Influence of Xanthines on Gastroesophageal Reflux in Infants at Risk for Sudden Infant Death Syndrome

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ABSTRACT. Theophylline and caffeine are two drugs frequently administered to infants at risk for sudden infant death syndrome, because of their stimulatory effects on the respiratory system. These drugs are known to increase gastric acid secretion and to decrease lower esophageal sphincter pressure that, in turn, possibly increases gastroesophageal reflux (GER). Thirty babies were tested for GER before and during caffeine treatment. Eighteen were studied under the same conditions while undergoing theophylline treatment. All results of pH monitoring before treatment were within normal ranges. Episodes of GER increased significantly ($P < .001$) in about 50% of the group treated with caffeine and in 66% of the group treated with theophylline. These results were independent of plasma xanthine concentrations (within or below therapeutic ranges) and of the efficacy of the drug. In addition, an increase was noted for the number of episodes of GER in 24 hours (from 5.3 to 17.1 in the caffeine group and from 5.3 to 24.3 in the theophylline group) and for the time pH was <4 (from 0.87% to 6% in the caffeine group and up to 13% in the theophylline group). Because GER is another known risk factor for sudden infant death syndrome, the administration of xanthine derivatives in babies at risk for sudden infant death syndrome should be carefully considered in each case. *Pediatrics* 1986;77:807–810; *sudden infant death syndrome, gastroesophageal reflux, continuous pH monitoring, caffeine, theophylline, xanthine derivative.*

The continuing care of the child who shows signs of "infant apnea" or a "near miss" sudden infant death syndrome (SIDS) episode is difficult in many respects for both parents and physicians. Much of the difficulty results from the inability to determine the precise cause of the observed event. Of all hypotheses proposed to explain SIDS, those relating to defective control of ventilation provide the major focus for current research. Caffeine and theophylline, two xanthine derivatives, are frequently administered to these infants because of their potent effects as central nervous system stimulants. These drugs are reported to stimulate gastric acid secretion as well as to diminish lower esophageal sphincter pressure. Therefore, they could increase episodes of gastroesophageal reflux and consequently induce aspiration and respiratory problems.

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MATERIALS AND METHODS

Infants studied were at risk for SIDS. Simultaneous cardiorespiratory monitoring for detection of risk for SIDS and continuous esophageal pH monitoring were performed at the age of 6 to 8 weeks in a routine screening program. All infants were born at term from mothers who had uneventful pregnancies and uncomplicated deliveries. In a group of 48 infants at risk for SIDS, xanthine derivatives were administered. "Risk for SIDS" was defined either as respiratory ataxia with central apnea episodes lasting longer than 10 seconds, accompanied in some cases by cardiac ataxia and a decrease of the transcutaneous Po_2, or as a periodic respiration of more than 7% of the tracing. For all investigations the infants were admitted to our "sleep-unit." At home, all infants were observed by respiratory monitoring.

A continuous 24-hour esophageal pH monitoring, using a Memolog 600 system (Novo Diagnostics), was performed in all infants before caffeine or theophylline administration. Monitoring of esophageal pH is one of the investigations in the routine screening program for infants at risk for SIDS. The system collects the registered data and when the memory is fully loaded it switches off automatically. During 24 hours, memory storage of 1 pH value per 7.5 seconds is carried out. The readout of data stored in the Memolog was performed with an Apple II computer with a central memory capacity

of 128K bits. The pH electrode was a flexible glass electrode (type MI 506; Microelectrodes, Inc.) with a maximal outer body diameter of 1.6 mm. Maximal pH error in vivo was 0.5 pH unit; the response time of the electrode was about 5 seconds. Location in the middle third of the esophagus was determined with the aid of radioscopy.

The position of the babies was taken into account[1]; all infants were studied in the prone position.

Caffeine (caffeine citrate) treatment was started at regular doses (5 mg/kg/d) in 30 infants.[2] The drug was administered as oral drops, two doses daily.

