α-Methyldopa selectively reduces alae nasi activity

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SUMMARY

1. Sedatives such as the benzodiazepines and alcohol reduce upper airway muscle activity. We hypothesized that a sedating antihypertensive, α-methyldopa, might have similar effects. To investigate this hypothesis we studied the effect of α-methyldopa on alae nasi electromyographic (EMG) activity during hypercapnia.

2. We studied ten healthy subjects and three subjects with obstructive sleep apnoea during CO₂-stimulated breathing. In a preliminary study four subjects demonstrated a fall in alae nasi EMG activity 4 h after the ingestion of 500 mg of α-methyldopa during CO₂ rebreathing.

3. In six additional normal subjects and three subjects with obstructive sleep apnoea, we studied the alae nasi EMG activity during steady-state hypercapnia with $P_{CO_2}$ held constant 5 torr (0.7 kPa) above baseline. On 2 separate days we studied subjects before and 2 h after they had ingested 750 mg of α-methyldopa or placebo.

4. In the normal subjects the mean alae nasi EMG activity fell by 34% 2 h after ingestion of α-methyldopa ($P<0.05$) without a change in other ventilatory parameters.

5. In the sleep apnoea group the individual mean alae nasi EMG activity fell 16–49%, with ventilation and tidal volume falling in one patient.

6. We conclude that α-methyldopa selectively reduces upper airway motor activity.

Key words: α-methyldopa, sleep apnoea, upper airway muscles.

Abbreviations: EMG, electromyographic; OSA, obstructive sleep apnoea.

INTRODUCTION

Hypertension is found in up to 90% of patients with the sleep apnoea syndrome [1]. In addition, screening of asymptomatic patients in hypertension clinics reveals unsuspected sleep apnoea in as many as 30% of those screened [2–5]. Therefore, physicians often prescribe antihypertensive medications for patients with this disorder. Many antihypertensives, particularly those acting via central mechanisms, produce sedation as a common side-effect. Sedating agents such as the benzodiazepines and alcohol have been shown selectively to decrease upper airway tone in man and experimental animals [6–11] as well as increase the severity of sleep apnoea in patients [12]. Considerable evidence exists that decreased tone in upper airway muscles accompanying sleep in patients with sleep apnoea syndrome permits collapse of the upper airway due to the negative pressure produced by the diaphragm [13]. We speculated that a sedating antihypertensive, α-methyldopa, might selectively decrease upper airway muscle tone. To test this hypothesis, we assessed the effects of α-methyldopa on alae nasi activity in ten normal volunteers and three patients with obstructive sleep apnoea (OSA) during hypercapnic breathing.

METHODS

Subjects

We studied ten normal subjects, aged 18–36 years. Two additional subjects were excluded from the study before any investigations because no alae nasi electromyographic (EMG) activity was obtained during resting breathing. All subjects were healthy and without respiratory or sleep-related complaints other than a history of mild asthma in two subjects. The OSA group consisted of two women and one man, aged 40–53 years. Their apnoea index (apnoeas plus hypopnoeas per hour of sleep as measured during polysomnography, with apnoeas defined as a complete cessation of breathing of greater than 10 s and hypopnoeas defined as a reduction in ventilation of greater
than 50% with an oxygen desaturation of greater than 5% \) ranged from 40 to 130. One of the OSA subjects had hypertension and was treated with nifedipine at the time of the study. The other two OSA subjects were taking no medications. All subjects gave informed consent according to the guidelines of the hospital Committee on Clinical Investigations.

Protocol

All subjects were studied during CO₂-stimulated breathing. A mass spectrometer (Perkin-Elmer 1100) was used to sample \( P_{ETCO_2} \) at the mouth. Flow and volume were measured with a Wedge spirometer (Med Science 570). Inspiratory ventilation was determined from flow with a respiratory integrator (Hewlett Packard 8815A). Cup electromyograph electrodes were placed superior and lateral to the alar cartilage. Surface EMG signals from the alae nasi were amplified (Tektronix AM502), band-pass filtered (10–1000 Hz), full-wave rectified and averaged over 150 ms to obtain a moving time average of activity. The peak of the moving time average during each respiratory cycle was used for data analysis. Volume, flow, ventilation, \( P_{ETO_2} \), electrocardiogram and integrated EMG signal were simultaneously recorded on an eight-channel strip chart recorder.

