Adverse Drug Reactions in the Newborn

SAVITRI P. KUMAR, M.D.

Department of Pediatrics,
University of Pennsylvania School of Medicine,
Philadelphia, PA 19104

ABSTRACT

Adverse drug reactions have been noted to occur in one of three newborns admitted to intensive care units. The factors associated with adverse drug reactions and the adverse reactions to commonly used medications in neonatal intensive care units are discussed. Methods of preventing or reducing these undesired effects are suggested.

Introduction

Adverse drug reactions (ADR) occur more frequently in sick neonates than in adult patients. These undesirable and unintended effects of drugs administered for therapeutic or diagnostic purposes have been noted to occur in 10 to 30 percent of infants in intensive care units, with 7.5 percent experiencing life-threatening reactions. Studies of drug utilization in an intensive care unit have shown that three-fourths of all infants admitted received between one to 26 drugs, with the average number of drugs used being six per baby.

Infants with ADR were noted to have significantly lower births weights and gestational ages, with marked reductions in such reactions observed in babies greater than 33 weeks. Cardiovascular drugs, diuretics, antibiotics, and components of parenteral nutrition solutions were the most commonly suspected agents. The increased frequency and high fatality rate associated with ADR make it a major health care problem in the neonatal period.

Factors Implicated in Adverse Drug Reactions in Newborn Infants

The vulnerability of the neonate to adverse drug reactions results from several factors:

1. Increased Drug Exposure: The neonate is exposed postnatally to a large number of drugs in addition to those acquired transplacentally and from the breast milk.

2. Immaturity of Systems: The immaturity of the drug metabolizing and eliminating systems, and the added strain of disease, can adversely affect pharmacokinetics, leading to accumulation of drugs to toxic concentrations.

3. Paucity of Pharmacologic Data: Many potent drugs are used in neonates, in spite of inadequacy of pharmacologic data, leading to adverse effects.

4. Practice of Polypharmacy: The presence of multiple disorders (e.g., RDS, PDA, apnea) in a single infant, leading to the practice of
polypharmacy, increases the risk of drug interactions.\textsuperscript{3}

(5) Medication Errors: Errors in drug computation increase the risk of medication errors in newborns, leading to overdosage and ADR.\textsuperscript{30}

Adverse drug reactions may be classified as resulting from (a) overdosage or exaggeration of the desired pharmacologic effect of the drug; (b) side effect or undesired but known pharmacologic effect of the drug; (c) cytotoxic effect, e.g., liver necrosis or abnormal blood morphology, from the drug causing unwanted morphologic changes in tissues. These reactions may be severe or life-threatening, moderate requiring therapy or prolonged hospitalization, or mild with spontaneous resolution. The purpose of this paper is to review the adverse reactions to the commonly used drugs in neonatal intensive care units. This review will not include adverse reactions to oxygen, parenteral fluids, or components of intravenous nutrition solutions.

Adverse Reactions to Drugs Commonly Used in Neonatal Intensive Care Units

Aminoglycosides

These antibiotics are widely used in the treatment of neonatal sepsis and are potentially ototoxic and nephrotoxic. Aminoglycoside ototoxicity can be explained by progressive accumulation of the drug that occurs in the inner ear upon repetitive administration or continuous infusion. Risk factors associated with aminoglycoside ototoxicity include high daily and total dosage, elevated peak and trough concentrations, previous aminoglycoside treatment, concomitant diuretic administration, and familial predisposition to aminoglycoside ototoxicity. Hypoxia increases the risk of aminoglycoside ototoxicity. Among the commonly used compounds, kanamycin and amikacin are the most cochleotoxic, followed by gentamicin and tobramycin. Vestibular toxicity follows a different order: streptomycin is most toxic, followed by gentamicin, tobramycin, and amikacin.\textsuperscript{4} Although several studies exist evaluating the ototoxicity of aminoglycoside antibiotics, in the neonate, it is difficult to estimate accurately the true incidence of drug-induced ototoxicity from various reports available. Estimates derived from audiometric measurements of cochlear function show extreme variability ranging from four to 15 percent.\textsuperscript{13} Eviatar and Eviatar demonstrated laboratory evidence of vestibular dysfunction and delays of head and postural control in eight of 43 infants tested between two and five years.\textsuperscript{12} Aminoglycoside nephrotoxicity results from tubular damage and measurements of proteins or enzymes of tubular origin have been used as indicators of tubular toxicity. It is suggested that urinary elimination of lysosomal enzyme N-acetyl glucosaminidase (NAG) may be a more sensitive indicator of tubular damage than serum creatinine.\textsuperscript{29}

