A. INGREDIENT NAME:

CAFFEINE CITRATED

B. Chemical Name:

C. Common Name:

Citrated Caffeine, Coffeinum Citricum

D. Chemical grade or description of the strength, quality, and purity of the ingredient:

	(Specifications)	*(Result)*
Assay (citric acid)	48.0-52.0%	50.5%

E. Information about how the ingredient is supplied:

White Crystalline Powder, Odorless Powder having a slightly bitter, acrid taste

F. Information about recognition of the substance in foreign pharmacopeias:

Pharmacopeias. In Aust., Hung., Ind., Roum., and Span.
B.P.C.1959
U. S. Pharmacopeia/BP 1959

G. Bibliography of available safety and efficacy data including peer reviewed medical literature:

Aldridge, A. Caffeine metabolism in the newborn. *Clin. Pharmacol. Ther.*, 1979;25:447.

LeGuennec, J. C. Maturational changes of caffeine concentration and disposition in infancy during maintenance therapy for apnea of prematurity: influence of gestional age, hepatic disease, and breast-feeding. *Pediatrics*, 1985;76: 834.

Aranda, J. V. Maturation of caffeine elimination in infancy. *Arch Dis Child*, 1979; 54: 946.

Brouard, C. Comparative efficacy of theophylline and caffeine in the treatment of idiopathic apnea in premature infants. *Am. J. Dis. Child*, 1985;139:698.

Eisenberg, M. G. and Kang, N. Stability of citrated caffeine solutions for injectable and enternal use. *Am. J. hosp. Pharm.*, 1984;41(11):2405-2406.

Brouard, C., Moriette, G., and Murat,I. Comparative efficacy of theophylline and caffeine in the treatment of idiopathic apnea in premature infants. *Am. J. Dis. Child.*, 1985; 139(7): 698-700.

H. Information about dosage forms used:

Solution

I. Information about strength:

20mg

J. Information about route of administration:

Oral or Intravenous

K. Stability data:

L. Formulations:

M. Miscellaneous Information:

34. S.M. was given aminophylline 6 mg (6 mg/kg of aminophylline, 4.8 mg/kg theophylline) as an IV loading dose over 20 min. Maintenance doses of 1 mg Q 8 hr have been ordered. Describe your pharmacotherapeutic monitoring plan for S.M. Include monitoring parameters for efficacy and toxicity and duration of therapy.

The goal of methylxanthine therapy in the treatment of apnea of prematurity is to decrease the number of episodes of apnea and bradycardia. Continuous monitoring of heart rate and respiratory rate is required for proper evaluation. The time, duration, and severity of episodes; activity of the infant; and any necessary intervention performed should be documented. Relationships between the apneic episodes and the feeding schedule and volume of feeds, as well as the dosing schedule of theophylline (e.g., trough), should be examined.

Apnea of prematurity usually resolves after 36 weeks postconceptional age; however, it may persist in some infants up to or beyond 40 weeks postconceptional age.[136] Therefore, methylxanthine therapy usually is discontinued at 35 to 37 weeks postconceptional age provided that the infant has not been having apneic spells.[141] Infants that require therapy for longer periods of time may be discharged home on methylxanthines with apnea monitors.

Toxicities noted in neonates include tachycardia, agitation, irritability, hyperglycemia, feeding intolerance, gastroesophageal reflux, and emesis or occasional spitting up of food. Tachycardia is the most common toxicity and usually responds to a downward adjustment of the theophylline dose. Tachycardia may persist for one to three days after dosage reductions due to the decreased elimination of theophylline-derived caffeine. Seizures also have been reported with accidental overdoses. Methylxanthine toxicity can be minimized with careful dosing and appropriate monitoring of serum concentrations. Serum theophylline concentrations should be monitored 72 hours after initiation of therapy or after a change in dosage. Serum concentrations of theophylline also should be measured if the infant experiences an increase in the number of apneic episodes, signs or symptoms of toxicity, or a significant increase in weight. In asymptomatic neonates, once steady-state levels are obtained, theophylline concentrations may be monitored every two weeks.

35. S.M. now is 3 weeks old (32 weeks postconceptional age) and weighs 1100 gm. His septic work-up was negative. Currently S.M. has several apneic spells per day which respond to tactile stimulation; his apneic episodes have not required ventilatory assistance. S.M. receives 1 mg aminophylline IV Q 8 hr and his trough theophylline level this morning was 5.7 µg/mL. The medical team is considering switching S.M.'s theophylline therapy to caffeine because of possible improved benefits. How does caffeine compare to theophylline with regard to its pharmacokinetics, efficacy, and toxicity? What treatment should be selected?

