ORIGINAL ARTICLE

Caffeine Therapy for Apnea of Prematurity

Barbara Schmidt, M.D., Robin S. Roberts, M.Sc., Peter Davis, M.D., Lex W. Doyle, M.D., Keith J. Barrington, M.D., Arne Ohlsson, M.D., Alfonso Solimano, M.D., and Win Tin, M.D., for the Caffeine for Apnea of Prematurity Trial Group*

ABSTRACT

BACKGROUND

Methylxanthines reduce the frequency of apnea of prematurity and the need for mechanical ventilation during the first seven days of therapy. It is uncertain whether methylxanthines have other short- and long-term benefits or risks in infants with very low birth weight.

METHODS

We randomly assigned 2006 infants with birth weights of 500 to 1250 g during the first 10 days of life to receive either caffeine or placebo, until drug therapy for apnea of prematurity was no longer needed. We evaluated the short-term outcomes before the first discharge home.

RESULTS

Of 963 infants who were assigned to caffeine and who remained alive at a postmenstrual age of 36 weeks, 350 (36 percent) received supplemental oxygen, as did 447 of the 954 infants (47 percent) assigned to placebo (adjusted odds ratio, 0.63; 95 percent confidence interval, 0.52 to 0.76; P<0.001). Positive airway pressure was discontinued one week earlier in the infants assigned to caffeine (median postmenstrual age, 31.0 weeks; interquartile range, 29.4 to 33.0) than in the infants in the placebo group (median postmenstrual age, 32.0 weeks; interquartile range, 30.3 to 34.0; P<0.001). Caffeine reduced weight gain temporarily. The mean difference in weight gain between the group receiving caffeine and the group receiving placebo was greatest after two weeks (mean difference, –23 g; 95 percent confidence interval, –32 to –13; P<0.001). The rates of death, ultrasonographic signs of brain injury, and necrotizing enterocolitis did not differ significantly between the two groups.

CONCLUSIONS

Caffeine therapy for apnea of prematurity reduces the rate of bronchopulmonary dysplasia in infants with very low birth weight. (ClinicalTrials.gov number, NCT00182312.)

From the Departments of Clinical Epidemiology and Biostatistics (B.S., R.S.R., A.O.) and Pediatrics (B.S.), McMaster University, Hamilton, Ont., Canada; the Department of Obstetrics and Gynaecology, University of Melbourne, Melbourne, Australia (P.D., L.W.D.); the Department of Pediatrics, McGill University, Montreal (K.J.B.); the Department of Pediatrics, University of Toronto, Toronto (A.O.); the Department of Pediatrics, University of British Columbia, Vancouver, Canada (A.S.); and the Department of Pediatrics, James Cook University, Middlesbrough, United Kingdom (W.T.). Address reprint requests to Dr. Schmidt at the McMaster University Medical Center, Rm. 3N11E, 1200 Main St. W., Hamilton, ON L8N 3Z5, Canada, or at schmidt@mcmaster.ca.

*Members of the Caffeine for Apnea of Prematurity Trial Group are listed in the Appendix.

N Engl J Med 2006;354:2112-21.

Apnea of prematurity — defined as cessation of breathing that lasts for more than 15 seconds and is accompanied by hypoxia or bradycardia — occurs in at least 85 percent of infants who are born at less than 34 weeks of gestation.[1] Widely used treatments include the application of continuous positive airway pressure and the prescription of a methylxanthine.[2] The methylxanthines — aminophylline, theophylline, and caffeine — reduce the frequency of apnea and the need for mechanical ventilation during the first seven days of therapy.[3] However, it has remained uncertain whether methylxanthines have any additional short- and long-term benefits or risks in preterm infants.[3-5] Despite this uncertainty, methylxanthines have been the mainstay of the pharmacologic treatment of apnea for the past 25 years.[2] Methylxanthines are typically prescribed in very preterm infants until they reach a postmenstrual age of 34 to 35 weeks.[6] Drug exposure may last even longer. A recent study from the Neonatal Research Network of the National Institute of Child Health and Human Development showed that among infants with very low birth weight, 44 percent of those with bronchopulmonary dysplasia and 21 percent of those without such disease were still receiving methylxanthines at a postmenstrual age of 36 weeks.[7]

The potential for harm exists because methylxanthines are inhibitors of adenosine receptors.[8] Adenosine preserves brain ATP levels and protects brain cells during experimental hypoxia and ischemia in a variety of animal models.[9-11] Methylxanthines also increase oxygen consumption in preterm infants and may therefore diminish growth.[12-15] We conducted this randomized, placebo-controlled, multicenter trial of caffeine to study the short- and long-term efficacy and safety of methylxanthine therapy in infants with very low birth weight.

