Effect of Acute Aminophylline Administration on Diaphragm Function in High Cervical Tetraplegia*

A Case Report

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Theophylline has been shown to have beneficial effects on phrenic nerve and diaphragm activation. This case report involves a C5-C6 chronic tetraplegic patient with acute respiratory failure and ventilator dependence. IV aminophylline was administered in increasing doses (2 mg/kg, 4 mg/kg, and 6 mg/kg) over the course of 1 day. Diaphragm surface electromyography (sEMG), measures of respiration (tidal volume, minute ventilation, and frequency), and serum theophylline levels were captured. Diaphragm sEMG activity increased by a maximum of 50% at therapeutic levels. The rapid shallow breathing index dropped from 112 to 86. The subject was successfully weaned from ventilatory support. We conclude that administration of aminophylline facilitated weaning from ventilatory support in this tetraplegic patient.

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Key words: aminophylline; diaphragm; tetraplegia; theophylline; ventilator; weaning

Abbreviations: *f* = respiratory frequency; RSBI = rapid shallow breathing index; SCI = spinal cord injury; sEMG = surface electromyography; VT = tidal volume

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Respiratory insufficiency resulting from diaphragm palsy and/or paralysis is a common sequela of cervical spinal cord injury (SCI) and may result in ventilator dependency. Tetraplegic patients who are ventilator dependent have the highest mortality rate of all spinal cord-injured persons.[1] Currently there is no pharmacologic treatment available to improve respiratory muscle function in tetraplegia and prevent or treat respiratory failure.

The methylxanthine, theophylline (or its IV administered counterpart, aminophylline) may be effective in treating respiratory muscle-related insufficiency. Theophylline has been shown to exert notable effects by increasing respiratory muscle strength.[2–5] However, the effect of theophylline on respiratory muscles is somewhat controversial.

In the animal model of cervical SCI of Nantwi and colleagues[6–10] and Goshgarian and colleagues[11,12], systemic theophylline administration has been shown to restore phrenic nerve activity and hemidiaphragm function acutely in rats that have been subjected to an ipsilateral C2 spinal cord hemisection. A case report[13] by the same laboratory citing the use of theophylline in a nonventilator-dependent tetraplegic patient noted improvement in measures of pulmonary muscle strength after 3 weeks of oral administration. Based on the efficacy of theophylline in numerous animal-based studies[6–12] and in the above case report,[13] theophylline may improve function of the compromised respiratory system in tetraplegics and enable them to be weaned from ventilatory support.

Case Report

A 54-year-old, African-American man with a functionally complete C5-C6 spinal cord injury from a gunshot wound received 30 years prior to hospital admission presented to an urban medical center ICU. His neurologic examination indicated a C5 injury on the right side and C6 injury on the left side. Bacterial pneumonia and septicemia were found, and respiratory failure developed subsequent to hospital admission. The patient was placed on mechanical ventilation and was aggressively treated with appropriate antimicrobial and supportive therapy. Following resolution of the primary infections, weaning from ventilatory support was unsuccessful due to respiratory muscle insufficiency, and a tracheostomy was performed. The patient was receiving ventilatory support for approximately 1 month prior to initiation of our protocol. We hypothesized that IV administration of aminophylline would increase diaphragm activation and thus improve respiratory function in the patient, allowing him to be weaned from ventilatory support.

Experimental Protocol

The following protocol was carried out in the course of 1 day. Following informed consent, baseline measurements of respira-

tion and surface electromyography (sEMG) signals (Viking IV; Viasys Healthcare; Madison, WI) were obtained. Rectified and moving-time averaged sEMG were measured from the sixth, seventh, and eighth intercostal spaces for eight consecutive spontaneous breaths while the patient was receiving continuous positive airway pressure, 5 cm H_2O with no pressure support, through the ventilator (Puritan Bennett 7200; Tyco Healthcare; Pleasanton, CA). Maximal sEMG activity during inspiration to minimal sEMG activity at end-exhalation was examined. Simple measures of ventilation (tidal volume [Vt], minute ventilation, and frequency [*f*]) were captured through the ventilator display, and a serum theophylline level was obtained. The rapid shallow breathing index (RSBI) [*f*/Vt] was calculated from the obtained *f* and Vt. IV aminophylline was then administered at gradually increasing doses with the intention of reaching the therapeutic level that yielded the best results in terms of sEMG and respiratory measurements. A bolus of 2 mg/kg was administered over 30 min, followed by a continuous infusion of 0.6 mg/kg for 30 min. Measurements of respiration, sEMG, and serum theophylline were obtained immediately following completion of the continuous infusion. Separate measurements were made following the same protocol after boluses of 4 mg/kg of aminophylline followed by 30 min infusion of 0.6 mg/kg, and finally 6 mg/kg aminophylline followed by 30 min of a 0.6 mg/kg infusion. Several hours elapsed between each increase in drug dose.