Pharmacokinetics. The plasma clearance of caffeine is considerably lower and the half-life is extremely prolonged in the premature newborn (see Table 96.2). The low clearance is a reflection of the decreased neonatal hepatic metabolism and a resultant dependence of elimination on the slow urinary excretion. In the preterm neonate, the amount of caffeine excreted unchanged in the urine is 85%, compared to less than 2% in adults. Adult urinary metabolite patterns are seen by seven to nine months of age.[154] The half-life of caffeine decreases with increasing postconceptional age[155] and plasma clearance reaches adult levels after 3 to 4.5 months of life.[156] As a result of the maturational changes, doses usually need to be adjusted after 38 weeks postconceptional age and dosing intervals need to be shortened to eight hours after 50 weeks postconceptional age.[155]

Efficacy, Toxicity, and Dosing. Comparative studies have found similar efficacy for theophylline and caffeine in the control of apnea of prematurity.[157,158] Caffeine, however, may have some advantages over theophylline including a wider therapeutic index. Adverse effects such as tachycardia, CNS excitation, and feeding intolerance are reported more frequently with theophylline than with caffeine. The prolonged half-life of caffeine in premature neonates results in less fluctuation in plasma concentrations and permits the use of a 24-hour dosing interval. Since the half-life is prolonged and dosing requirements do not change quickly over time, caffeine serum concentrations can be monitored less frequently. Oral or IV loading doses of 10 mg/kg of caffeine base (20 mg/kg of caffeine citrate), followed by maintenance doses of 2.5 mg/kg (5 mg/kg caffeine citrate) given daily will maintain plasma caffeine concentrations in the therapeutic range (5 to 20 µg/mL).[144]

Although infants who are unresponsive to theophylline may respond to caffeine,[159] S.M.'s theophylline therapy presently is not optimized; his serum concentration is less than 6 µg/mL. S.M. appears to have partially responded to theophylline and may benefit from an increase in the dose with resultant therapeutic serum concentrations. S.M.'s aminophylline dose should be increased to 1.5 mg every eight hours to achieve serum concentrations of around 8 µg/mL. Although caffeine may have several advantages over theophylline, the IV product marketed in the U.S. is only available as the sodium benzoate salt. Benzoic acid has been associated with the gasping syndrome and also may displace bilirubin from albumin binding sites.[34,35] Because of these toxicities, caffeine sodium benzoate should not be used in neonates. It is possible, however, to compound an acceptable IV and oral caffeine preparation.[160] As for any compounded injectable preparation, quality control must be done to assure sterility, stability, and lack of pyrogen contamination. If the hospital currently is not compounding an IV caffeine product, it could take months to institute quality control measures.

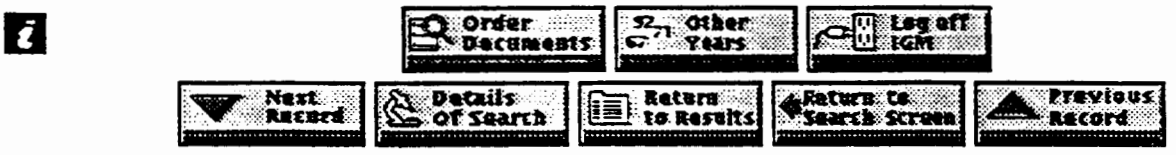
Other Agents

36. S.M.'s dose of theophylline has been optimized and theophylline serum concentrations now are 12.4 µg/mL. S.M. continues to have apneic episodes. What other pharmacologic agents can be used?

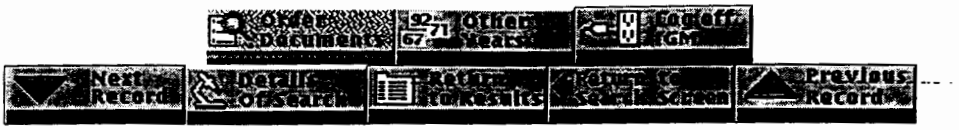
Doxapram, an analeptic agent, has been shown to be as effective as theophylline for the treatment of apnea of prematurity.[161,162] Due to the limited number of investigations and uncertain side effects, however, the use of doxapram should be restricted to patients who are refractory to methylxanthine therapy.[144] In addition, the IV preparation commercially available in the U.S. contains 0.9% benzyl alcohol and should be used with caution. Although doses are not well defined, a loading dose of 2.5 to 3 mg/kg given IV over 15 to 30 minutes followed by a 1 mg/kg/hour continuous infusion has been recommended.[144,163] Doses may be increased by 0.5 mg/kg/hour increments to a maximum dose of 2.5 mg/kg/hour.[144] Lower doses have been used in infants receiving concomitant methylxanthine therapy with approximately 50% responding to IV doxapram doses of 0.5 mg/kg/hour.[164] A few studies have administered doxapram enterally; however, bioavailability in preterm newborns is not yet well defined.[144,165] Side effects associated with doxapram include: increased blood pressure (usually with doses >1.5 mg/kg/hour);[164] GI disturbances such as abdominal distension, regurgitation, increased gastric residuals, and vomiting; and CNS adverse effects such as increased agitation, excessive crying, jitteriness, irritability, disturbed sleep, and seizures. Further studies of doxapram are needed in order to better delineate its adverse effects and to help define its safety and efficacy for the treatment of apnea of prematurity.