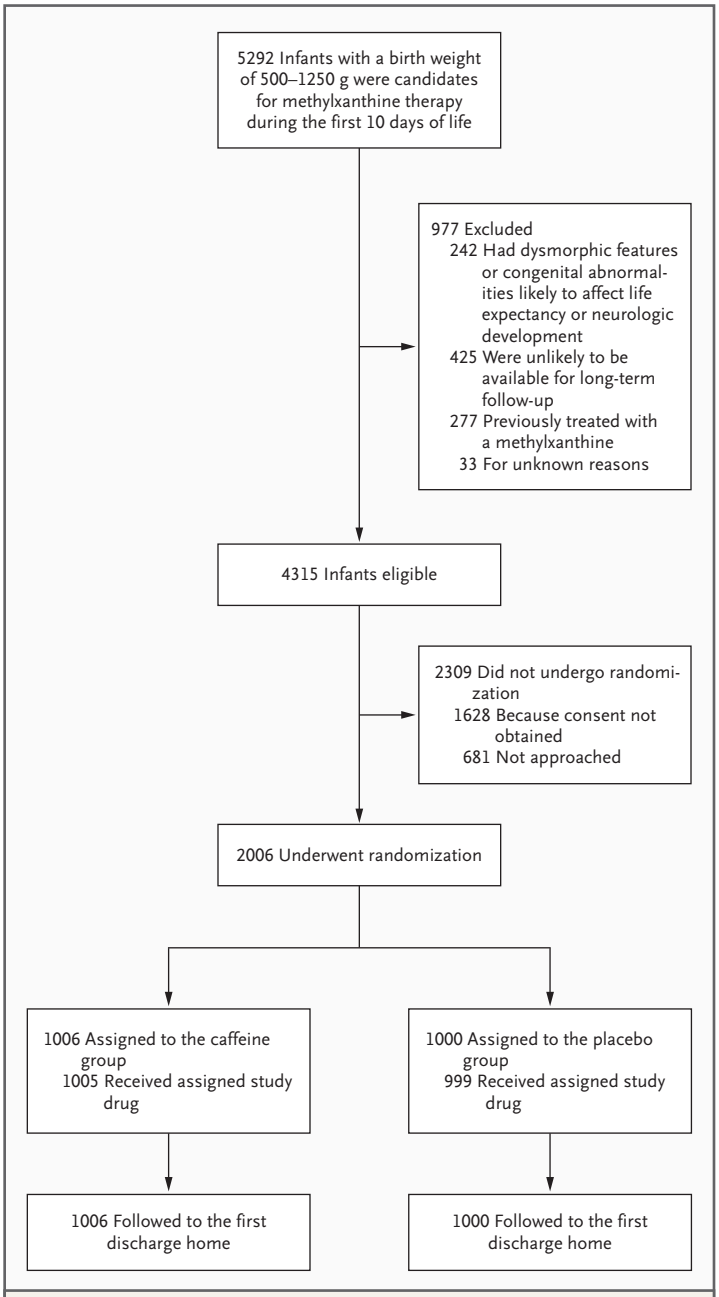

Figure 1. Numbers of Infants Who Were Eligible for the Study and Randomly Assigned to Receive Caffeine Citrate or Placebo.

METHODS

STUDY INFANTS

Infants with a birth weight of 500 to 1250 g were eligible for enrollment if their clinicians considered them to be candidates for methylxanthine therapy during the first 10 days of life. We documented the following reasons why clinicians intended to use methylxanthines: to prevent apnea, to treat apnea, or to facilitate the removal of an endotracheal tube. The reasons for exclusion are listed in Figure 1. The research ethics boards of all clinical centers approved the protocol. Written informed consent was obtained from a parent or guardian of each infant. An investigational new drug application was filed with Health Canada because caffeine is not approved for the treatment of apnea of prematurity in Canada. Clinical-trial-notification applications were filed in Australia. Appropriate regulatory approvals were obtained elsewhere.

