Lung function, hypoxic and hypercapnic ventilatory responses, and respiratory muscle strength in normal subjects taking oral theophylline

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Abstract

Methylxanthines are known to be respiratory stimulants and are thought by some to augment hypercapnic and hypoxic ventilatory drive and improve respiratory muscle strength. Hypoxic and hypercapnic ventilatory responses were measured in 10 normal subjects before, during, and after administration of theophylline for three and a half days. Pulmonary function, carbon dioxide production, and mouth pressures during maximal static inspiratory and expiratory efforts were also measured. The mean (SD) serum theophylline concentration was 13·8 (3·2) mg/l. Lung volumes and flow rates did not change significantly with theophylline. The mean (SD) values for maximum static inspiratory pressure were 152 (27), 161 (25), and 160 (24) cm H_2O, respectively before, during, and after theophylline. Neither these values nor peak expiratory pressure measurements were significantly changed. The slopes of the hypercapnic ventilatory responses were 2·9 (0·9), 3·3 (1·2), and 3·3 (1·4) l/min/mm Hg carbon dioxide tension (PCO_2) respectively before, during, and after theophylline administration. The respective values for the slopes of the hypoxic response were $-1·4$ (0·9), $-1·3$ (0·8), and $-1·1$ (0·9) l/min/1% oxyhaemoglobin saturation. None of these values changed significantly with theophylline. Theophylline, however, increased carbon dioxide production (200 to 236 ml/min) and alveolar ventilation (4·7 to 5·7 l/min) significantly, with a concomitant fall of end tidal PCO_2 (35·5 to 32·9 mm Hg). It is concluded that in man oral theophylline at therapeutic blood concentrations increases carbon dioxide production and ventilation without changing pulmonary function, respiratory muscle strength, or the hypoxic or hypercapnic ventilatory response significantly.

Methylxanthines are respiratory stimulants,[1] and have been used as such to treat infants[2] and adults[3] with central apnoea and Cheyne-Stokes respiration[4][5] successfully for 50 years.

1 mm Hg $\approx$ 0·133 kPa.

The mechanisms by which theophylline mediates the improvement in ventilation are not clear; augmentation of hypoxic and hypercapnic ventilatory responses has, however, been suggested.[1]

Several studies have looked at the effects of theophylline on the ventilatory response to hypoxia and hypercapnia in man,[6–10] though in some,[8][10] in which theophylline augmented hypercapnic ventilatory response or diminished carbon dioxide retention after oxygen breathing, the studies were performed in patients with chronic obstructive lung disease in whom theophylline caused bronchodilatation. The increase in hypercapnic response might therefore have been due to the decrease in airways resistance rather than a change in chemosensitivity to carbon dioxide.[11][12]

Only three systematic studies to our knowledge have been concerned with the ventilatory effects of theophylline in normal man.[6][7][9] Stroud and associates[9] showed that intravenous administration of aminophylline (3 and 6 mg/kg) in man displaced the ventilation carbon dioxide curve (measured by a steady state technique) upward and to the left (to a higher ventilation for a given expired carbon dioxide concentration). In contrast, Lakshminarayan and colleagues[6] reported that intravenous administration of 5 mg/kg of aminophylline had no significant effect on the slope or intercept of hypercapnic response in six normal subjects but significantly augmented the response to hypoxia measured at the prevailing carbon dioxide tension (PCO_2). In the study of Sanders and associates,[7] however, aminophylline did not augment the ventilatory response to hypoxia when measurements were performed at the prevailing PCO_2 (which was lower in those given aminophylline than in the control subjects). Aminophylline rather than theophylline was used in all these studies, most were performed after intravenous administration, and the number of subjects studied was usually small.

In this study we report the effects of maintained treatment with oral theophylline on lung function, hypoxic and hypercapnic ventilatory responses, and respiratory muscle strength in 10 normal subjects. Because subjects usually recognise theophylline, a double blind approach is difficult, so we performed measurements before, during, and after administration of theophylline.

Our specific aim was to investigate whether

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oral theophylline increases ventilatory responses, and if so whether the augmentation is due to bronchodilatation, to an increase in respiratory muscle strength, or to a rise in metabolic rate.

Methods
We studied 10 healthy non-smoking men aged 22–39 years. All were medical personnel but unaware of the reason for the experiment. The protocol was approved by the Institutional Review Board at the University of Cincinnati College of Medicine.

TESTS
Spirometric and ventilatory measurements and tests of muscle strength were carried out before the drug trial and served as a training run. Tests were performed two hours after a meal and at the same time of day for each subject. All subjects refrained from beverages containing caffeine derivatives on the day of the study.

