Impact of Caffeine Boluses and Caffeine Discontinuation on Apnea and Hypoxemia in Preterm Infants

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Background: Apnea of prematurity often occurs during and following caffeine therapy. We hypothesized that number of apnea events would be impacted by adjustments in caffeine therapy.

Materials and Methods: An automated algorithm was used in all infants ≤ 32 weeks gestation admitted to a level IV Neonatal Intensive Care Unit from 2009 to 2014 to analyze chest impedance, electrocardiogram, and oxygen saturation data around the time of serum caffeine levels, caffeine boluses while on maintenance therapy, and caffeine discontinuation. Episodes of central apnea/bradycardia/desaturation (ABDs), and percent time with $\text{SpO}_2 < 88\%$ and $< 75\%$ were measured.

Results: ABDs were analyzed in 302 preterm infants (mean gestational age 27.6 weeks) around the time of 485 serum caffeine levels, 90 caffeine boluses, and 273 episodes of caffeine discontinuation. Higher serum caffeine levels were not associated with fewer ABDs or higher heart rate. For caffeine boluses given due to clinically recognized spells, hypoxemia and algorithm-detected ABDs decreased day 1–2 after the bolus compared to the day before and day of the bolus (mean 4.4 events/day after vs. 6.6 before, $p = 0.004$). After caffeine discontinuation, there was no change in hypoxemia and a small increase in ABDs (2 events/day 3–5 days after discontinuation vs. 1 event/day before and > 5 days after, $p < 0.01$). This increase in ABDs occurred irrespective of gestational age, respiratory support, or postmenstrual age at the time caffeine was stopped.

Conclusions: In this retrospective analysis, caffeine boluses and caffeine discontinuation were associated with a small change in the number of ABD events in preterm infants.

Keywords: apnea, preterm infant, caffeine, hypoxemia

Introduction

CAFFEINE IS COMMONLY used to treat apnea of prematurity (AOP), which occurs in nearly all infants < 28 weeks gestational age (GA) and many of those < 32 weeks GA.^{1–3} Caffeine has generally been found to be efficacious and safe with a wide therapeutic index,^{3–5} and some reports suggest that higher doses of caffeine may be more beneficial.^{6,7} However there is also some evidence of potential detrimental effects of caffeine, particularly at high doses.^{8–10} Balancing the potential toxicities of the drug with the potential adverse effects of hypoxemia associated with significant apnea events is challenging, and more data are needed to establish optimum dosing and duration of caffeine therapy in preterm infants with AOP.

Research in AOP is complicated by difficulty in accurately quantifying events in large numbers of infants over long periods of time. To address this issue, we previously developed an automated apnea detection system that stores bedside monitor cardiorespiratory data for later analysis of central “ABD” (apnea, bradycardia, and desaturation) events. In our apnea detection algorithm, an ABD event is defined as the presence of very low variance in the chest impedance signal for at least 10 seconds indicating central apnea, with associated bradycardia < 100 bpm, and desaturation $< 80\%$.^{11,12} This validated system has allowed us to answer a number of questions about AOP, including its association with common pathologic conditions in very low birth weight (BW) preterm infants.^{1,13,14} In this analysis, we tested the hypothesis that adjustments in caffeine dosing would impact the number of central ABD events

in preterm infants. First, we sought to determine whether serum caffeine levels were correlated with number of ABD events. Second, we evaluated the impact of bolus doses of caffeine during maintenance therapy. Third, we studied ABDs and hypoxemia after discontinuation of caffeine therapy.

Materials and Methods

Patient population

Infants ≤ 32 weeks gestation admitted to the University of Virginia Neonatal Intensive Care Unit (NICU) from January 2009 to December 2013 who received caffeine for at least 7 days and had sufficient stored bedside monitor data for apnea analysis around the time of caffeine events were included in this study. The apnea analyses were performed retrospectively and the study was approved by the University of Virginia Institutional Review Board with waiver of consent since there were no interventions and the data were deidentified. Infants with multiple congenital anomalies, critical congenital heart disease, posthemorrhagic hydrocephalus requiring shunt placement, or electroencephalogram-confirmed seizures were excluded. In the caffeine discontinuation analysis, we also excluded six infants who remained on caffeine beyond term corrected age: five for severe bronchopulmonary dysplasia (BPD) and one for bowel surgery and risk for postoperative apnea.