Table 1. Baseline Characteristics and Status of the Infants at Randomization and Their Mothers.*

Characteristic	Caffeine Group (N=1006)	Placebo Group (N=1000)
Mothers		
Age — yr	30±6	30±6
Race or ethnic group — no. (%)†		
White	797 (79)	789 (79)
Black	67 (7)	71 (7)
Asian	84 (8)	82 (8)
Other or unknown	58 (6)	58 (6)
Antenatal corticosteroids —— no. (%)	890 (88)	873 (87)
Clinical chorioamnionitis — no. (%)	138 (14)	133 (13)
Cesarean section — no. (%)	628 (62)	626 (63)
Infants at birth		
Birth weight — g	964±186	958±181
Gestational age — wk	27±2	27±2
Female sex — no. (%)	508 (50)	470 (47)
Birth weight <10th percentile for gestational age — no. (%)‡	161 (16)	158 (16)
Born at study hospital — no. (%)	903 (90)	890 (89)
Singleton birth — no. (%)	721 (72)	712 (71)
Apgar score at 5 min		
Median	8	8
Interquartile range	7–9	7–9

RANDOMIZATION

A computer-generated randomization scheme was used to assign the infants to treatment groups in a 1:1 ratio. Randomization was stratified according to the study center and balanced in random blocks of two or four patients. A designated pharmacist at each center received a binder containing the prespecified sequence of treatment-group assignments from a statistician at the coordinating center who was not otherwise involved in the trial. Access to the binder was restricted to selected pharmacy personnel. The pharmacy study logs were retrieved after the completion of recruitment to ensure that all randomly assigned infants were included in the analysis. Infants were considered to have been randomly assigned at the time the first prescription for study drug was signed.

STUDY INTERVENTION AND COINTERVENTIONS

As soon as possible after random assignment, eligible infants received an intravenous loading dose of either 20 mg of caffeine citrate per kilogram of body weight or an equivalent volume of normal saline. This was followed by a daily maintenance dose of 5 mg per kilogram. If apneas persisted, the daily maintenance dose could be increased to a maximum of 10 mg of caffeine citrate per kilogram. The maintenance doses were adjusted weekly for changes in body weight and could be given orally once an infant tolerated full enteral feedings. The drug was monitored according to its clinical effect only.[16] Blood levels of caffeine were not measured. Doses of the study drug were held or reduced for symptoms suggestive of caffeine-induced toxicity (e.g., tachycardia, tachypnea, jitteriness, tremors, and unexplained seizures and vomiting) or for other clinical reasons. The study drug was discontinued permanently at the discretion of the local clinicians. However, it was recommended to continue therapy with the study drug until the infant had tolerated at least five consecutive days without the use of positive airway pressure.

Caffeine citrate for injection was supplied by Sabex. In the single study site in the United States, Cafcit (Roxane Laboratories) was used.

Table 1. (Continued.)

Characteristic	Caffeine Group (N=1006)	Placebo Group (N=1000)
Infants at randomization		
Age — days		
Median	3	3
Interquartile range	2–5	1–5
Indication for use of methylxanthines		
Treatment of documented apnea — no. (%)	429 (43)	401 (40)
Prevention of apnea — no. (%)	234 (23)	220 (22)
Facilitation of removal of endotracheal tube — no. (%)	341 (34)	378 (38)
Other — no. (%)	2 (<1)	1 (<1)
Supplemental oxygen — no. (%)	478 (48)	474 (47)
Any use of positive airway pressure — no. (%)	822 (82)	845 (84)
Endotracheal tube in situ — no. (%)	519 (52)	543 (54)
Therapies between birth and randomization — no. (%)		
Surfactant	679 (67)	677 (68)
Pleural drainage of pneumothorax	14 (1)	14 (1)
Postnatal corticosteroids	40 (4)	44 (4)
Prophylactic indomethacin	64 (6)	69 (7)
Indomethacin for patent ductus arteriosus	159 (16)	178 (18)
Ibuprofen for patent ductus arteriosus	11 (1)	8 (<1)
Surgical closure of patent ductus arteriosus	5 (<1)	1 (<1)
Blood products for pulmonary hemorrhage	14 (1)	3 (<1)

* Plus–minus values are means ±SD.
† Race or ethnic group was self-reported.
‡ The 10th percentile for gestational age in a normal population has been reported previously.[23]

To prevent contamination, the study protocol strongly discouraged the use of open-label methylxanthines. The use of doxapram — a respiratory stimulant — was also discouraged because of limited evidence of its safety and efficacy.[17] Nonpharmacologic therapies such as continuous positive airway pressure were used as necessary to control apnea.

