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Aminophylline increases respiratory muscle activity during hypercapnia in humans

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ABSTRACT

Background: Theophylline is an old drug traditionally used as a bronchodilator, although it was recently shown to possess anti-inflammatory properties, enhance the actions of corticosteroid actions, and stimulate the respiratory neuronal network. Theophylline has been recognized as an important drug for not only asthma but also corticosteroid-insensitive chronic obstructive pulmonary disease (COPD). To clarify the role of theophylline in hypercapnic ventilatory responses in humans, we analyzed the effects of aminophylline administered at the usual clinical therapeutic doses on ventilation and augmentation of respiratory muscle contractility in room air and under 3 conditions of hypercapnia.

Study design: We performed electromyography (EMG) of the parasternal intercostal muscle (PARA) and transversus abdominis muscle (TA) in 7 healthy subjects and recorded both ventilatory parameters and EMG data in room air and under 3 conditions of hypercapnia before (control) and during aminophylline administration.

Results: Before aminophylline administration (control), hypercapnic stimulation elicited ventilatory augmentation in a hypercapnia intensity-dependent manner. Ventilatory parameters (tidal volume, frequency of respiration, and minute ventilation) showed significant increases from lower $PaCO_2$ levels during aminophylline administration when compared with the corresponding values before aminophylline administration. EMG activity of both PARA and TA increased significantly at each level of hypercapnia, and those augmentations were shown from lower $PaCO_2$ levels during aminophylline administration.

Conclusion: Aminophylline administered at the usual clinical therapeutic dose increases ventilation and EMG activity of both inspiratory and expiratory muscles during hypercapnia in healthy humans.

1. Introduction

Theophylline is an old drug traditionally used as a bronchodilator for the treatment of bronchial asthma. Recently, it was shown that aminophylline, a compound consisting of two molecules of theophylline and one molecules of ethylenediamine, causes bronchodilation, controls inflammation, enhances corticosteroid actions, and stimulates the respiratory neuronal network [1–4]. Theophylline had been recognized as an important drug for the management of patients with not only bronchial asthma but also corticosteroid-insensitive chronic obstructive pulmonary disease (COPD) [5–10].

In a previous study, respiratory rate and tidal volume increased during hypercapnia [11]. While other studies demonstrate increased electromyography (EMG) activity of the diaphragm and abdominal muscles in awake canines [12–14]. In contrast,

Abbreviation: DIV, intravenous drip.

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aminophylline increases transdiaphragmatic pressure (Pdi) during hypoxia and delays the onset of diaphragmatic fatigue in COPD patients with hypoxic hypercapnia [15,16]. We previously reported that aminophylline augments the hypoxic ventilatory response and increases EMG activity of the parasternal intercostal muscle (PARA), one of the major inspiratory muscles, in humans [17]. In order to better understand the action of aminophylline in humans, we thought to elucidate its mechanism of action under non-hypoxic hypercapnic conditions, which has not been well described. We hypothesize that aminophylline administered at standard clinical doses increases not only inspiratory muscle activity but also expiratory muscle activity during hypercapnia in humans inducing a significant change in chest wall musculature in its entirety. To evaluate respiratory muscle activity, we analyzed EMG data for PARA [18–23] and the transversus abdominis muscle (TA), the latter being one of the major expiratory muscles [12]. In addition, because aminophylline essentially exerts pharmacological effects identical to those of theophylline [1], we need not discriminate between aminophylline and theophylline hereafter in this study.

2. Material and methods

Seven healthy young men (age, 20–23 years; height, 162–178 cm; weight, 52–73 kg) were enrolled. None of these subjects had prior experience with respiratory maneuvers or experimentation. No history of pulmonary or neuromuscular disorder was reported. All subjects underwent thorough pre-study evaluation, including electrocardiography and echocardiography by a cardiologist to rule out the presence of underlying cardiac disease. Subjects were asked to refrain from consuming any caffeine- or theophylline-containing substances for minimum 24 h prior to the study. Each subject provided informed consent to participate in the study, which was approved by the Ethics Committee of Kitasato University.

2.1. Measurement of ventilatory parameters

The subjects maintained a supine position throughout the study. Ventilatory parameters were recorded as described previously [12,24]. The parameters were recorded with the subjects breathing via a mouthpiece through a one-way, low-resistance breathing circuit (<1 cm H_2O/L/s) that was connected to a hot-wire pneumotachograph for measuring respiratory airflow. During the entire study, end-tidal CO_2 ($ETCO_2$) and transcutaneous oxygen saturation (SpO_2) were monitored and analyzed continuously using an infrared CO_2 analyzer and a pulse oximeter, respectively. The inspiratory flow signal was used to calculate respiratory timing, i.e., inspiratory time (T_I), expiratory time (T_E), and total time per breath (T_T), breath-by-breath as well as the frequency of respiration (f). The inspiratory flow signal was digitally integrated and the tidal volume (V_T) and minute ventilation (V_I) were calculated.

