The effect of aminophylline on respiratory and limb muscle contractility in man

C. Brophy, A. Mier, J. Moxham, M. Green

ABSTRACT: The effect of oral aminophylline on respiratory muscle and quadriceps femoris strength was compared with placebo in five normal subjects. A double-blind randomized cross-over protocol, spanning 2-3 wks, was followed. Aminophylline was taken before both placebo and active drug periods to establish correct dosage, to allow tolerance to side-effects to develop, and to keep the two limbs of the study identical and double-blind. Maximal static inspiratory and expiratory mouth pressures at residual volume and total lung capacity, respectively, maximal sniff transdiaphragmatic pressure, maximal voluntary quadriceps femoris contraction force and theophylline levels were measured during placebo and active drug periods. For the group, there were no significant differences between respiratory or quadriceps muscle strength on aminophylline and on placebo although there was a tendency for greater values on aminophylline. Mean theophylline level was 14.6 $\text{mg} \cdot \text{L}^{-1}$ (range 8.4-25.0 $\text{mg} \cdot \text{L}^{-1}$). We conclude that aminophylline produces no enhancement of skeletal muscle strength, at therapeutic dosage in normal subjects.


For many years aminophylline has been used in the treatment of asthma. Traditionally, the mode of action has been thought to be bronchodilatation and central nervous system stimulation. However, with the identification of an inotropic action on skeletal muscle [1], it has been postulated that aminophylline may act both to increase respiratory muscle contractility and to protect against respiratory muscle fatigue [2]. Whether this action is important at therapeutic drug levels is the subject of debate. Jones et al. [1] produced low-frequency fatigue in animal and human skeletal muscle, including diaphragm strips, and observed prompt return of force with aminophylline. Enhancement of twitch tension was seen in fresh and fatigued muscle, with a less marked effect at higher frequencies of stimulation. They observed an effect only at theophylline levels which would be toxic in man. Subsequently, Wiles et al. [3] found low-frequency fatigue of human adductor pollicis muscle, in vivo, to be unchanged at therapeutic levels of theophylline, and Moxham et al. [4] were unable to identify any increase in twitch tension with stimulation of the fresh diaphragm via the phrenic nerve in man.

During a maximum voluntary effort, motor nerve firing frequencies are high and aminophylline, at a dose sufficient to augment twitch tension, could be expected to have little effect on maximum tension. However, Aubier and co-workers [5] have reported that, in dogs, aminophylline increases diaphragm contractility at high as well as low frequencies of stimulation, while Murgiano et al. [6] have described a 16% increase in transdiaphragmatic pressure measured during maximal inspiratory efforts in patients with chronic obstructive pulmonary disease, at therapeutic doses of theophylline.

To determine whether aminophylline can increase maximum voluntary contraction force, we studied the effects of the drug on global respiratory muscle and diaphragm strength in normal subjects. We also studied the effect of the drug on the quadriceps femoris muscle for which contraction force can be measured more directly.

Methods

Five normal nonsmoking subjects, 4 males and 1 female, aged 28-32 yrs, were studied. They were familiar with the techniques involved and two had performed the manoeuvres on several previous occasions. All gave their informed consent and were aware of the study hypothesis. Studies were performed 3-6 h after drug ingestion. Subjects sat before a Tektronix oscilloscope displaying an uncalibrated feedback of pressure or force, as an incentive, and individuals were enthusiastically encouraged to perform at their best. Measurements were stored on magnetic tape (Racal Store 7, Ampex tape) and displayed on a chart recorder (Mingograf 800).

Measurements

Global respiratory muscle strength was assessed by measurement of maximal static inspiratory and expiratory mouth pressures ($P_{\text{IMax}}$ and $P_{\text{EMax}}$), whilst measure-
ment of transdiaphragmatic pressure (Pdi) was used to provide a more specific index of diaphragm strength [7].

**Maximal static mouth pressures.** Vital capacity (VC) was measured with an Ohio spirometer before each manoeuvre. \( P_{\text{max}} \) and \( P_{\text{max}}' \) were performed at residual volume and total lung capacity, respectively. A leak, 2 mm \( \pm \) and 37 mm long, in the mouthpiece prevented discomfort and glottic closure [8]. A noseclip was worn, and a standard flanged rubber mouthpiece proved comfortable, producing a satisfactory seal at the mouth. No restriction was placed on the method of obtaining maximal pressures, but subjects were asked to sustain the maximal effort for 2 s. The greatest pressure maintained for one second was measured with a Validyne differential pressure transducer (range \( \pm 500 \) mmHg). Three technically satisfactory recordings for both \( P_{\text{max}} \) and \( P_{\text{max}}' \) were taken at each of the morning and afternoon sessions on each study day.

