Current Options in the Management of Apnea of Prematurity

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Summary: Apnea of prematurity (AOP) is a common problem that affects premature infants and, to a lesser degree, term infants. Apnea of prematurity appears to be due to immaturity of the infant's neurologic and respiratory systems. Apnea of prematurity is a diagnosis of exclusion that can be made only when other possible infectious, cardiologic, physiologic, and metabolic causes of apnea have been ruled out. The fundamental principles for managing apnea of prematurity include monitoring the infant closely while instituting supportive care measures such as tactile stimulation, continuous positive airway pressure, or mechanical ventilation. When necessary, pharmacologic therapy may be used to stimulate breathing. The first-line agents of choice for the management of AOP are the methylxanthines. And, for second-line therapy, a switch to a different class of agent, such as the respiratory stimulant doxapram, is an option. Of the methylxanthines, theophylline is the most extensively used. However, a review of the literature suggests that caffeine citrate may be the agent of choice for AOP. Comparative clinical studies have demonstrated that caffeine is at least as effective as theophylline, has a longer half-life, is associated with fewer adverse events, and, in addition, has a greater ease of administration. Caffeine stimulates the respiratory and central nervous systems more effectively and penetrates into the cerebrospinal fluid more readily than theophylline. In addition, because of stable plasma levels, caffeine has a wide therapeutic margin and few side effects. In contrast, theophylline plasma levels may fluctuate widely, which necessitates frequent monitoring and has a higher incidence of adverse events than caffeine. Before the FDA approval of caffeine citrate (Cafcit®) for administration either intravenously and/or orally, caffeine preparations were "homemade." A few studies suggest that use of pharmacotherapy to treat AOP is not generally associated with long-term sequelae, although more data are needed before this can be definitively concluded. *Clin Pediatr.* 2000;39:327-336

Introduction

Apnea is the most important disorder in the control of breathing in the neonate and is one of the most common problems in the neonatal intensive care unit.[1] Apnea of prematurity (AOP) is defined as the cessation of breathing for periods from 10 to 20 seconds, with

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or without bradycardia or cyanosis.[2,3] The term generally applies to infants of less than 37 weeks' gestation who develop apnea without an identifiable cause. Episodes of AOP may begin within 1 day after birth but are most common in infants who are between 5 and 10 days old.[4] The incidence is inversely correlated with gestational age and weight. Approximately 25% of premature infants who weigh less than 2,500 g experience at least one apneic episode during the first 10 days of life; for those under 1,000 g at birth, the incidence approaches 90%.[5]

The fundamental principles for managing AOP have remained constant over the last 25 years. The infant must be monitored closely while continuous positive airway pressure, tactile stimulation, mechanical ventilation, supplemental oxygen, avoidance of flexion of the neck, and other supportive measures are provided. Frequently, methylxanthine therapy with theophylline or caffeine is instituted to stimulate breathing. In light of some studies,[6-8] however, there has been increased interest in the use of caffeine citrate. These studies recommend the use of caffeine because it was found to be as efficient as theophylline and easier to administer, plasma concentrations with caffeine are more predictable, and caffeine offers a wider therapeutic range than theophylline.

The advent of a ready-to-use, premixed formulation of caffeine citrate may prompt reevaluation of the choice of theophylline for treatment of AOP. This article briefly discusses current theories about the pathophysiology of AOP and then reviews clinical studies concerning pharmacologic management.

Definition

By definition, apnea is a clinical syndrome that may be attributable to a variety of underlying disorders.[9] Factors contributing to apnea include prematurity, gastroesophageal reflux, sepsis, metabolic errors, poor thermoregulation, seizures, and electrolyte and anatomic abnormalities.

