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The Effect of Chloral Hydrate on Genioglossus and Diaphragmatic Activity

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Summary

A child presented with obstructive sleep apnea (OSA) and a near-fatal airway obstruction and respiratory arrest shortly after receiving chloral hydrate (CH). We, therefore, hypothesize that CH might selectively depress upper airway maintaining muscles such as the genioglossus and so predispose to airway obstruction.

Genioglossus (GG) and diaphragmatic (DIA) integrated electromyograms (I EMGs) were recorded in four cats and four rabbits before and after hypnotic doses of CH ranging from 200–1000 mg/kg. Results were similar in both species. Peak GG I EMG decreased within 10–20 min after CH in seven of eight animals. Average peak GG I EMGs were decreased from 100% before CH to as low as 37.0 ± 27.2% (SD) after CH ($P < 0.001$). Minimum GG I EMGs fell from 47.2 ± 27.2% of peak values before CH to as low as 16.0 ± 9.7% after CH ($P < 0.01$). Phasic GG I EMGs decreased from 53.8 ± 25.1% of peak control activity to as low as 20.6 ± 24.6% after CH ($P < 0.05$). By contrast, peak and phasic DIA I EMGs after CH were not significantly different from those before CH administration. We conclude that hypnotic doses of CH may preferentially depress GG activity as compared with DIA activity. Selective depression of airway-maintaining muscular contraction by CH may place susceptible patients at risk for life-threatening airway obstruction and may preclude the use of CH to facilitate sleep for polygraphic evaluations in patients suspected of having OSA.

Abbreviations

CH, chloral hydrate
DIA, diaphragm
GG, genioglossus
I EMG, integrated electromyogram
OSA, obstructive sleep apnea
$tcPo_2$, transcutaneous partial pressure of oxygen

CH is a widely used hypnotic drug. Miller and Greenblatt (12) reported that 21% of hospitalized medical patients received CH, and, in some hospitals, as many as one-third of patients receive CH (8). One reason for this popularity is that, unlike barbiturates and other sedative-hypnotics, therapeutic doses of CH are not thought to diminish inspiratory drive. If true, this property of CH would greatly facilitate investigations of sleep-related breathing abnormalities in patients who have difficulty falling asleep spontaneously.

Recently, a child with OSA had a respiratory arrest shortly after CH administration. Observation just before the respiratory arrest suggested that the patient had upper airway obstruction. We therefore designed the present study to investigate whether CH selectively depresses upper airway-maintaining musculature and so might predispose to life-threatening OSA.

The GG was chosen for study because GG contraction, which pulls the tongue forward out of the pharyngeal airway, is thought to help maintain pharyngeal airway patency (13). Recent studies have shown that other pharyngeal muscles besides the GG also are involved in the maintenance of upper airway patency (4, 7).

CASE REPORT

A 15-mo-old black male was referred for evaluation of recurrent pneumonia. Physical examination revealed a cachectic boy with moderately enlarged tonsils but no evidence of airway obstruction during wakefulness; however, examination during sleep revealed snoring and episodes of labored breathing without air movement, suggestive of OSA (4). Cardiomegaly on chest x-ray and right ventricular hypertrophy on both electrocardiogram and echocardiogram indicated cor pulmonale (9). Polygraphic monitoring revealed intermittent obstructive apnea during sleep associated with hypercarbia and severe hypoxia ($tcPo_2$ as low as 35 mm Hg). After diagnostic bronchoscopy under general anesthesia, the patient would not resume spontaneous breathing. A tracheostomy was then performed. Thereafter, the patient had no difficulties with breathing during sleep. Weight increased from the 5th to greater than the 95th percentile and, by age 28 mo, laboratory evidence of cor pulmonale disappeared.

