Therapy of neonatal seizures

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DIAGNOSIS AND TREATMENT OF UNDERLYING CAUSES

LIKE all therapies, the treatment of neonatal seizures is dependent on proper diagnosis. Thus, it is essential to determine if the seizures are of metabolic, toxic, or structural origin, since treatment of each of these disorders is quite different. Diagnosis of the etiology of neonatal seizures begins with a proper history (*Figure 1*).

Frequently the infant's mother is remote from the neonatal intensive care unit; and if the child is outborn, family members are not easily accessible. Hence, there is frequently a delay in obtaining a family history, and details regarding the labor and delivery period are often missing. It is important to obtain a maternal drug history, details suggestive of infections during pregnancy as well as those surrounding the labor and delivery process, and a family history of neonatal seizures or deaths. Although hypoxic ischemic encephalopathy is currently regarded as the most common cause of neonatal seizures, without a proper history many entities masquerading as perinatal asphyxia are missed.

A physical examination frequently furnishes clues to the etiology of the seizure state. Blood pressure should not be overlooked, as hypertensive encephalopathy may cause seizures in neonates.[1] Treatment of this disorder employs agents to control blood pressure rather than standard anticonvulsive drugs. Skin lesions are a clue to both infection and neurocutaneous syndromes. Visualization of the retina is frequently difficult with a standard ophthalmoscope, but indirect funduscopy should be performed by a qualified professional, since retinal hemorrhages are indicative of trauma and chorioretinitis suggestive of infection. Examination of the scalp for needle marks may reveal a clue to inadvertent local anesthetic toxicity during labor and delivery. A tense, bulging fontanelle is indicative of intracranial hemorrhage, but it may also be seen in hyperammonemic disorders. The child's mental status is a clue to the etiology of seizures, being preserved in the interictal

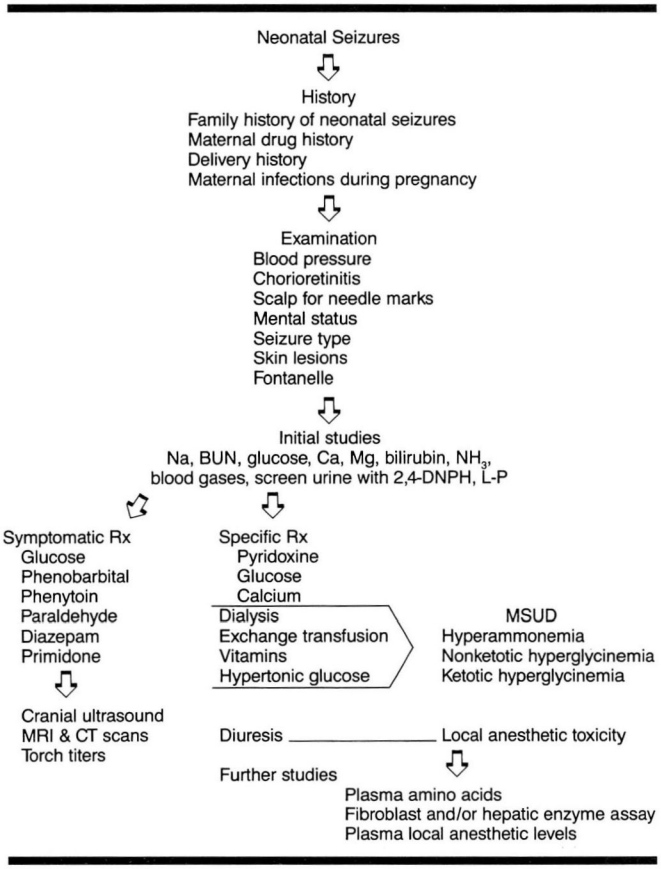

FIGURE 1. Flow diagram of an approach to neonatal seizures.

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state of hypocalcemic seizures but significantly impaired in structural and other metabolic disorders.

Appropriate laboratory investigations of neonates with seizures are imperative. Every infant with neonatal seizures should have a cerebrospinal fluid examination, determinations of serum sodium, BUN, glucose, calcium, magnesium, bilirubin, and blood gases, and a urine 2,4-dinitrophenylhydrazine screen.

