Dosing and Safety of Off-label Use of Caffeine Citrate in Premature Infants

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Objective To characterize the dosing and safety of off-label caffeine citrate in a contemporary cohort of extremely premature infants.

Study design We used electronic health records (2010-2013) from 4 neonatal intensive care units to identify infants of ≤28 weeks of gestational age exposed to caffeine citrate. Safety outcomes included death, bronchopulmonary dysplasia, necrotizing enterocolitis, spontaneous intestinal perforation, intraventricular hemorrhage, patent ductus arteriosus ligation, seizures, and arrhythmias. We used multivariable logistic regression to evaluate the association of caffeine citrate exposure with clinical events.

Results Of 410 infants with a median (IQR) gestational age of 26 (24-27) weeks, 95% received caffeine citrate for >0 days. Infants received a median (IQR) daily dose of 8 (5-10) mg/kg/day. Incidences of clinical events on day of caffeine citrate exposure were death 2%, patent ductus arteriosus ligation 12%, and medical and surgical necrotizing enterocolitis 5% and 4%, respectively. Bronchopulmonary dysplasia occurred in 37% of infants and was not associated with caffeine dose. Increased caffeine citrate dose was associated with lower odds of patent ductus arteriosus ligation and necrotizing enterocolitis.

Conclusions Caffeine citrate was used in extremely premature infants at younger gestation, at higher doses, and for longer durations than recommended on the drug label. Increased caffeine citrate exposure, dose, or therapy duration was not associated with increased risk of necrotizing enterocolitis. *(J Pediatr 2019;211:27-32)*.

Caffeine citrate is the most common nonantimicrobial medication used in the neonatal intensive care unit (NICU) and is used primarily to treat apnea of prematurity (AOP).[1] Infants with AOP experience frequent episodes of apnea, resulting in hypoxemia and bradycardia, placing the infant at risk for prolonged mechanical ventilation, retinopathy of prematurity, bronchopulmonary dysplasia (BPD), and long-term neurodevelopmental impairment.[2-4] Approximately 85% of infants born at <34 weeks of gestational age and almost all infants born at <29 weeks of gestational age develop AOP.[5,6]

The drug label for caffeine citrate was last updated by the US Food and Drug Administration (FDA) in 1999. The label recommends using caffeine citrate for short-term treatment of AOP in infants between 28 and 33 weeks of gestational age.[7] The label dose recommendation includes a single loading dose of 20 mg/kg intravenously followed by maintenance doses of 5 mg/kg administered intravenously or orally every 24 hours.[7,8] However, in clinical practice, caffeine citrate is frequently used off-label among extremely premature infants born as early as 22 weeks of gestational age and is continued at higher doses (>5 mg/kg/day) for several weeks.[8,9]

The caffeine citrate label also includes a warning of a possible association with necrotizing enterocolitis (NEC) based on findings from an older randomized,

AOP	Apnea of prematurity
BPD	Bronchopulmonary dysplasia
CAP trial	Caffeine for Apnea of Prematurity trial
FDA	US Food and Drug Administration
IVH	Intraventricular hemorrhage
NEC	Necrotizing enterocolitis
NICHD	National Institute of Child Health and Human Development
NICU	Neonatal intensive care unit
PDA	Patent ductus arteriosus
PMA	Postmenstrual age

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double-blind, placebo-controlled trial involving 85 premature infants.[7,10] Subsequent studies have examined the safety and efficacy of caffeine citrate in neonatal populations.[3,5,8,9,11] Most notably, in the large, randomized, placebo-controlled, multicenter Caffeine for Apnea of Prematurity (CAP) trial, caffeine citrate exposure in infants with a birth weight of 500-1250 g was associated with lower rates of BPD and patent ductus arteriosus (PDA) and improved survival without neurodevelopmental impairment.[9,12,13] The CAP trial demonstrated no difference in the incidence of NEC between the caffeine citrate and control groups.[9] However, because the trial was not performed under an investigational new drug application, the resulting data were not available to the FDA to consider a label change.