Details of the techniques used for the pulmonary function tests in our laboratory have been published.[14] Spirometric tests were performed in triplicate (Collins/DS, W E Collins, Braintree, Montana) and the highest value was used. Transfer factor for carbon monoxide (TLCO) was determined by the single breath technique, and functional residual capacity (FRC) by helium rebreathing.

The ventilatory tests were measured with the subject sitting, wearing a nose clip and breathing through a mouthpiece connected to a low resistance two way valve (Hans-Rudolph, Kansas City, Missouri). Auditory distraction was provided by radio headphones. Inspiratory flow and volume were measured by a pneumoscan S-301 spirometer (KL Engineering, Sylmar, California), calibrations were performed on the basis of using known flow rates from a pneumatic calibrator (Model 65–250, Pennwalt Corporation, Belleville, New Jersey) and 3 litre syringes for volume. End tidal carbon dioxide was sampled at the mouthpiece by an infrared carbon dioxide analyser (Beckman Medical Gas Analyzer, LB-2, Beckman Cardiopulmonary Instruments, Fullerton, California). Arterial oxygen saturation (SaO$_2$) was measured by ear oximetry (BTI Biox II A, Bioximetry Technology, Boulder, Colorado).

Measurements started after achievement of a steady state as shown by a stable end tidal P_{CO_2}. Resting ventilation was measured with the subject breathing room air and a timed volume of exhaled gas was collected for calculation of carbon dioxide production ($\dot{V}_{CO_2}$). Deadspace and alveolar ventilation were calculated from the Bohr equation and the alveolar ventilation equation on the basis of known end tidal carbon dioxide, mixed expired carbon dioxide, carbon dioxide production, and minute ventilation.

The hypercapnic ventilatory response was determined by the rebreathing method of Read.[15] Data points after the appearance of a mixed venous P_{CO_2} plateau were used in the calculations. Linear regression was used to derive the equation $\dot{V}_E = S(P_{CO_2} - B)$, where S is the slope of response and B is the intercept

on the P_{CO_2} axis. The isocapnic hypoxic ventilatory response was performed by the rebreathing method of Rebuck and Campbell.[16] End tidal P_{CO_2} was maintained at the prevailing levels by removing carbon dioxide from the circuit by two variable speed pumps connected to a carbon dioxide absorber. Rebreathing was stopped when arterial oxygen saturation reached 70%. Data points from 90% to 70% saturation were used to relate ventilation to saturation by least squares regression analysis. A minimum of 10 minutes was allowed between each test.

Respiratory muscle strength was assessed by measuring mouth pressures during maximal static inspiratory (PIPmax) and expiratory (PEPmax) efforts against an obstructed mouthpiece with a small leak to minimise oral pressure artifacts.[16 17] The pressures were measured at residual volume (PIPmax) and at total lung capacity (PEPmax), maintained for one second and determined three to five times until at least two technically satisfactory measurements were recorded.

Theophylline serum concentration was determined with the Kodak Ektachem 700 (Rochester, New York).

EXPERIMENTAL DESIGN
Training studies were performed two days before baseline measurements, to acquaint subjects with the laboratory and equipment and minimise their anxiety, and to enable them to practise PIP and PEP manoeuvres. Baseline measurements (run I) were performed the day before subjects were given sustained release theophylline (Theo-Dur, Key Pharmaceutical, Kenilworth, New Jersey), 10 mg/kg/day in two divided doses (every 12 hours), by mouth. Measurements were repeated (run II) on the fourth day and a venous blood sample obtained for determination of theophylline concentration. A third set of measurements (run III) was obtained at least two weeks after theophylline administration had been stopped.

STATISTICAL ANALYSIS
Slopes of ventilatory responses were calculated without knowledge of drug treatment. Statistical significance was determined by analysis of variance with repeated measures and multiple paired t tests. The Bonferroni correction factor was used when more than two variables were compared. The SAS computer system, University of Cincinnati, was used for calculations. Data are presented as means with standard deviations in parentheses. Values of p below 0·025 were considered significant.

Results
The mean (SD) age was 31·2 (5·4) years, height 176 (7) cm, and body weight 78 (15) kg. The mean serum theophylline concentration was 13·8 (3·2) (range 7·4–17·8) mg/l during the second study; eight subjects had concentrations above 12 mg/l.

Mean baseline FRC total lung capacity (TLC), and TLCO were 2·82 (0·87), 6·54 (0·77), 1·38 (0·46) l, and 35·0 (3·0) ml/min/mm Hg.

