Intravenous aminophylline in patients admitted to hospital with non-acidotic exacerbations of chronic obstructive pulmonary disease: a prospective randomised controlled trial.

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Abstract

Background  Intravenous aminophylline is commonly used in the treatment of exacerbations of chronic obstructive pulmonary disease (COPD), despite limited evidence for its efficacy and known risks of toxicity. We hypothesised that adding intravenous aminophylline to conventional therapy would not produce clinically important changes in the speed of spirometric or symptomatic recovery or shorten hospital stay in exacerbations of COPD.

Methods  80 patients hospitalised with non-acidotic exacerbations of COPD were recruited at admission to a randomised, double-blind, placebo-controlled study comparing intravenous aminophylline 0.5 mg/kg/hour after an appropriate loading dose with an equivalent volume of 0.9% saline. The primary outcome was the change in post-bronchodilator forced expiratory volume in 1 sec (FEV₁) over the first five days of admission. Secondary end-points were changes in self-reported breathlessness, arterial blood gases, forced vital capacity (FVC) and length of hospital stay.

Findings  There was no difference in the post-bronchodilator FEV₁ over the first five days between the aminophylline and placebo groups. In the aminophylline group, 2 hours of treatment produced a small but significant rise in arterial pH (p=0.001) and fall in PaCO₂ (p=0.01) compared to placebo treatment. There were no differences in the severity of breathlessness, post-bronchodilator FVC or the length of hospital stay between groups. Nausea was a more frequent side effect in the aminophylline group (46% vs. 22%; p<0.05), but palpitations and headache were noted equally in both groups.

Interpretation  Although intravenous aminophylline produced small improvements in acid-base balance, these did not influence the subsequent clinical course. We found no evidence for any clinically important additional effect of theophylline treatment when used with high dose nebulised bronchodilators and oral corticosteroids and, given its known toxicity, cannot recommend intravenous aminophylline in the treatment of non-acidotic COPD exacerbations.

Keywords: COPD exacerbation, intravenous aminophylline
Introduction

Hospitalisation due to an exacerbation of chronic obstructive pulmonary disease (COPD) is a major cause of morbidity and mortality worldwide (1). Treatment of these episodes is relatively standardised comprising controlled oxygen therapy, high dose nebulised beta agonist and/or anticholinergic drugs, oral corticosteroids (2;3) and ventilatory support as needed (4). Several guidelines recommend that intravenous aminophylline be considered as an option when response to the above treatment is not adequate (5;6), since theophylline shows some additivity with the effects of other treatment in stable disease (7). Demonstrating that this occurs in acute exacerbations has been difficult, and although a recent meta-analysis could not exclude a positive beneficial effect, it did confirm that significant adverse effects were present when theophylline was used (8).

Of only four trials considered suitable for the meta-analysis, two looked at treatment effects over two hours in the emergency room, one over three days in hospital and one, published only as an abstract, gave oral theophylline and evaluated its effect on patients still hospitalised after 48 hours (9-12). All trials were relatively small, with the best designed underpowered to exclude a treatment effect (9). Two of the studies suggested additional benefits of treatment, either in preventing hospitalisation or reducing subsequent relapse rate but these findings were inconsistent (10;11).

Given the limited data available, we hypothesised that intravenous aminophylline would not change post-bronchodilator lung function or the rate of symptom recovery in patients hospitalised with their COPD exacerbations and would not reduce the time to discharge or the subsequent relapse rate. To test these hypotheses we conducted a prospective double-blind randomised parallel group trial comparing intravenous aminophylline and placebo given from the time of hospital presentation and followed throughout the admission and where possible until six weeks after discharge.
Patients and Methods

Patients

Patients with a clinical diagnosis of COPD (13) presenting to the emergency department of University Hospital Aintree were considered eligible if they complained of increased breathlessness and two or more of the following symptoms for at least 24 hours; increased cough frequency or severity, increased sputum volume or purulence, increased wheeze. Patients were aged 40-80 years with at least a 20 peak-year smoking history, an initial FEV\textsubscript{1} <70% predicted and FEV\textsubscript{1}/forced vital capacity ratio <70% predicted for age.

We excluded patients with a clinical history of asthma or atopy, uncontrolled cardiac disease, advanced malignancy, clinical or radiological evidence of pneumonia, pneumothorax or chest wall deformity. Additionally those patients with an arterial blood pH below 7.32 were excluded to ensure that the use of non-invasive ventilation (NIV) was not a confounding factor when analysing the data. Anyone with a contra-indication to aminophylline, corticosteroids, beta-agonists or anticholinergics was also excluded.

The study protocol was approved by the South Sefton Research Ethics committee and informed consent was obtained from all patients before study entry.