Aminoglycoside antibiotics potentiate or prolong muscle weakness in patients with postsynaptic defects of cholinergic function or presynaptic defects resulting from decreased acetylcholine release.\textsuperscript{23} The decreased acetylcholine release that occurs in magnesium intoxication in infants results in a clinical syndrome characterized by poor feeding, weak cry, muscle weakness, and respiratory failure, a syndrome that appears similar to infant botulism. When these infants require antimicrobial therapy, alternate drugs should be used, or if aminoglycoside antibiotics are administered, the infants should be closely monitored for possible development of respiratory failure. As the difference between effective and toxic doses of aminoglycosides is narrow, infants being treated with these
drugs should have peak and trough blood levels measured.\textsuperscript{9}

\textbf{Chloramphenicol}

Despite well-known toxic effects of chloramphenicol, especially the Gray Baby Syndrome, errors in prescription and administration of the drug still occur, leading to fatal reactions. No infant should be treated with chloramphenicol without monitoring serum concentrations. Immaturity of hepatic and renal functions can result in toxic concentrations with circulatory collapse and death.\textsuperscript{24} Charcoal hemoperfusion has been shown to be effective in reducing toxic blood levels.\textsuperscript{21}

\textbf{Vancomycin}

The increased incidence of coagulase negative staphylococcal infections in sick neonates has led to the increased use of this drug. This drug is potentially ototoxic and nephrotoxic, especially with concurrent administration of aminoglycosides. Recent studies suggest that the liver may be involved in metabolism of vancomycin. In very low birth weight infants, hepatic immaturity, in addition to renal immaturity, may lead to drug accumulation. Monitoring of blood levels is mandatory to ensure therapeutic efficacy without toxicity.

A high incidence of histamine-like skin eruptions has been noted to occur during infusion of the drug, accompanied by hypotension in an occasional infant.\textsuperscript{5}

\textbf{Nafcillin}

Subcutaneous extravasation of parenteral nafcillin sodium can cause deep tissue necrosis, sometimes necessitating multiple debridements and skin grafting. This nafcillin extravasation injury has been shown to be prevented by clysis of hyaluronidase at the site of infiltration.\textsuperscript{34}

\textbf{Furosemide}

Furosemide, a potent diuretic, is extensively used in low birth weight (LBW) neonates in the treatment of congestive heart failure associated with patent ductus arteriosus and in bronchopulmonary dysplasia (BPD). Prolonged use of furosemide leads to hypokalemia and metabolic alkalosis. Furosemide markedly increases calcium excretion in the urine and renal calculi are frequently seen with prolonged use of this drug in LBW infants. Autopsies of infants have shown that parenchymal calcium deposits are mainly in the interstitial areas of the renal papillae rather than in the tubules. Calculi are frequently composed of calcium oxalate and calcium phosphate.\textsuperscript{20} Secondary hyperparathyroidism and bone disease have also been reported to complicate long-term furosemide therapy.\textsuperscript{30} Furosemide-related renal calcification can be reversed by concurrent administration of chlorothiazide, a diuretic which promotes tubular reabsorption of calcium. It has been suggested that prophylactic use of chlorothiazide can prevent renal calcification in infants with chronic lung disease who require long-term diuretic therapy.\textsuperscript{20}

Although furosemide has been used in the management of hemodynamically patent ductus arteriosus, Green et al\textsuperscript{15} suggest that furosemide can interfere with ductal closure by stimulating the renal release of prostaglandin E\textsubscript{2}, a potent dilator of immature ductus arteriosus and by causing hypocalcemia, which can inhibit ductal closure.

Cholelithiasis has been seen in some infants receiving total parenteral nutrition. It has been suggested that furosemide may predispose to biliary lithogenesis by increasing biliary calcium
excretion. Furosemide potentiates ototoxicity of aminoglycoside antibiotics. Methyl Xanthines

The adverse reactions of these drugs are principally the exaggeration of their pharmacologic actions. Although theophylline and caffeine are primarily used in the management of apnea of prematurity, caffeine continues to be used infrequently as a respiratory stimulant in the asphyxiated infant, where it is not only ineffective but also may lead to worsening of hypotension. As the neonate can metabolize theophylline to caffeine, unlike the adult, possible additive or potentiating effects should be taken into consideration.