Theophylline was administered to 18 infants, also at usual doses (6 mg/kg/d).[3] The drug was administered three times a day, as oral drops. The plasma xanthine level was monitored at least once a week. A second cardiorespiratory monitoring and tracing and continuous pH monitoring were performed after 3 to 4 weeks of treatment. A third pH monitoring was performed 3 to 4 weeks after the treatment was stopped.

The following parameters for gastroesophageal reflux were studied: periods with a pH <4; the duration of the longest reflux episode; the total number of reflux episodes; and the number of reflux episodes longer than five minutes. In addition to these parameters, the program (developed by our unit) provides a pH tracing (Figure). These values were compared with the results of a control group (60 healthy newborns).[1] For all these parameters the mean value and standard deviation were calculated. With the aid of a *t* test we checked whether the results were different in a statistically significant way.

RESULTS

For both the caffeine and the theophylline groups, all results of pH monitoring before treatment were within normal ranges (Table 1), established previously by our team.[1]

Group 1: Caffeine

Thirty babies were treated with caffeine. Before caffeine administration, pH <4 represented 0.91 ± 0.54% (mean value ± SD) of the total investigated time. The longest episode of reflux lasted 3.15 ± 1.83 minutes. In 24 hours, 7.52 ± 2.21 episodes of reflux were observed, and the number of episodes lasting longer than five minutes was 0.81 ± 0.51. No statistically significant difference from the control group was found. Results are shown in Table 2.

Caffeine was administered daily, and plasma levels were monitored at least once a week. In about 20% of the infants the levels were below therapeutic ranges, and in 80% of the infants levels were within therapeutic ranges (5 to 15 μg/mL). A toxic level was never detected.

The second cardiorespiratory monitoring and tracing, taken 3 to 4 weeks later, failed to show any improvement in 90% of the infants. In 10% risk for SIDS had decreased.

Results of the second pH monitoring, performed under similar conditions to the first, were within normal ranges in 50% of the infants studied (subgroup A, Table 2). In the other 50%, however (subgroup B), values for all parameters studied were statistically significantly higher. Duration of pH >4

TABLE 1. Normal Ranges for Results of pH Monitoring (N = 60)*

Parameter	Prone Position	Supine Position
Duration pH <4 (%)	0.87 ± 0.75	5.47 ± 1.71
Longest episode (min)	2.85 ± 2.23	13.30 ± 10.31
No. of episodes (in 24 h)	7.45 ± 2.81	25.59 ± 12.94
No. of episodes >5 min	0.84 ± 0.70	3.09 ± 0.98

* Values are means ± SD.

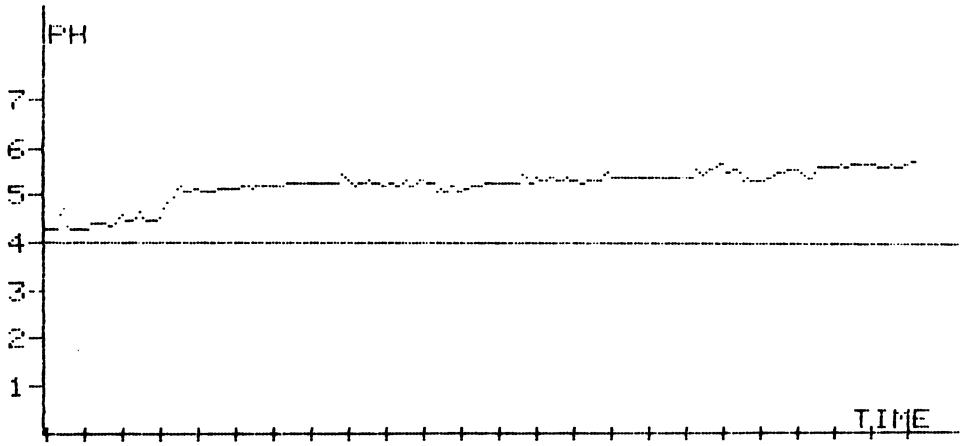

Figure. Normal pH tracing. Each point represents pH at 7.5-second time interval.