National Library of Medicine: IGM Full Record Screen

TITLE:	Stability of citrated caffeine solutions for injectable and enteral use.
AUTHOR:	Eisenberg MG; Kang N
SOURCE:	Am J Hosp Pharm 1984 Nov;41(11):2405-6
NLM CIT. ID:	85069497
MAIN MESH SUBJECTS:	Caffeine/*ADMINISTRATION & DOSAGE
ADDITIONAL MESH SUBJECTS:	Administration, Oral Chromatography, High Pressure Liquid Drug Stability Human Injections Solutions Time Factors
PUBLICATION TYPES:	JOURNAL ARTICLE
LANGUAGE:	Eng
REGISTRY NUMBERS:	0 (Solutions) 58-08-2 (Caffeine)



National Library of Medicine: IGM Full Record Screen



TITLE: Population pharmacokinetics of intravenous caffeine in neonates with apnea of prematurity.

AUTHOR: Lee TC; Charles B; Steer P; Flenady V; Shearman A
AUTHOR AFFILIATION: School of Pharmacy, University of Queensland, St. Lucia, Australia.

SOURCE: Clin Pharmacol Ther 1997 Jun;61(6):628-40
NLM CIT. ID: 97352987

ABSTRACT: OBJECTIVE: The study the population pharmacokinetics of caffeine after intravenous administration to premature infants with apnea. METHODS: A prospective, blinded parallel study in which daily caffeine citrate doses of 30, 15, and 3 mg/kg were administered over 7 days by intermittent intravenous infusion. Arterial blood samples (three to six per patient) were assayed for caffeine content by means of HPLC. Population pharmacokinetic modeling was performed with NONMEM. RESULTS: Clearance (L/hr) = (0.00000399 . current weight [grams]) + (0.000128 . postnatal age [days]). For gestational age > 28 weeks, volume of distribution (L) = (0.000764 . weight [grams] + (0.0468 . postnatal age [days]); for gestational age < or = 28 weeks, volume of distribution (L) = (0.000755 . weight [grams]) + (0.0224. postnatal age [days]). Interpatient variability (coefficient of variation, in percent) was approximately 25% for clearance and approximately 11% for volume of distribution. Intrapatient error (standard deviation) was 3.9 mg/L. There was insignificant bias between observed and model-predicated serum caffeine concentrations in a separate group of 30 infants. CONCLUSIONS: Caffeine was well tolerated at all doses. Clearance was markedly lower and volume of distribution was higher than the values reported previously for term infants and adults. Both parameters were significantly influenced by postnatal age and current body weight, whereas volume of distribution in infants > 28 weeks' gestational age was higher than that in more premature babies. The predictive performance and the clinical application of the derived population models was satisfactorily shown.

MAIN MESH SUBJECTS:
Apnea/*BLOOD
Caffeine/ADMINISTRATION & DOSAGE/*PHARMACOKINETICS
Infant, Premature/*BLOOD

ADDITIONAL MESH SUBJECTS:
Chromatography, High Pressure Liquid
Female
Gestational Age
Human
Infant, Newborn
Infusions, Intravenous
Male
Predictive Value of Tests
Prospective Studies
Reproducibility of Results
Single-Blind Method
Support, Non-U.S. Gov't

No.	Records	Request
1	57	Eisenberg
2	103	Kang
3	1047	caffeine
* 4	1	Eisenberg and Kang and caffeine

Record 1 of 1 - IPA 1970-3/98

TI: Stability of citrated caffeine solutions for injectable and enteral use
AU: Eisenberg-MG; Kang-N
SO: Am-J-Hosp-Pharm (American-Journal-of-Hospital-Pharmacy); 1984; 41(Nov); 2405-2406
PY: 1984
AB: The stability of extemporaneous citrated caffeine (I) solutions formulated in the hospital pharmacy for parenteral and enteral use was studied. To prepare the I injection, 10 g of I powder was dissolved in 250 ml of sterile water for injection, USP, and further diluted to 500 ml. The resulting solution was autoclaved in vials and tested for sterility and stability at time zero and at monthly intervals for 4 months. I enteral solution was prepared by dissolving 10 g of I in 250 ml of sterile water for injection, USP, and further diluting with a flavoring agent to 500 ml. Both the injectable and enteral products are stable for at least 90 days, with the reported concentration \GE/ 90% of the original intended concentration. Results for the injectable batches and for one enteral batch indicate the possibility of extending usable shelf-life to 120 days. It was concluded that extemporaneously prepared solutions of I in sterile water and in sterile water and syrup are stable for at least 3 months.
AN: 22-03531

CAFFEINE CITRATED

As a 50/50 mixture, the human oral dose is 5-20 mg daily if used as a stimulant.