The current medical literature indicates a significant gap between the caffeine citrate label recommendations and contemporary clinical practice. Therefore, the National Institute of Child Health and Human Development prioritized investigating dosing and safety of caffeine citrate in treating AOP under an investigational new drug application with the FDA. We conducted this study to better characterize safety and exposure-response of caffeine citrate in extremely premature infants receiving the drug off-label, and to provide data to the FDA for consideration of revising the pediatric labeling of caffeine citrate.

Methods

Electronic health records from four NICUs were used to identify premature infants born at ≤28 weeks of gestational age who received at least 1 dose of caffeine citrate prior to day of life 120. We excluded infants with a congenital anomaly. Infants were selected consecutively in reverse chronological order, from 2013 to 2010. Data collected from electronic health records included basic maternal demographics, infant birth characteristics, laboratory and radiology reports, procedures, medication records, weights, caffeine citrate plasma concentration (when available), and diagnoses. Prior to its start, the study was approved by an institutional review board at participating sites, and a waiver of informed consent was granted.

Study Outcomes

Clinical events of interest included BPD, medical and surgical NEC, spontaneous intestinal perforation, grade II-IV intraventricular hemorrhage (IVH), seizure, arrhythmia, PDA ligation, and death. BPD was defined as the need for supplemental oxygen at 36 weeks of postmenstrual age (PMA). NEC was defined by modified Bell staging criteria, stage IIA or greater.[14] The diagnosis of IVH was based upon head ultrasound results with the highest grade II, III, or IV hemorrhage in either ventricle.[15] NEC, spontaneous intestinal perforation, PDA ligation, seizure, and arrhythmia events were included if the event occurred on a day of caffeine citrate dosing. All BPD and IVH events occurring after initiation of caffeine therapy were included in this analysis regardless of whether the infant received caffeine citrate on the day of the event. Death was reported after initiation of caffeine therapy, as well as on the day of caffeine citrate dosing.

Table II. Cohort characteristics

Characteristics	N = 410
Gestational age (wk)	26 (24, 27)
Birth weight (g)	800 (660, 950)
Male	55%
Singleton birth	70%
Inborn	83%
Cesarean delivery	72%
Hospital stay (d)	87 (68, 104)
White	50%
Antenatal steroids	90%
Surfactant therapy	95%

Data presented as % or median (IQR).

Statistical Analyses

The planned sample size was 400, which was based on the 95% CI (exact binomial) for a clinical event of interest of 0.04%-8.9%. We used descriptive analysis to examine the frequency of clinical events of interest as well as the mean, median, and range of caffeine citrate exposures. For each participant, we evaluated caffeine exposure regarding loading dose (defined as day 1 of caffeine), average daily maintenance dose (mg/kg) (defined as cumulative caffeine doses excluding loading day 1 divided by number of dose days), the maximum dose of caffeine after loading day 1, and cumulative exposure (including all caffeine doses). In addition, we evaluated age at start of therapy, duration of exposure, and individual average plasma concentrations when available as part of clinical care. Indications for the use of caffeine citrate or the reason why concentrations were obtained were not available in this cohort. We reported medians (IQRs) of individual caffeine citrate exposures for the cohort.

We evaluated the association between caffeine citrate exposure and select clinical events of interest with a higher event rate at the participant level using logistic regression controlling for site, gestational age, birth weight, and concomitant medications (**Table I**; available at www.jpeds.com). Specific clinical-event-of-interest outcomes were BPD, NEC, and PDA ligation. Two separate adjusted analyses were performed for each event outcome to evaluate exposure based on either caffeine citrate dose information or serum concentrations, where available, for a total of 6 models. For analyses with caffeine citrate dose, we considered mean daily caffeine citrate dose (mg/kg/day) and duration of therapy. For regression, the average daily caffeine dose predictor was calculated as the cumulative caffeine dose (including the day 1 loading dosage) divided by the number of dose days until the event day for participants who experienced the clinical event of interest, and over the full study period for participants who did not. For analyses with caffeine citrate plasma concentrations, we used the maximum plasma level for BPD and the most recent plasma level seven days before or after the event for NEC and PDA ligation in the subset of participants with

