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ORIGINAL ARTICLE

Apnea of prematurity and caffeine pharmacokinetics: potential impact on hospital discharge

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OBJECTIVE: To determine the half-life of serum caffeine concentrations and its relation to apnea of prematurity (AOP) after caffeine is discontinued in preparation for hospital discharge.

STUDY DESIGN: Prospective cohort study involving preterm infants with gestational ages $\leqslant 33$ weeks at birth. After caffeine was discontinued, serum caffeine concentrations and electronic detection of pathologic apnea, defined *a priori*, were obtained at 24 and 168 h, respectively.

RESULT: Caffeine levels decreased from 13.3 ± 3.8 to 4.3 ± 2 mg l^{-1} ($n = 50$, mean ± s.d.) at 24 and 168 h, respectively ($P < 0.01$). The mean caffeine half-life was 87 ± 25 h at 35 ± 1 weeks postmenstrual age. Seven days after discontinuation of caffeine, 64% of the infants had pathologic apnea.

CONCLUSION: Hospital discharge planning for preterm infants with a history of AOP should be carefully considered after discontinuing caffeine. This study showed that caffeine may not reach subtherapeutic levels until around 11–12 days.

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INTRODUCTION

Caffeine citrate is one of the most commonly used medications in the preterm infant because it reduces the frequency of apnea, decreases the duration of mechanical ventilation and supplemental oxygen, and decreases the incidence of patent ductus arteriosus.[1,2] In large, randomized multicenter clinical trials, caffeine was prescribed for very low birth weight infants within 5 days of life and was discontinued ~6–7 weeks later, at a postmenstrual age of 34–35 weeks. However, extremely preterm infants, especially those born at 24–26 weeks gestational age, may continue to have clinically significant apnea even after 37 weeks post-menstrual age (PMA).[3–5] Resolution of apnea of prematurity (AOP) is one essential factor in determining the timing of a safe hospital discharge for the preterm infant.

The long therapeutic half-life of caffeine in preterm infants confounds the issue of safe hospital discharge. In a previous pharmacokinetic study of infants born at < 30 weeks gestation that had been intubated, the mean caffeine elimination half-life was found to be 101 hours.[6] In that study, caffeine elimination increased nonlinearly with postnatal age, with a more rapid increase in clearance during the first 2 weeks.[6] More recent studies would suggest that serum caffeine concentrations are not necessary to measure since caffeine has a large therapeutic index of efficacy and safety.[7] However, no previous study has focused on caffeine pharmacokinetics near the date of hospital discharge, when caffeine is discontinued, whereas looking at recorded cardiorespiratory patterns specifically for AOP.

Using a standard loading and maintenance dose of caffeine,[8] in the present study it was hypothesized that after discontinuing caffeine, concentrations would be in a therapeutic range for > 1 week. As a corollary, by determining the caffeine half-life, one could determine when caffeine concentrations would be subtherapeutic in considering hospital discharge.

METHODS

The data from this prospective, single-regional-perinatal center, pragmatic cohort study were obtained in 2013 and 2014 from preterm infants with a gestational age of $\leqslant 32$ weeks at birth that were treated with caffeine citrate. Exclusion criteria were birth weight < 500 g, infants requiring any respiratory support at the time caffeine was discontinued, major anomalies or chromosomal disorders, a history of seizures, grade 3 or 4 intracranial hemorrhage or hydrocephalus. This study and the informed consent process were approved by the Committee on Research Involving Human Subjects established at Stony Brook State University of New York. Informed consent was obtained from the parents of all study subjects.