*Ventilation and gas exchange (mean (SD) values) before, during, and after theophylline administration**

Run†	RR (/min)	VT (ml)	$\dot{V}E$ (l/min)	$\dot{V}CO_2$ (ml/min)	$\dot{V}A$ (l/min)	$\dot{V}D$ (l/min)	$PECO_2$ (mm Hg)
I	12·4 (4·2)	676 (162)	8·00 (2·11)	200 (59)	4·72 (1·50)	3·28 (0·95)	35·5 (2·3)
II	14·0 (4·7)	718 (129)	9·63‡ (2·23)	236‡ (50)	5·77‡ (1·19)	3·88 (1·15)	32·9‡ (2·5)
III	13·4 (2·4)	619 (128)	8·29 (2·09)	207 (57)	4·77 (1·24)	3·52 (0·80)	35·0 (2·0)

*$\dot{V}CO_2$ is at STPD and the other measurements at BTPS.
†I—before theophylline; II—on theophylline; III—after theophylline.
‡p < 0·025 v baseline value.

RR—respiratory rate; VT—tidal volume; $\dot{V}E$—minute ventilation; $\dot{V}CO_2$—carbon dioxide production; $\dot{V}A$—alveolar ventilation; $\dot{V}D$—deadspace ventilation; $PECO_2$—end tidal carbon dioxide tension.

Mean baseline values for forced vital capacity (FVC), FEV_1, FEV_1/FVC, peak expiratory flow (PEF), and peak inspiratory flow (PIF) were 5·04 (0·42) l, 4·36 (0·54) l, 86% (5%), 12·5 (1·5) l/s, and 9·1 (1·3) l/s. There were no significant changes in any of these measurements during the study.

Mean PIP was 152 (27), 161 (25), and 160 (24) cm H_2O for runs I, II, and III. The corresponding values for PEP were 227 (17), 234 (27), and 231 (31) cm H_2O. The maximum difference between the mean value of the best and the next best value for a given measurement was 3·8%, indicating good reproducibility. Theophylline had no significant effect on either PIPmax or PEPmax.

Carbon dioxide production, minute ventilation, and alveolar ventilation increased significantly with theophylline and end tidal carbon dioxide tension ($PECO_2$) fell significantly (table). These variables returned to baseline values after theophylline had been stopped.

Mean values for S of the ventilatory response and the intercept of the response did not change significantly with theophylline administration. For the hypercapnic responses the mean values of B (x-intercept) were 39·5 (2·6), 38·7 (2·9), and 40·9 (3·1) mm Hg for runs I, II, and III. The corresponding S values were 2·9 (0·9), 3·3 (1·2), and 3·3 (1·4) l/min/mm Hg PCO_2. Ventilation for runs I, II, and III at a PCO_2 of 60 mm Hg was 59·9 (20·9), 71·4 (26·8), and 62·3 (25·5) l/min and did not differ significantly. The S values for the hypoxic response were −1·4 (0·9), −1·3 (0·8), and −1·1 (0·9) l/min/1% oxyhaemoglobin saturation for runs I, II, and III. There were no significant correlations between serum theophylline concentrations and the S values of ventilatory response or their respective changes from baseline.

We attempted to standardise the ventilatory responses. During the hypoxic test the mean time spent between 90% and 70% oxyhaemoglobin saturation did not differ significantly (169 (22), 154 (34), and 158 (30) seconds for runs I, II, and III). Mean $PECO_2$ values during the three hypoxic response measurements were also similar (34·9 (2·0). 33·7 (2·5), 34·9 (1·7) mm Hg).

Discussion

From this study in normal man we draw four main conclusions. Theophylline at therapeutic plasma concentrations increases carbon dioxide production and alveolar ventilation and decreases end tidal PCO_2; theophylline does not significantly change lung volumes or flow rates

(thus confirming the results of Estenne et al[18]); theophylline does not significantly affect inspiratory or expiratory muscle strength; and, importantly, it does not significantly change the slopes or intercepts of hypoxic and hypercapnic ventilatory responses.

THEOPHYLLINE AND MUSCLE STRENGTH
Care was taken in measuring inspiratory and expiratory muscle strength, and subjects were trained to carry out the manoeuvre. Measurements were reproducible, as the closeness of the mean values of the two highest observations showed. The lung volumes at which PEPmax and PIPmax were performed (TLC and RV) remained virtually unchanged.