Table III. Summary of caffeine citrate doses and concentration by site

	Site 1 (N = 100)	Site 2 (N = 108)	Site 3 (N = 107)	Site 4 (N = 95)	Total (N = 410)
Postnatal age at start of caffeine (d)	1 (0-1)	0 (0-0)	0 (0-1)	0 (0-1)	0 (0-1)
Loading dose d 1 (mg/kg/d)	20 (19-22)	17 (13-25)	20 (20-25)	20 (20-20)	20 (19-23)
Daily maintenance dose (mg/kg/d)*	9 (8-10)	7 (5-10)	5 (5-6)	9 (8-10)	8 (5-10)
Maximum daily dose (mg/kg/d)	20 (12-24)	11 (8-19)	13 (10-15)	19 (17-20)	16 (10-20)
Cumulative dose (mg/kg)	666 (584-852)	380 (295-517)	263 (201-333)	538 (412-718)	455 (292-640)
Duration of treatment (d)	77 (62-97)	55 (45-65)	52 (35-64)	63 (51-80)	60 (46-75)
	Site 1 (N = 24)	**Site 2 (N = 3)**	**Site 3 (N = 101)**	**Site 4 (N = 46)**	**Total (N = 174)**
Average plasma concentration (mg/L)†	26 (22-30)	24 (22-26)	16 (14-18)	24 (18-29)	18 (15-24)
Maximum plasma concentration (mg/L)	29 (26-33)	24 (22-26)	24 (21-27)	27 (18-35)	25 (21-29)
Postnatal age at first collection (d)	21 (15-38)	40 (38-43)	4 (3-6)	22 (17-31)	7 (4-20)

Data presented as median (IQR) in cohort; individual variables represent summary statistics per participant.
Multiple doses administered in a calendar day were combined as the daily dose.
*For each participant, maintenance dose was defined as the average of all caffeine doses after loading dose day 1.
†For each participant, average plasma concentration was defined as the average of all available plasma concentrations.

available plasma concentration information. In the BPD analyses, all infants discharged or transferred from the hospital before 36 weeks of PMA were not considered at risk of BPD and were excluded.

Results

The analysis included 410 infants (Table II) from the following participating sites: Children's Hospitals and Clinics of Minnesota (n = 100), Coastal Carolina Neonatology (n = 108), Children's Hospital of Philadelphia Newborn Care at Pennsylvania Hospital (n = 107), and Hackensack University Medical Center (n = 95). The studied infants had a birth weight range of 340-1460 g and a gestational age range of 22-28 weeks. The median (IQR) first-day loading dose was 20 (19-23) mg/kg/day, and the subsequent median of the individual average daily maintenance caffeine citrate dose for the study cohort was 8 (5-10) mg/kg/day, excluding the first (loading) day of dosing; total duration was 60 (46-75) days (Table III). Median (IQR) postnatal age at the start of caffeine citrate therapy was 0 (0-1) days, the median (IQR) PMA on the last day of caffeine citrate dosing was 34 (33-36) weeks, and the median (IQR) postnatal age at hospital discharge or transfer was 87 (68-104) days. Overall, 389 (95%) infants started caffeine citrate therapy by 2 days of age, and 390 (95%) infants received caffeine citrate for ≥10 days. Plasma caffeine concentrations were available for 174 infants, with a median (IQR) of 4 (2-10) concentrations recorded per infant. The median (IQR) of the individual average plasma concentration was 18 (15-24) mg/L (Table III). The postnatal age at first plasma collection varied, with an overall median of 7 (4-20) days.

Altogether, 209 (51%) infants experienced at least 1 clinical event of interest, and their incidence varied across sites (Table IV). We identified 10 infants (2%) who experienced a clinical event of interest (other than BPD or IVH) on a day without caffeine and, per study design, were not included in this analysis. Death occurred in 28 infants (6.8%), of whom 9 (2%) died on a day of caffeine citrate exposure. The median (IQR) gestational ages for the deceased (on a caffeine dose date) and surviving infants were 24 (23-24) weeks and 26 (25-27) weeks, respectively. The median (IQR) birth weights for the deceased and surviving infants were 595 (510-710) g and 810 (670-950) g, respectively. The median (IQR) durations of therapy for the deceased and surviving infants were 9 (3-12) days and 60 (47-76) days, respectively. Overall, the most common clinical events of interest included BPD (37%), grade III-IV IVH (13%), and PDA ligation (12%). NEC (medical or surgical) occurred in 35 (9%) infants. Seizures were reported in 13 infants (3%), all of whom received phenobarbital. No arrhythmias were reported.