Excessive doses and high plasma concentrations of these drugs have led to overt central nervous system (CNS) excitation. Opisthotonus, fine tremors, and clonic and tonic movements with exaggeration of reflexes have been described in newborn infants with overdoses of caffeine sodium benzoate. Sinus bradycardia has also been observed during concurrent therapy with digitalis, suggesting an additive effect of the two vagotonic drugs.

Tachycardia is a well-known side effect of theophylline which has been noted even at therapeutic serum levels. Sudden death from bolus injections of theophylline, presumably from cardiogenic origin, has also been noted. Administration of theophylline should be over 15 to 20 minute periods. Gastrointestinal symptoms with vomiting, increased gastric acid secretion, is seen with serum theophylline concentrations greater than 20 µg per ml. A possible relationship of theophylline usage and necrotizing enterocolitis (NEC) has been raised. A decrease in lower esophageal sphincter pressure has been noted with large doses of theophylline. Although methylated xanthines act as mild diuretics, marked diuresis and dehydration, as well as electrolyte abnormalities have been noted in infants overdosed with aminophylline. Hyperglycemia may result from aminophylline overdosage. Mechanisms proposed are stimulation of glycogenolysis in muscle and liver, and stimulation of gluconeogenesis. Theophylline stimulates glucagon release. Methyl xanthines may also induce insulin release in the premature infant. Stimulation of lipolysis, with increases in free fatty acids (FFA), triglycerides, and glycerol have also been noted.

Theophylline and caffeine inhibit the synthesis of cholesterol in cultured glial cells, implying a possible impairment of neuronal development. However, a followup study by Nelson et al failed to show any difference in growth or development between the theophylline treated infants and matched controls. The adverse effects of methyl xanthines could be avoided by monitoring plasma concentrations. Owing to the long half-life and narrow serum fluctuations of caffeine in infants, weekly monitoring of caffeine is usually satisfactory, while theophylline with a much shorter half-life should be monitored more often. Prostaglandin E

Currently, prostaglandin E is being widely used in ductal-dependent cyanotic heart disease to maintain ductal patency. Well-documented side effects encountered with this drug infusion include hyperthermia, hypotension, skin flushing and edema, diarrhea, apnea, and bradycardia. Prostaglandins are rapidly inactivated by tissues, especially with passage through the lungs. These side effects are often noted at the onset of treatment and are reversible with reduction or discontinuation of infusion. Damage to the wall of the ductus with aneurysm formation has resulted from a three to six day infusion of the drug. Pro-
longed infusions of prostaglandin $E_1$ and $E_2$ have been associated with widespread cortical hyperostosis resembling Caffey’s disease.\textsuperscript{35} Serum calcium has been noted to be normal. The etiology of these skeletal changes remains unknown.

**Tolazoline**

This pulmonary vasodilator drug is used frequently in the syndrome of “persistent pulmonary hypertension” of the newborn. In addition to blocking alpha adrenergic receptors, it has sympathetic and cholinergic activity and is a histamine agonist. Although 30 to 62 percent of infants with “pulmonary vasospasm” treated with tolazoline have responded with transient and sometimes marked increases in $P_{O_2}$, the rate of complications has been unfortunately very high. Serious complications of this drug have included pulmonary and gastrointestinal hemorrhage, systemic hypotension, renal dysfunction, and thrombocytopenia.\textsuperscript{10} Although tolazoline can increase $P_{O_2}$ in some patients, and especially when used with drugs that augment systemic hypertension, such as dopamine, its therapeutic inconsistency and high complication rate make this an ineffective agent in the newborn.

**Dopamine**

Dopamine has been used extensively in pediatric intensive care units because of its ability to raise blood pressure and increase urine output in patients with shock. Increase in heart rate, myocardial contractility, coronary and renal blood flow, and cardiac output are the major cardiovascular effects. However, overdosage with this medication has led to intense peripheral vasoconstriction, metabolic acidosis, dry gangrene of the extremities and midgut infarction.\textsuperscript{18,26} Any infant receiving peripheral infusion of the drug should have frequent examinations of the extremities throughout the period of infusion. Meticulous attention must be paid to the calculation of the dose, dilution, and infusion rates to avoid these side effects.