2.2. EMG recordings

Details of the fine wire EMG techniques used in this study are published elsewhere [12,24–26]. Briefly, pair of fine wire electrodes were inserted, approximately 10 mm apart, into 3rd parasternal intercostal muscle (PARA) and transversus abdominis muscle (TA) 1 cm below the right costal margin on the anterior axillary line guided by high resolution ultrasound echo graph.

The EMG signals from the electrodes were band-pass filtered (10 Hz–1 kHz), rectified and processed by a resistance capacitor with a time constant of 50 ms to provide continuous moving average EMG data for PARA and TA. Those moving average EMG signals were then directly merged with respiratory airflow and $ETCO_2$ data on the hard disk of a microcomputer at 100 Hz.

2.3. Loading hypercapnia

Subjects rebreathed 6.9% CO_2 balanced O_2 from a 6 L bag [27] until the observed $ETCO_2$ was approximately 10% or until the subjects exhibited signs of dyspnea. To ensure subject safety, EMG data, $ETCO_2$, SpO_2, facial expressions, and the fraction of inspired oxygen (FIO_2) were monitored throughout hypercapnic loading.

2.4. Administration of aminophylline

Aminophylline (Eisai Co., Ltd.: Tokyo, Japan) was diluted with 0.9% NaCl solution and administrated intravenously using a syringe pump. A loading dose of 9 mg/kg was administrated in the first hour, followed by a maintenance dose of 0.75 mg/kg/h. The maintenance dose used is equivalent to a standard clinical therapeutic dosage. Venous blood was sampled and serum theophylline concentrations were measured at 0, 60, 90, and 120 min after the initiation of aminophylline administration (Fig. 1).

2.5. Experimental protocol

Ventilatory parameters and EMG data under hypercapnia were recorded before and continuously during aminophylline administration 1 h after initiation. All recordings were obtained under two conditions: room air and progressive hypercapnia.

2.6. Analysis of breathing pattern and EMG activity

The flow signal was evaluated for respiratory timing and digitally integrated. T_I, T_E, T_T, V_T, f, and V_I were determined and the mean inspiratory flow (V_T/T_I), and inspiratory fraction of respiration (T_I/T_T) were calculated breath-by-breath.

Resting EMG activity was defined as the lowest moving average EMG activity measured during expiration and inspiration. Tidal EMG was calculated as the maximum difference per breath between resting EMG activity and the peak height of the moving average EMG signal. These measurements defined tidal activity of respiratory airflow and timing as well as EMG activity of PARA and TA. Mean tidal EMG activity was calculated from 10 sequential breaths in each condition. The tidal moving average EMG activity of each respiratory muscle was expressed as $\%EMG_{max}$ [12,17,24].

Indices of breathing pattern and EMG activity were calculated in the supine position during breathing at rest (REST) and at 3 levels of CO_2 stimulation (mild, moderate and severe) before and after aminophylline administration. Similar to the definition in previous reports [12,24], we defined severe CO_2 (CO_{2Sev}) as the highest $ETCO_2$ ($PaCO_2$) level tolerated comfortably by each subject with a minimum valve of numerical rating scale. Moderate and mild hypercapnic stimulation levels (CO_{2Mod} and CO_{2Mild}, respectively) were selected at 10 and 20 Torr below maximum levels, respectively. Those conditions were denoted as C-REST, C-CO_{2Mild}, C-

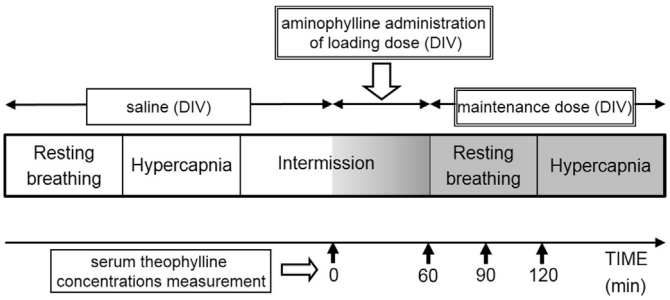

Fig. 1. Aminophylline was administrated with 9 mg/kg as loading dose, then followed by 0.75 mg/kg/h as maintenance doses intravenously.

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