Apnea of prematurity may be attributable to immaturity of the respiratory and central nervous systems and generally resolves by the time the infant reaches a postconceptual age of 36 to 38 weeks, although occasionally it may persist for several weeks longer.[3] Inappropriate or delayed treatment of AOP may cause considerable morbidity and possible mortality; repeated episodes may result in irreversible neurologic damage (e.g., blindness from bilateral retrolental fibroplasia, sensorineural deafness, spastic diplegia or quadriplegia, retardation, or death).[10] However, it is unclear whether the severe sequelae associated with repeated apneic episodes relate to apnea alone or hypoxic ischemic injury, given that hypoxia acts as a respiratory depressant, rather than respiratory stimulant, in preterm infants and neonates.[4,11]

Pathophysiology

Apnea in the infant may be classified as one of three types: central apnea is a complete cessation of breathing; obstructive apnea refers to an absence of nasal airflow despite respiratory efforts; and mixed apnea, the most common type of apnea observed in premature infants, refers to a central respiratory pause that either preceeds or is followed by airway obstruction.[3,4,11,12] Apnea may also be classified as AOP, apnea of infancy, or obstructive sleep apnea. In premature infants, apnea is usually of mixed origin with about 65% central and 35% obstructive episodes. However, AOP does not predict the later occurrence of sudden infant death syndrome (SIDS) or apnea of infancy.[3,4]

The mechanisms by which mixed and obstructive apnea occur may be initiated by a sleep-related decrease of pharyngeal airway dilation.[12] Subsequent breathing efforts may cause the pharyngeal airway to collapse, resulting in reflex swallowing manuevers and/or reflex central apnea and culminating in a blunted chemoreceptor response to hypoxia.[11,12] Control of breathing is more disorganized during rapid eye movement (REM) sleep, which is the predominant mode of sleep in premature infants.

Hypopharyngeal function is very important in the maintenance of upper airway patency in infants. Pharyngeal collapse is the chief cause of obstructive apnea, and when hypopharyngeal tone is poor, airway collapse occurs at very low pressures. Integration of pharyngeal muscle function is reduced during sleep, resulting in collapse and subsequent apnea in susceptible infants. Postural changes, such as flexion of the neck, may further exacerbate apnea owing to compromise of the airway.

Although the pathogenesis of AOP has not been fully elucidated, it is probably related to both the overall neurologic and cardiorespiratory immaturity of the infant whereby the central respiratory center appears to have an altered response to hypoxemia and hypercapnia. Normally, the response to a decrease in partial pressure of oxygen (P_{O_2}) or an increase in partial pressure of car-

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bon dioxide (P_{CO_2}) is an increase in minute ventilation. However, premature infants respond to decreased P_{O_2} by a transient increase in minute ventilation and then a return to baseline or below baseline ventilation.[13] Infants respond to elevated P_{CO_2} levels by diminished, rather than increased, inspiratory effort. The preterm infant's blunted response to hypoxia further depresses the respiratory center's sensitivity to elevated levels of carbon dioxide (CO_2).[3,11] The unstable response to low inspired oxygen may also play a role in the pathogenesis of apnea.[14]

In addition, neurologic stimulation of the primary muscles of respiration, the diaphragm and the intercostals, may be inadequate.[4] Poor compliance of the chest wall in premature infants may fail to maintain an adequate resting lung volume, and in addition, chest wall stability may be reduced in REM sleep. A contributing factor may be abnormality of the brain stem.[9] One hypothesis is that the preterm infant's breathing may be depressed by the release of adenosine, a metabolite of adenosine triphosphate, that has neuroregulatory effects including inhibition of respiration.[15]

Diagnosis of AOP

Most cases of apnea are usually promptly detected in infants at highest risk. Routine monitoring for apnea in infants at risk includes heart and respiratory rates as well as oxygen saturation.

Once monitoring has detected pauses in breathing of at least 10 seconds in duration, a pneumogram may be obtained to determine the frequency and severity of the respiratory pauses, and a polysomnogram may be used to measure cardiorespiratory patterns, muscular activity, end-tidal carbon dioxide levels, transcutaneous oxygen levels, oral or nasal airflow, and chest wall and abdominal movements.[9] However, these are not usually obtained routinely in clinical practice.

Once apnea has been diagnosed, the clinician must investigate a variety of possible causes while continuing to monitor and provide supportive therapy. The causes of apnea in preterm infants are indicated in Table 1. Appropriate laboratory tests include complete blood count, differential cell count, and urinalysis. Other tests that may be undertaken, depending on the individual circumstances, include electrocardiogram, electroencephalogram, chest radiograph, and analysis of spinal fluid for protein, glucose, and bacteria. Infants should also be evaluated for stability of the thermal environment, resting oxygenation, and relationship to feeding.