To assess upper airway patency at age 3 yr, a small tracheostomy tube was plugged. The patient could breathe easily around the plug when awake, and, for the next 3 d the patient did well during natural sleep with only minimal retractions and no identifiable apneic spells. To further evaluate whether partial airway obstruction during sleep would cause difficulty if the tracheostomy tube was removed, polygraphic monitoring and upper airway fluoroscopy during an afternoon nap were planned. To facilitate sleep, the patient was given 55 mg/kg CH orally. Because the patient remained alert, a second dose of 55 mg/kg CH was given 1 h later. Within 15 min after the second CH dose, the bedside nurse witnessed a period of vigorous respiratory movements without airflow (obstructive apnea). The patient then stopped breathing, became bradycardic and required resuscitation and intermittent positive pressure ventilation. Subsequently, the patient was re-evaluated during a daytime nap without sedation. We found sleep-related tonsillar obstruction and, after tonsillectomy, tracheal decannulation was accomplished.

MATERIALS AND METHODS

Four New Zealand white rabbits and four cats were anesthetized by intraperitoneal injection of 25 mg/kg ketamine and 5 mg/kg of xylazine. Additional doses were given as needed. Two percent xylocaine was used for local anesthesia.

EMGs were recorded from fine wire electrodes (1) placed in a GG muscle and in the DIA as previously described (5, 6). A nasogastric tube was inserted for CH administration. After insertion of the electrodes and nasogastric tube, the animals were allowed to recover from anesthesia for at least 2 h. Adequate

recovery was judged to be present when the animal exhibited spontaneous body movements, sniffing and chewing, and responded to touch.

EMGs were amplified (Grass P15) 100–1000 times with 30 and 1000 Hz low and high frquency filters. Raw EMGs were rectified and electrically integrated with a RC circuit (Beckman 9852A). The integrator response time to a step increase in activity was 90% complete in 250 ms (6). Raw and integrated EMGs were recorded on a polygraph for later analysis. During recordings each animal was tightly placed in a metal screened restraining cage to reduce background electrical noise and to maintain the animals as much as possible with the neck extended in the "sniffing position."

After recovery from anesthesia, GG and DIA EMGs were recorded for 30 min before CH administration (control period). CH was then administered by nasogastric tube and recordings continued for at least 60 min by which time trichloroethanol, the active metabolite of CH, would have peaked (3). Subsequent CH doses were administered in two animals in which the initial CH dose failed to induce sleep. For each animal, the first dose which induced sleep was chosen for analysis. Sleep was judged to be present when the animal was quiet without vigorous movements, had eyes closed, and exhibited little or no response to stimuli. The initial CH dose was 250 mg/kg in six animals, 125 mg/kg in one animal, and 1000 mg/kg in one animal. From previous work, 250 mg/kg was considered the smallest dose likely to induce sleep (2, 10) and this initial CH dose did indeed induce sleep in six animals. In one animal in which 125 mg/kg did not induce sleep, a subsequent dose of 200 mg/kg did; in one animal doses of 250 and 500 mg/kg failed to induce sleep but a subsequent dose of 1000 mg/kg did.

Data analysis. Integrated GG and DIA EMGs were analyzed at 10-min intervals from 30 min before until 60 min after CH administration. Peak (inspiratory) I EMGs and minimum (expiratory) I EMGs were measured from six consecutive breaths at each time. The phasic change in I EMGs was calculated as the difference between peak I EMG and minimum I EMG for each muscle. Peak, minimum, and phasic values from the six individual breaths at each time were averaged. The average peak activity in the control period was obtained by averaging the values for peak I GG EMG and peak I DIA EMG in the control period. Values for peak, minimum, and phasic I EMG for each muscle and at each time were then expressed as a percentage of average peak I EMG in the control period. Graphs were constructed to show the values of peak, minimum, and phasic I EMGs for individual animals against time.

Data from individual animals were averaged to obtain group means. Because results from rabbits and cats were similar, data from the two species were pooled. To demonstrate the differential effect of CH on GG EMG, peak I GG EMG was divided by peak I DIA EMG at each time, and then expressed as a percentage of the average ratio in the control period. The ratio of peak I GG EMG to peak I DIA EMG was displayed graphically both for individual animals and for the group mean. Statistical significance of results was assessed by the two-tailed paired t test comparing peak, minimum and phasic values for I GG EMG and for I DIA EMG at each time to corresponding values in the control period. All values are shown as mean ± SD.