Of the metabolic abnormalities causing neonatal seizures, the two most common are hypoglycemia and hypocalcemia. On the basis of statistical considerations, a preterm infant with a whole blood glucose level below 20 mg/dL or a term infant with a whole blood glucose level below 30 mg/dL is regarded as hypoglycemic. After 72 hours of age, the blood glucose level should be above 40 mg/dL in all neonates. When hypoglycemia is present, treatment consists of a slow infusion of 10% dextrose, 2 mg/kg intravenously (IV) followed by 6 to 10 mg/kg/minute (i.e., 80 mg/kg/24 hours) of 10% dextrose. In certain hypoglycemic states, steroids or more hypertonic glucose solutions may be required. Infants with low birth weight for gestational age are at particular risk for symptomatic hypoglycemia. It is important to realize, however, that hypoglycemia may also occur in conjunction with asphyxia, maple syrup urine disease (MSUD), methylmalonic and proprionic acidemia as well as disorders of lactate metabolism.

Hypocalcemia is most likely to be present when serum calcium levels are below 8 mg/dL in the term infant or below 7.5 mg/dL in the preterm infant. If hypocalcemia is found, a serum magnesium level should be obtained since hypocalcemia accompanying hypomagnesemia will respond only if hypomagnesemia is treated. Therapy consists of a slow IV infusion of 200 mg/kg of calcium gluconate. Hypomagnesemia is corrected by the administration of 0.2 mL/kg of 50% magnesium sulfate intramuscularly. Hypocalcemia is seen in low birthweight infants, infants of hyperparathyroid mothers, infants of diabetic mothers, and those with the DiGeorge syndrome. In these circumstances, hypocalcemia tends to occur in the first three days following birth. Hypocalcemia related to high phosphate feedings, immature renal and parathyroid function and maternal vitamin D deficiency is uncommon but occurs between the fourth and seventh days of life. Infants with convulsions due to hypocalcemia are usually alert between seizures, which are most often multifocal and migratory. Hypocalcemia, like hypoglycemia, frequently occurs in association with asphyxia and/or hemorrhage. Nonspecific responses to IV calcium infusions do not exclude consideration of such primary causes.

A major toxic cause of neonatal seizures is the inadvertent administration of local anesthetic to the infant during the administration of saddle, paracervical, or pudendal blocks during the labor and delivery process.[2] These infants are meconium-stained, flaccid and apneic. Brain stem abnormalities and cardiac arrhythmias are frequently present, and the determination of local anesthetic levels confirms the diagnosis. As these procaine derivatives are rapidly metabolized, plasma levels must be measured shortly after birth. Neonates with this condition are frequently thought to have intrapartum asphyxia. Treatment of local anesthetic toxicity consists of diuresis and acidification of the urine.[2] The seizures ar self-limited; their time of occurrence correlates best with the time of highest local anesthetic levels. Conventional anticonvulsants are of limited benefit.

Drug-withdrawal seizures occasionally occur in the neonatal period; hypnotics and analgesics are the primary offenders.[3] Although most physicians think in terms of "street" drugs (heroin and methadone) when drug-withdrawal symptomatology is noted in the neonate, the use of shorter-acting barbiturates such as secobarbital during the last trimester of pregnancy should be considered. The incidence of withdrawal seizures is approximately 1.4% in the case of heroin and 7.8% following methadone.[4] It is important to realize that in infants of an addicted mother, the time of occurrence of neonatal seizures varies from three to 34 days and may occur even after the child has left the nursery.

Pyridoxine-dependency seizures characteristically appear shortly after or at birth. These infants closely resemble neonates with perinatal asphyxia. Meconium staining and flaccidity are frequent.[5] Pyridoxine is an essential cofactor in the synthesis of glutamic acid decarboxylase, which is an essential enzyme in the synthesis of gamma-aminobutyric acid. The diagnosis of pyridoxine-dependency seizures is confirmed when 100 mg of pyridoxine is given IV with electroencephalographic (EEG) monitoring. The seizures are characteristically generalized and clonic, and respond within minutes to pyridoxine administration. The EEG may take hours to normalize. Pyridoxine therapy is necessary for life.