An external safety monitoring committee reviewed the study data every four to six months during the enrollment phase. With the exception of this committee and the study pharmacists, no one involved in the study or in the care and assessment of outcomes of the infants was aware of the individual treatment-group assignments.

OUTCOMES

The primary outcome of this study is a composite of death, cerebral palsy, cognitive delay, deafness, or blindness at a corrected age of 18 to 21 months. Ascertainment of this outcome is under way and is expected to be completed by December 2006. The steering committee followed a recommendation by the external safety monitoring committee and agreed to analyze the protocol-specified secondary short-term outcomes after the completion of recruitment and the initial hospitalization of the study infants, including bronchopulmonary dysplasia, ultrasonographic signs of brain injury, necrotizing enterocolitis, retinopathy of prematurity, and growth.

Bronchopulmonary dysplasia was defined by the need for supplemental oxygen at a postmenstrual age of 36 weeks.[18] Cranial ultrasonography was recommended between the 14th and the 28th days of life, and between 34 and 36 weeks of postmenstrual age if the infant was still hospitalized in the study center at that time. The scans were read locally, and copies of the written reports were sent to the coordinating center. The follow-

Table 2. Use of Study Drug, Open-Label Methylxanthines, and Cointerventions.

Variable	Caffeine Group (N=1006)	Placebo Group (N=1000)	P Value
Study drug			
Postmenstrual age at first dose — wk			0.09
Median	28.1	27.7	
Interquartile range	26.6–29.3	26.4–29.1	
Postmenstrual age at last dose — wk			0.05
Median	34.4	34.7	
Interquartile range	33.0–35.9	32.9–36.1	
Dose reduction due to suspected caffeine-induced toxicity — no. (%)	23 (2.3)	14 (1.4)	0.18
Open-label methylxanthines — no. (%)			
Any use	90 (9.0)	100 (10.0)	0.45
Permanent switch	43 (4.3)	69 (6.9)	0.01
Cointerventions			
Postmenstrual age at last use of endotracheal tube — wk*			<0.001
Median	29.1	30.0	
Interquartile range	28.0–31.0	28.7–31.9	
Postmenstrual age at last use of positive airway pressure — wk*			<0.001
Median	31.0	32.0	
Interquartile range	29.4–33.0	30.3–34.0	
Postmenstrual age at last use of supplemental oxygen — wk*			<0.001
Median	33.6	35.1	
Interquartile range	30.6–36.9	32.0–37.6	
Doxapram — no. (%)	12 (1.2)	37 (3.7)	<0.001
Postnatal corticosteroids — no. (%)	145 (14.4)	202 (20.2)	<0.001
No. of transfusions of red cells			<0.001
Median	1	2	
Interquartile range	0–3	0–4	

* This outcome excludes 52 infants in the caffeine group and 55 infants in the placebo group who died.

ing lesions are indicative of brain injury and were analyzed as a group: intraparenchymal echodense lesions, cystic periventricular leukomalacia, porencephalic cysts, and ventriculomegaly with or without intraventricular hemorrhage.[19] Necrotizing enterocolitis was diagnosed during surgery, at autopsy, or by a finding of pneumatosis intestinalis, hepatobiliary gas, or free intraperitoneal air on radiography. All stages of retinopathy were recorded according to the international classification.[20,21] Weight and head circumference were recorded weekly.

The use of drug or surgical therapy to close a patent ductus arteriosus was documented but was not a prespecified outcome. However, after noticing a higher incidence of patent ductus arteriosus in the placebo group than in the caffeine group, the external safety monitoring committee recommended to the steering committee in June 2001 that additional data be collected for all infants whose duct was closed surgically. All decisions pertaining to the diagnosis and treatment of a patent ductus arteriosus were at the discretion of the local clinicians.

