicol was implicated in the fatal vascular collapse of three newborn infants exposed to excessive doses of the drug. The mechanisms responsible for this toxic effect in neonates, the so called “gray baby syndrome,” are failure of the drug to be conjugated with glucuronic acid and inadequate renal excretion of unconjugated drug.

In some cases, this glucuronyl transferase deficiency can be compensated for by the early development of sulphate conjugation. This pathway has been documented as operative with acetaminophen as the substrate in the neonate. It remains as the major path of excretion until age 10 to 12 years when glucuronidation becomes the dominant path of conjugation of acetaminophen. It is postulated that other drugs are conjugated by this pathway, but little is known at this time.

Such a situation, when combined with the lack of predictability in neonatal drug disposition and metabolism already mentioned, stresses the importance of measuring the plasma drug concentration in the therapeutic management of newborn infants.

**Indications for Drug Monitoring**

As in other areas of scientific research, progress in a given field is usually preceded by improvements in analytical methodology. The advances in technology outlined earlier have had dramatic impact on clinical medicine. It is now recognized that for many drugs there are individual ranges of plasma concentrations which will produce the desired therapeutic effect in most patients. Similarly, levels below or above this range will generally result in a suboptimal or toxic response, respectively. However, having the technical ability to measure plasma levels of many drugs and correlate these with clinical response is not sufficient reason for doing so. The question now is not why one should monitor drug concentrations, but rather which drugs should be monitored.

From the previous presentation, it can be appreciated that in the neonate the answer to this question may differ from that in any other patient population. There are, however, two basic requirements which must be met if drug monitoring is to be of any clinical utility: the action of the
drug must be reversible and, secondly, there must be a correlation between the drug’s plasma concentration and its pharmacological effects.\(^5\)

An implicit assumption in drug monitoring is that the concentration of free drug in plasma reflects the concentration at the receptor site which in turn is proportional to the intensity of the pharmacologic effect.

Although most therapeutic drug monitoring involves measuring total drug levels, individuals vary in their degree of protein binding and thus in the percentage of biologically active free drug. Importantly, in certain disease states the “bound” drug—“free” drug equilibrium is altered such that the total drug concentration does not accurately reflect the free drug concentration. For example, uremic patients often lack the ability to bind phenytoin (normally highly protein-bound). For these patients, total drug concentrations one-tenth the normal effective concentration will be therapeutic. In addition to phenytoin and valproic acid which are highly protein-bound, drugs such as disopyramide which exhibit concentration-dependent binding are variable and thus frequent candidates for the new ultra-filtration methods for free drug monitoring. For irreversibly acting drugs the pharmacologic effect does not diminish as the drug is cleared from the plasma. These drug effects are indirectly mediated where the rate limiting step in reversal of effect involves synthesis of new enzymes, biogenic amines, or even the production of new cells as in the case of antiproliferative agents. Additionally, some drugs may concentrate in cellular reservoirs which prolong potent drug action long after plasma levels are undetectable.

For drugs that meet the criteria as outlined previously, there are several indications for therapeutic drug monitoring summarized in table I. Some of these indications assume less importance in the perinatal patient while additional ones are unique to this age group.

It is implicit that when other readily available tests reflect the effect of the drug of interest (e.g., glucose/insulin), they should be used. Additionally, the use of non-invasive techniques such as transcutaneous PO\(_2\) measurements can be used to help regulate neonatal treatment of cardiopulmonary problems.\(^29\)

### TABLE I

Indications for Plasma Drug Monitoring

<table>
<thead>
<tr>
<th>Indication</th>
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<tbody>
<tr>
<td>I. Drugs having low therapeutic index</td>
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<tr>
<td>II. Drugs having narrow, established therapeutic range</td>
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<tr>
<td>III. Clinical effect not achieved or toxicity observed</td>
</tr>
<tr>
<td>IV. Suspected drug interactions</td>
</tr>
<tr>
<td>V. Drug disposition altered by disease/physiological state</td>
</tr>
<tr>
<td>VI. Suspected noncompliance</td>
</tr>
<tr>
<td>VII. Overdose</td>
</tr>
</tbody>
</table>

**Therapeutic Index**

Drugs with a large therapeutic index (the difference between toxic and therapeutic drug levels is wide) can be safely given in doses well in excess of the minimum concentration required for therapeutic effects, as exemplified by penicillin and cephalosporin antibiotics.

The conventional approach of scaling down adult doses according to weight or surface area is satisfactory only for drugs with a large therapeutic index. However, this method is unsuitable for most of the drugs used in neonatal drug therapy (anti-convulsants, aminoglycoside antibiotics, anti-inflammatory agents, and cardiac glycosides) which have a relatively low therapeutic index.

**Therapeutic Range**

It is clearly an advantage to adjust the dose regimen to achieve a plasma drug concentration associated with optimal therapeutic effect without any undue adverse effects. Unfortunately, well defined relationships between plasma drug concen-
trations and therapeutic response applicable to the neonate are quite scarce relative to the ever increasing numbers of drugs used in newborn intensive care. Clinical experience has suggested therapeutic plasma ranges for a number of drugs as shown in table II. These will hopefully serve as general guidelines to therapeutic decisions. As more data are accumulated and correlated with clinical effects, the more valuable such information will become. However, the drug concentrations should always be interpreted in the total clinical setting, thus treating the patient, not the drug concentration.13,34

INEFFECTUAL RESPONSE OR TOXICITY

Owing to the wide inter-individual variation in neonatal metabolism and excretion, a standard drug regimen for the average newborn may either produce the desired effect, provide a poor therapeutic response, or lead to signs of toxicity. In the latter two cases, obtaining a plasma drug level with knowledge of the presumptive therapeutic range would indicate direction for proper management.