Infants with MSUD characteristically have prominent vomiting, generalized clonic convulsions, and hypertonia. Abnormalities of gaze have also been noted with this disorder.[6] MSUD is due to the inability to

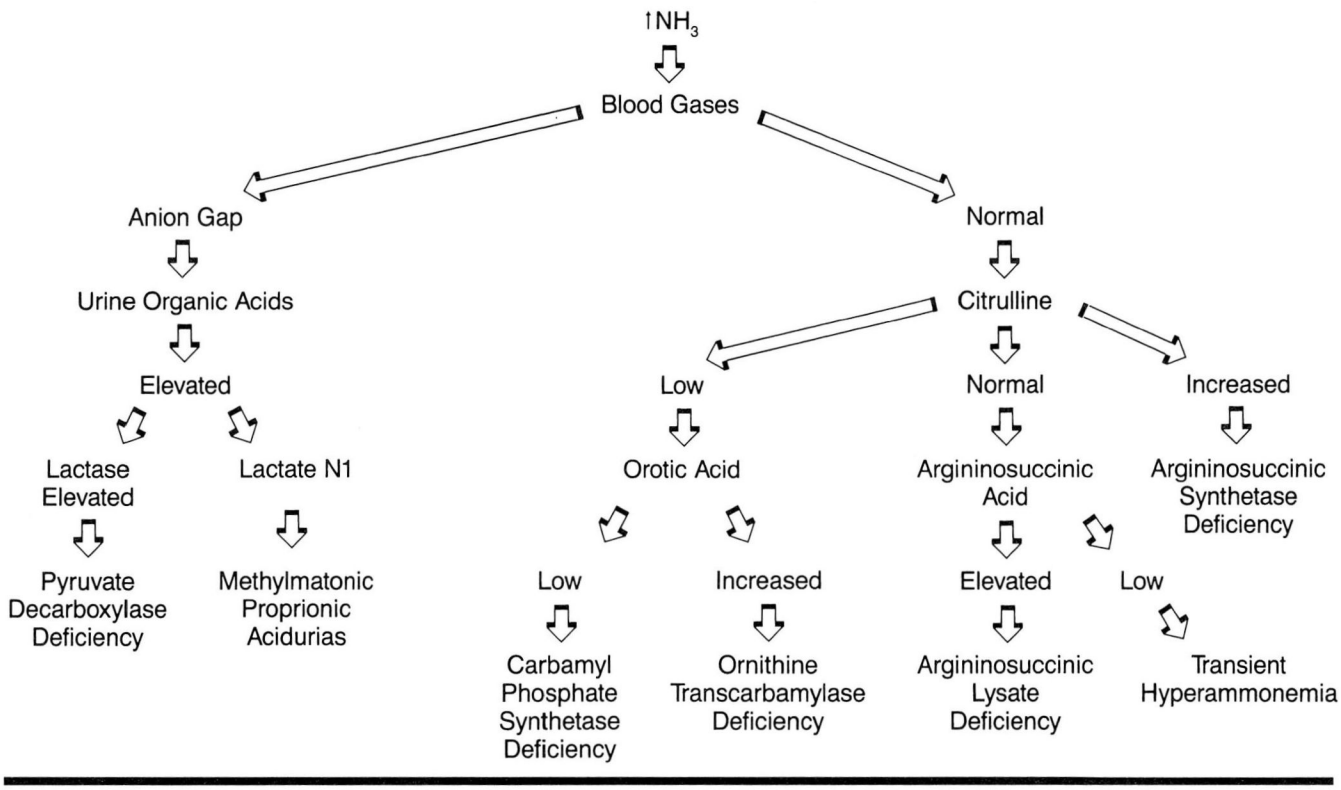

FIGURE 2. Flow diagram of an approach to hyperammonemia.

decarboxylate leucine, isoleucine and valine. The circulating keto derivatives of these amino acids cause a severe metabolic acidosis and also impart the odor of maple syrup to the urine. A rapid screen for MSUD consists of briefly boiling urine to remove nonspecific ketones and then mixing it with an equal volume of 2,4-dinitrophenylhydrazine. In the presence of keto derivatives, a fluffy yellow precipitate forms. Plasma amino acid chromatography and absence of the decarboxylase enzymes in cultured fibroblasts confirm the diagnosis. The goals of treatment are to lower plasma leucine levels and correct the accompanying hypoglycemia. Peritoneal dialysis and exchange transfusion as well as the IV infusion of hypertonic glucose may be required acutely.[7] Since a response to thiamine in MSUD has been recognized, all infants should receive vitamin B-1 administered at a dosage of 10 mg/day. Subsequent therapy consists of a diet deficient in long-chain amino acids and a high caloric intake of approximately 150 calories/kg/day.