Our results strongly suggest, therefore, that in normal man oral theophylline does not improve respiratory muscle strength as measured by this technique. These data are consistent with the findings of Moxham et al,[19] who showed that theophylline had no effect on diaphragmatic contractility evoked by percutaneous phrenic nerve stimulation. Similar results were reported for the sternomastoid muscle.[20] The results differ, however, from those obtained by Murciano and associates in normal subjects[21] and in patients with chronic obstructive lung disease.[22][23] Improved inspiratory muscle contractility after theophylline in patients with chronic obstructive lung disease does not necessarily mean that theophylline has a direct effect on the diaphragm. As theophylline improves pulmonary function in these patients this might have resulted in improvement of respiratory muscle strength.[22]

EFFECT OF THEOPHYLLINE ON VENTILATORY RESPONSES
Although methylxanthines are often said to augment hypoxic and hypercapnic ventilatory responses,[1] theophylline had no significant effect in either test in our subjects. The lack of effect on the carbon dioxide response contrasts with the results of some earlier studies[9] but is in agreement with the findings of Lakshminarayan et al[6] and Sanders et al.[7] Lakshminarayan et al did, however, show an increase in the hypoxic ventilatory response with intravenous aminophylline.

Hypoxic ventilatory response may not be measuring a single factor as is commonly assumed. When man is subjected to sustained hypoxia, ventilation increases initially owing to stimulation of carotid bodies; later ventilation falls.[24] Hypoxic ventilatory depression is most easily shown in anaesthetised animals with

denervation of the carotid body.[25][26] Changes in ventilation during hypoxia may represent the algebraic sum of peripheral chemoreceptor stimulation and central ventilatory depression, the contribution of the latter depending on the degree and duration of hypoxia. Our observations in anaesthetised, spontaneously breathing animals[26] and the results of Easton and Anthonisen in man[24] indicate that hypoxic ventilatory depression usually takes several minutes to develop. We believe that respiratory depression is unlikely to have occurred during our hypoxic ventilatory tests, as they lasted less than three minutes. Hypoxic ventilatory depression might, however, have occurred in the study of Lakshminarayan *et al*[6] as the hypoxia lasted seven minutes; the hypoxaemia was also more severe, arterial oxygen tension (PaO_2) falling to around 30 mm Hg (4·0 kPa) whereas in our study the minimum PaO_2 was about 40 mm Hg (5·3 kPa). If our assumption is correct and hypoxic depression occurred in the studies of Lakshminarayan and associates, the augmentation of hypoxic response by aminophylline noted in that study may have been due to reversal of the central depression.[24-26] Theophylline has been shown to reduce ventilatory depression in man[24] and in anaesthetised cats whether breathing spontaneously[26] or paralysed and mechanically ventilated.[25]

THEOPHYLLINE AND VENTILATION

Our results show that oral theophylline at therapeutic plasma concentrations increases resting minute and alveolar ventilation and decreases end tital PCO_2. Deadspace did not change, which is consistent with the lack of bronchodilatation with theophylline. The increase in ventilation was not associated with any significant improvement in inspiratory or expiratory muscle strength. Aubier and associates[27] found that aminophylline increased ventilation in anaesthetised dogs by improving diaphragmatic strength.

Theophylline has increased carbon dioxide production significantly in man,[6] rat,[28] and dog.[29] The rise in carbon dioxide production was in part due to the increased work of breathing (as reflected by the increase in ventilation), but is probably due mainly to an increase in metabolic rate related to a generalised potentiation of muscular contractions as a result of facilitation of neuromuscular transmission.[30] Alveolar ventilation rose more than was accounted for by increased carbon dioxide production, so that $PECO_2$ fell. A fall in PCO_2 would tend to depress ventilation, so the theophylline induced augmentation of ventilation may be underestimated. Eldridge and associates[31] and Javaheri and colleagues[32] showed that aminophylline increased ventilation considerably in anaesthetised cats when end tidal and arterial PCO_2 were kept relatively constant.

The increase in ventilation seen with theophylline may be related to inhibition of adenosine at A-1 receptors, adenosine being inhibitory in the central nervous system and in the neuronal circuit concerned with breathing.[26][31][32] As theophylline increased ventilation in the present study in the absence of sig-

nificant change in hypoxic and hypercapnic ventilatory responses, respiratory muscle strength, or lung function, we may reasonably suggest that in man, as in the cat,[31][32] this action is due to inhibition of adenosine, which should be tonically inhibiting ventilation. Theophylline, at therapeutic plasma concentrations, is believed to be a specific inhibitor of adenosine.[1] This mechanism of action may also account for the therapeutic effect of theophylline on central apnoea and Cheyne-Stokes respiration[3-5] as adenosine is released in the brain during hypoxia.[33] Further work, however, is necessary to show the relation between theophylline, adenosine, and these breathing disorders.

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