Clinical data were obtained from the NICU and hospital databases, including GA, BW, gender, respiratory support, and caffeine administration. The general practice in the unit over the 5-year period of study was to administer caffeine empirically to all infants < 32 weeks GA and as indicated for recurrent apnea in infants ≥ 32 weeks GA. The initial bolus dose was 20 mg/kg of caffeine citrate and the standard maintenance dose was 5 mg/(kg·day) of caffeine citrate. Caffeine was generally discontinued once an infant was > 32 weeks post-menstrual age (PMA), off continuous positive airway pressure, and having minimal or no clinically significant apnea requiring intervention.

Serum caffeine levels were obtained at clinicians' discretion, generally either because an infant was having events or due to tachycardia. Bolus doses were given based on conventional bedside monitoring and medical record reporting of apnea events. We analyzed bolus doses recorded in the Medical Administration Record (MAR) database as at least 5 mg/kg given in addition to the regular daily dose. For infants receiving multiple boluses, only the first bolus was included in this analysis. Medical records were reviewed to determine the reason for the bolus.

Apnea analysis

Central apnea events with associated bradycardia and desaturation were analyzed when infants were not on

mechanical ventilation. In the University of Virginia (UVA) NICU, all bedside monitor waveform and vital sign data are continuously collected and stored using a central network server (BedMaster Ex; Excel Medical, Jupiter, FL) and later analyzed using an algorithm that underwent rigorous validation.¹² The algorithm detects episodes of low variance in the chest impedance waveform signal after eliminating heart beat and motion artifact. It then identifies "ABD events" as central apnea of at least 10 seconds with associated decline in heart rate to < 100 bpm and oxygen saturation to $< 80\%$. We analyzed ABDs each day when complete bedside monitor data were available at least 25% of the day (excluding days that the infant was on mechanical ventilation for any part of the day). For the caffeine bolus analysis, we included all events for which ABD data were available, at minimum, the day of the bolus, and 1 day before and after. For the caffeine discontinuation analysis, we included events for which there were at least 3 days of data in the week before and the week after discontinuation (mean 19 hours/day analyzed).

Of note, algorithm-detected apnea events were analyzed retrospectively by the research team, and decisions about caffeine boluses and discontinuation were based solely on conventional clinical practices, including nursing reports and bedside monitor displays.

Hypoxemia analysis

Oxygen saturation values from the bedside monitor pulse oximeter, recorded every 2 seconds using the default 8-second SpO₂ averaging time and lower alarm limit of SpO₂ of 88%, were continuously collected and stored. We calculated the percentage of SpO₂ values $< 88\%$ and $< 75\%$ for all times that data were available around the time of caffeine levels, caffeine boluses, and caffeine discontinuation.

Statistical analysis

Data are expressed as mean and standard deviation unless otherwise noted. Paired sign rank testing was used to compare the number of ABD events and hypoxemia before and after caffeine boluses or caffeine discontinuation. Linear regression was used to analyze ABDs or heart rate in relationship to serum caffeine levels. Statistical significance was set at $p < 0.05$ and analyses were performed in GraphPad Prism 7.01 (San Diego, CA).

Results

Patient demographics

In the 5-year period, 826 infants ≤ 32 weeks gestation were admitted to the UVA NICU (mean GA and BW 28.5 weeks and 1245 g, respectively), and 642 of these infants were treated with caffeine for at least 7 days. Of these, 302 infants had bedside monitor data available for ABD analysis around the time of caffeine levels,

boluses, and discontinuation. Reasons for exclusion included inadequate chest impedance, electrocardiogram, and pulse oximeter data, being on mechanical ventilation, not having levels obtained or boluses given, and death or transfer before caffeine discontinuation.