**Indomethacin**

This drug is a prostaglandin synthetase inhibitor frequently used in the pharmacologic closure of patent ductus arteriosus in preterm infants. Indomethacin causes platelet dysfunction and increases the risk of intracranial and gastrointestinal hemorrhage. Necrotizing enterocolitis with gastrointestinal perforation has been noted to occur following indomethacin therapy in low birth weight infants.\textsuperscript{27} Transient renal dysfunction is usually seen, although acute renal failure may occur on occasion. The drug is contraindicated if serum creatine is greater than 1.6 mg per dl. Acute hyponatremia, with rise in urinary osmolality and body weight, secondary to transient increase in antidiuretic hormone, has also been reported. The use of furosemide together with indomethacin therapy has been advocated to reduce this effect.\textsuperscript{28} Elevation of serum digitalis levels to toxic ranges, with prolongation of half-life, has been noted in infants treated with indomethacin, following medical therapy for congestive heart failure.\textsuperscript{32} Blindness secondary to intense vasoconstriction and obliteration of ophthalmic vessels has been reported.\textsuperscript{20}

**Digoxin**

Although the newborn appears to be less sensitive to digoxin than the adult, toxicity and fatal adverse reactions do occur in the neonatal period. High serum levels of digoxin are associated with poor feeding, persistent vomiting, and electrocardiographic abnormalities, mostly atrial in origin with or without atrioventricular nodal block. Ventricular arrhythm-
mias are rarely noted. Assay of serum digoxin levels, if obtained after a week or more of administration and five to eight hours after the dose, may be of assistance in diagnosing toxicity. Levels less than two ng per ml exclude digoxin toxicity. Computation errors frequently lead to overdosage, which may be life-threatening.

Phenytoin

Dilantin* is added to the anticonvulsant therapy in the newborn infant when seizure activity is not controlled by phenobarbital alone. In this age group, the pharmacokinetics of dilantin are unpredictable because of delays in absorption when administered by mouth and delays in elimination in both term and preterm infants. Cardiovascular toxicity with atrial fibrillation, hypotension, sinus bradycardia, sinus arrhythmia, and incomplete bundle branch block has been noted in adults and older children. Recently, persistent bradycardia and lethargy has been reported in a preterm infant with toxic levels (60 μg per ml) of dilantin.37

Calcium Salts

The majority of premature infants routinely receive parenteral calcium infusion to prevent early onset hypocalcemia. A rapid bolus administration of calcium gluconate is associated with severe bradycardia and extravasation of calcium containing fluids cause necrosis and calcification of soft tissues. Recently, calcification of the brain has been reported at autopsy in severely stressed newborns following parenteral calcium therapy.7

Calcium glubionate (Neo-calglucon)† administered orally, has a high osmolality and is associated with the risk of necrotizing enterocolitis.11

Sodium Bicarbonate:

This commonly used drug has an osmolality of 1555 mOsm per kg of water in the concentration of one mEq per ml. Liberal use of this drug has been associated with intraventricular hemorrhage in low birth weight infants.12

Vitamin E

Low birth weight infants frequently receive vitamin E for the treatment of vitamin E deficient hemolytic anemia, and to reduce the incidence of the serious sequelae of retinopathy of prematurity. Increased incidence of sepsis and necrotizing enterocolitis has been reported in low birth weight infants receiving large oral doses of Aquasol E,‡ the currently available oral preparation.14 Aquasol E is hyperosmolar (15 IU per 0.3 ml, 3990 mOsm per kg H2O), and the hyperosmolality is related in large part to the propylene glycol contained in the preparation. Consideration should be given to the use of a parenteral form of vitamin E in the first few days of life, until oral administration may be safely instituted.

A recently available intravenous vitamin E preparation (E-Ferol aqueous solution)§ containing 25 mg per ml vitamin E, has been associated with an unusual syndrome of hepatomegaly, splenomegaly, cholestatic jaundice, azotemia, thrombocytopenia, and fatalities in over half the infants less than 1500 grams receiving this preparation. The reported outbreaks from the two hospitals ceased shortly after discontinuation of E-Ferol.6

---

* Parke Davis, Morris Plains, NJ 07950.
† Dorsey Pharmaceuticals, Lincoln, NE 68501.
‡ Armour Pharmaceutical, Tarrytown, NY 10591.
§ O’Neal, Jones & Feldman, St. Louis, MO.
Additives and Preservatives in Parenteral Preparations