Controlling for birth weight, gestational age, site, and concomitant medications, increased average caffeine citrate daily dose was associated with reduced odds of NEC and PDA ligation, with aORs (95% CIs) of 0.78 (0.63-0.92) and 0.74 (0.61-0.86), respectively. There was no significant association between dose and BPD (P = .33). In addition, increasing the duration of therapy was not associated with increased odds of BPD, NEC, or PDA ligation. In the subset of infants with plasma concentrations and adjusting as

Table IV. Summary of clinical events of interest diagnosed on a day of caffeine citrate exposure by site

	Site 1 (N = 100)	Site 2 (N = 108)	Site 3 (N = 107)	Site 4 (N = 95)	Total (N = 410)
Death	0%	2%	4%	3%	2%
BPD*,†	49%	27%	29%	40%	37%
Medical NEC	1%	8%	4%	5%	5%
Surgical NEC	4%	3%	8%	3%	4%
SIP	5%	7%	5%	2%	5%
Grade II IVH†	7%	7%	8%	7%	7%
Grade III or IV IVH†	17%	9%	14%	11%	13%
PDA ligation	14%	19%	8%	6%	12%
Seizures	2%	8%	2%	0%	3%
Arrhythmia	0%	0%	0%	0%	0%

SIP, spontaneous intestinal perforation.
*Per BPD definition, participants discharged or transferred from hospital before 36 weeks of PMA are excluded from this analysis.
†All BPD and IVH (grade II, III, or IV) are included in this analysis regardless of whether the infant was receiving caffeine on the day of the event.

Table V. Comparison of prior studies of caffeine citrate reporting NEC frequency

	N caffeine	Sites	Population	NEC, n/N (%)	Median duration of therapy (d)
FDA label[10,*]	46	9	28 to <33 wk of gestational age	2/46 (4.3%)	10
CAP trial[9,†]	1006	35	500-1250 g	63/1006 (6.3%)[‡]	37
NICHD NRN[28,§]	9575	20	22-28 wk of gestational age Birth weight 401-1500 g	11%	Not reported
VON[29,§]	38 017	669	Birth weight 501-1500 g	2015/38, 017 (5.3%)	Not reported
Current study[§]	410	4	22-28 wk of gestational age	35/410 (8.5%)	60

NICHD NRN, The National Institute of Child Health and Human Development Neonatal Research Network study from 2003 to 2007; *VON*, The Vermont Oxford Network study from 2009. No studies have shown a significant caffeine-related increase in NEC.
*Randomized controlled trial, post-hoc analysis with no significant increase in NEC with caffeine treatment compared with placebo.
†Randomized controlled trial with no significant increase in NEC with caffeine treatment compared with placebo ($P = .63$).
‡Placebo group reported NEC in 67 of 1000 (6.7%).
§Retrospective analysis.

possible for site, gestational age, birth weight, and concomitant medications, increasing plasma concentrations of caffeine citrate were not associated with BPD, NEC, or PDA ligation.

Discussion

Our study demonstrated that caffeine citrate is administered to neonates born at younger gestational age (22-28 weeks of gestational age) at higher doses and for longer durations than recommended by the FDA-approved drug label. Increasing caffeine citrate dose in this population is associated with decreased rates of NEC and PDA ligation. Most infants in this study received doses that were higher than recommended by the drug label; however, plasma concentrations remained in the therapeutic window. The CAP trial also supported higher dosing in these infants, with a daily maintenance dose of up to 10 mg/kg.[9]

No clinical trials have definitively determined when to discontinue caffeine citrate therapy in preterm infants. However, because AOP is uncommon beyond 34 weeks of gestational age, caffeine citrate therapy is often continued until preterm infants are 34-36 weeks of corrected gestational age and free of any apnea episodes for at least 8 days.[16] In the CAP trial, the median PMA at discontinuation of caffeine citrate was 34 weeks and the median duration of therapy was 37 days.[9] The data in our study align with the CAP trial, as caffeine citrate was used for a median of 60 days, which is 6 times longer than recommended in the FDA-approved label, and the median PMA on the last day of caffeine citrate dosing was 34 weeks.