While safer than theophylline, it has produced diuresis, nausea, tinnitis, palpitations, arrhythmias in foeti and neonates from mothers who drink excess coffee, wakefulness and convulsions. Caffeine is NOT a human teratogen. The powder can produce eye and pulmonary irritation.

REFERENCES

1. Eisenberg MG, Kang. Stability of citrated caffeine solutions for injectable and enteral use. Am J Hosp Pharm 1984; 41(11):2405-6.

2. Brouard C, Moriette G, Murat I, et al. Comparative efficacy of theophylline and caffeine in the treatment of idiopathic apnea in premature infants. Am J Dis Child 1985; 139(7):698-700.

3. Donnelly RF, Tirona RG. Stability of citrated caffeine injectable solution in glass vials. Am J Hosp Pharm 1994; 51(4):512-4.

4. Fraser BD. Stability of caffeine citrate injection in polypropylene syringes at room temperature. Am J Health Syst Pharm 1997; 54(May 1):1106, 1108.

5. Janke KK, Leger J, Mansour S. Identifying patient-specific outcomes in lower back pain. Can Pharm J 1995; 12(May):22-3, 54.

6. Barnes AR, Hebron BS, Smith J. Stability of caffeine oral formulations for neonatal use. J Clin Pharm Ther 1994; 19(6):391-6.

7. Romagnoli C, De Carolis MP, Muzii U, et al. Effectiveness and side effects of two different doses of caffeine in preventing apnea in premature infants. Ther Drug Monit 1992; 14(1):14-9.

8. Hopkin C, Taylor A, Hanson S. Stability of caffeine citrate. Br J Pharm Prac 1990; 12(Apr):133.

9. Nahata MC, Zingarelli J, Durrell DE. Stability of caffeine citrate injection in intravenous admixtures and parenteral nutrition solutions. J Clin Pharm Ther 1988; 44(Aug):145-51.

10. Yoovathaworn KC, Sriwatanakul K, Thithapandha A. Influence of caffeine on aspirin pharmacokinetics. Eur J Drug Metab Pharmacokinet 1986; 11(1):71-6.

11. Le Guennec JC, Billon B. Delay in caffeine elimination in breast-fed infants. Pediatrics 1987; 79(Feb):264-8.

12. Hughes AM, Cannon LA. Analgesic abuse. Pharm J 1986; 236(Apr 19):475.

13. Autret E, Breteau M, Laugier J, et al. Comparison of two different maintenance doses of caffeine in the treatment of apnea in premature infants. Therapie 1985; 40(Jul-Aug):235-9.

14. Charney DS, Heninger GR, Jatlow PI. Increased anxiogenic effects of caffeine in panic disorders. Arch Gen Psychiatry 1985; 42(Mar):233-43.

15. Frakenburg FR. Chronic Tylenol #1 abuse. Can J Hosp Pharm 1983; 36(Winter):86.

16. Dandurand KR. Use of caffeine in neonates. Am J Hosp Pharm 1984; 41(August):1520-1.

17. Chait LD, Griffiths RR. Effects of caffeine on cigarette smoking and subjective response. Clin Pharmacol Ther 1983; 34(Nov):612-22.

18. Eswarasankaran S, Ramakrishnan PN, Palanichamy S, et al. Influence of drugs on the transfer of paracetamol across everted rat intestine. Indian J Hosp Pharm 1982; 19(May-Jun):103-5.

19. Dobmeyer DJ, Stine RA, Leier CV, et al. Arrythmogenic effects of caffeine in human beings. N Engl J Med 1983; 308(Apr 7):814-6.

20. Ammar HO, Ibrahim SA, El-Faham TH. Interactions of chlorothiazide and hydrochlorothiazide with certain amides, imides and xanthines. Pharm Ind 1981; 43(3):292-5.

21. Khanna NN, Bada HS, Somani SM. Use of salivary concentrations in the prediction of serum caffeine and theophylline concentrations in premature infants. J Pediatr 1980; 96(Mar (Part I)):494-9.

22. Bada HS, Khanna NN, Somani SM, et al. Interconversion of theophylline and caffeine in newborn infants. J Pediatr 1979; 94(Jun):993-5.

23. Lehmann HE, Black P, Ban TA. Effect of psychostimulants on psychometric test performance with special reference to conflict avoidance behavior. Curr Ther Res 1970; 12(Jun):390-2.