Urea cycle abnormalities may manifest shortly after birth, with vomiting, generalized clonic seizures, lethargy progressing to coma, hypotonia and tense, bulging anterior fontanelles.[8] Hyperammonemia is common to all the urea cycle enzyme deficiencies and transient hyperammonemia of the newborn (*Figure 2*) but is also encountered in the methylmalonic and proprionic acidemias.

If the blood ammonia level is elevated in association with an anion gap and metabolic acidosis, methylmalonic or proprionic acidemia should be suspected. In the event that an anion gap is not present, plasma amino acid levels should be determined rapidly. If citrulline is absent or severely reduced and the urinary orotic acid level is high, ornithine transcarbamoylase deficiency is the most likely diagnosis. If the urinary orotate level is low, the diagnosis of carbamoylphosphate synthetase deficiency should be considered. If the argininosuccinic acid level is elevated, argininosuccinic aciduria is suggested, particularly if normal transient hyperammonemia of the newborn is likely. The acute treatment consists of peritoneal dialysis, which has been found superior to exchange transfusion, arginine supplementation to maintain functioning segments of the urea cycle, and sodium benzoate to decrease blood ammonia by increasing nitrogen re-

moval through hippurate synthesis. During the acute phase of treatment, protein is withheld, and hypertonic glucose infusions are utilized.[9]

Nonketotic hyperglycemia is due to lack of a glycine cleavage enzyme, so that glycine is not metabolized to carbon dioxide ammonia and a 1-carbon-tetrahydrofolate fragment. The defect has been demonstrated in liver fibroblasts and brain tissue. These infants characteristically present with refractory, stimulus-sensitive seizures, and are deeply comatose between spells.[10] Glycine levels of plasma and cerebrospinal fluid are markedly elevated. A successful therapy for this disorder is not currently available, and most neonates succumb within days to months after diagnosis.

The so-called ketotic hyperglycinemias, proprionic or methylmalonic acidemia, may occur in the neonatal period with vomiting, dehydration, coma, acidosis and seizures. Hyperammonemia, ketosis with an anion gap, ketone bodies in the urine and thrombocytopenia suggest this diagnosis. The finding of elevated levels of the appropriate short-chain organic acid in the urine confirms the diagnosis. Treatment consists of correction of the acidosis with sodium bicarbonate, limitation of protein, and the administration of biotin for proprionic acidemia and vitamin B-12 for methylmalonic acidemia.

Isovaleric acidemia is a very rare disorder and is due to the inability to decarboxylate the amino acid isovaline. These infants manifest with seizures, vomiting, acidosis, ketosis, and an offensive body odor.

Of the neurocutaneous syndromes, incontinentia pigmenti and tuberous sclerosis have caused neonatal seizures. Incontinentia pigmenti is characterized by a vesicular crusting rash similar to herpes simplex. The rash heals leaving a filmy pigmented cutaneous lesion because melanocytes are incontinent of pigment. Two neonates with symptomatic subependymal giant cell astrocytomas have been described, one of whom had refractory seizures.[11] Unusual patches of hair pigmentation were observed in the infant with refractory seizures.

Neonatal adrenoleukodystrophy is an autosomal recessive disorder affecting both males and females, characterized by hypotonia and refractory neonatal seizures.[12] Seizures are of the generalized clonic and myoclonic varieties. Neonates with adrenoleukodystrophy are deficient in oxidizing long-chain fatty acids, with resultant accumulation of long-chain fatty acids in plasma and cultured fibroblasts.