Study Design

One investigator (ND) took a detailed medical history and examined patients within 4 hours of hospitalisation. On admission, blood was taken for a full blood count, including absolute eosinophil count. An arterial blood sample was taken, with patients breathing room air whenever possible, for blood gas analysis; this was repeated after two hours of treatment. Serum theophylline level was measured if the patient was receiving an oral theophylline preparation (Olympus turbidometric assay; with the lower limit <5, the curve is linear to 160 µmol/l: normal range is 55-110 µmol/l). Sputum was collected, if produced, for microscopy, culture and sensitivity. A score for the severity of breathlessness at the time of admission was recorded using both the modified Borg category scale and by showing patients a 100mm visual analogue scale with the two ends described as “No Shortness of Breath” (=0) going up to “Shortness of Breath as bad as can be” (=100) and asking them to score their condition relative to these points. Finally, post-bronchodilator spirometry was recorded using a dry bellows spirometer (Vitalograph volumetric spirometer, model 2150 Buckingham, UK) to American Thoracic Society standards (14). At least three forced expiratory manoeuvres were obtained on each occasion until two were within 5%. Data are expressed relative to European Steel and Coal Company predicted values. All patients were treated with both a nebulised beta-agonist (salbutamol 5mg) and an anticholinergic (ipratropium 500 mcg) every 6 hours, controlled oxygen therapy, intravenous or oral antibiotics at the physician’s discretion and oral prednisolone 30mg daily for fourteen days.

Patients were randomly assigned to treatment with intravenous Aminophylline or saline; the study drug (which was identically packaged) was diluted in saline to a concentration of 1mg Aminophylline/ml and a loading dose of 5mg/kg body weight was given over 30 minutes. Subsequently an infusion at a rate of 0.5 mg/kg body weight/ hour was continued until the physician in charge of the patient, who was not a study investigator, felt it appropriate to discontinue treatment because of clinical
improvement or adverse effect. The placebo was given in the same manner so that a similar volume of fluid was infused. If the patient were taking an oral theophylline preparation before admission, the loading dose was omitted and the oral preparation was discontinued. Randomisation was performed using a computer generated random number table. Packages of treatment were numbered in advance and used sequentially.

Blood was taken on day 1 of the study for serum theophylline level. The result was sent to another team member (not an investigator) who issued dummy results where appropriate to maintain the blinding. The rate of infusion was adjusted as appropriate and serum theophylline levels rechecked as needed. All patients, investigators, and other hospital staff were masked to treatment status throughout the study.

Further assessments were carried out at 12 hours and then daily for five days (unless discharged from hospital before this time) and again on the day the patient was thought fit for discharge. At each assessment, made 30 minutes after the bronchodilator was given, spirometry was repeated, a daily symptom score was recorded by assessing whether patients felt the same, better or worse overall compared to the previous day; a Borg score for breathlessness, measurements of respiratory rate, and percentage oxygen saturation were recorded. Additionally we asked about possible side effects of aminophylline (headache, nausea and palpitations).

Patients could be withdrawn at any time if they or their physician (not an investigator) felt clinical improvement was unsatisfactory and patients were automatically withdrawn if the arterial pH fell below 7.32. The patient’s physician decided when they were medically fit for discharge, and this date was used in the study analysis. At discharge, spirometry and the visual analogue breathlessness score was repeated, a St George’s Respiratory Questionnaire was completed to assess the patients’ health status (15) and an assessment was made by the investigator as to whether the study treatment had been helpful.

At six weeks after discharge we reviewed patients and repeated spirometry after 5mg nebulised salbutamol and the St George’s Respiratory Questionnaire. We collected data about any treatment changes since discharge and whether there had been any further exacerbations. The six week visit was postponed if the patient had had a further exacerbation. Patients not returning were contacted by telephone and their vital status and exacerbation history confirmed. The study funders had no part in the design, the running of the study or the data analysis.

Statistical analysis

The primary endpoint was the change in post-bronchodilator FEV₁ over the first 5 days post admission; secondary endpoints were changes in breathlessness as measured by the Borg and VAS scales, changes in arterial blood gases from baseline to two hours after treatment, changes in FVC and length of hospital stay.

Given the hazards of theophylline therapy, we decided that it could only be justified if it was accompanied by a clinically important improvement in FEV₁, equivalent to an improvement of 200ml within the study period. We calculated that a sample size of 37 in each group would give 80% power to detect a difference of 200ml in FEV₁ between Aminophylline and placebo, assuming that the common
standard deviation is 300ml using a two group t-test with a 5% two-sided significance level. Hence we aimed to recruit 40 patients per group. All data were analysed using SPSS version 11; we used Student’s t test, ANCOVA and ANOVA to compare normally distributed data. Data are expressed as mean and 95% confidence intervals (CI). The assumptions of the model were checked by inspection of the residuals.
Results

We screened 320 patients for the study and 132 met the inclusion criteria (figure 1). The most common reason for exclusion was for attending with breathlessness for reasons other than COPD.