All study patients received a loading dose of caffeine citrate of 20 mg kg^{-1} within the 1-week of life followed by a starting maintenance dose of 5 mg kg^{-1} per day.[8] The attending neonatologists could use a higher maintenance dose and rebolus caffeine at their discretion for recurrent apnea. The decision to discontinue oral caffeine was also made clinically by the attendings on service. Upon discontinuation of caffeine, consent for the study was obtained. Serum caffeine concentrations were obtained at 24 and 168 h after the last caffeine dose was administered. Using these concentrations, the caffeine elimination rate constant (k_e) was calculated using the formula $k_e = \ln(C_1/C_2)/(t_1 - t_2)$. The half-life was then determined by dividing 0.693 (the natural log of 2) by the elimination rate constant.[9]

To identify pathologic apneas, 24 h continuously recorded cardiorespiratory waveforms (heart rate and respiratory rate by electrical impedance) were downloaded at 24 h and at 7 days, coinciding with the days that caffeine samples were obtained. In addition, these recordings were obtained daily from the cardiorespiratory monitors to objectively identify events and were scored by an investigator who was unaware of the clinical condition of the infant, serum caffeine concentrations or postnatal age. Pathologic apnea at rest (events not associated with feeding) was defined *a priori* as apnea > 20 s or apnea < 20 s associated with bradycardia (heart rate < 80 bpm for $\geqslant 5$ s). Pulse oximeters are routinely used in all the neonatal intensive care unit patients until the time of hospital discharge. The finding of pathologic apnea on the recording download was prospectively reported to the attenders on service to consider any changes in medical management. The neonatal staff was masked from the caffeine half-life calculations and cardiorespiratory recording results and nurses were instructed to continue to record

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Table 1. Demographic characteristics of the infants in the study group ($n = 50$)

Patient profile	
Gestational age (weeks)	29 ± 2^a
Birth weight (g)	1273 ± 356^a
Male	48%
HCT at caffeine discontinuation (%)	30 ± 5^a
PMA at caffeine discontinuation (weeks)	35 ± 1^a
Initiation of caffeine (days)	1 ± 1^a
Caffeine duration (days)	41 ± 20^a
Average LOS after caffeine d/c (days)	19 ± 11^a

Abbreviations: HCT, hematocrit; LOS, length of stay; PMA, post-menstrual age. [a]Values are mean ± s.d.

significant events into the medical record. To identify hospital readmissions to our medical center for an apparent life-threatening event, we placed a phone call to the mother and reviewed the patients' medical record at least 3 months after hospital discharge.

Statistical analysis

The analysis was carried out after 50 patients were enrolled in the study period of August 2013–July 2014 to get a robust calculation of caffeine half-life. After discontinuing caffeine, the half-lives were calculated and compared with 1 week postmenstrual age intervals using analysis of variance. Serum caffeine concentrations and the number of pathologic apnea events at 24 and 168 h (1 and 7 days) after caffeine was discontinued were compared using a one-tailed and two-tailed paired *t*-test, respectively.

RESULTS

There were 138 patients eligible for the study during the enrollment period. Of these 138 patients, 50 completed the study. Of the 88 patients not enrolled, 60 were lost due to missed opportunity, 11 died, 6 were excluded because they continued to require respiratory support (nasal cannula) at the time that caffeine was discontinued, 3 patients had incomplete data, 4 had social services restrictions, 3 parents refused to be in the study and 1 was transferred to another institution. Eighty-six percent of the study patients were on the standard maintenance dose of 5 mg kg^{-1} per day and 56% received at least one caffeine bolus at some point during their hospitalization. Seven out of the 50 patients had higher daily maintenance doses ranging from 6 to 8 mg kg^{-1} per day. Three patients had cholestasis as defined by a direct bilirubin >2 mg dl^{-1} and were included in the study. Demographic characteristics of the infants who completed the study are shown in Table 1.

Serum caffeine concentrations at 24 and 168 h after discontinuation of caffeine are shown in Figure 1. There was a 67% decrease in caffeine concentrations from 24 h (13.3 ± 0.5 mg l^{-1} (mean ± s.e.)) to 168 h (4.3 ± 0.3 mg l^{-1}). The mean calculated half-life of caffeine for our study population was 87 ± 25 h at a postmenstrual age of 35 ± 1 weeks (mean ± s.d.). The caffeine half-lives did not differ by the postmenstrual age at which the medication was discontinued (Figure 2). In addition, there was no correlation between postnatal age and caffeine half-life (data not shown).