Several families have been described with generalized and focal clonic seizures occurring during the first two weeks of life. The peak time of onset is the fifth day, and seizures cease within 15 days. These infants appear to be refractory to anticonvulsant therapy, but their general outlook is good.[13]

Perinatal hypoxic ischemic central nervous system (CNS) injury is currently regarded as the single most common cause of neonatal seizures and is noted in 8% to 22% of infants with low Apgar scores. A study of 131 neonates at Magee Women's Hospital noted that this combination of entities accounted for 58% of neonates with seizures.[14] Volpe estimated that 60% to 65% of his series was composed of neonates with hypoxic ischemic CNS insults.[15] Seizures are more likely to occur in infants with a marked delay in the onset of respiration.[16] Seizures due to asphyxia and/or hemorrhage are usually a mixture of generalized clonic and subtle seizure activity. These seizures are usually most severe for approximately 72 hours after onset and subside irrespective of therapy.

It is important to remember that pyridoxine-dependency seizures, local anesthetic toxicity, and occasionally metabolic abnormalities may trigger seizures that closely mimic postasphyctic seizures. Hyponatremia, hypoglycemia, and hypocalcemia are all known to complicate asphyxia. Asphyctic cardiac involvement may also compromise cerebral blood flow.

Seizures occurring secondary to hypoxic ischemic encephalopathy, trauma, and neonatal stroke are treated with conventional anticonvulsants. The intelligent selection of anticonvulsant agents is limited, however, by our current understanding of neonatal seizures. As documented by the work of Mizrahi and Kellaway[17] and Scher,[18] it has become evident that a significant number of abnormal movements in neonates, previously thought to be seizures, do not have an accompanying cortical electric discharge. It is clear that tonic seizures described in many infants with perinatal asphyxia and intracranial hemorrhage are not truly seizure activity but release of brain stem reflexes due to forebrain destruction. Previous classifications which have relied entirely upon clinical descriptions have been called into question. A significant percentage of what has been previously regarded as subtle seizure activity may in fact be abnormal neonatal movements of nonictal origin. Generalized or focal clonic activity with eye deviation appears to have the best correlation with concomitant EEG seizure patterns. In addition, it is evident that a significant number of infants have electrical seizure discharges which are unaccompanied by clinical movements because of concomitant use of paralyzation[19] to facilitate

pulmonary ventilation, and because neonates do not appear to generate accompanying clinical activity consistently and predictably.

The choice of anticonvulsants is also limited by the fact that most series reporting the efficacy of anticonvulsant agents do not define the seizure characteristics being treated, nor is EEG documentation used. Only one controlled study utilizing EEG documentation is currently in progress and that as yet has not been completed.[20] The choice of anticonvulsants in the treatment of neonatal seizures has been based on tradition rather than on the proven efficacy of one agent compared to another. The toxicity of anticonvulsants has been only casually assessed, and the time of response following administration of the anticonvulsants has not been detailed.

TREATMENT WITH ANTIEPILEPTIC MEDICATIONS

Phenobarbital is the drug most frequently chosen as the initial agent in the treatment of neonatal seizures. In order to obtain therapeutic but nontoxic levels promptly, phenobarbital should be administered IV as a loading dose. Three series are in close agreement regarding the efficacy of phenobarbital as the initial agent in the treatment of seizures in the newborn. In a study of 39 neonates utilizing doses approximating 20 mg/kg, Lockman et al[21] noted seizure control in 32%, while Van Orman and Darrvish,[22] in a study of 81 neonates who had received adequate loading doses, reported a response of 33%. In our study of 77 neonates,[23] we noted that seizures were controlled in 36% following the administration of loading doses of 15 to 20 mg/kg of phenobarbital. Gal et al[24] reported a quite different response in their population. First, almost 60% responded with plasma levels equal to those achieved in the other studies—an almost twofold difference. Second, in a group of 13 neonates with seizures due to hemorrhage, with whom phenobarbital was used as monotherapy at doses of 35 to 40 mg/kg, they noted an 85% success rate—again distinctly different from the 35% to 38% success rate reported by other investigators. There would appear to be a difference in the populations described by Gal et al,[24] and those of Lockman et al,[21] Painter et al,[23] and Van Orman and Darrvish.[22] The lack of electrical or clinical seizure definition in all of these series makes interpretation of the data difficult. The potential toxicity of phenobarbital in the neonate has been inadequately addressed. All of the series previously summarized note only lethargy and no apparent change in cardiovascular status specifically related to the drug. However, in none of these series were sequential heart rate and blood pressure recorded and reported. Svenningsen et al,[25] however, noted an invariable decrease in heart rate below 100 bpm in the presence of plasma phenobarbital concentrations of 52 mg/L. This is important as such relative bradycardia in neonates may result in significant decreases in cardiac output and compromise of cerebral blood flow. Donn et al[26] studied pharmacokinetic and cardiovascular parameters in ten severely asphyxiated term newborns given loading doses of 30 mg/kg of phenobarbital over 15 minutes. Unfortunately, the observations were only made immediately and 30 minutes after the loading dose. Although there was a trend to decreasing heart rate and increasing blood pressure, this was not statistically significant. Since the time parameters of optimal distribution of phenobarbital to the CNS in neonates are unknown, but may be as long as 60 minutes, an observation time of 30 minutes may not have been sufficient.

