Safety of Off-label use of Caffeine Citrate in Premature Infants

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Background: Caffeine citrate is labeled by the FDA for short-term treatment of apnea of prematurity (AOP) for infants born between 28 and 33 weeks gestational age (GA). The label includes an association with necrotizing enterocolitis (NEC) based on a trial of 45 infants exposed to the drug. Caffeine citrate is often used for long-term treatment of infants born <28 weeks GA, and NEC has not been observed with caffeine citrate use in subsequent larger trials.

Objective: Characterize the safety of caffeine citrate in premature infants receiving caffeine off-label.

Design/Methods: We used Electronic Health Records (EHR) from 2005-13 from four neonatal intensive care units (NICUs) to identify all infants <28 weeks GA, <120 days of age, without major congenital anomalies exposed to caffeine citrate. Safety outcomes of interest included death, NEC (either medical or surgical), spontaneous perforation (SIP) and laboratory abnormalities. We used logistic regression models controlling for GA, birth weight, caffeine dose, and duration of caffeine citrate therapy to evaluate the association of caffeine exposure with NEC. NEC was evaluated through logistic regression model by whether the event occurred or did not occur on a day of caffeine dosing at infant level. The independent factors included site, GA (weeks), birth weight (by units of 100 grams), mean study dose (mg/kg/day), duration of therapy (day) and concomitant medications by classification.

Results: The cohort comprised 410 infants (Table); 94% received caffeine citrate for > 13 days (median 60 days; range 1-144). The median daily and cumulative study dose per kg of participant dosing weight were 8 mg/kg (4 – 25) and 455 mg/kg (20 – 1231), respectively. Increasing caffeine citrate dose was associated with lower risk of NEC events (medical or surgical), odds ratio = 0.78 (0.63, 0.92), and increased caffeine citrate duration was associated with lower risk of NEC events (medical or surgical), odds ratio=0.93 (0.91, 0.96).

Conclusions: In this cohort of infants <28 weeks GA, increased exposure to caffeine (dose or duration) was not associated with increased risk of NEC. This study adds significant data for the safety of caffeine use in clinical practice in premature infants born < 28 weeks. The results from this research are being submitted to FDA for review and possible labeling change.

Table 1. Cohort 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)
Race	
White or Caucasian	50%
Black or African American	34%
Other/Not reported	17%
Antenatal steroids	90%
Surfactant therapy	95%
Outcomes	
Death	2%
NEC (either medical or surgical)	9%
Medical NEC	5%
Surgical NEC	4%