Demographics and clinical characteristics of the entire population and of the subsets of infants included in each of the analyses are shown in Table 1.

Relationship between serum caffeine levels, ABD events, and heart rate

We identified 485 serum caffeine levels obtained in 238 infants on maintenance caffeine therapy with sufficient stored bedside monitor data to analyze ABDs on the day of the level. The mean level was 15.3 ± 5.0 mcg/mL, 67 levels (14%) were >20 mcg/mL, and 28 (6%) were <8 mcg/mL. There was a weak, but statistically significant *positive* correlation between the serum caffeine level and the daily number of ABDs (higher caffeine levels associated with slightly more ABDs) (Fig. 1A, $R^2=0.02$, $p=0.002$). There was no correlation between serum caffeine level and mean heart rate on the day of the level (Fig. 1B), $R^2 < 0.001$, $p=0.50$).

Apnea and hypoxemia after caffeine boluses

We identified 210 caffeine boluses given to infants while on maintenance caffeine therapy, (at least 5 mg/kg given in addition to the daily dose). Of these, 119 were given while the infant was not on mechanical ventilation. Some infants received multiple boluses and we analyzed only the first one for which we were able to retrieve sufficient stored bedside monitor data to analyze ABDs before and after ($n=67$). For 62 of these boluses (93%) a serum caffeine level was obtained within 1–2 days prior. Medical record review revealed that 50

boluses were given due to clinically recognized ABDs with variable combination of apnea, bradycardia, and desaturation. Eleven boluses were given due to a low serum caffeine level or severe lung disease without mention in the medical record of ABDs, and six boluses were given to infants with ABDs and suspected sepsis (in three cases with positive cultures and in one case with suspected necrotizing enterocolitis [NEC]). Table 2 shows characteristics of the infants in each group and the mean number of ABD events the day before and day of the bolus (day –1 to 0) compared to the number of ABD events day 1–2 after the bolus. There was a significant decrease in algorithm-detected ABDs after the bolus in infants with clinically recognized ABDs. Percentage of time with $SpO_2 < 88\%$ was also significantly lower after the bolus for infants with clinically recognized ABDs ($21.9\% \pm 11.5\%$ before vs. $20.8\% \pm 12.7\%$ after, $p=0.049$), but time with $SpO_2 < 75\%$ was not different (data not shown).

Apnea and hypoxemia after caffeine discontinuation

For 273 infants, sufficient stored monitor data were available to analyze ABDs in the week before and after discontinuation of caffeine therapy. Seventeen of these infants (6%) were on continuous positive airway pressure (CPAP), 98 (36%) on nasal cannula, and 159 (58%) on no respiratory support when caffeine was stopped. PMA at the time caffeine was stopped was inversely associated with GA (Fig. 2A). During the earlier years of the study, it was routine in our unit to check a serum caffeine level after discontinuing therapy to determine when to start an “apnea countdown” before discharge.¹⁵ In the 273 infants in this analysis, 165 caffeine levels were obtained within 10 days of stopping caffeine (Fig. 2B). The mean time for checking a level was 6 days after caffeine discontinuation, at which time the mean level was 4.1 mcg/mL and maximum level was 7 mcg/mL.

TABLE 1. CLINICAL CHARACTERISTICS OF INFANTS IN EACH ANALYSIS AND ENTIRE POPULATION

	<i>Serum caffeine levels</i>	<i>Caffeine bolus</i>	<i>Caffeine discontinuation</i>	<i>All ≤ 32 week infants 2009–2013</i>
No. of infants	238	67	273	826
GA (weeks)	27.7 ± 2.4	26.0 ± 2.0	27.8 ± 2.4	28.5 ± 2.9
BW (g)	1124 ± 383	869 ± 248	1147 ± 377	1245 ± 475
Female	107 (45)	30 (45)	137 (50)	389 (47)
IVH grade 3–4	13 (5)	10 (15)	17 (6)	55 (7)
Septicemia	23 (10)	11 (16)	25 (9)	89 (11)
NEC	10 (4)	4 (6)	10 (4)	36 (4)
BPD	77 (32)	36 (54)	75 (27)	229 (28)
Ventilator days	12 ± 20	22 ± 19	11 ± 19	13 ± 26
Length of stay (days)	66 ± 30	87 ± 30	64 ± 29	53 ± 40
Age at analysis (days)	36 ± 24	39 ± 21	39 ± 24	n/a
PMA at analysis (weeks)	31 ± 3	31 ± 2	33 ± 2	n/a