STATISTICAL ANALYSIS

Assuming an incidence of death or neurodevelopmental disability of 20 percent, we needed 1000 infants in each group for the study to have a statistical power of 80 percent to detect a 25 percent

relative reduction in the risk of the primary outcome. The current analyses of secondary outcomes were adjusted according to study center with the use of a logistic-regression model that included terms for treatment and center. The regression coefficient associated with treatment in the fitted model yielded a point estimate and 95 percent confidence interval for the treatment effect expressed as an odds ratio. The quotient of the estimated coefficient and its standard error was used as a z-test statistic for the null hypothesis of no treatment effect. Mean weight gain and head circumference were compared between the two groups at weekly intervals with the use of Student's t-test. Nonparametric tests or Fisher's exact test were used as appropriate to analyze the use of the study drug and cointerventions. All P values are two-sided.

RESULTS

STUDY INFANTS

The numbers of infants who were deemed eligible for the study and the numbers randomly assigned to receive caffeine citrate or placebo are shown in Figure 1. A total of 2006 infants were enrolled between October 11, 1999, and October 22, 2004 — 994 in Canada, 58 in the United States, 520 in Australia, and 434 in Europe and Israel. Six infants (four in the caffeine group and two in the placebo group) did not meet the eligibility criteria but were included in the analysis. All patients were followed to their first discharge home. Long-term follow-up is under way.[22] With the exception of sex, the baseline characteristics of the infants in the two groups at birth and of their mothers were similar. The status of the infants at randomization was also similar in the two groups (Table 1).

STUDY INTERVENTION AND COINTERVENTIONS

The use of the study drug and the use of cointerventions in the two groups are shown in Table 2. Study infants received their first doses of caffeine or placebo at a median postmenstrual age of 28 weeks and were weaned off the study drug before reaching a median postmenstrual age of 35 weeks. The median number of days of administration of the study drug was 37 in the caffeine group (interquartile range, 24 to 46) and 36 in the placebo group (interquartile range, 23 to 46; P=0.68). Only 37 infants (1.8 percent) — 23 in the caffeine group and 14 in the placebo group — had doses of the study drug withheld or reduced because of clinical symptoms and signs suggestive of caffeine-induced toxicity.

One hundred ninety infants (9.5 percent) received at least one dose of open-label methylxanthines, either because of an administrative error or intentionally. Of those, 112 infants were switched permanently to open-label methylxanthines at the request of the parents or clinical staff. A permanent switch to open-label methylxanthines occurred more frequently in the placebo group than in the caffeine group (P=0.01).

The administration of positive airway pressure through an endotracheal tube, the use of any positive airway pressure, and oxygen therapy were each discontinued approximately one week earlier for infants in the caffeine group than for infants in the placebo group (P<0.001 for each comparison). In addition, the following cointerventions were used less frequently in the caffeine group than in the placebo group: doxapram, postnatal corticosteroids, and red-cell transfusions (P<0.001 for each comparison). All cointerventions were prescribed at the discretion of the local clinicians.

OUTCOMES

Outcomes in the two groups before the first discharge home are shown in Table 3. Caffeine significantly reduced the frequency of bronchopulmonary dysplasia. Of the 963 infants who were assigned to caffeine and who were alive at a postmenstrual age of 36 weeks, 350 (36.3 percent) received supplemental oxygen, as compared with 447 of the 954 infants (46.9 percent) assigned to placebo (adjusted odds ratio, 0.63; 95 percent confidence interval, 0.52 to 0.76; P<0.001). The rates of death before the first discharge home, ultrasonographic signs of brain injury, and necrotizing enterocolitis did not differ significantly between the two groups. Adjustments for prespecified and prognostically important baseline characteristics yielded odds ratios for these outcomes that further attenuated the associations with the assigned treatment.

During the first three weeks after randomization, infants in the caffeine group gained less weight than infants in the placebo group (Fig. 2). No significant differences in weight gain were observed between four and six weeks after randomization. Mean head circumferences in the two groups remained similar throughout the entire