This study shows that increasing the duration of therapy with caffeine citrate was not associated with increased odds of BPD. Other studies have demonstrated the important role of duration of therapy with caffeine citrate in decreasing the risk of BPD.[17-19] In the CAP trial, there was a significant reduction of BPD incidence in infants who received caffeine citrate (36% vs 47% in the placebo group). The authors attributed the decrement of BPD rates to a shorter duration of endotracheal intubation and positive pressure ventilation in the caffeine citrate-treated patients compared with the controls.[9]

In the current study, caffeine citrate therapy was initiated early, as is consistent with previous studies.[20] In a large multicenter cohort study using data from 62 056 very low birth weight infants, the use of early caffeine citrate therapy within the first 3 days of life was associated with a lower odds of BPD in survivors compared with later use (23% vs 31%; OR 0.68 [95% CI 0.63-0.73]).[21] In our study, the median start day was zero, suggesting that many clinicians are using caffeine citrate shortly after birth to prevent apnea, effectively maintain noninvasive support, or decrease risk of BPD rather than waiting for apnea to occur. In a pilot trial, infants of <29 weeks of gestational age were randomized to early prophylactic use of caffeine before 2 hours of age or caffeine initiation at 12 hours of age.[22] The study reported that fewer infants in the early caffeine treatment group required intubation by 12 hours of age, compared with those receiving caffeine at 12 hours of age (27% vs 70%; $P = .08$).

Other benefits of caffeine citrate include decreased need for treatment (medical and surgical) of PDA.[21,23,24] This association could be explained by different primary or secondary mechanisms, including a diuretic effect, vasoconstrictor effect, adenosine antagonism, reduction in duration of invasive ventilation, or improvement in cardiac output and blood pressure.[25] The decreased need for respiratory or cardiac support may reduce the likelihood of a clinician evaluating the patency of a PDA or choosing to treat a PDA. In our cohort, increased mean caffeine citrate dose was significantly associated with a reduction in surgical treatment for PDA. However, the indications for ligation of a PDA were not evaluated in this study and are controversial in the literature.[26] In the CAP trial, the post-hoc analysis revealed that infants in the caffeine citrate group were significantly less likely to require pharmacological treatment or surgical ligation compared with infants in the control group.[9] Other retrospective studies also found that early caffeine citrate therapy within the first 3 days of age was associated with a significant reduction of incidence of PDA requiring treatment compared with later initiation of therapy.[16,20,21]

NEC is a devastating complication of prematurity.[27] The FDA's label warning for caffeine citrate's potential association with NEC[7] is based on post-hoc analysis of an older randomized, double-blind, placebo-controlled trial of 85 premature infants (caffeine citrate = 46, placebo = 39) in whom the incidence of NEC was not significantly different between the caffeine group (4.3%) and the placebo group

(2.6%).[10] In contrast, our results as well as those from other large cohorts and the pivotal CAP trial did not demonstrate any association between caffeine citrate exposure and NEC (**Table V**).[28,29] The primary data from CAP were not made available to the FDA, and in general, published studies alone are insufficient for the FDA to make decisions.

Strengths of this study include that the data are recent (2010-2013), representing current care of extremely preterm infants from 4 large NICUs, and the availability of caffeine citrate dosing data. This study was performed under an investigational new drug application and with primary data sources available to the FDA.

As with all retrospective analyses of electronic medical records, weaknesses include an absence of data regarding indication for use and variation in the administration of caffeine citrate per local standard NICU practices (ie, not as a study drug). There was no placebo group involved because nearly all infants in this gestational age group received caffeine citrate. Because caffeine citrate treatment was administered via standard of care, potential modeling biases were inherent in the selection of dosage and treatment duration based on participant response and changes in condition. Given the study design, clinical events of interest (except for BPD and IVH) were included only if they occurred on the day of caffeine citrate dosing. Characterization of infant death was limited to birth characteristics and exposure to caffeine. Changes in clinical practice over the study period could not be taken into consideration.