Physical examination should include observation of the infant's breathing pattern, in sleep and while awake, and careful cardiac, neurologic, and respiratory examinations. The physician should look for an accumulation of fluid or solid material in the oropharynx, which may have resulted in a reflex-mediated closure of the glottis. Absence of this reflex may result in occlusion of the airway by the foreign material. Alternatively, hyperactivity of this reflex may mean that the glottis has remained closed after removal of the obstruction. Any of these physical obstructions may precipitate central apnea, since, as described earlier, hypoxia may depress central respiratory activity.[4]

Table 1

COMMON CAUSES OF APNEA IN PRETERM INFANTS

- Airway obstruction
- Impaired oxygenation
- Temperature instability
  - Hyperthermia
  - Hypothermia
- Infection
- Neurologic disorders
- Metabolic disorders
- Abdominal disorders
- Congenital heart disease
- Arrhythmia
- Maternal drugs
- Congenital anomalies of the central nervous system
- Prostaglandin E infusion

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Only after a thorough investigation has failed to reveal a specific cause can the diagnosis of AOP be made and appropriate pharmacotherapy instituted. It is particularly important to rule out systemic conditions (e.g., sepsis), seizure disorders, and gastroesophageal reflux before administering methylxanthine therapy (theophylline or caffeine), for these agents are known to lower the seizure threshold and decrease the muscle tone of the esophageal sphincter.[16]

Treatment of AOP

Treatment of AOP should be as noninvasive as possible and typically employs both nonpharmacologic and pharmacologic measures.

Physiological Stimuli

Supportive therapy may involve placing the infant with the head in the midline and the neck in the neutral position or slightly extended to minimize upper airway obstruction. Lowering the environmental temperature slightly to lower the skin temperature (e.g., from 36.5°C to 36.2°C) may reduce the frequency of apnea in some infants but is not commonly practiced. Other nonpharmacologic measures may include tactile stimulation, an oscillating waterbed, continuous positive airway pressure, and mechanical ventilation.[3,17]

Pharmacologic Therapy

There appears to be no consensus as to when treatment is necessary. If apneic spells continue despite supportive measures, pharmacologic intervention may become necessary. Because of their respirogenic effects, methylxanthines (e.g., theophylline and caffeine citrate) are considered the primary pharmacologic treatment options for apnea.[18]

Although the mechanism of action for the methylxanthines on the control of breathing has not been conclusively established, they have been shown to increase respiratory center output, leading to increased ventilation and the transmission of neural impulses; reduce REM sleep; improve skeletal muscle contraction, metabolic homeostasis, and oxygenation secondary to increased cardiac output; increase ventilation; and decrease hypoxic episodes.[2,9,19]

The specific effects appear to vary to some degree between theophylline and caffeine (Table 2). Caffeine is considered to be more effective in stimulating the central nervous and respiratory systems and appears to penetrate the cerebrospinal fluid more readily than theophylline.[2,9] Theophylline is considered a more potent cardiac stimulator and has greater efficacy as a diuretic and bronchodilator but is associated with a higher incidence of tachycardia. The bronchodilatory action of theophylline does not appear to play a significant therapeutic role in AOP, however, because the disorder is caused by a lack of driving force of respiration rather than by increased airway resistance.[9]

Theophylline. Since 1973, when theophylline was first used to treat AOP, clinical studies have repeatedly demonstrated its effectiveness, even in oxygen-dependent infants of less than 31 weeks' gestational age.[7,8,20] When administered to the premature infant, theophylline, through a central stimulating effect, has been shown to increase ventilation, increase ventilatory response to CO_2, improve blood gases, and decrease the frequency of apneic episodes.[2] A concurrent rise of 20% in metabolic rate may be seen.[21] Other postulated mechanisms of xanthine action on the respiratory system include effects on phosphodiesterase, adenosine, and calcium flux, and, at

Table 2

COMPARATIVE PHARMACOLOGIC ACTIVITY OF CAFFEINE AND THEOPHYLLINE

Action	Caffeine	Theophylline
CNS and respiratory stimulation	+++	++
Cardiac stimulation	+	+++
Smooth muscle relaxation	+	+++
Skeletal muscle stimulation	+++	++
Diuresis	+	+++

+++ = most active.

Adapted with permission of the publisher from Aranda JV, Cook CE, Gorman W, et al. Pharmacokinetic profile of caffeine in the premature newborn infant with apnea. *J Pediatr.* 1979;94:663-668.