RESULTS

The dose of CH required to induce sleep was 250 mg/kg in five animals, 200 mg/kg in one animal, and 1000 mg/kg in the other two animals. Peak I GG EMG decreased within 10–20 min after the hypnotic dose of CH in seven of eight animals. By contrast, no consistent effect on peak I DIA EMG was seen. As shown in Figure 1, the decrease in peak GG EMG activity was due in part to a depression of tonic (minimum expiratory) I GG EMG activity and, in part, to a depression of the phasic inspiratory increase in I GG EMG.

Figures 2A and B show graphs of I GG EMGs and I DIA

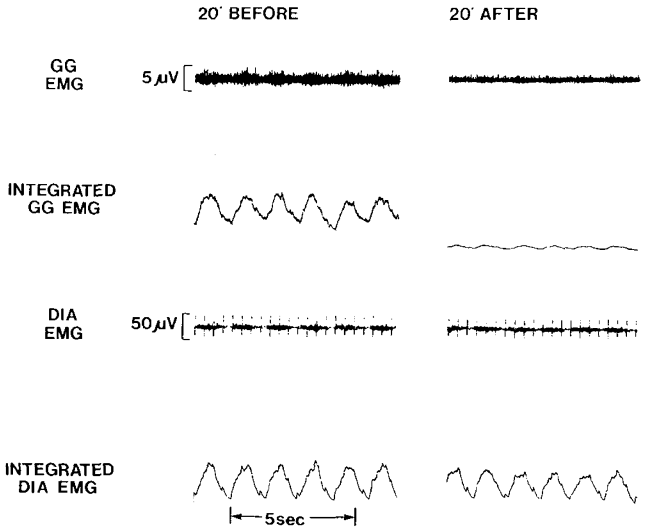

Fig. 1. Raw and integrated GG EMG and raw and integrated DIA EMG tracings obtained 20 min before and 20 min after administration of 250 mg/kg CH to a rabbit. Note the marked decrease in GG EMG activity and relatively unchanged DIA EMG activity. The decrease in peak GG activity is due to decreases in both tonic (minimum expiratory) activity and phasic inspiratory activity.

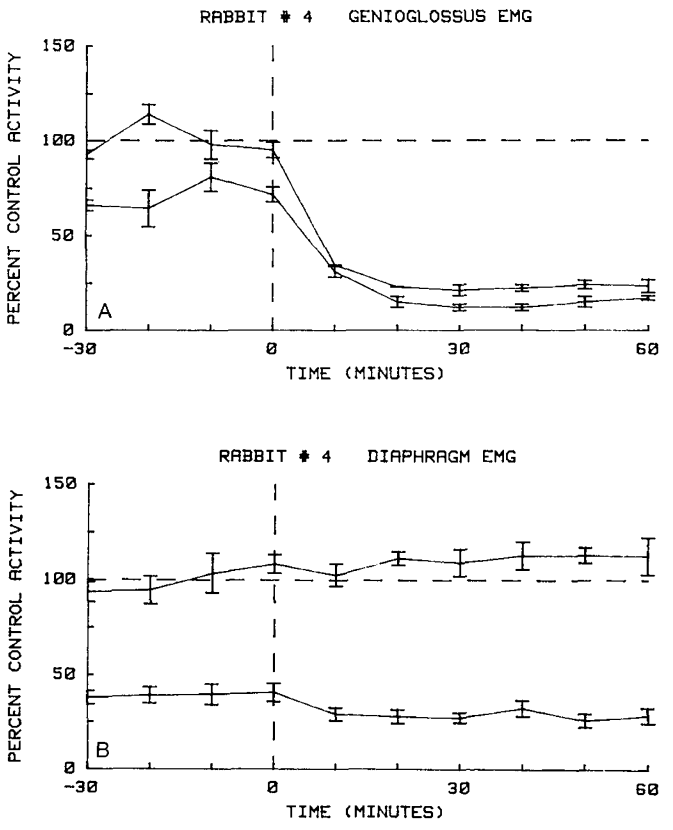

Fig. 2. Integrated EMGs before and after CH administration in a rabbit. The *horizontal dotted line* indicates average peak activity in the control period (100%). The *vertical dotted line* indicates time of CH administration. *Upper trace* on each graph shows peak I EMG (± SD) and *lower trace* shows minimum I EMG (± SD). (*A*) Peak I GG EMG decreases 10 min after CH is given. The decrease in peak I GG EMG is due to decreases in both tonic (minimum expiratory) activity and phasic inspiratory activity. (*B*) Values of peak, minimum, and phasic I DIA EMGs are relatively unchanged after CH.