We found no correlation between the caffeine concentration after 7 days and the frequency of pathologic apneas (Figure 3). Those with the most pathologic events on the download did not have the lowest caffeine levels. The mean number of events per day was 1.3 ± 1.8 vs 2 ± 2.2 (mean ± s.d., $P = 0.015$), 1 and 7 days after discontinuation, respectively. Two of the study patients were identified as having pathologic AOP after stopping caffeine who were restarted on caffeine at PMA 34 and 36 weeks and treated for an additional 2 weeks. They were included in this study at the time when their caffeine was finally discontinued. Most of our babies (64%) had at least one pathologic apnea event documented by cardiorespiratory monitoring 7 days after discontinuing caffeine.

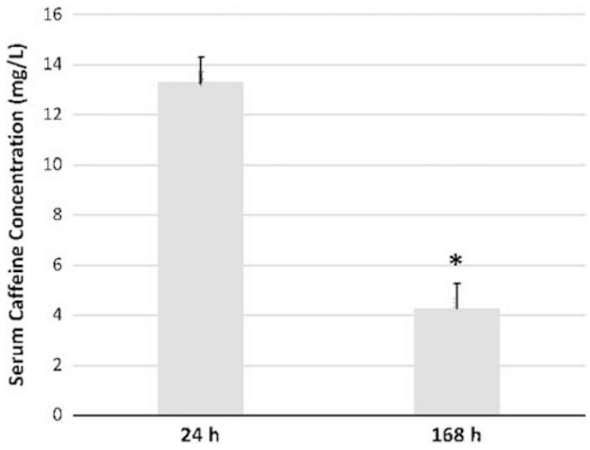

Figure 1. Serum caffeine concentrations at 24 and 168 h after discontinuation of caffeine ($n = 50$). Values are mean ± s.e. *Represents different from 24 h value, $P < 0.001$.

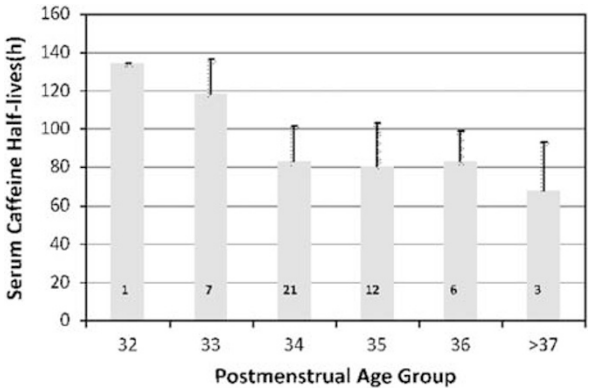

Figure 2. Elimination half-lives of caffeine by 1 week intervals at the postmenstrual age of caffeine discontinuation ($n = 50$). Caffeine values are mean ± s.d. The number inside the bar represents the number of patients in each postmenstrual age group.

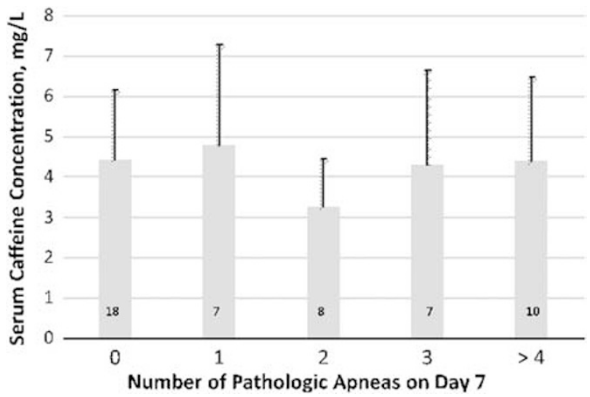

Figure 3. Serum caffeine concentrations for the number of patients (number inside the bar) having different numbers of apneic events at 168 h after discontinuation of caffeine ($n = 50$). Caffeine values are mean ± s.d.

At the time caffeine was discontinued, three patients had direct hyperbilirubinemia, 3.6 ± 1 mg dl^{-1} (mean ± s.d.). The serum caffeine *t*½ was 87 ± 25 h ($n = 50$) vs 86 ± 10 h ($n = 3$) for all patients

vs the three and patients with cholestatic jaundice, respectively. Fifteen (30%) of the study patients were diagnosed with gastroesophageal reflux based on clinical symptoms of emesis, regurgitation of formula, apnea and bradycardia, and irritability after feeds. Seven out of the 15 (46%) study patients had an impedance probe study, which confirmed gastroesophageal reflux.