**Sniff Transdiaphragmatic pressure (sniff Pdi).** Transdiaphragmatic pressure was measured with two balloon catheters (P.K. Morgan). Passed under local anaesthesia through the nose, one was positioned in the mid-oesophagus \( 40-45 \) cm from the nares [9] to register oesophageal pressure (Poes), and one in the stomach \( 65-70 \) cm from the nares, to register gastric pressure (Pg). Both catheters were attached to differential pressure transducers (Validyne range \( \pm 150 \) cm H\( \text{O} \)). Electrical subtraction of the signals from the two transducers gave a value for transdiaphragmatic pressure (Pdi=Pg-Poes) with zero Pdi at resting end-expiration. The seated subjects were asked to perform maximal sharp sniffs from functional residual capacity, without a noseclip [7]. Practice sniffs were performed until Pdi no longer increased, after which ten maximal sniffs were recorded.

**Maximal voluntary quadriceps contraction force (MVC).** Subjects were seated in a specially designed chair for the measurement of isometric quadriceps force [10]. An inextensible strap connected to a strain gauge (Strain­stall, range \( 0-100 \) kg) was passed round the ankle just proximal to the malleoli, and subjects were instructed to contract their quadriceps maximally against the strap for at least one second. The best three contractions for each leg were measured.

**Protocol**

An acclimatization period (fig. 1) comprising several measurement sessions spaced over ten days enabled all subjects to master the techniques of mouth pressure and quadriceps strength measurements. This ensured that the learning effect previously noted for serial mouth pressure measurement in normals occurred before formal studies began [11].

The study began with a period on aminophylline during which the appropriate dosage regime was established for each subject and tolerance to side-effects developed. Random double-blind allocation to placebo or aminophylline followed, and after 3–5 days on either active drug or placebo subjects performed the full measurement protocol. On two days the three best \( P_{\text{max}} \) and \( P_{\text{max}}' \) values were recorded in the morning and afternoon, and the three best MVCs for each leg were recorded once. On the second day the ten best sniff Pdi values were included in the measurements. Subjects then changed back to aminophylline for several days, after which they crossed-over, double-blind, to either placebo or active drug. Measurements were repeated after a further 3–5 days on the trial drug. Blood samples for theophylline assay were taken on both aminophylline and placebo study days at the same time, between 5–8 h after dosing.

**Statistical analysis**

The data were analysed by testing the difference between placebo and aminophylline study day measurements using a one sample t-test. Statistical significance was taken as a p value <0.05.

![fig. 1. - Study protocol: the acclimatization period ensured that measurements were performed reproducibly before formal studies began. Aminophylline was taken for several days before each double-blind treatment period.](image-url)

**Results**

The coefficient of variation (CV) expressed in terms of standard error of the mean (SEM) for measurements made over three days at the end of the acclimatization period was 3.7% for \( P_{\text{max}} \), 4.2% for \( P_{\text{max}}' \), and 3.9% for mean right and left leg MVC measurements. The direction of individual differences in measurements on
subjects were performing truly maximal efforts. All subjects showed small increases in $P_{E_{\text{max}}}$ on aminophylline. Whilst two subjects had increases in $P_{E_{\text{max}}}$, two had decreases, and one had the same mean $P_{E_{\text{max}}}$ value on aminophylline and on placebo. Four subjects had higher sniff Pdi values on aminophylline and one on placebo. The difference in aminophylline and placebo values for right and left MVCs were similarly inconsistent, and in addition there were inconsistent changes for each leg within individuals. Table 1 presents group mean values for each parameter during both treatment periods. There were no significant differences between the mean $P_{E_{\text{max}}}$, sniff Pdi and right and left MVC values on aminophylline and those on placebo, although all mean values tended to be slightly greater on aminophylline. Mean theophylline level was 14.6 mg·l$^{-1}$ on aminophylline (range 8.4–25.0 mg·l$^{-1}$ and therapeutic range 10–20 mg·l$^{-1}$). On placebo all theophylline values were below measurable levels.

Table 1. - Mean values for the group (±SEM) of sniff Pdi, $P_{E_{\text{max}}}$ and MVC measurements on aminophylline and on placebo, with associated p values.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Placebo</th>
<th>Aminophylline</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>$P_{E_{\text{max}}}$ cmH$_2$O</td>
<td>104 (8)</td>
<td>111 (9)</td>
<td>0.58</td>
</tr>
<tr>
<td>$P_{E_{\text{max}}}$ cmH$_2$O</td>
<td>94 (11)</td>
<td>98 (14)</td>
<td>0.83</td>
</tr>
<tr>
<td>sniff Pdi cmH$_2$O</td>
<td>131 (11)</td>
<td>135 (12)</td>
<td>0.82</td>
</tr>
<tr>
<td>MVC rt kg</td>
<td>47 (5)</td>
<td>49 (5)</td>
<td>0.89</td>
</tr>
<tr>
<td>MVC lt kg</td>
<td>46 (4)</td>
<td>47 (4)</td>
<td>0.85</td>
</tr>
</tbody>
</table>

$P_{E_{\text{max}}}$ and $P_{E_{\text{max}}}$: maximal static expiratory and inspiratory mouth pressure, respectively; Pdi: transdiaphragmatic pressure; MVC: maximal voluntary quadriceps contraction force.

