

Safety of Off-Label Use of Caffeine Citrate in Premature Infants

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Disclosures

Speaker:

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1. Dr. Puia Dumitrescu has no financial relationships to disclose or Conflicts of Interest to resolve. Any real or apparent conflicts of interest related to the content of this presentation have been resolved.
2. Dr. Puia Dumitrescu is supported by a Pediatric Departmental NIH T32 (PI Benjamin).
3. The use of caffeine described in this population is off-label.

Caffeine citrate

- 3rd most commonly used medication in neonatal intensive care units after ampicillin and gentamicin.
- FDA Label
 - Indicated for short-term (10 days) treatment of apnea of prematurity (AOP)
 - 28 and <33 weeks gestational age (GA)
 - Associated with necrotizing enterocolitis (NEC)

Caffeine citrate

- In clinical trials of premature infants
 - Reduces the frequency of AOP
 - Reduces bronchopulmonary dysplasia (BPD)
 - No association with NEC
- In clinical practice is frequently used off-label
 - 22-27 weeks GA
 - >10 days duration



Objective

- Characterize the safety of off-label caffeine citrate in premature infants

Data source

- Used electronic health records from four sites in the Pediatric Trials Network
 - Children's Hospitals and Clinics of Minnesota
 - Coastal Carolina Pediatrics
 - Children's Hospital of Philadelphia
 - Hackensack University Medical Center

Study population

- Inclusion Criteria
 - 2005 to 2013
 - <28 weeks GA
 - <120 days postnatal age (PNA)
 - ≥ 1 day of caffeine therapy
- Exclusion Criteria
 - Known major congenital anomaly

Outcomes

- Clinical Events of Interest
 - NEC
 - Bronchopulmonary dysplasia (BPD)
 - Patent ductus arteriosus (PDA) ligation

Association between caffeine exposure and clinical events of interest

- Models
 - Study dose, maximum plasma level - predictors for BPD
 - Study dose, most current plasma level - predictors for NEC, PDA
- Logistic regression used to evaluate the association of clinical events of interest at infant level
 - BPD was evaluated at 36 weeks of PMA assessment
 - NEC and PDA were evaluated on a day of caffeine dosing.
- Controlled for: site, GA, BW, mean dose, duration of therapy, plasma levels and concomitant medication

Baseline Characteristics

	N = 410 % or median (min, max)
Postnatal age at start of caffeine (days)	0 (0 - 44)
Gestational age (weeks)	26 (22 - 28)
Birth weight (g)	800 (340 - 1460)
Male	55%
Singleton	70%
Inborn	83%
Race	
White or Caucasian	50%
Antenatal steroids	90%
Surfactant therapy	95%

Caffeine citrate exposure

- 95% received caffeine citrate for >10 days
- Median (range of caffeine exposure)
 - duration of therapy - 60 days (1-144)
 - daily dose per kg - 8 mg/kg (4 - 25)
 - maximum dose - 20 mg/kg (5 - 46)
 - cumulative dose - 455 mg/kg (20 - 1231)

Clinical events of interest

		Total (N=410)
BPD		37 %
NEC (medical and/or surgical)		9 %
	Medical NEC	5 %
	Surgical NEC	4 %
PDA requiring surgical treatment		12 %

Adjusted ORs - caffeine exposure association with clinical events of interest

	BPD (N=119)	NEC (N=37)	PDA (N=50)
Mean Dose (mg/kg/day)	0.91 (0.75, 1.10)	0.78 (0.63, 0.92)	0.74 (0.61, 0.86)
Duration of Therapy (day)	0.96 (0.94, 0.99)	0.93 (0.91, 0.96)	0.90 (0.87, 0.93)
Maximum Plasma Concentration (mg/L)	0.96 (0.90, 1.03)	N/A	N/A
Current Plasma Concentration (mg/L)	N/A	1.10 (0.99, 1.23)	1.02 (0.90, 1.16)

Conclusions

- Increased caffeine citrate dose was associated with lower risk of NEC and PDA
- Increased caffeine citrate duration was associated with lower risk of NEC, BPD and PDA

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Extra slides

Data Summary

	N - caffeine	Sites	Population	NEC	Median duration, days
Current Label	46	9	28 to <33 wk GA	4.3%#	10
CAP Trial	1006	35	500-1250 g	6.3%*	37
Retrospective EHR Data	410	4	22-28 wk GA	4.4%	60
Pediatrix Data	86,647	299	21-32 wk GA	1.3%	29
PROP Data	794	8	23-28 wk GA	2.1%	47

#2.6% in placebo group

*6.7% in placebo group

Clinical events of interest

	Total (N=410)
	%
Death - Number of Participants	2
BPD	37
NEC (medical and/or surgical)	9
Medical NEC	5
Surgical NEC	4
SIP	5
Grade II IVH	7
Grade III or IV IVH	13
PDA requiring surgical treatment	12
Seizures	3
Arrhythmia	0