Table 3. Outcomes before the First Discharge Home.*

Outcome	Caffeine Group (N=1006)	Placebo Group (N=1000)	Unadjusted Odds Ratio	Odds Ratio Adjusted for Center (95% CI)	P Value	Odds Ratio Adjusted for Center and Patient Characteristics (95% CI)†
Death — no. (%)	52 (5.2)	55 (5.5)	0.94	0.93 (0.63–1.38)	0.73	0.96 (0.64–1.44)
Bronchopulmonary dysplasia — no. (%)‡	350 (36.3)	447 (46.9)	0.65	0.63 (0.52–0.76)	<0.001	0.64 (0.52–0.78)
Retinopathy of prematurity — no. (%)§	322 (39.2)	362 (43.2)	0.84	0.84 (0.68–1.03)	0.09	0.88 (0.70–1.10)
Brain injury — no. (%)¶	126 (13.0)	138 (14.3)	0.90	0.90 (0.69–1.18)	0.44	0.97 (0.74–1.28)
Necrotizing enterocolitis — no. (%)	63 (6.3)	67 (6.7)	0.93	0.93 (0.65–1.33)	0.63	0.94 (0.65–1.34)
Drug therapy only for closure of patent ductus arteriosus — no. (%)‖**	293 (29.3)	381 (38.1)	0.67	0.67 (0.55–0.81)	<0.001	0.67 (0.54–0.82)
Surgical closure of patent ductus arteriosus — no. (%)**	45 (4.5)	126 (12.6)	0.33	0.32 (0.22–0.45)	<0.001	0.29 (0.20–0.43)

* CI denotes confidence interval.
† The odds ratio has been adjusted for the gestational age and sex of the infant, as well as for the presence or absence of antenatal administration of corticosteroids, a multiple birth, and an endotracheal tube at randomization.
‡ This outcome is for infants who were alive at a postmenstrual age of 36 weeks (963 in the caffeine group and 954 in the placebo group).
§ This outcome is for infants who were examined for retinopathy in the 35 study centers where the infants were enrolled (822 in the caffeine group and 838 in the placebo group). A total of 531 infants (53 percent) in the caffeine group and 490 infants (49 percent) in the placebo group were transferred to another hospital before their first discharge home. Data on retinal examinations performed after those transfers will be collected at the 18-month follow-up.
¶ This outcome is for infants who underwent cranial ultrasonography at least once after randomization (967 in the caffeine group and 966 in the placebo group). In the caffeine group, 33 infants had intraparenchymal echodense lesions, 24 had cystic periventricular leukomalacia, 6 had a porencephalic cyst, and 93 had ventriculomegaly (with or without intraventricular hemorrhage); in the placebo group, 41 infants had intraparenchymal echodense lesions, 37 had cystic periventricular leukomalacia, 16 had porencephalic cysts, and 99 had ventriculomegaly (with or without intraventricular hemorrhage).
‖ Fourteen infants in each group received ibuprofen, and 282 in the caffeine group and 372 in the placebo group received indomethacin.
** This outcome excludes infants who underwent surgical closure of a patent ductus arteriosus before randomization (five in the caffeine group and one in the placebo group).

six weeks (data not shown). In a post hoc analysis, the infants randomly assigned to caffeine were significantly less likely to undergo therapy (in particular, surgery) to close a patent ductus arteriosus than were the infants in the control group (Table 3).

DISCUSSION

We designed this large, multicenter, randomized, placebo-controlled trial of caffeine to resolve the long-standing uncertainty about the short- and long-term efficacy and safety of methylxanthine therapy for apnea of prematurity.[3-5] This article focuses on secondary short-term outcomes; we report these early because of their clinical relevance, pending ascertainment of the primary outcome (a composite of death, cerebral palsy, cognitive delay, deafness, or blindness at a corrected age of 18 to 21 months). We found that caffeine substantially reduced the frequency of bronchopulmonary dysplasia. Caffeine had the potentially adverse effect of diminishing weight gain for the first three weeks after the start of therapy but had no significant effects on the rates of death before the first discharge home, ultrasonographic signs of brain injury, and necrotizing enterocolitis.

Previous data have established that methylxanthines reduce the frequency of apnea,[3] but their effects on the duration of assisted ventilation and their other short- and long-term benefits and risks (including effects on bronchopulmonary dysplasia, brain injury, and growth) have remained uncertain.[3,4] One published trial enrolling a total of 85 infants randomly assigned to either caffeine or placebo reported 4 patients with necrotizing enterocolitis in the caffeine group, as compared with 2 in the placebo group.[24] When the Food and Drug Administration approved caffeine citrate (Cafcit) for the treatment of apnea of prematurity, a warning was included in the label about the possible association between the use of methylxanthines and the development of necrotizing enterocolitis.[25] The absence of any discernible effect of caffeine on the incidence of necrotizing enterocolitis in our study is reassuring.