All 50 patients had daily monitor downloads during the week, accounting for 350 patient-days of cardiorespiratory recordings. Seven patients had only one documented pathologic apnea on download over the course of 7 days and one patient had none. We found at least one pathologic apnea event on 192 cardiorespiratory recordings. Most of the pathologic events identified on these recordings were not identified clinically by nursing documentation; just 36% were identified by nursing.

At time of hospital discharge, five of the infants were followed at home by the Infant Apnea Program on apnea monitors (Respironics Smart Monitor-4003, Philips Respironics, Murrysville, PA). All five infants discharged home with monitors had pathologic apneas at 7 days post caffeine. The other 29 infants with pathologic apneas at 7 days post caffeine had clinically resolved their events by the time of hospital discharge. Follow-up phone calls were completed for 83% of all the patients, and a review of our medical center electronic records indicated that there were no readmissions for an apparent life-threatening event in any of our study patients.

DISCUSSION

One of the considerations for the safe hospital discharge of preterm infants is a period of monitoring for apnea recurrence over 7–10 days after discontinuing caffeine citrate.[10] Other factors that may affect the length of stay include maturation of the feeding coordination, adverse nosocomial events and financial pressures.[4] Accordingly, the present study determined serum caffeine concentrations and its relation to cardiorespiratory events after caffeine was discontinued in preparation for hospital discharge. It was found that after discontinuing caffeine only 33% of the study infants had normal cardiorespiratory recordings at 7 days and the majority still had a potentially therapeutic serum caffeine concentration.[7] Using the caffeine half-life data from the present study cohort, we extrapolated that the serum caffeine concentration would likely be in a subtherapeutic range after 11 days.

Caffeine has been shown to be a safe and efficacious drug in premature neonates with numerous benefits.[1,2,11,12] Caffeine has a wide therapeutic index with serum concentrations usually maintained between 5 and 20 mg l^{-1}, but it has been previously shown that its efficacy could be as low as 2.9 mg l^{-1}.[7] It is known that there is a decrease in the elimination half-life of caffeine, in the first few weeks after birth.[6] However, in the present study, we did not find any significant difference in the caffeine elimination half-life, closer to hospital discharge, between 33 weeks and term, but there appeared to be trend. However, our present study was underpowered to demonstrate a small statistically significant effect. In contrast, in a smaller study performed in 1985, there appeared to be gestational age-associated and postmenstrual age-associated decreases in caffeine half-life, but the caffeine concentrations in that study were not obtained near hospital discharge.[13]

The average caffeine half-life for the entire cohort in the present study was 87 ± 25 h (mean ± s.d.) and the average caffeine concentration 24 and 168 h after the last dose of caffeine was 13.3 ± 3.8 and 4.3 ± 2.0 mg l^{-1} (mean ± s.d.), respectively. The half-life data suggest that it would require, on average, ~3 half-lives or ~11–12 days, with considerable variation, before the caffeine concentration in our patients would reach subtherapeutic concentrations of < 2.9 mg l^{-1}.[7] A longer time interval would be needed if higher serum caffeine concentrations are targeted as maintenance as recently suggested.[14]

Caffeine is metabolized in the liver via microsomal cytochrome P-450 monooxygenase and the soluble enzyme xanthine oxidase.[15] Caffeine has also been found in the urine unmetabolized in infants.[16] Mild direct hyperbilirubinemia in three of the study patients at the time caffeine was discontinued did not seem to be associated with a prolongation of the caffeine elimination half-life, but this study was underpowered to find this difference if it truly exists.

Previous studies have shown that 50% of documented apneic events are missed clinically by nurses even after education.[17,18] In our study we found that nursing reports of symptomatic apneas were far less (36%) than those documented by daily cardiorespiratory recordings. However, this study was performed when the nursing documentation was transitioning to the electronic record and some nurses were documenting on paper record or not documenting events at all.