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least in adults, diaphragm activity. Both caffeine and theophylline are believed to stimulate diaphragmatic contractility and prevent diphragmatic fatigue.[17,22]

The mean half-life of theophylline is approximately 30 hours in infants, which is five to six times longer than in adults.[2] Theophylline undergoes a methylation reaction to produce caffeine, and during theophylline therapy, plasma concentrations of caffeine may approach 50% of the theophylline concentration in the preterm infant.[23] Because caffeine is eliminated slowly in this age group, it can accumulate in substantial quantities.[9]

Oral theophylline or intravenous aminophylline is given with a loading dose of 5 mg/kg followed by a maintenance dose of 1–2 mg/kg every 8 hours.[3] Generally, a plasma concentration of at least 5 mg/L is necessary to produce therapeutic effects, although benefits have sometimes been reported at lower levels.[9] A target plasma concentration of 10 mg/L is generally accepted.[2] Plasma concentrations of theophylline may vary widely at the same dosage levels, which necessitates frequent monitoring and dose adjustments.[7]

Toxicity, which may occur at plasma concentrations above 13 mg/L, generally affects the central nervous system and cardiovascular system. Side effects include tachycardia, jitteriness, irritability, vomiting, abdominal distension and feeding intolerance, seizures, hyperglycemia, and electrolyte imbalances.[3] Although theophylline toxicity may occur at concentrations about 13 mg/L, significant side effects such as seizure occur at much higher levels.

Because theophylline has a narrow therapeutic window, close monitoring of plasma levels is essential.

Caffeine. The efficacy of caffeine in the treatment of AOP has been demonstrated in several studies.[2,18,22,24] Caffeine has been found to decrease the number of apneic spells, P_{CO_2}, and hydrogen ion concentration, as well as the need for and duration of mechanical ventilation in premature infants with apnea. It also increases minute ventilation by increasing central inspiratory drive without altering respiratory timing.[25] Evidence suggests that caffeine is a more potent centrally acting respiratory agent with fewer side effects than theophylline.[22,23] Caffeine penetrates into the cerebrospinal fluid more readily than theophylline, possibly because of its higher lipophilicity,[9] and can be effective in infants who are refractory to standard theophylline treatment.[22]

Caffeine is rapidly absorbed in preterm infants, with plasma concentrations reaching 6 to 10 mg/L within 30 minutes to 2 hours after administration of an oral dose of 10 mg/kg.[25] Compared with theophylline, clinical studies have shown that plasma concentrations of caffeine do not usually fluctuate widely.[7]

Caffeine citrate can be administered either orally or intraveneously. The recommended loading dose of 10 mg/kg of caffeine (equivalent to 20 mg per kg of caffeine citrate) followed 24 to 48 hours later by a single daily maintenance dose of 2.5 mg/kg caffeine (5 mg per kg of caffeine citrate). This dose regimen will achieve plasma concentrations of caffeine of 8 to 14 mg per liter after the loading dose and 7 to 20 mg per liter during the maintenance dose. These recent premixed, standardized, commercially available IV and PO preparations make caffeine citrate an attractive alternative treatment for AOP. Because of the narrow fluctuations in plasma concentrations of caffeine owing to its very long half-life (102.9 hours), it may be necessary to monitor plasma concentrations once or twice a week. Note that caffeine sodium benzoate should not be given to neonates with hyperbilirubinemia, since benzoate can interact competitively with bilirubin at the albumin-binding site.[1,2] Because of the longer half-life, a longer duration of observation may be required after discontinuation of caffeine therapy to assure that the infant will not manifest apnea once the drug concentrations have reached subtherapeutic levels. Since elimination of caffeine is affected by postnatal age, it may be prudent to observe infants for 7 to 10 days after discontinuation of therapy.

Caffeine toxicity is rarely observed at plasma serum concentrations below 50 mg/L, which is markedly higher than the serum concentrations of 5 to 20 mg/L that have been found to be effective in clinical studies.[2,7,20] In one pharmacokinetic study of caffeine, plasma concentrations as high as 84.2 mg/L were reached.[25] The major adverse event reported was jitteriness, which occurred in an infant with a plasma concentration of caffeine at 61.7 mg/L. The jitteriness resolved within 48 hours after cessation of caffeine. These observations indicate that caffeine has a wide therapeutic index.