We measured each subject’s blood pressure 10 and 5 min before the initiation of the experiment. The mean arterial pressure was calculated as two-thirds of the diastolic pressure plus one-third of the systolic pressure. The subjects then sat comfortably in a semi-recumbent position in a chair specifically designed to keep body position constant. Subjects breathed on a closed circuit employing a tight-fitting face mask (dead space 75 ml; Respironics) which allowed them to breathe freely through nose and mouth. Before each study, mask fit was assessed by monitoring CO₂ at all points around the outside of the mask.

In a preliminary study four subjects were studied during CO₂ rebreathing using the method of Read [14]. After a 5 min equilibration period, subjects breathed from a 7 litre rebreathing bag which initially contained 93% O₂ and 7% CO₂. Subjects breathed to a \( P_{ETCO_2} \) that was 25 torr (3.3 kPa) above baseline, at which time the run was concluded. Two runs were performed. The subjects then ingested 500 mg of \( \alpha \)-methyldopa and the rebreathing runs were repeated at 2 and 4 h. We analysed all breaths occurring at \( P_{ETCO_2} = 50–52 \) torr (6.7–6.9 kPa). An average of 26.2 breaths (18–40 breaths) was analysed per subject. The processed EMG signal amplitudes were arbitrarily expressed as a percentage of the maximal value of the peak EMG signal observed during the equilibration period. We used the Freedman’s rank sum test blocked with 0 h as control to evaluate the data [15]. Significance was reached with \( P<0.05 \).

Because we found considerable breath-to-breath variability in the amplitude of the alae nasi EMG signal during CO₂ rebreathing and the small number of breaths at any \( P_{ETO_2} \), we modified our protocol to study the additional nine subjects. Six normal and three OSA subjects performed steady-state hypercapnic breathing before and after ingesting 750 mg of \( \alpha \)-methyldopa. Using the same tight-fitting mask described, subjects breathed on a closed circuit containing 100% O₂. Expired ventilation was selectively channelled through calcium carbonate in order to maintain \( P_{ETCO_2} \) at the target level. Low flow O₂ was added to the system to maintain constant volume. Alae nasi EMG signal, volume, flow, \( P_{ETCO_2} \) and inspiratory ventilation were processed and recorded as in the preliminary study. During each trial, the subjects breathed for 5 min while all expired ventilation was channelled through calcium carbonate. This maintained \( P_{ETCO_2} \) in the isocapnic range \( [P_{ETCO_2} = 38–42 \) torr (5.1–5.6 kPa)] \). \( P_{ETCO_2} \) was then allowed to rise 5 torr (0.7 kPa) above this baseline. Subjects breathed at this increased \( P_{ETCO_2} \) for 10 min, the last 4 min being used for data collection. Subjects were studied on 2 days. On 1 day, the subjects performed a trial immediately before and 2 h after ingesting 750 mg of \( \alpha \)-methyldopa. On the other day, subjects were studied 2 h apart with no medication given. Subjects were randomized as to which trial, \( \alpha \)-methyldopa or control, occurred first. Three of six normal subjects and the three OSA subjects were given placebo during their control day, but due to the marked sedation produced by the \( \alpha \)-methyldopa, blinding was impossible. Therefore, the remaining three normal subjects did not receive placebo. We used the Freedman’s rank sum test, blocked without control, to analyse the data. Significance was reported at \( P \) values < 0.05.

To determine whether \( \alpha \)-methyldopa influenced upper airway motor activity by altering breathing route, we studied the effect of 750 mg of \( \alpha \)-methyldopa in comparison with placebo on the route of breathing in a randomized double-blinded manner. Two individuals who had served as subjects during the steady-state protocol served as subjects for this study. Nasal ventilation was measured with a Fleisch no. 3 pneumotachograph connected to a tight-fitting nasal continuous positive pressure mask (Respironics) while total ventilation was measured using an impedance plethysmograph (Respirac). The percentage of nasal versus total ventilation was compared before and 2 h after the ingestion of \( \alpha \)-methyldopa or placebo.

RESULTS

All subjects perceived side-effects related to the \( \alpha \)-methyldopa. All subjects complained of sleepiness approximately 1.5 h after drug ingestion. Other comments included feelings of fatigue, dysphoria and, in one subject, lightheadedness.

In the preliminary study, mean (± SD) arterial pressure fell by 5 ± 4 mmHg at 4 h. During steady-state hypercapnia, the mean arterial pressure fell by 7 ± 5 mmHg (from 87 to 80 mmHg) at 2 h after 750 mg of \( \alpha \)-methyldopa. The heart rate did not change in either study. There were no changes in the blood pressure or pulse in the OSA patients after \( \alpha \)-methyldopa.