TABLE 2. Results of pH Monitoring (Prone Position) in Groups Receiving Caffeine and Theophylline*

Group and Parameter	Before Treatment		Treatment (3–4 wk)			After Treatment
			Subgroup A		Subgroup B	
Group 1: Caffeine (n = 30)						
Duration pH <4 (%)	0.91 ± 0.54	NS	0.98 ± 0.82	S	6.84 ± 2.03	0.98 ± 0.71
Longest episode (min)	3.15 ± 1.83	NS	4.03 ± 2.03	S	25.20 ± 8.17	2.61 ± 2.46
No. of episodes (in 24 h)	7.52 ± 2.21	NS	8.01 ± 2.54	S	17.10 ± 5.20	7.45 ± 2.93
No. of episodes >5 min (in 24 h)	0.85 ± 0.51	NS	0.93 ± 0.56	S	5.61 ± 1.24	0.94 ± 0.86
Group 2: Theophylline (n = 18)						
Duration pH <4 (%)	0.75 ± 0.58	NS	0.81 ± 0.63	S	13.00 ± 3.21	0.80 ± 0.76
Longest episode (min)	2.88 ± 2.35	NS	3.05 ± 2.78	S	28.38 ± 10.25	4.15 ± 2.66
No. of episodes (in 24 h)	5.80 ± 3.14	NS	7.07 ± 3.26	S	24.33 ± 6.31	6.58 ± 5.15
No. of episodes >5 min (in 24 h)	0.90 ± 0.76	NS	1.08 ± 0.98	S	7.69 ± 1.24	0.96 ± 0.84

* Values are means ± SD. NS, not significant; S, significant ($P < .001$). For caffeine treatment, subgroup A: n = 15; subgroup B: n = 15. For theophylline treatment, subgroup A: n = 6; subgroup B: n = 12.

increased to 6.8 ± 2.03% of the total investigation time (or 70.1 minutes in 24 hours). The longest reflux episode increased to 25.20 ± 8.17 minutes. The number of episodes of reflux reached 17.10 ± 5.20 in 24 hours, or nearly one episode per hour. The number of episodes of reflux lasting longer than five minutes increased in a comparable way: 5.61 ± 1.24 in 24 hours. Neither a correlation between these results and the efficacy of the drug, nor a correlation between these results and the xanthine plasma level could be detected.

Results of pH monitoring performed 3 to 4 weeks after treatment was stopped, were always within normal ranges (pH <4: 0.89 ± 0.71%; longest episode: 2.61 ± 2.46 minutes; number of episodes: 7.45 ± 2.93; and number of episodes of lasting longer than five minutes: 0.94 ± 0.89).

Group 2: Theophylline

Eighteen babies were treated with theophylline. All investigations before treatment were within normal ranges (pH <4: 0.75 ± 0.58%; longest episode: 2.88 ± 2.35 minutes; number of episodes: 5.80 ± 3.14; and number of episodes lasting longer than five minutes: 0.90 ± 0.76).

Theophylline was administered daily. Plasma levels were below therapeutic ranges in ±10% of all infants and within therapeutic ranges in 90% of infants. No toxic levels were detected.

The second cardiorespiratory monitoring and tracing showed a diminished risk for SIDS in only 5% of infants. In 95% of the infants, tracings were similar to the first ones.

Results of the second pH monitoring were within normal ranges in six infants (33%) (subgroup A, Table 2). In the other 12 infants, values for all parameters were significantly higher (subgroup B). Mean duration of pH >4 increased to 13.0 ± 3.21% of the total investigation time. The longest episode of reflux increased to 28.38 ± 10.25 minutes. The number of episodes of reflux increased to 24.33 ± 6.31 in 24 hours, of which 7.69 ± 1.24 lasted longer than five minutes. A correlation between the efficacy of the drug and the plasma levels or pH monitoring could not be observed.