The observation of abnormal clinical symptoms does not necessarily indicate an adverse drug reaction as the toxic presentation may often be similar to that of the underlying disease. As an example, a patient receiving digoxin may develop cardiac arrhythmias owing to digoxin toxicity or as the result of the patients underlying disease. With a knowledge of the plasma drug level it is possible to decide whether to decrease or increase the drug dose or, in the case of continued symptoms at therapeutic drug levels, change to more effective medication.

DRUG INTERACTIONS

The increase in frequency of multidrug therapy in pediatric practice has similar but more profound effects than are seen in the adult, largely due to the rapid maturation changes in newborn drug metabolism and excretion.22 While it is often essential to use two drugs to achieve a therapeutic objective (e.g., the concurrent use of cardiac glycoside plus diuretic to maintain cardiac output and prevent edema), most attention given to drug-drug interactions results from the potential for adverse reactions. One drug may compete with another for the same metabolic site, alter absorption or protein binding, al-

### TABLE II

<table>
<thead>
<tr>
<th>Drug</th>
<th>Peak Range</th>
<th>Trough Range</th>
<th>Ref.</th>
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</thead>
<tbody>
<tr>
<td>Amikacin</td>
<td>15 - 25 µg/ml at 1 hour postdose</td>
<td>2 - 4 µg/ml at 6 hours predose</td>
<td>Howard 1975</td>
</tr>
<tr>
<td>Caffeine</td>
<td>5 - 20 µg/L</td>
<td></td>
<td>Aranda 1981</td>
</tr>
<tr>
<td>Carbamazepine</td>
<td>3 - 12 µg/ml</td>
<td></td>
<td>Rane 1990</td>
</tr>
<tr>
<td>Chloramphenicol</td>
<td>10 - 20 µg/L</td>
<td></td>
<td>Black 1978</td>
</tr>
<tr>
<td>Digoxin</td>
<td>1 - 3 µg/L</td>
<td></td>
<td>Leitman 1979</td>
</tr>
<tr>
<td>Diazepam</td>
<td>0.15 - 0.3 µg/L</td>
<td>0.2 - 0.3 µg/L</td>
<td>Nyberg and Wattrell 1980</td>
</tr>
<tr>
<td>Ethosuximide</td>
<td>40 - 100 µg/ml</td>
<td></td>
<td>Langslet et al 1978</td>
</tr>
<tr>
<td>Gentamicin</td>
<td>Peak 4 - 8 µg/ml at 1 hour</td>
<td>Trough 1 - 2 µg/ml at 6 hours</td>
<td>McCracken 1977</td>
</tr>
<tr>
<td>Phenobarbital</td>
<td>15 - 25 µg/ml</td>
<td></td>
<td>Szefer 1980</td>
</tr>
<tr>
<td>Phenytoin</td>
<td>10 - 20 µg/ml</td>
<td></td>
<td>Pippenger 1975</td>
</tr>
<tr>
<td>Theophylline</td>
<td>5 - 10 µg/ml</td>
<td></td>
<td>Jailing 1975</td>
</tr>
<tr>
<td>Tobramycin</td>
<td>Peak 4 - 6 µg/ml at 1 hour postdose</td>
<td>Trough 0.5 - 1 µg/ml at 8 hours predose</td>
<td>McCracken, J. Ped. 1976</td>
</tr>
<tr>
<td>Valproate</td>
<td>40 - 50</td>
<td></td>
<td>Gram 1979</td>
</tr>
</tbody>
</table>
nder metabolism by enzyme induction, or change the rate of renal excretion. The rapidity at which these parameters change in neonates often exaggerates the adverse effects whether it involves toxicity or a compromise in therapeutic efficacy.

The clinician can be alert for such interactions for many drugs through extrapolation of the data base applicable to the adult. The alterations in steady state drug concentrations are variable and often unpredictable in the newborn. Therefore, monitoring the plasma concentration of a given drug, along with adequate clinical observation, is often invaluable in avoiding adverse effects.

**Drug Disposition in Pathophysiologic States**

Drug concentration monitoring is generally indicated in patients with impaired elimination owing to renal or hepatic failure. In the case of small premature infants who already have functionally impaired elimination, this additional insult makes the monitoring of drugs, particularly those with a low therapeutic index, virtually essential in avoiding toxicity in this high-risk group.

As can be seen, many of the indications for plasma drug concentration measurements in the neonate are equally applicable to all patient populations, while others are quite unique. In contrast, a number of adult indications are rarely encountered in neonatal drug therapy. For example, non-compliance, which is a major factor in therapeutic failure in many patients, is rarely a consideration in the hospitalized infant. The use of plasma blood levels is quite important in accidental or intentional overdose situations where quantitative information is useful both in management and prognosis. In the newborn intensive care unit, this is hopefully a rare situation although with arithmetical errors this catastrophic complication is still occasionally seen. A more common cause not widely appreciated is toxic effects in otherwise normal infants owing to transplacentally acquired drugs.

**References**


14. **KNUDSEN, F. U.:** Plasma diazepam in infants after rectal administration in solution and by