In general, adverse events associated with caffeine usually involve the central nervous system (irritability and convulsions).[3] Other, infrequently reported, adverse events include tachycardia,[26] constipation, gastroesophageal reflux,[16,24] increased urinary output and creatinine clearance,[27] and increased sodium and calcium excretion.[28] Clinical

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effects (tachycardia and gastrointestinal intolerance), however, are rare.

The majority of these studies were conducted before a premixed, standardized solution of caffeine citrate became commercially available in 1999. The safety and efficacy of this formulation of caffeine citrate have been evaluated in a phase III, placebo-controlled, randomized, double-blind trial involving 82 infants whose mean gestational age was less than 30 weeks.[24] Caffeine citrate was administered to 46 infants in a loading dose of 10 mg/kg IV followed by a daily maintenance dose of 2.5 mg/kg, either IV or orally. Another 39 infants were assigned to the placebo control group. Both groups received treatment for 10 days. Efficacy was defined as either complete elimination of apnea on days 2 through 10 or as a reduction of at least 50% in the number of apnea episodes from baseline on days 2 through 10.

Eighty-two infants were included in the efficacy analysis. Active treatment for 7 to 10 days was associated with elimination of apnea in 11 (24%) infants and at least a 50% reduction of apnea episodes in 31 (67%) within the 10-day period. By contrast, 16 (41%) infants given placebo had a reduction in apnea episodes of at least 50%, and none had elimination of apnea.[24] In particular, caffeine was significantly better than placebo in reducing apnea episodes by at least 50% on days 4, 5, 7, 8, 9, and 10, and the difference approached significance on days 2, 3, and 6. Caffeine was significantly better than placebo in eliminating apnea episodes on days 2, 4, 7, 8, and 9, and the difference approached significance on days 3 and 6. No clinically significant differences in the overall incidence of adverse events were identified between treatment groups.[24]

A study conducted by Lee et al[22] demonstrated caffeine's potential to provide safer and more convenient treatment of apnea than theophylline. Despite a very wide range of maintenance doses (3, 15, and 30 mg/kg), there was no evidence of dose-dependent pharmacokinetics. In this study in which >90% of patients were younger than 6 days of age, the elimination half-life of caffeine was 86 to 277 hours, compared with 5 hours in adults.[22] Owing to the inability of the neonate to metabolize caffeine through hepatic pathways, the majority of the drug was cleared by the kidneys, as reflected in linear drug disposition even at high doses.[22] And although most other sources have recommended caffeine doses based only on current body weight, this study demonstrates that caffeine clearance was influenced by postnatal age as well. For example, a 2-day-old infant weighing 1,000 g would require a maintenance intravenous caffeine citrate dose of 7.1 mg every 24 hours to achieve a steady state concentration of 35 mg/L. Subsequently, if this infant's body weight remained unchanged 10 days later, a 31% dosage increase to 9.3 mg would be required to maintain the same steady-state concentration of 35 mg/L.[22]

Discontinuation of Methylxanthine Therapy. Apnea of prematurity is generally resolved by 34–36 weeks postconceptional age, although it may persist past 37 weeks in some infants. The decision to discontinue methylxanthine therapy is largely empirical. Once the preterm infant is asymptomatic, and has reached a postconceptional age where AOP is not expected, it is reasonable to discontinue the drug on a trial basis while monitoring for apnea.

Choice of Methylxanthine Therapy. Although in the United States, theophylline is commonly used for AOP, the evidence increasingly suggests that caffeine may provide comparable efficacy with fewer drawbacks.[7,20] Caffeine is generally regarded as being a more potent stimulator of both the central nervous system and the respiratory system. Dosing regimens of caffeine appear to be simpler and provide more predictable results than with theophylline, most likely as a result of its smaller fluctuations in plasma concentrations and longer half-life.[9] Moreover, caffeine appears to have a wider therapeutic window and to produce fewer side effects (Table 3).