Results

Diaphragm sEMG activity (rectified/moving-averaged peak to baseline) increased by a maximum of 50% on the more-affected right side (C5 injury) and 16.9% on the left side (C6 injury) at a dose of 4 mg/kg and a corresponding serum level of 12.4 μg/mL (Table 1). Additionally, the RSBI dropped from a baseline of 112 to 86 at a dose of 6 mg/kg (Table 1, Fig 1). At serum levels greater than the clinically therapeutic range for aminophylline (10 to 20 μg/mL), extinction of the positive effects of aminophylline on diaphragm sEMG was observed (Fig 2). The overshoot in theophylline level was not intentional. The serum theophylline level was returned to a therapeutic level by immediately titrating the dose of aminophylline. As soon as the theophylline level had returned to a therapeutic level, the subject was removed from ventilatory support successfully. Aminophylline administration was discontinued after 2 days. The patient maintained stable respiratory function and was discharged from the ICU and then from the hospital after decannulation and observation.

Discussion

This case report demonstrates a clinically significant improvement in diaphragm sEMG activity, RSBI, and ability to maintain spontaneous respiratory function after the administration of aminophylline. Diaphragm sEMGs in this case were obtained as a trending tool for gross diaphragm activation. The outcome measures studied responded to treatment in a dose-related fashion (except RSBI, see below), improving with increasing serum theophylline levels and then decreasing when a theophylline serum level that exceeded the therapeutic threshold was reached (Table 1).

RSBI is a commonly used index of probability of ventilator weaning success that is derived by dividing the patient's spontaneous *f* by the spontaneous Vt.[14] However, the utility of the RSBI has not been evaluated in a population of spinal cord-injured patients. Interestingly, in this case report the RSBI continued to improve (reflected as a downward trend) at the highest theophylline serum level despite the fact that the diaphragm EMG decreased (Fig 1). The decrease in the RSBI was due to a steady decrease in the patient's *f* over the study period from an initial rate of 29 to 24 breaths/min while Vt remained constant.

Table 1 illustrates that at a serum theophylline level of 12.4 μg/mL, the right sEMG exhibited a 50% increase in activation from baseline, while the left side sEMG increased by 16.9% from baseline. The differences between sEMG gains in the left and right hemidiaphragm during the study may be explained by the fact that the right hemidiaphragm had much lower activation to begin with, compared to the left. Indeed, the neurologic level on the patient's right side was determined to be at C5, while on the left it was at C6. Therefore, the right phrenic nerve would be more affected by his injury. Starting at a lower level of activation, the right phrenic nerve was predisposed to respond to aminophylline with greater magnitude compared to its low baseline. Both the left and right baseline sEMGs were considerably lower than would be expected in healthy individuals due to bilateral cervical SCI and recent critical illness of this patient with mechanical ventilation. Furthermore, extinction of sEMG activity gains at serum levels above therapeutic range correlates with findings in the Nantwi C2 spinal hemisection animal

Table 1—*Respiratory Function vs Aminophylline Dose**

Variables	Baseline (No Drug)	2 mg/kg Aminophylline	4 mg/kg Aminophylline	6 mg/kg Aminophylline
Left average sEMG, mV/s	14.3 ± 1.02	11.9 ± 0.92	16.7 ± 1.29	5.7 ± 0.51
Left average sEMG, % change from baseline	baseline	−17.1 ↓	16.9 ↑	− 60.4 ↓
Right average sEMG, mV/s	4.9 ± − 0.46	5.8 ± 0.35	7.5 ± − 0.28	4.3 ± − 0.37
Right average sEMG, % change from baseline	baseline	16.5 ↑	50 ↑	− 13.2 ↓
$\dot{V}_E$, L	7.5	6.75	6.9	6.7
f, breaths/min	29	27	25	24
RSBI, *f*/Vt	112	108	91	86
Serum level, μg/mL	0	5.2	12.4	22.7

*Data are presented as mean ± SD unless otherwise indicated.