In the preliminary study during CO₂ rebreathing, at 2 h the mean alae nasi EMG activity decreased by 11%,
which was not significantly different from baseline. At 4 h the mean alae nasi EMG activity was 28% less than baseline ($P<0.05$) but not significantly different from the activity at 2 h. Inspiratory ventilation, tidal volume and respiratory frequency were not significantly changed at any time. Ventilatory responsiveness to hypercapnia as measured by the slope of the CO$_2$ response curve was also unchanged by α-methyldopa.

During steady-state hypercapnia the mean alae nasi EMG activity fell 35% in the normal group after the ingestion of 750 mg of α-methyldopa ($P<0.05$). During the control day, the mean alae nasi EMG activity at 2 h was 23% higher than at 0 h, a difference which was not statistically significant (Fig. 1, Table 1). Ventilation, tidal volume and respiratory frequency were not significantly different on either day. In the three subjects with OSA (Fig. 2) the mean alae nasi EMG activity fell by 16–49% after α-methyldopa ingestion. During the control day the alae nasi EMG activity increased by 7–16% after placebo. One subject, who demonstrated a 49% decrease in alae nasi EMG activity, decreased her ventilation (from 10 to 5 litres/min) and tidal volume (from 0.9 to 0.45 litres) after α-methyldopa.

The percentage of nasal ventilation compared with total ventilation was not affected by the ingestion of α-methyldopa in the two subjects studied. Both of these subjects had previously shown a marked drop in alae nasi activity after α-methyldopa but not placebo. Nasal ventilation accounted for over 95% of total ventilation after ingestion of both placebo and α-methyldopa.

**DISCUSSION**

Our results demonstrate that normal subjects had a significant decrease in alae nasi activity during hypercapnic breathing after the oral administration of α-methyldopa. This reduction was seen during CO$_2$ rebreathing as well as during steady-state hypercapnia. This finding was observed without significant change in inspiratory ventilation, tidal volume or respiratory frequency. Although we did not measure diaphragm or other pumping muscle activity directly, the absence of change in the indirect measures of respiratory pumping activity (i.e. ventilation and tidal volume) suggests that the sum of diaphragmatic and intercostal muscle contraction was not altered. Thus α-methyldopa appears to selectively reduce upper airway muscle activity. Patients with OSA demonstrated a similar decrease in alae nasi activity, although one patient also demonstrated a decrease in ventilation and tidal volume. The route of breathing was not altered by α-methyldopa in the two subjects studied. This suggests that a shift from nose to mouth breathing did not influence our results.

We employed the alae nasi as a representative upper airway muscle. Patrick et al. [16] described a close relationship between activity of the alae nasi and the genio-

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**Table 1. Peak alae nasi EMG activity and respiratory variables during steady-state hypercapnia**

Values are expressed as means ± sd. $P_{ETCO_2}$ was maintained at 5 torr (0.7 kPa) above the resting value. Abbreviations: $V_T$, tidal volume; $f_R$, respiratory frequency; NS, not significant.

<table>
<thead>
<tr>
<th></th>
<th>EMG signal (% of maximal peak EMG signal during equilibration period)</th>
<th>$V_T$ (litres)</th>
<th>$P$ (litres/min)</th>
<th>$f_R$ (breaths/min)</th>
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<tbody>
<tr>
<td>Control</td>
<td></td>
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<tr>
<td>0 h</td>
<td>48 ± 19</td>
<td>1.1 ± 0.3</td>
<td>21 ± 7</td>
<td>17 ± 4</td>
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<tr>
<td>2 h</td>
<td>59 ± 19</td>
<td>1.1 ± 0.4</td>
<td>20 ± 6</td>
<td>17 ± 4</td>
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<tr>
<td>$P$</td>
<td>NS</td>
<td>NS</td>
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<tr>
<td>α-Methyldopa</td>
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<tr>
<td>0 h</td>
<td>52 ± 10</td>
<td>1.1 ± 0.3</td>
<td>19 ± 4</td>
<td>16 ± 5</td>
</tr>
<tr>
<td>2 h</td>
<td>34 ± 6</td>
<td>1.1 ± 0.3</td>
<td>18 ± 3</td>
<td>16 ± 5</td>
</tr>
<tr>
<td>$P$</td>
<td>&lt;0.05</td>
<td>NS</td>
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sented by different symbols.