The safety and efficacy of both agents in reducing the frequency of apnea has been evaluated in three small comparative trials.[7,8,20] All three studies involved infants with a mean gestational age <31 weeks who were randomly assigned to either theophylline or caffeine therapy for AOP. The results are not directly comparable because different outcome measures, loading doses, and maintenance doses were used. Nevertheless, it is worthwhile noting that all three trials reported no significant difference between treatments in mean reduction of the frequency of apnea episodes. In one study, caffeine appeared to have a faster effect on respiratory rate.[20]

In all three studies, theophylline was associated with more adverse events.[7,8,20] The most common was tachycardia, which in one study necessitated a dosage adjustment in five of 12 infants receiving theophylline.[8]

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Table 3

COMPARISON OF CAFFEINE AND THEOPHYLLINE IN THE TREATMENT OF AOP

	Caffeine	Theophylline
Mechanism of action	Increase central inspiratory drive Increase minute ventilation Increase respiratory rate	Increase ventilatory response to CO_2 Increase ventilation
Route	IV, oral	IV, oral
Onset of toxicity	Rare below plasma serum levels <50 mg/L	May occur at plasma levels of 13 mg/L
Therapeutic range	5–25 mg/L	5–13 mg/L
Half-life	100 hours	30
Loading dose	10 mg/kg	5 mg/kg
Maintenance dose	2.5 mg/kg qd	2 mg/kg q 6–8hr
Time to steady state	14 days	5 days
Side effects	Comparable to placebo Mild excitability	GI intolerance Irritability Tachycardia
Monitoring for plasma concentrations	Infrequently	Frequently
Drug interactions	None	None

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Other adverse events included gastrointestinal (GI) intolerance and excitability.

Adverse events related to caffeine administration were less common. There was one report of tachycardia necessitating dosage adjustment in a caffeine-treated infant.[8] None of the studies reported GI intolerance or significant excitability in infants treated with caffeine.

In these three studies, the investigators concluded that caffeine and theophylline are comparable in significantly reducing the number of apneic episodes in the preterm infant. They recommended clinical use of caffeine, because of its wider therapeutic window, fewer side effects, and ease of administration (once a day vs. three times a day). One author concluded that plasma concentrations of caffeine need to be monitored only if the infant fails to respond.[8] The others recommended monitoring plasma concentrations once or twice a week.[7,20]

Doxapram. Doxapram, an analeptic agent with potent respiratory stimulant properties that exert predominantly peripheral chemoreceptor effects, is used when a methylxanthine does not significantly reduce the frequency of apnea episodes. In low doses (0.5–1.0 m/kg) doxapram may stimulate the peripheral chemoreceptors. It also increases minute ventilation and tidal volume with effect on respiratory timing. At higher doses, it appears to exert a central effect.[29]

Doxapram has been widely studied in adults, but less is known about its use in children and infants. The half-life is reported to be about 10 hours in the first few days of life, and about eight hours at 10 days of age.[29] The recommended dosage is 1 to 2.5 mg/kg/h given by continuous IV infusion. That dosage can be decreased to 0.5 to 0.8 mg/kg/h when apnea episodes become less frequent. However, therapeutic serum drug levels can only be achieved when the drug is given by continuous IV infusion.[3]

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The recommended plasma levels have not been determined. Serum drug levels of less than 5 mg/L have been found effective in the treatment of apnea. However, adverse events have been reported with plasma concentrations greater than 3.5 mg/L. In general, the side effects appear to be similar to those of theophylline.[3] Because doxapram contains benzyl alcohol, it must be used with caution in neonates.[30] More research is needed to determine the safe and effective doses of doxapram in infants.

Long-Term Safety of Pharmacotherapy. Since methylxanthine agents alter both cerebral blood flow and metabolism (decreasing cerebral blood flow while increasing cerebral metabolic rate for both oxygen and glucose), concern exists regarding long-term effects on preterm infants.[31] Athough there is not sufficient evidence to allay those concerns conclusively, several clinical studies are available that suggest that these agents do not have long-term sequelae.[31-33]

Infants with germinal matrix and/or intraventricular hemorrhage (GMH/IVH) require methylxanthine therapy in the neonatal period more often than infants without IVH. Because the combined presence of GMH/IVH and methylxanthine therapy may compound the potential for adverse effects, Ment et al[31] analyzed the neurodevelopmental outcome of very-low-birth-weight neonates with respect to the presence of GMH/IVH and neonatal methylxanthine therapy. Methylxanthine therapy was given to 26 infants who experienced hemorrhage and to 17 of those who did not and the infants were evaluated at 18 months by use of the Bayley developmental index (MDI). Infants who had received methylxanthine therapy scored significantly better in terms of mean MDIs indicative of developmental status (p=0.033), regardless of whether they had experienced a hemorrhage, than the infants who had not been treated.[31] In addition, infants were measured for length/height, weight, and occipitofrontal head circumference and received comprehensive neurodevelopmental assessment. Results demonstrated no harmful effects of neonatal methylxanthine therapy on cognitive functioning at 18 months.