Mean $\pm$ standard deviation or n (%).

BPD, bronchopulmonary dysplasia (supplemental oxygen at 36 weeks PMA); BW, birth weight; GA, gestational age; IVH, intraventricular hemorrhage; LOS, length of stay; NEC, necrotizing enterocolitis; PMA, postmenstrual age.

FIG. 1. Serum caffeine levels, ABD events, and heart rate. Serum caffeine levels were obtained during maintenance therapy when clinically indicated (485 levels in 238 infants). We retrospectively analyzed the number of ABD events (**A**) and mean heart rate (**B**) on the day of the caffeine level. Linear regression (solid line) and 95% confidence intervals (dotted lines) are shown. ABD, apnea/bradycardia/desaturation; HR, heart rate.

On the day caffeine was discontinued, 192 infants (70%) had no algorithm-detected ABD events, and 94 infants (34%) had no ABDs for 5 days prior. On the other hand, 46 infants (17%) had three or more ABDs on the day caffeine was stopped. In the overall group, there was a small, statistically significant increase in ABD events 3–5 days later (2 events/day 3–5 days after discontinuation and 1 event/day before and after, $p < 0.01$) (Fig. 2C). Considering separately the 81 infants with at

least one ABD event on the day caffeine was discontinued compared to the 192 with no events, both groups had a similar small increase in events within 3–5 days after stopping. By 8–10 days off caffeine, the number of ABD events had returned to baseline (Fig. 2C). With regard to hypoxemia, in the days before stopping caffeine, infants were spending an average of 11% of the time with $\text{SpO}_2 < 88\%$. There was no significant change after stopping (Fig. 2D), nor was there a significant difference in percent of time with $\text{SpO}_2 < 75\%$ after stopping caffeine (data not shown).

We sought to determine whether the small increase in apnea 3–5 days after discontinuing caffeine was more pronounced in subgroups of infants. Figure 3 shows that the increase of about 1 ABD event per day occurred irrespective of whether or not infants were on respiratory support (Fig. 3A), were $<$ or ≥ 28 weeks GA (Fig. 3B), or were $<$ or ≥ 33 weeks PMA (Fig. 3C).

Discussion

Caffeine has been shown to reduce apnea and improve a number of important outcomes of preterm infants,^{3,4,16,17} but questions remain regarding optimum dosing and duration of treatment. Using our automated algorithm to retrospectively analyze stored bedside monitor cardiorespiratory data, we found that higher serum caffeine levels were not associated with higher heart rate or with fewer ABD events. Furthermore, we found only small changes in ABD events related to caffeine boluses and caffeine discontinuation.

Dosing of caffeine is variable between institutions and has changed over time. In the years of this study, the starting maintenance caffeine dose in our NICU was 5 mg/kg and some infants remained on this dose, while others received one or more boluses, usually followed by an increase in the daily dose. We found that some infants receiving a caffeine bolus for ABD spells also had antibiotics started for suspected or proven sepsis, while other infants were given a bolus due to a serum caffeine level in the lower end of the therapeutic range or due to severe lung disease. For the majority of infants that received a bolus, there was documentation in the medical

TABLE 2. NUMBER OF ALGORITHM-DETECTED APNEA/BRADYCARDIA/DESATURATION 2 DAYS BEFORE AND AFTER CAFFEINE BOLUS BASED ON REASON FOR BOLUS