On the basis of experimental data in an elegant rat pup model, controlled for nutrition, Diaz et al[27] have noted that phenobarbital interferes with brain growth. The metabolism and distribution of phenobarbital in the rat are distinctly different from those in the human, and the rate of brain growth is significantly different between the species, so that the relevance of these data to the human condition is uncertain. Further studies of the effects of phenobarbital on CNS metabolism and growth in neonates is certainly justified.

The pharmacologic properties of phenobarbital favor use of this drug in the treatment of neonatal seizures. The volumes of distribution reported by Donn et al[26] of 0.97 ± 0.1 L/kg in term infants, by Painter et al[23] of 0.93 ± 0.15 L/kg in all neonates, and by Lockman et al[21] of 0.81 ± 0.12 L/kg at loading doses of 15 to 20 mg/L are remarkably similar. These volumes of distribution indicate a rather predictable plasma level achieved following the administration of loading doses. Plasma levels can be predictably maintained at 20 mg/L following oral or IV administration of 3 to 4 mg/kg/day. The neonate, however, binds phenobarbital less well than the older child or adult.[28] In 11 neonates, we found that phenobarbital binding ranged from 6% to 41% with a mean of $24.1\% \pm 8.7\%$ in 56 determinations. This is dramatically different from the $41.3\% \pm 8.4\%$ binding that we have found in older children and adults. Binding appeared to be most impaired in very sick preterm infants; in one of our 11 neonates, an unexplained cardiorespiratory arrest occurred with a

free level of 38.5 mg/L. Because of the implications concerning phenobarbital's effect on brain growth and cardiovascular stability, further observations concerning the variability of protein binding and its association with toxicity and seizure control are important. Phenobarbital appears to be distributed to the neonatal brain in roughly the same proportion as has been reported in adults. The brain plasma ratio of phenobarbital has been found to be 0.71±0.2, a figure not significantly different from that reported in adults. The tissue distribution to heart, however, is significantly greater than that to brain, highlighting the importance of observations concerning this drug's effect on cardiovascular status.

Phenytoin is the second most frequently used anticonvulsant in the treatment of neonatal seizures and in most series is used as an adjunctive agent to phenobarbital. Van Orman and Darrvish[22] noted a response rate of 2 of 7 (28%) when the drug was used initially; in this same series, 44 infants who had not responded to phenobarbital as the initial agent had a 41% response rate (18/44) following a 15 mg/kg loading dose of phenytoin. In 49 infants who had not responded to phenobarbital as an initial agent, we noted a 31% response rate to both agents in combination. Albani[29] in a study of 16 newborns (11 term and five preterm) noted an 87.5% (14/16) response rate when phenytoin was utilized as the sole agent. Time to response, however, is not clearly specified in that study.

The major toxic effect of phenytoin is the production of cardiac arrhythmias when administered IV. The drug must be given slowly at a rate not to exceed 1 mg/kg/minute. Detailed cardiovascular parameters are not reported in any of the series, and arrhythmias were not mentioned.