A normal predischarge event-recording analysis just before hospital discharge can identify preterm infants at extremely low risk for a significant apneic episode at home.[19] We found cardiorespiratory recordings at 168 h or ~7 days after discontinuing caffeine showed a small but statistically significant increase in the number of predefined pathologic apneic events. Thus, with two elimination half-lives of caffeine (~7 days), a therapeutic effect could still be observed in some infants at serum caffeine concentrations of 4.3 ± 2 mg l^{-1} (mean ± s.d.). In addition, we did not identify a threshold caffeine level below that infants became symptomatic. Moreover, we found that most infants who clinically failed their cardiorespiratory recording studies did so for significant desaturations either at rest or around feedings and our criteria for scoring pathologic apnea were not a sensitive or specific indicator of their clinical status. This reinforces the recent recommendations from the American Academy of Pediatrics to not routinely screen preterm infants before hospital discharge with a cardiorespiratory recording study.[20]

There are some limitations of the present study. First, this cohort of patients represented generally healthy premature infants due to our exclusion criteria. The therapeutic efficacy of caffeine could vary among subgroups excluded.[12,13] Neonates with severe neurological diagnoses and those who were still requiring supplemental oxygen or any respiratory support including nasal cannula at the time of caffeine discontinuation were excluded. There were only eight infants who were born at $\leqslant 26$ weeks gestational age; these patients could be expected to have delayed resolution of apnea beyond 40 weeks PMA.[3] However, *post hoc* analysis of the infants in our cohort with gestational ages $\leqslant 26$ weeks showed the average caffeine half-life was 83.1 ± 13.3 mg l^{-1} (mean ± s.d.), no different from the entire cohort.

Another limitation of the study was that the cardiorespiratory recordings were reviewed only up to 7 days after discontinuing caffeine. This design was based on the earliest time frame suggested to observe infants for an apnea free period before hospital discharge.[10] In retrospect, recordings could have been carried out beyond the 7 days as most study patients were still hospitalized. The study infants were discharged home at a mean of 19 ± 11 days after caffeine was discontinued at a PMA of 35 ± 1 weeks. This means that the majority of infants in this cohort had other medical reasons for continued hospitalization and were simply not waiting for caffeine to clear their system. On the other hand, we had two patients who failed to successfully wean off caffeine and their caffeine was restarted. This represented a 4% failure rate, lower than that observed in a recently reported retrospective study, which included all patients at 33–35 weeks.[21]

As it has been shown that preterm infants on home cardiorespiratory monitors may have extreme events up to 43 weeks postmenstrual age,[5] we completed a home telephone follow-up. Eighty-three percent of the parents of the study infants were successfully contacted and none of these infants had an apparent life-threatening event (ALTE). A review of our medical center electronic records confirmed that there were no

readmissions for an ALTE in our study patients. Most infants in our region who present with ALTE are transferred to our institution for work-up.

In this study patient cohort, the caffeine concentrations 7 days after discontinuation were still in a therapeutic range and there was a small but significant increase in pathologic apneas. There was no correlation identified between the caffeine concentration and number of pathological apneas at 7 days after discontinuation of caffeine. We conclude that hospital discharge planning for preterm infants with apnea should be carefully considered after discontinuing caffeine for recurrence of apnea. Our patients did not reach subtherapeutic concentrations until around 11–12 days, but it would have been even longer if higher caffeine levels were targeted as recently suggested.[14] In the present study the caffeine concentration at 24 h after the last dose was administered was $13.3 \pm 3.8\ mg\ l^{-1}$ (mean±s.d.). A retrospective, hypothesis-generating study suggested that higher concentrations of serum caffeine $>14.5\ mg\ l^{-1}$ during maintenance therapy are associated with a shorter duration of ventilation, less oxygen therapy needed at hospital discharge, shorter length of stay and lower total hospital charges.[14] Therefore, consideration of caffeine trough level at 24 h after the last dose could help clinicians to calculate when the caffeine levels would fall below therapeutic values, knowing the 87-h half-life.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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