Discussion

We have found no significant improvement in respiratory muscle or quadriceps strength with therapeutic levels of theophylline. Previously, we have shown that a short learning period may be necessary before reproducible $P_{E_{\text{max}}}$ and $P_{E_{\text{max}}}$ measurements can be made [11]. The sniff, a comfortable and familiar manoeuvre, has a CV of less than 1% and so does not require a learning period [7]. In the present study, subjects performed maximal static mouth pressures as well as MVCs on several occasions before making formal measurements. Repeatability has been expressed in terms of coefficient of variation, to allow comparison with previous work, and confirm that these measurements were satisfactorily reproducible. Despite the use of different techniques, studies of maximal inspiratory efforts have shown that normal subjects can maximally activate the respiratory muscles [12, 13], and together with the small between-day CV in this work, support the contention that the subjects were performing truly maximal efforts.

Chest wall configuration was not controlled during $P_{E_{\text{max}}}$, $P_{E_{\text{max}}}$ and sniff manoeuvres. However, $P_{E_{\text{max}}}$ and $P_{E_{\text{max}}}$ vary little near total lung capacity or residual volume, respectively [14], and vital lung capacity, which was performed immediately before each static effort, did not appreciably alter for any individual. Sniffs were performed from resting end-expiration, which in healthy subjects varies little, and would be unlikely to alter systematically. The study design enabled a double-blind randomized protocol to be followed. Administration of aminophylline knowingly for several days before both placebo and active drug ingestion ensured that the two limbs of the study were identical, allowed tolerance to side-effects to develop, and obscured the identity of the succeeding agent. Indeed none of the subjects was able to actually identify the active drug period.

MURCIANO et al. [6] reported that mean Pdi, recorded during maximal inspiratory efforts in chronic obstructive pulmonary disease patients, was 16% higher than on theophylline than on placebo. Accompanying this change, forced expiratory volume in one second (FEV$_1$) increased and functional residual capacity (FRC) decreased on aminophylline compared to placebo, and it is probable that the consequent change in diaphragmatic length improved force-length relationships thereby improving diaphragmatic contractility. In contrast, theophylline has no bronchodilatory action on normal airways [15] so that lung mechanics, and diaphragmatic force-length relationships, would not be expected to alter in normal subjects.

Only two research groups have described improvement in inspiratory muscle contractility of normal subjects with theophylline [2, 16]. AUBER and co-workers [2] found a 15% increase in submaximal diaphragm contractility, while SUPINSKI et al. [16] reported an increase of 16%. Other investigators have shown no effect on normal human skeletal muscle, in particular respiratory muscle, contractility at various levels of activation [3, 4, 17–19]. Studies of the frequency-force relationship of the adductor pollicis and the sternomastoid muscles found no effect of aminophylline on either fresh or fatigued muscle [3, 17, 18]. In previous work from this laboratory, acute administration of aminophylline produced no enhancement of unilateral diaphragm twitch pressures [4], and recently an investigation of the bilateral diaphragm twitch confirmed these findings [19]. The present work supports these negative studies and those of JOMES et al. [1] who predicted that, although very high concentrations of aminophylline increase diaphragmatic twitch tension, significant enhancement of diaphragmatic contractility would not be seen at therapeutic concentrations.

We conclude that oral aminophylline produces no effect on respiratory muscle or quadriceps strength at therapeutic doses in normal subjects.

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References


RéSUMé: Les effets de l'Aminophylline orale sur le muscle respiratoire et sur la force développée par le quadriceps fémoral ont été comparés chez 5 sujets normaux avec l'effet du placebo.

Nous avons suivi un protocole en double aveugle avec randomisation et permutation croisée, s'étendant sur 2 à 3 semaines.

L'Aminophylline a été prise avant les périodes de placebo et d'administration de drogues actives pour en établir un dosage correct pour permettre le développement de la tolérance à des effets collatéraux et pour que les deux bras de l'étude apparaissent identiques et en double aveugle. Les pressions buccales maximales statiques inspiratoires et expiratoires au volume résiduel et à la capacité pulmonaire totale, et expiratoires au volume résiduel et à la capacité pulmonaire totale, et respectivement les pressions trans-diaphragmatique du renflement, la force de contraction maximale volontaire du quadriceps fémoral et les niveaux de Théophylline ont été mesurés pendant les périodes de placebo et d'administration de drogues actives.

Dans l'ensemble du groupe, on n'a pas noté de différence significative entre la force des muscles respiratoires ou quadriceps entre la période d'Aminophylline et la période placebo quoiqu'il y ait une tendance pour des valeurs légèrement plus élevées sous Aminophylline. Le niveau moyen de Théophylline était de 14.6 mg par litre (extrêmes: 8.4-25.1 mg/L). Nous concluons que l'Aminophylline ne produit pas de renforcement de la force des muscles squelettiques aux dosage thérapeutiques chez des sujets normaux.