Benzyl Alcohol

Benzyl alcohol, used as a preservative in a wide variety of parenteral medications and fluids, has been associated with a syndrome of severe metabolic acidosis, encephalopathy, respiratory depression with gasping, leading to death in several infants receiving large volumes of fluids containing 0.9 percent benzyl alcohol. Metabolically, benzyl alcohol is oxidized to benzoic acid, conjugated with glycine in the liver and excreted as hippuric acid. This metabolic pathway may not be functional in premature infants, leading to accumulation of benzoic acid with resulting metabolic acidosis and toxicity. It has been recommended that flush solution containing 0.9 percent benzyl alcohol not be used in infants and parenteral medications be reviewed for the quantity of benzyl alcohol contained. Infants who died of this suspected iatrogenic syndrome received 99 to 234 μg per kg per day. Since the minimum toxic level is still unknown, awareness of this potential problem in infants receiving multiple drugs containing benzyl alcohol is essential.

Propylene Glycol

Although thought to have low toxicity and used in many drug preparations, propylene glycol has been associated with central nervous system depression and is one-third as intoxicating as ethanol. As propylene glycol is metabolized to lactate, metabolic acidosis may occur in susceptible individuals. Iatrogenic hyperosmolality has been noted in very small infants receiving medications containing propylene glycol.

Oral Medications

The majority of oral drug preparations used in intensive care units have osmolalities in excess of 1000 mOsm per kg of water, and often several-fold greater than parenteral preparations when corrected for the same concentrations, such as multivitamins, vitamin E, theophylline, calcium gluconate, furosemide, and phenobarbital. The high osmolalities found in some preparations are not due to drugs themselves but secondary agents such as propylene glycol, ethanol, sorbitol, and other pharmaceutical additives. Necrotizing enterocolitis has been associated with hyperosmolar feedings. The fact that several hyperosmolar medications, such as vitamin E, theophylline, multivitamins, are given together with formula fluids may be responsible for necrotizing enterocolitis frequently seen in low birth weight infants.

Medication Bezoars

Bezoar formations in the stomach, small intestine, and colon have been associated with cholestyramine, polystyrene (Kayexalate)* and Amphojel.† Bezoar formation and fecal impaction occurs when intestinal motility is reduced, as seen in premature infants. Medication bezoars are often asymptomatic although intestinal obstruction or hemorrhage may occur. Presence of bezoar should be suspected if large "fecal" masses are noted in radiographs of the small bowel or colon in low birth weight infants receiving these medications.

Topical Agents

Mydriatics

Ophthalmologic examination of low birth weight infants is a routine procedure in intensive care units. Phenylephrine 10 percent ophthalmic solution has

---

* Breon Labs, New York.
† Wyeth Labs, Philadelphia, PA 19101.
caused adverse reactions in adults and children with blood pressure elevation, and blanching of the skin, particularly the lower eyelid. Currently, medications used most frequently for dilating the pupils are phenylephrine, 2.5 percent solution, and Mydriacyl 0.5 to one percent solution. The known metabolic pathways for phenylephrine inactivation include hepatic conjugation and monoamine oxidase and tyrosinase degradation. These pathways are not yet mature in early infancy, leading to prolonged blood levels.

In a study evaluating the systemic effect of mydriatic eye drops, phenylephrine 2.5 percent solution and Mydriacyl 0.5 percent solution, although achieving the maximum mydriasis, was noted to consistently increase mean blood pressure by 20 percent and by 50 percent in one fourth of the group. The combination of eyedrops of one percent phenylephrine and 0.2 percent cyclopentolate has been suggested as the agent of choice for mydriasis in low birth weight infants.²²

POVIDONE IODINE

Perinatal iodine exposure causes transient hypothyroidism in a significant number of newborns. Although hypothyroidism is transient and lasts less than two weeks, careful monitoring of these infants and followup of thyroid function is necessary.²²

ISOPROPYL ALCOHOL

Isopropyl alcohol is a commonly used disinfectant. Alcohol pledgets have occasionally been used as substitutes for conducting electrode paste beneath limb electrodes. Second and third degree burns with fatal outcomes have been reported in premature infants.³¹ As keratinization of the skin is incomplete until 25 weeks, isopropyl alcohol should be used with extreme caution in very low birth weight infants.

Summary

Adverse drug reactions can be prevented or reduced by increasing the awareness of the problem in neonates, especially premature infants, cautious use of drugs, with avoidance of therapeutic agents whose pharmacologic data is inadequately known, monitoring of therapeutic drug concentrations where feasible, and the institution of a unit-dose system of drug dispensing to reduce medication errors.

References

11. Ernst, J. A., Williams, J. M., Glick, M. R.,