In summary, caffeine citrate was routinely administered off-label to extremely premature infants during their first 2 months after birth. Duration of therapy was not associated with increased odds of BPD. Furthermore, the dose and duration of therapy were not associated with increased odds of PDA ligation or NEC. This study (and the CAP trial) does not support an association between caffeine citrate exposure and NEC. Additional studies are necessary to optimize the timing of caffeine citrate initiation, dose, and the duration of therapy. Given differences between the FDA-approved label and the published literature, results from this research are being submitted to the FDA for review. ■

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50 Years Ago in *The Journal of Pediatrics*

Active Chronic Hepatitis in Infancy: Possible Presence of the Disease in Siblings

Benjamins D, Sunshine P. J Pediatr 1969;75:294-8.

In 1969, Benjamins and Sunshine described a 7-month-old infant with jaundice, elevated liver enzymes, positive autoantibodies, an elevated IgG concentration, and a liver biopsy revealing marked portal lymphoplasmacytic infiltrate and piecemeal necrosis. Her liver enzymes and IgG normalized after a 2-month course of corticosteroid therapy. Interestingly, this patient had an older sister with adrenal insufficiency diagnosed at 42 months; she died at 46 months of life and at autopsy was also found to have a cirrhotic liver.

Over the last 50 years, autoimmune liver diseases have been increasingly recognized in the pediatric population. In the 1990s, the International Autoimmune Hepatitis Group was developed to establish criteria to define autoimmune hepatitis (AIH). In 2008, this group developed simplified criteria using autoantibodies, IgG concentrations, histology, and the absence of viral hepatitis to diagnose AIH, an approach subsequently validated in children.[1] Based on the information provided, the 7-month-old infant would have been classified as having "probable" AIH. Had the presence of chronic viral hepatitis been excluded, she would have fit the criteria for "definite" AIH.

The infantile onset of AIH is atypical and should raise the concern for an immunodeficiency. Lankisch et al describe a series of children 6 months to 3 years of age with AIH.[2] They report 3 patients with pathologic mutations in the autoimmune regulator gene (AIRE), which is critical for immune tolerance. AIRE mutations are associated with autoimmune polyendocrinopathy-candidiasis-ectodermal dysplasia (APCED) and are inherited in an autosomal recessive manner. Although typically associated with candidiasis, hypoparathyroidism, and adrenocortical failure, AIH can be present in up to 20% of patients. Indeed, this case series revealed that 2 patients with confirmed AIRE mutation presented with AIH as the only manifestation. Generally, children with APCED respond to immunosuppression.

Since Benjamins and Sunshine described what may have been the first siblings with AIH secondary to APCED, significant strides have been made in the recognition and diagnosis of patients with AIH. However, the underlying pathomechanisms of this disorder remain elusive.

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Appendix

The PTN Publications Committee:
Additional members of the Best Pharmaceuticals for Children Act–Pediatric Trials Network Steering Committee

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Table I. Concomitant medications

1. Furosemide	12. Fentanyl	23. Miconazole	34. Midazolam
2. Bumetanide	13. Hydromorphone	24. Nifedipine	35. Pentobarbital
3. Ethacrynic acid	14. Methadone	25. Omeprazole	36. Phenytoin
4. Hydrochlorothiazide	15. Amiodarone	26. Propranolol	37. Dopamine
5. Chlorothiazide	16. Amlodipine	27. Ranitidine	38. Dobutamine
6. Spironolactone	17. Dexmedetomidine	28. Sildenafil	39. Epinephrine
7. Acetazolamide	18. Erythromycin	29. Carbamazepine	40. Milrinone
8. Indomethacin	19. Fluconazole	30. Phenobarbital	41. Norepinephrine
9. Ibuprofen	20. Ketoconazole	31. Rifampin	42. Phenylephrine
10. Hydrocortisone	21. Lidocaine	32. Fosphenytoin	43. Vasopressin
11. Morphine	22. Methimazole	33. Lorazepam	44. Acetaminophen