The metabolism of phenytoin in the neonate has been quite variable. Bourgeois and Dodson[30] reported apparent half-life of phenytoin 30 times in 16 infants, aged 2 to 36 days, and noted a range of six to 140 hours. It would appear that phenytoin given as an IV loading dose produces predictable therapeutic nontoxic plasma levels, but its metabolism thereafter is unpredictable. Albani and Wernicke[31] reported the necessity of using 9 to 29 mg/kg of phenytoin by the oral route to maintain therapeutic plasma levels, but Painter was unable to maintain effective plasma levels of phenytoin at 12 mg/kg/day orally by any preparation in nine neonates. As with phenobarbital, the neonate appears to bind phenytoin less well than older children or adults do. In 25 determinations, we noted that phenytoin binding ranged from 39% to 91% with a mean of 70.2%±14.0%. The phenytoin-bound fractions were reduced 27% compared to those in older children. This problem appears to be most acute in sick preterm infants; we have noted an exacerbation of seizures in a premature infant with a free phenytoin level of 8 mg/L and cardiac arrhythmias in three neonates with free phenytoin fractions in excess of 4 mg/L. Like that of phenobarbital, the distribution of phenytoin to brain tissue appears to be similar in neonates and in adults. The mean brain plasma ratio was found to be 1.28± 0.32. Tissue distribution of phenytoin to heart, however, has been found to be 9.1±0.1, emphasizing the importance of observations of this drug on cardiovascular parameters in neonates.

Diazepam has regained attention in the treatment of neonatal seizures. Thong and Abramson[32] reported on five infants with severe recurrent convulsions refractory to conventional anticonvulsant therapy, treated with continuous IV infusions of diazepam. The dosages of diazepam required by continuous infusion varied between 3 and 12 mg/kg/day given for 21 hours to 18 days. Pharmacokinetic parameters were not reported. Gamstorp and Seden[33] treated eight term infants with seizures from severe perinatal asphyxia for six to 11 days with continuous IV infusions of diazepam. Effective infusion rates of 0.7 to 2.75 mg/hour were noted. When the infants were seizure-free for 12 to 24 hours, the dosage was slowly tapered. Duration of therapy was three to 11 days. Seizures did not recur during infusion of the highest dosage used in each patient. Deshmukh et al[34] reported a pilot study of seven neonates with severe unresponsive seizures treated with lorazepam. Cessation of seizure activity occurred in all patients within five minutes. Two infants demonstrated recurrent seizures eight hours after a dose of 0.05 mg/kg of lorazepam, but severity and frequency were diminished. The dose was administered IV over two to five minutes. In three infants undergoing EEG monitoring, marked generalized suppression of the background activity and cessation of electrographic seizures were noted.

Hypotension, hypoventilation, and lethargy are all concerns when diazepam is administered in the treatment of neonatal seizures. Since many preparations contain sodium benzoate, there is concern regarding displacement of bilirubin from albumin binding sites. In the series reported by Gamstorp and Seden,[33] lethargy was noted but adverse cardiovascular effects or the need for assisted ventilation was not noted. Hypotension or apnea was not mentioned in the reports of Thong and Abramson[32] and Deshmukh et al.[34] Experimental studies in Gunn rats would appear to indicate

that the amount of sodium benzoate contained in the volume of diazepam utilized in the treatment of neonatal seizures is of little concern regarding bilirubin metabolism.[35] Kernicterus has not been reported as a complication of the use of diazepam, but careful consideration should be given to use of this drug in jaundiced infants since sodium benzoate is an effective uncoupler of bilirubin from albumin in vitro.[36] Effects of diazepam upon brain growth have not been well studied in the immature brain, but diazepam may impair the proliferation of cortical neurons in culture.

In the series of Gamstorp and Seden,[33] plasma concentrations of diazepam exceeded 35 μmol/L in half the population. Infusion rates of 0.3 to 0.8 mg/kg/hour produced mean concentrations above 10 μmol/L in the majority of determinations. The volume of distribution of diazepam has been reported to vary between 1.3 and 2.6 L/kg with half-lives varying between 50 and 400 hours. Experimentally, diazepam enters the brain very rapidly, but data in the human neonate are not available.