Reason for bolus in medical record	"ABD spells" (n=50)	Suspected sepsis with ABD (n=6)	Low level or lung disease (n=11)
GA (weeks)	26.0 $\pm$ 2.0	28.0 $\pm$ 2.0	25.2 $\pm$ 1.5
PMA (weeks)	31.4 $\pm$ 2.5	31.3 $\pm$ 2.7	34.3 $\pm$ 2.9
Serum level (mcg/mL)	13.4 $\pm$ 2.5	13.7 $\pm$ 1.6	12.7 $\pm$ 1.9
No. of ABDs before (mean)	6.6	11.8	0.7
No. of ABDs after (mean)	4.4	6.9	0.8
ABDs before/after <i>p</i>	0.004	0.438	0.875

ABD, apnea/bradycardia/desaturation.

FIG. 2. Impact of caffeine discontinuation on ABD events and hypoxemia. For 273 infants, ABDs and hypoxemia were analyzed around the time of caffeine discontinuation. (A) PMA at the time of caffeine discontinuation was higher for lower GA infants. (B) For a subset of infants, serum caffeine levels were obtained within 10 days of discontinuing caffeine, and all levels were <8 mcg/mL within 6 days. (C) Mean number of ABD events per day before and after caffeine discontinuation. (D) Mean percent time with SpO₂ <88%. Standard error bars are shown. GA, gestational age; PMA, post-menstrual age.

record of clinically recognized ABDs with some combination of apnea, bradycardia, and desaturation, and these infants had a significant decrease in events after the bolus. Several randomized studies have suggested that starting with higher maintenance doses of caffeine may

be beneficial. In a retrospective report, infants receiving maintenance dosing of at least 8 mg/(kg·day) required fewer dose changes and maintained serum caffeine levels within the standard accepted range.¹⁸ Even higher maintenance doses of caffeine [20 mg/(kg·day)] have been

FIG. 3. ABD increase after caffeine discontinuation based on respiratory support, GA, and PMA. Mean number of ABD events per day is shown 3–5 days after caffeine discontinuation compared to 0 to 2 days before discontinuation. Infants were analyzed based on whether they were on no respiratory support or CPAP, or nasal cannula (A, filled vs. open circles); whether they were < or ≥28 weeks GA (B, filled vs. open triangles); and whether they were < or ≥33 weeks PMA at the time of caffeine discontinuation (C, filled vs. open squares). Asterisks indicate a significant increase in ABDs after caffeine discontinuation for each of the three groupings ($p < 0.01$). CPAP, continuous positive airway pressure; NC, nasal cannula; RA, room air.

shown, in randomized trials, to increase the chance of successful extubation for preterm infants on mechanical ventilation.^{6,7} Studies have also shown a lower rate of BPD with caffeine compared to placebo⁵ and with earlier compared to later initiation of caffeine.¹⁹ In one retrospective report, infants with higher serum caffeine levels (>14.5 mg/dL) were less likely to be diagnosed with BPD or to need home oxygen, and had shorter length of NICU stay compared to infants with lower serum levels.²⁰ None of these studies quantified apnea events, and it is possible that some of the beneficial effects of higher caffeine doses and levels are not mediated by suppression of apnea, but by effects on the lungs.

Toxicity of caffeine is generally thought to be minimal, although there are reports of tachycardia,⁷ poor growth,^{5,21} reduced cerebral and intestinal blood flow velocity,²² and increased serum levels of proinflammatory cytokines related to caffeine therapy.⁹ A very high dose of caffeine shortly after birth [80 mg/(kg·day)] was also associated, in a randomized clinical trial, with increased incidence of cerebellar hemorrhage.⁸ Further randomized studies would be required to determine to what extent higher doses or higher serum levels of caffeine result in more side effects, or whether they more effectively reduce apnea compared to conventional doses and levels. We found, somewhat counterintuitively, that higher serum caffeine levels were associated with a slightly *higher* number of ABDs. Although we were unable to assess the decision-making process behind obtaining caffeine levels in this retrospective review, we speculate that levels were more likely to be checked in infants for whom caffeine did not seem to be effective, in other words in those receiving higher doses yet having more frequent events. Individual variability in caffeine efficacy is an important phenomenon that is not well understood. Polymorphisms in adenosine receptors have been reported to render some infants less susceptible to caffeine's apnea-suppressing effects.²³ Since some infants continue to experience significant central apnea while on caffeine, and since the associated hypoxemia might have long-term adverse consequences, adjunct therapies should be investigated. Nonpharmacologic modalities such as gentle sensory afferent stimulation have recently been reported, in small studies, to reduce apnea and improve oxygen saturation^{24,25}