Results of pH monitoring 3 to 4 weeks after theophylline administration was stopped were normal for all infants (Table 2).

DISCUSSION

The incidence of SIDS in the general population is about two per 1000 live births, with notable regional and ethnic variations.[3] The etiology of this syndrome remains unknown, although a lot of research on its origin has been done in recent years. Most of the observed factors in SIDS could be explained on the basis of a mild primary defect of autonomic control of respiration.[4] Some authors[5] reported that 7% of children at risk for SIDS have gastrointestinal reflux associated with apnea. Our subjects did not belong to this group, as symptoms of gastrointestinal reflux were absent, and results of continuous pH monitoring were initially within normal ranges.

The efficacy of theophylline (average dose 6 mg/kg/d), administered to full-term infants, aged 0 to 6 weeks, has been reported in infants with a history of unexplained apnea and respiratory abnormalities on pneumogram recording.[6] The interconversion of theophylline and caffeine in newborn infants is 100%.[2] Caffeine, as well as theophylline, has been administered frequently to preterm and term infants with respiratory problems.[2,5–7]

The adverse effects of caffeine and theophylline are many. They produce excitation of the central nervous system at all levels. Increased transmission of impulses across nerves and synapses and stimulation of the motor end-plate have been demonstrated.[7] Episthotonus, fine tremors, and clonic and tonic movements with exaggeration of reflexes have been described. Caffeine is a direct cardiac muscle stimulant, and it causes an increase of inotropy and

chronotropy.[7] Effects on the vascular system include pulmonary and systemic vascular dilatation and cerebral constriction. Smooth muscles are relaxed by the drug, whereas skeletal muscles are stimulated. There is increased renal blood flow and accentuated diuresis. Multiple effects on the endocrine system are recognized. A mild increase in clotting time and a shortened coagulation time are known. Basal metabolic rate is increased.[7]

Effects on the gastrointestinal tract are many. Gastric acid secretion is stimulated, and, therefore, fluid secretion is increased. Occasional transient abdominal distention is a well-documented observation. A decrease in lower esophageal sphincter pressure has been reported.[8,9] This can have adverse implications for the young infant, eg, episodes of reflux and aspiration.[7] The influence of caffeine on lower esophageal sphincter pressure seems variable and a decrease has been reported[8] as well as contradicted.[7] More recent experience with manometric studies demonstrated the difficulties of reproducing consistent results, especially in small infants. This technique only measures lower esophageal sphincter pressure and does not indicate whether reflux is really present.[10]

The use of continuous esophageal pH monitoring, which was popularized by Tuttle in adults, has been extended to the newborn, infant, and child.[1] The accuracy of extended pH monitoring has been shown to be as high as 90%.[10] We recently published normal data in asymptomatic newborns showing that gastrointestinal reflux is physiologic between certain ranges.[1]

The administration of caffeine to newborns increased the total reflux time dramatically ($P < .001$), and the number of episodes of reflux in half of the patients studied. A correlation with plasma levels of caffeine could not be demonstrated, although levels were within therapeutic ranges (5 to 20 μg/ml)[11] in 80% of infants, and higher, toxic levels[11] were not detected. In 20% of infants levels did not reach therapeutic ranges.

The finding of normal results for esophageal pH monitoring in all infants before and 3 to 4 weeks after the administration of the xanthines was stopped indicates that gastrointestinal reflux was not present before therapy. Therefore, there is a correlation with the administration of xanthines, as this was the only parameter that had changed. No reason could be detected for the difference of response in the infants studied, except for the presence of individual (hyper) sensitivity toward the drug, a well-known effect of xanthines.[11]

Gastroesophageal reflux is a well-known risk factor for SIDS.[12] Abnormal results of cardiorespiratory monitoring in infants with gastrointestinal reflux can be normalized when gastrointestinal reflux is treated correctly.[12] Therefore, we discourage the administration of caffeine in infants at risk for SIDS, if screening for gastrointestinal reflux is not performed routinely.

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