EMGs, respectively, for a single animal from 30 min before to 60 min after CH. Both peak inspiratory and minimum expiratory I GG EMG values are decreased from the corresponding values before CH. Phasic I GG EMG, represented as the distance between the upper and lower lines at each time, is similarly depressed. No such dramatic change is evident for I DIA EMG.

Figures 3A and B and Table 1 present group mean data for I GG EMG and I DIA EMG, respectively. Average peak I GG EMGs were significantly decreased from 100% before CH to as low as 37.0 ± 27.2% after CH ($P < 0.001$). Minimum I GG EMGs fell from 46.2 ± 26.1% of peak values before CH to as low as 16.0 ± 9.7% after CH ($P < 0.01$). Phasic I GG EMG decreased from 53.8 ± 25.1% of peak control activity to as low as 20.6 ± 24.6% after CH ($P < 0.05$). By contrast, peak and phasic I DIA EMGs were not significantly different than those in the control period. Minimum I DIA EMGs decreased from 27.8 ± 17.1% before CH to as low as 14.9 ± 11.8% after CH ($P < 0.01$).

Peak I GG EMG and peak I DIA EMGs for individual animals are shown in Figs. 4A and B, respectively. Peak I GG EMG decreased in seven of eight animals. One animal had increases in both peak I GG EMG and peak I DIA EMG after CH whereas one animal demonstrated markedly increased peak I DIA EMG (200–300% of control) and decreased peak I GG EMG after CH. Peak I DIA EMGs for individual animals increased in two, decreased in three, and did not change in three.

Figures 5A and B show values for the ratio of peak I GG EMG to peak I DIA EMG for individual animals and for group mean data, respectively. A decrease in this ratio expresses a differential depressant effect of CH upon GG activity compared with DIA activity. The ratio of peak I GG EMG to peak I DIA EMG decreased in seven of eight animals and was virtually unchanged in the one animal in which both EMGs increased. Group mean data for the ratio of peak I GG EMG to peak I DIA EMG decreased to as low as 30.0 ± 17.7% of the pre-CH ratio.

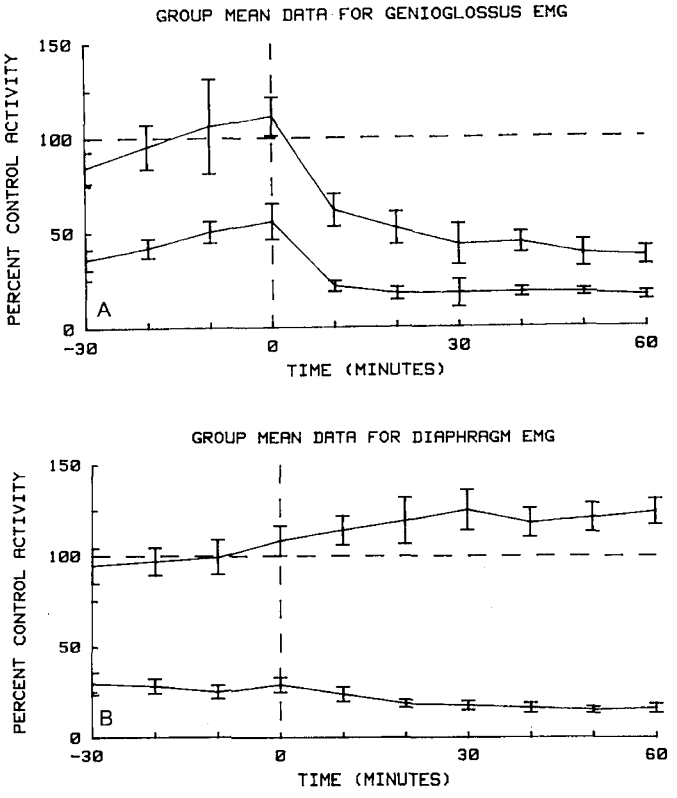

Fig. 3. Group mean I EMGs for all animals are shown (see also Table 10. (*A*) Note the decreases in peak, minimum, and phasic I GG EMGs after CH. (*B*) Peak (inspiratory) I DIA EMG after CH is not significantly different from control. Minimum I DIA EMG decreases after CH.