Primidone can only be administered by the oral route, and early plasma levels vary between 3 and 18 mg/L. The lowest effective plasma concentration appears to be 6 mg/L, observed in infants given 15 to 25 mg/kg as a loading dose followed by maintenance of 12 to 20 mg/kg/day.

A single study by Powell et al[37] noted the efficacy of primidone as an adjunctive agent in the treatment of 24 neonates with severe refractory repetitive convulsions. Thirteen of 24 (54%) responded to this adjunctive agent, but the response time was in terms of hours.

The toxic effects of primidone of concern in neonates are somnolence and hypotension. Its limitations include the lack of parenteral preparations and its marked effect on phenobarbital clearance, rendering it unattractive as a drug in the treatment of neonatal seizures.

Paraldehyde is frequently used as an adjunctive agent in the treatment of neonatal seizures. Koren et al,[38] in a study of 14 neonates with severe refractory seizures, noted that paraldehyde was efficacious in 50% of the population. Similarly, Giacola et al[39] reported that 56% of neonates (5/9) responded to paraldehyde as an adjunctive agent. In both of these studies, it is difficult to tell how rapidly the infants responded; but response time would appear to be in hours rather than in minutes.

The toxic effects of paraldehyde include hypotension and lipoid pneumonitis, but neither of these complications was noted in the series reported. The effects of paraldehyde on brain growth in the neonate have not been studied.

Paraldehyde given as an IV infusion of 200 mg/kg followed by 15 mg/kg/hour, or 200 mg/kg/hour for two hours, or 150 mg/kg/hour for three hours have all been utilized in the treatment of neonatal seizures. The minimal effective plasma level appears to be 100 mg/L; and peak levels of 247±11 mg/L are achieved in the neonate with apparent safety.

Paraldehyde is distributed to brain very rapidly in experimental animals, but no human data are available.

Lidocaine has been advocated for the treatment of neonatal seizures.[40] In ten infants, the majority of whom were refractory to other anticonvulsants, reported by Norell and Gamstorp,[40] lidocaine was administered IV at a dosage of 4 mg/kg/hour. Eight of ten (80%) of this population responded over a four-day period.

The toxic effects of lidocaine include seizures, arrhythmias, and hypotension. This agent appears to be an anticonvulsant at levels of 0.5 to 4 mg/L, but a convulsant at levels of 7.5 mg/L, and produces bradycardia at concentrations of 8 to 12 mg/L. The half-life of lidocaine has been reported to be 2.9 to 3.2 hours. The volume of distribution of 2.75 L/kg in neonates is higher than that reported in adults, with whom values approximate 1.11 L/kg. Lidocaine binding in neonates appears to be 20%, compared to 70% reported in adults.[39] Raddanyl-Boyvet has reported treating 24 newborns (15 premature, 8 term) with lidocaine for persistent refractory seizures. Seizures ceased within 30 minutes in 18 infants and at 18 hours in one. This agent appeared ineffective in five neonates. Seizure control was accomplished at levels that varied between 3.4 and 10.5 mg/L; no significant changes in heart rate or blood pressure were observed. The EEG was analyzed in 18 neonates before and during lidocaine infusion; it remained unchanged in seven but became markedly discontinuous in 11. Half-lives within this population varied from 30 to 116 minutes.

Experience with *valproic acid* and *carbamazepine* in treating neonatal seizures is too limited to assess.

CONCLUSIONS

An intelligent approach to the use of anticonvulsants in neonates has been limited by our ability to

diagnose neonatal seizures correctly. It is clear that the EEG as an aid to the diagnosis and treatment of neonatal seizures will become standard in the future. In addition to the limitations of diagnosis, attention has not been paid to the unique characteristics of neonatal seizures. An analysis of the efficacy of anticonvulsants in the treatment of this disorder is also limited by the lack of consistent clinical definitions of seizure activity and a paucity of randomized controlled studies. Very detailed and specific studies are needed to assess the effects of anticonvulsants on cardiac output and brain growth parameters. The majority of anticonvulsants used in the treatment of neonatal seizures are relatively predictable pharmacologically when loading doses are administered. It appears that the availability and affinity of anticonvulsant receptors are quite different in the immature brain compared to the mature brain; we have very little information concerning the ontogeny of these receptors.

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