We used a placebo to ensure masking of the assignment of the study drug. However, apneas that persisted despite optimal use of the study drug were treated if they required more than mild stimulation. Clinicians were instructed to control such apneas with all necessary nonpharmacologic therapies, including the use of assisted ventilation through an endotracheal tube, nasal continuous positive airway pressure, and supplemental oxygen.[2]

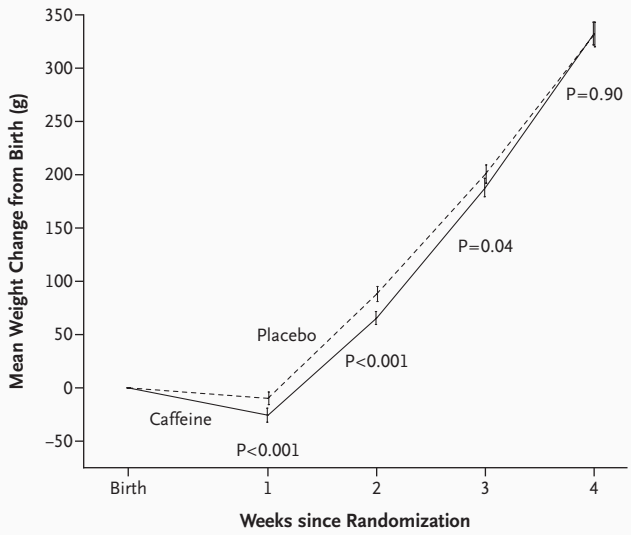

Figure 2. Mean Change in Body Weight during the First Four Weeks after Random Assignment to Caffeine or Placebo.

The mean difference in weight gain was –16 g after one week (95 percent confidence interval, –25 to –7), –23 g after two weeks (95 percent confidence interval, –32 to –13), and –13 g after three weeks (95 percent confidence interval, –25 to –0.4).

We stratified the random assignment to caffeine or placebo according to study center, and we adjusted for center in the analysis to eliminate the bias caused by the variability of practice among the clinical sites. We found that infants in the placebo group required each of three levels of respiratory support — positive airway pressure with an endotracheal tube in place, any positive airway pressure, and supplemental oxygen — for one more week than did infants in the caffeine group. We speculate that the increased incidence of bronchopulmonary dysplasia among infants treated with placebo was caused mainly by their longer exposure to positive airway pressure.

Caffeine appeared to reduce the frequency of a patent ductus arteriosus that was judged by the clinical staff to require closure with drug or surgical therapy. This finding was unexpected and post hoc and must be interpreted cautiously. We did not include patent ductus arteriosus among the short-term outcomes in our study protocol because it had not been suggested previously that methylxanthine therapy altered the rate of ductal

closure in the preterm infant. However, we recorded the use of drug or surgical therapy for closure of a patent ductus, prompting the external safety monitoring committee to monitor this outcome. Our study protocol did not mandate serial echocardiography in all study patients. Therefore, it is uncertain whether caffeine promoted the closure of a patent ductus arteriosus or whether the clinical staff were more likely to look for and close a patent ductus arteriosus in the placebo group than in the caffeine group because the infants in the placebo group required positive airway pressure and supplemental oxygen for a longer period than did infants assigned to caffeine. Additional studies are needed to clarify the effect of caffeine on ductal closure.

In summary, caffeine therapy for apnea of prematurity reduces the incidence of bronchopulmonary dysplasia. Except for a temporary reduction in weight gain, caffeine has no apparent short-term risks. At the doses used in this trial, the incidence of drug-induced toxicity is low. The recognition that bronchopulmonary dysplasia is an important risk factor for neurosensory impairment in early childhood[26] suggests the potential for long-term benefits of caffeine therapy in infants with very low birth weights. However, information on short-term outcomes is insufficient to assess the overall efficacy and risk of neonatal interventions.[27,28] Follow-up of our study cohort to the corrected ages of 18 to 21 months and 5 years, currently in progress, is needed before one can confidently recommend the standard use of methylxanthine therapy for apnea of prematurity.

Supported by the Canadian Institutes of Health Research and the National Health and Medical Research Council of Australia, which was a study sponsor in Australia.

No potential conflict of interest relevant to this article was reported.

We are indebted to the study pharmacists, to the nursing and medical staff at all the participating hospitals, and to Sabex in Boucherville, Que., Canada, for providing the caffeine citrate injection for the study.