Metabolism of caffeine is very slow at birth (half-life nearly 100 hours), and increases over time, reaching adult half-life of 6 hours around 6–9 months of age.²⁶ Caffeine metabolism has been reported to be increased in female infants²⁷ and with formula compared to breast milk feeding.²⁸ Monitoring of serum caffeine levels is generally not recommended, in part, due to the expense (several hundred dollars per test at our hospital and, in part, because neither toxicity nor efficacy appear to be predictable by the serum level.^{29,30} Rather, the trend in clinical practice seems to be either starting with high em-

piric dosing, or giving additional bolus and higher maintenance doses until either the apnea is improved or the infant shows obvious signs of toxicity (usually tachycardia). With this trend toward higher caffeine dosing and less monitoring of serum levels, combined with individual variability in infant responses to the drug, unexpected toxicities may emerge in some infants.

A final consideration in caffeine therapy is when to stop. Central apnea typically declines between 32 and 36 weeks' PMA and in most infants, clinically significant events resolve between 36 and 40 weeks PMA.¹ Discontinuing caffeine too early could lead to increased apnea and hypoxemia,³¹ whereas continuing caffeine too long might delay NICU discharge if an apnea-free observation period off caffeine is required.^{1,32} We found that the mean PMA of caffeine discontinuation in our unit was 33 weeks, with lower GA infants having caffeine stopped at higher PMA (Fig. 2A) likely reflecting persistence of clinically recognized events. A third of infants had no algorithm-detected ABDs for at least 5 days before stopping caffeine, suggesting that perhaps caffeine could have been discontinued sooner in some infants. The small increase in ABD events 3–5 days off caffeine likely corresponds to the time that levels fell below the therapeutic range, which is earlier than expected based on other reports,³³ likely reflecting relatively low serum levels at the time caffeine was stopped (Fig. 2B). Within a week, the number of ABD events declined to the baseline before discontinuing caffeine, which would be expected with neurologic maturation.

Limitations

There are a number of limitations to this retrospective review, including the inability to capture all caffeine adjustments due to gaps in monitor data and the inability to account for all clinical events and interventions that either contribute to or limit apnea. Also, our system does not capture obstructive apnea, but it does capture mixed obstructive/central events. We also use a rigorous definition of central apnea, requiring low variance in the chest impedance signal with both bradycardia <100 bpm and desaturation $<80\%$. It is possible that the frequency of milder events or of events with bradycardia *or* desaturation, but not both, might change with caffeine boluses or caffeine discontinuation. An additional consideration is that we studied all events, including those that were self-limited or feeding related, and may not have been considered clinically important or recorded in the medical record. We cannot exclude the possibility that more severe events or those requiring intervention were impacted by changes in caffeine therapy.

Conclusion

Many preterm infants continue to experience some central apnea while on caffeine therapy and it is not

clear from our retrospective review that increased dosing or higher serum levels has a major impact on these events. Following caffeine discontinuation, most infants did not have a significant change in ABD events or hypoxemia. We found marked individual variability in AOP and, since the hypoxemia associated with apnea may have adverse consequences,³⁴ prospective observational studies or randomized controlled trials are needed to elucidate optimum caffeine dosing and other interventions for reducing apnea. Even more importantly, the impact of apnea, hypoxemia, and therapeutic interventions on long-term neurodevelopmental outcomes deserves further study.

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Author Disclosure Statement

No competing financial interests exist.

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