Fig. 2. Peak integrated EMG signal from the alae nasi in patients with OSA during steady-state hypercapnia [P$_{CO_2}$ 5 torr (0.7 kPa) above baseline] before (0 h) and 2 h after either no intervention (a) or after ingesting 750 mg of $\alpha$-methyldopa (b). Individual subjects are represented by different symbols.

Glossus during chemical stimulation and loading. As opposed to other upper airway muscles such as the genioglossus, we found the alae nasi to be readily accessible and to demonstrate little change in EMG activity with changes in posture.

Multiple studies designed to demonstrate a differential effect of medications on upper airway muscle versus diaphragm activity have employed CO$_2$ rebreathing to stimulate ventilation [6, 7, 9, 17]. We began in our preliminary study using CO$_2$ rebreathing, but found that steady-state hypercapnia produced more consistent levels of stimulation, provided more breaths for analysis, and allowed for reduction in the duration of the study.

Our study did not employ a double-blind placebo controlled design. Blinding was not possible due to the dramatic sedation which resulted from ingesting either 500 or 750 mg of $\alpha$-methyldopa. We do not feel this influenced our results, as 11 of 13 subjects were naive to the purpose of the investigation and all subjects demonstrated a similar response to drug administration including six subjects who received a placebo on their control day.

An interesting, although not statistically significant, finding in our study was the 20% increase in alae nasi activity at 2 h during our control day. The subjects may have been 'alerted' by the anticipation of the mild discomfort produced by hypercapnia. This heightened arousal may have increased upper airway tone. However, this theory remains untested in the current study.

$\alpha$-Methyldopa is one of several sedating medications which produce a decrease in upper airway muscle activity in humans and animals [6–12]. Similar results have been found using sedatives such as flurazepam [8], diazepam [7] and chloral hydrate [10]. This selective reduction in upper airway activity is most dramatic in the case of alcohol, which has been found to decrease genioglossal activity during both quiet and hypercapnic breathing [9]. Presumably by reducing upper airway tone, alcohol worsens apnoea in patients with the sleep apnoea syndrome [12].

This study did not demonstrate that $\alpha$-methyldopa causes or worsens sleep-disordered breathing. Our subjects simply demonstrated a selective reduction in alae nasi activity during mild hypercapnia after drug administration. While $\alpha$-methyldopa has not been shown to worsen sleep apnoea, the importance of upper airway tone in the maintenance of airway patency [13] suggests that any medication differentially suppressing upper airway activity may produce sleep-related obstructions in susceptible individuals.

Other interventions have also been found to decrease upper airway muscle activity. Leiter et al. [17] explored the effect of sleep deprivation on the EMG activity of the genioglossus in normal volunteers. After sleep deprivation, genioglossal EMG activity decreased during tidal and hypercapnic breathing with no significant change in tidal volume, ventilation or respiratory frequency. This study may shed light on a common mechanism for decreasing upper airway muscle tone. The authors speculated that the effect of sedating medication as well as sleep deprivation may be secondary to a reduction in the activity of the reticular activating system.

$\alpha$-Methyldopa acts primarily by penetrating the brain where it is converted to $\alpha$-methylnoradrenaline [18]. This amine produces its blood pressure effect by stimulating the $\alpha$-adrenoceptors in the ponto-medullary region. In animal models, sedation appears to be mediated by these same receptors [18]. All of our study participants experienced sedation as the major side-effect of ingesting $\alpha$-methyldopa. In patients with hypertension being treated with $\alpha$-methyldopa, sedation is an extremely common side-effect of chronic administration. We speculate that sedation with its accompanying reduction in reticular activating system activity may produce the selective decrement in alae nasi activity.

The doses of $\alpha$-methyldopa employed in this study were higher than normally used when therapy with this medication is initiated but are well within the dose range employed in clinical practice. The implications of this study may be questioned because we studied subjects who had not previously received $\alpha$-methyldopa. The sedating effect of this medication is said to wane over time [18]. This decrease in sedation has never been documented, however, and anecdotes suggest that $\alpha$-methyldopa may produce significant sedation after years of use.

In summary, our study shows that $\alpha$-methyldopa decreases activity in an upper airway muscle in similar fashion to benzodiazipines and alcohol. Until studies are performed defining the effect of this medication on sleep-disordered breathing, we suggest that care be taken in prescribing this and any other sedating medication to patients with sleep apnoea.

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