APPENDIX

The following investigators, research nurses, and hospitals participated in the neonatal phase of the Caffeine for Apnea of Prematurity Trial (study sites are listed according to the number of infants they enrolled): McMaster University Medical Center, Hamilton, Ont., Canada — B. Schmidt, J. D'Ilario, J. Cairnie; Royal Women's Hospital, Melbourne, Australia — P. Davis, L. Doyle, B. Faber; Women's College Hospital, Toronto — E. Asztalos, L. Golec; Women's and Children's Hospital, Adelaide, Australia — R. Haslam, C. Barnett, L. Goodchild, R. Lontis; Mercy Hospital for Women, Melbourne, Australia — S. Fraser, J. Keng; Centre Hospitalier Universitaire de Quebec, Quebec, Canada — A. Bairam, S. Ferland, L. Laperriere; Ottawa Hospital, Ottawa — M. Blayney, D. Davis, J. Frank; British Columbia Children's Hospital, Vancouver, Canada — A. Solimano, A. Singh, M. Chalmers, K. Ramsay; Academic Medical Center, Amsterdam — M. Offringa, D. Nuytemans, E. Vermeulen; Meir General Hospital, Kfar-Saba, Israel — S. Arnon, A. Chalaf; Mount Sinai Hospital, Toronto — A. Ohlsson, K. Nesbitt; Royal University Hospital, Saskatoon, Sask., Canada — K. Sankaran, S. Morgan; the Brooklyn Hospital Center, Brooklyn, N.Y. — M. LaCorte, P. LeBlanc, A. Braithwaite; Soroka University, Beer Sheva, Israel — A. Golan, T. Barabi; the Canberra Hospital, Canberra, Australia — G. Reynolds, B. Dromgool, S. Meskell; Foothills Hospital, Calgary, Alta., Canada — D. McMillan, D. Schaab, L. Spellen; St. Boniface, Winnipeg, Man., Canada — R. Alvaro, A. Chiu, C. Porter, G. Turner; University Hospital Maastricht, Maastricht, the Netherlands — T. Muler; Kingston General Hospital, Kingston, Ont., Canada — M. Clarke, J. Parfitt; Hotel Dieu Grace Hospital, Windsor, Ont., Canada — C. Nwaesei, L. Kuhn; Ludwig Maximilian University, Munich, Germany — A. Schulze, P. Pudenz, M. Muller; Astrid Lindgren Children's Hospital, Stockholm — H. Lagercrantz, M. Bhiladvala, L. Legnevall; Victoria General Hospital, Victoria, B.C., Canada — D. Matthew, W. Amos, S. Tulsiani; Kaplan Medical Center, Rehovot, Israel — E. Shinwell, R. Levine; Royal Victoria Hospital, Montreal — K. Barrington, T. Kokkotis; James Cook University Hospital, Middlesbrough, United Kingdom — S. Sinha, W. Tin, S. Fritz; University of Sherbrooke, Sherbrooke, Que., Canada — H. Walti, D. Royer; Royal Maternity Hospital, Belfast, Northern Ireland — H. Halliday, D. Millar, A. Berry; Basel Children's Hospital, Basel, Switzerland — H. Fahnenstich, K. Philipp; Moncton Hospital, Moncton, N.B., Canada — R. Canning; Royal Victoria Infirmary, Newcastle, United Kingdom — U. Wariyar, W. Tin, S. Fritz; University Hospital Zurich, Zurich, Switzerland — H. Bucher, J.-C. Fauchere; Neonatal Nursing Initiative, Stockton on Tees, United Kingdom — W. Tin, S. Fritz; University Hospitals of Geneva, Geneva — R. Pfister, V. Launoy; University of Tuebingen, Tuebingen, Germany — C. Poets, P. Urschitz-Duprat; *Steering Committee* — B. Schmidt (chair), K. Barrington, P. Davis, L.W. Doyle, A. Ohlsson, R.S. Roberts, A. Solimano, W. Tin; *External Safety Monitoring Committee* — M. Gent (chair), W. Fraser, E. Hey, M. Perlman, K. Thorpe; *Consultant Pharmacist* — S. Gray; *Coordinating and Methods Center in Hamilton, Ont., Canada* — R.S. Roberts, C. Chambers, L. Costantini, E. McGean, L. Scapinello.

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