Table 1. *Values of integrated eletromyograms (EMGs) in the control period and at 10-minute intervals after chloral hydrate**, †*

Time (min)	Integrated genioglossus EMG		
	Peak	Minimum	Phasic
Control	100	46.2 ± 26.1	53.8 ± 25.1
10	61.7 ± 34.7**	21.3 ± 22.1**	40.3 ± 31.4
20	52.0 ± 52.6*	17.6 ± 17.5**	34.4 ± 35.9
30	43.3 ± 43.7**	17.7 ± 20.7*	25.7 ± 24.1*
40	44.2 ± 49.6**	17.9 ± 20.9**	26.3 ± 29.7
50	38.2 ± 42.2**	17.6 ± 20.1**	20.6 ± 24.6*
60	37.0 ± 27.2***	16.0 ± 9.7**	20.9 ± 20.5*

Time (min)	Integrated diaphragmatic EMG		
	Peak	Minimum	Phasic
Control	100	27.8 ± 17.1	72.2 ± 21.2
10	114 ± 38.9	23.7 ± 11.6	90.3 ± 37.8
20	119 ± 76.0	16.2 ± 11.1*	103 ± 72.2
30	125 ± 91.0	17.4 ± 14.5*	108 ± 87.6
40	118 ± 69.9	16.1 ± 12.7**	102 ± 66.1
50	121 ± 73.1	14.9 ± 11.8**	106 ± 70.5
60	124 ± 80.2	15.9 ± 11.4**	108 ± 75.9

* All values are expressed as a percentage of the average peak integrated EMG for that muscle in the control period: $\bar{x}$ + SD are shown.

† Peak, minimum, and phasic integrated EMGs at each time are compared with their respective values in the control period using the two-tailed, paried *t* test; *$P < 0.05$; **$P < 0.01$; and ***$P < 0.001$.

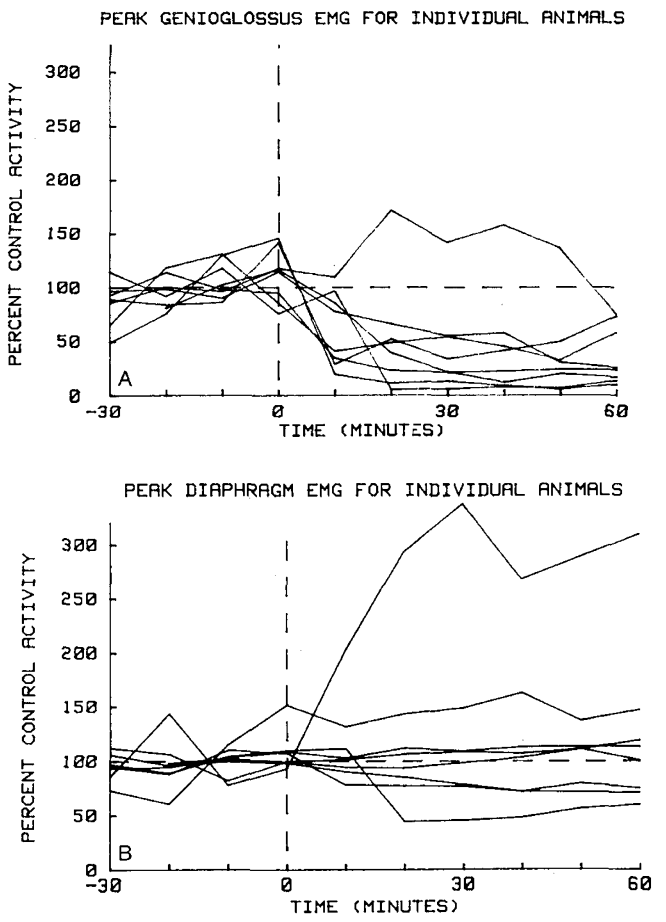

Fig. 4. Peak I EMGs for individual animals are shown. (*A*) Peak I GG EMG decreases in seven of eight animals after CH. (*B*) The effect of CH on peak I DIA EMG is more variable.