Le Guennec et al[33] assessed the effects of long-term (mean 23.8 weeks) caffeine therapy. Weight, length, and head circumference were measured in 28 preterm infants before institution of caffeine therapy, twice during therapy, and at 3 and 6 months after cessation of therapy. No adverse effects on these measures were apparent during early infancy.

Gunn et al[32] monitored the growth, development, and ophthalmologic status of 42 preterm infants with apnea: 21 who were treated with caffeine and 21 matched controls. The infants were examined every 3 months for up to 40 months. In the caffeine-treated group, a significant decrease was observed in both the number of infants who required intermittent positive pressure ventilation (IPPV) for apnea and the number of days that IPPV was required. Additionally, there were no significant differences in length, weight, or head circumference at 6 or 12 months between the two groups. Further, fewer neurolgic (i.e., seizures, hydrocephaly, intracranial hemorrhage) and opthalmologic (i.e., retrolental fibroplasia, myopia, esotropia) sequelae were observed in infants with apnea treated with caffeine compared to controls.[32]

As previously mentioned, while Apnea of Prematurity (AOP) does not predict the later occurrence of SIDS or apnea of infancy,[3,4] a small percentage (0.5–1%) of preterm infants may develop SIDS.[4,34] However, a discussion of SIDS/Acute Life Threatening Episode (ALTE) is outside of the scope of this article.

Cessation of Therapy/Home Monitoring. The majority of infants with AOP remain in the hospital until their apnea has resolved completely.[3] Generally, treatment with caffeine or theophylline reduces the number and severity of apneic episodes within 24–48 hours and continued therapy leads to complete resolution before hospital discharge.[9] However, as described above, home monitoring and continued methylxanthine therapy may be recommended following hospital discharge in a small percentage of infants. The development or persistence of apnea in infants over 37 weeks may indicate apnea of infancy, as opposed to AOP. Home monitoring is recommended for the small percentage of older infants who are diagnosed through pneumocardiogram and polysomnographs as having apnea of infancy and for those who have experienced an otherwise unexplained ALTE.[3]

Conclusion

Despite the fact that AOP is a common, potentially serious disorder, there are a large number of unanswered questions. The underlying causes have yet to be fully elucidated, and until they are, treatment will remain largely symptomatic. The primary agents used to treat AOP are the methylxanthines, particularly

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theophylline and caffeine. A few, small comparative trials indicate that both agents are effective but that caffeine has a markedly wider therapeutic margin. Caffeine also has the advantage in terms of ease of administration, particularly with the new ready-to-use formulation of caffeine citrate for both IV and oral administration. Doxapram may prove to be a useful agent as second- or third-line therapy, but its efficacy, safety, and administration in preterm infants have not been established. A few small studies suggest that the methylxanthine therapy does not have any long-term sequelae, but very little is known about doxapram. This issue must be addressed in extensive, long-term studies.

Fortunately, premature infants outgrow their apnea once the brain stem matures enough to assume respiratory control.[12] Similarities between sleep apnea and AOP exist in that both result from a sleep-related defect in the respiratory system. However, once secondary physiologic causes of apnea (i.e., airway obstruction, cardiac disease, seizure disorder) have been ruled out, AOP is attributed to incomplete neurologic development that resolves with time and supportive interventions such as physiologic stimuli and pharmacotherapy.

Clinical studies have demonstrated that caffeine is at least as effective as theophylline, has a longer half life, is associated with fewer adverse events, and, in addition, has a greater ease of administration. With the introduction of an intravenous and oral formulation, caffeine may be used with greater ease, eliminating the need for fomulation in hospital pharmacies. The newly introduced formulation of caffeine citrate has been shown to be safe and effective and may minimize the need for monitoring. As clinical experience with caffeine citrate increases, this agent may rapidly become the drug of choice in the treatment of AOP.

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