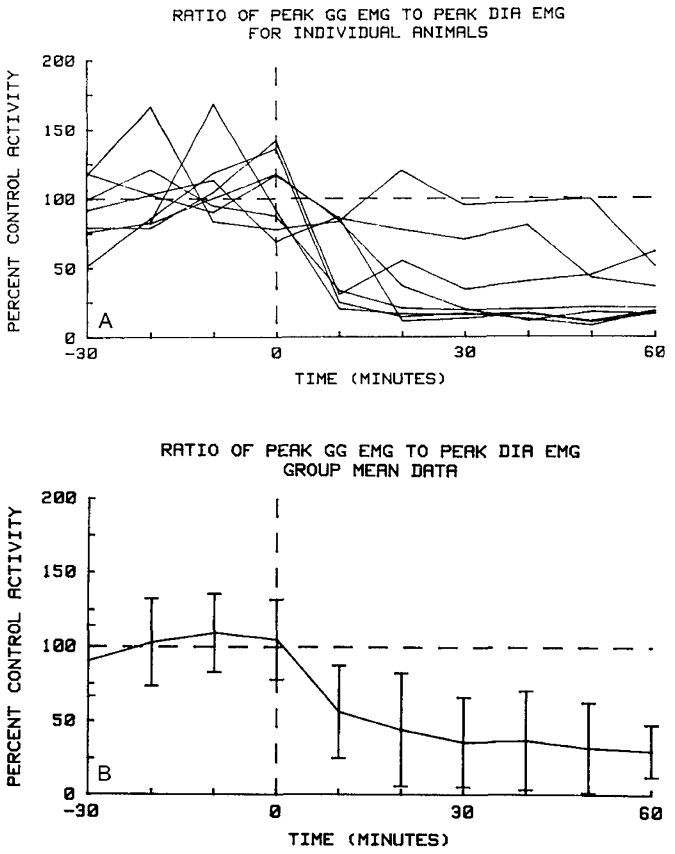

Fig. 5. The ratio of peak I GG EMGs to peak I DIA EMGs are shown. (*A*) The ratio of peak I GG EMG divided by peak I DIA EMG decreases after CH in seven of eight animals. (*B*) Group mean data for all animals are shown. The decrease in this ratio after CH expresses the differential depression of GG compared with DIA.

DISCUSSION

The results of this study demonstrate that in both cats and rabbits, hypnotic doses of CH selectively depress activity of the GG muscle compared with the DIA. The CH-induced GG depression was noticeable throughout the respiratory cycle with significant decreases in peak, minimum, and phasic I GG EMGs. Depression of GG activity began within 10–20 min after CH administration and lasted several hours. This time course of GG depression is consistent with the known time course of blood levels of trichloroethanol, the active metabolite of CH (3).

Previous studies have investigated the effects of CH on breathing but not explored the effects of CH on upper airway-maintaining musculature. Lees *et al.* (11) found no changes in baseline respiratory parameters or in hypercarbic ventilatory responses in tracheostomized puppies after 100 mg/kg of CH or in infants after 50 mg/kg of CH. Likewise, Hunt *et al.* (10) found no significant differences in baseline respiratory parameters or in hypercarbic or hypoxic ventilatory responses after 250 mg/kg of CH in tracheostomized rabbits (10). These studies suggested that, in patients who did not have a propensity towards airway obstruction, CH may be used for studies of sleep-related breathing control.

The finding that CH depresses GG but not DIA activity and the case report of a near-fatal airway obstruction after CH administration suggest that CH may depress GG and other airway-maintaining muscles in patients at risk for life-threatening airway obstruction including those with OSA. Such depression of upper airway-maintaining muscular activity could increase the frequency and/or duration of OSA episodes. Besides the immediate dangers of asphyxial brain damage and death, this effect could confound polygraphic evaluations of breathing in OSA patients. We, therefore, recommend that CH not be given to patients suspected of having OSA and that studies of sleep-related breathing control be performed only during nocturnal sleep or daytime naps (4).

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