Thirty nine patients received active treatment and 41 placebo. Of the 65 sputum specimens at admission, 43 were sterile, 10 grew Haemophilus influenzae, 8 Streptococcus pneumoniae and the remainder a range of other organisms. The presence of a positive sputum culture was unrelated to the subsequent progress. There were two deaths during hospital admission, both in the placebo group, both occurring after study medication was stopped due to clinical improvement. In one case the patient subsequently deteriorated, received Aminophylline out of the clinical trial setting and also non-invasive ventilation. The other subject died suddenly on day 3 from a myocardial infarction. In addition two further subjects in the aminophylline group were given unblinded aminophylline due to clinical deterioration the day after the study drug was discontinued.

The baseline characteristics of the two groups did not differ (Table 1).

<table>
<thead>
<tr>
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<th>Placebo n=41</th>
<th>Aminophylline n=39</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>67.4 (65.1-69.7)</td>
<td>69.6 (67.1-72.1)</td>
<td>0.22</td>
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<tr>
<td>Men / Women, n</td>
<td>22/19</td>
<td>13/26</td>
<td>0.07</td>
</tr>
<tr>
<td>BMI</td>
<td>22.9 (21.0-24.8)</td>
<td>24.1 (22.0-26.2)</td>
<td>0.41</td>
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<tr>
<td>Pack years</td>
<td>57.1 (47.5-66.7)</td>
<td>46.2 (35.2-55.2)</td>
<td>0.11</td>
</tr>
<tr>
<td>Symptoms for (days)</td>
<td>10.7 (8.4-12.0)</td>
<td>9.2 (6.8-11.6)</td>
<td>0.38</td>
</tr>
<tr>
<td>Years of COPD</td>
<td>12.0 (8.1-15.9)</td>
<td>9.3 (6.9-11.7)</td>
<td>0.24</td>
</tr>
<tr>
<td>VAS admission</td>
<td>74.7 (68.4-81.0)</td>
<td>66.4 (59.7-73.1)</td>
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</tr>
<tr>
<td>Borg admission</td>
<td>5.0 (4.4-5.6)</td>
<td>5.1 (4.4-5.8)</td>
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<tr>
<td>FEV₁ (L)</td>
<td>0.64 (0.54-0.74)</td>
<td>0.65 (0.57-0.73)</td>
<td>0.84</td>
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<tr>
<td>FVC (L)</td>
<td>1.76 (1.58-1.94)</td>
<td>1.65 (1.47-1.83)</td>
<td>0.40</td>
</tr>
<tr>
<td>Eosinophil count (%)</td>
<td>1.9 (1.3-2.5)</td>
<td>1.4 (0.7-2.1)</td>
<td>0.30</td>
</tr>
<tr>
<td>Number on oral theophylline</td>
<td>12 (29%)</td>
<td>8 (21%)</td>
<td>0.25</td>
</tr>
<tr>
<td>Theophylline level (µmol/l)</td>
<td>61 (47-75)</td>
<td>88 (72-104)</td>
<td>0.58</td>
</tr>
<tr>
<td>pH admit</td>
<td>7.41 (7.40-7.42)</td>
<td>7.42 (7.40-7.44)</td>
<td>0.26</td>
</tr>
<tr>
<td>pO2 admit</td>
<td>7.46 (6.98-7.94)</td>
<td>7.67 (7.21-8.13)</td>
<td>0.51</td>
</tr>
<tr>
<td>pCO₂ admit</td>
<td>5.96 (5.57-6.35)</td>
<td>5.46 (5.04-5.87)</td>
<td>0.07</td>
</tr>
</tbody>
</table>

Table 1: Baseline characteristics of the two groups. Values are means (95% CI) or numbers(%).

In the aminophylline group, the mean theophylline level of the 8 patients taking oral theophylline was 88 µmol/l (72-104) compared to 61µmol/l (47-75) in the 11 theophylline users in the placebo group.

The mean number of days the study drug was given was 1.7 (1.3-2.1) in the aminophylline group and 2.3 (1.0-2.0) in the placebo group (p=0.058). The mean theophylline level on the day following admission in the aminophylline group was 73.4µmol/l (62.9-83.9) whilst in the placebo group it was 2.5µmol/l (0.5-4.5); in the 11 subjects receiving placebo who used oral theophylline the mean level was 9.0µmol/l (3.3-14.7).
From admission to discharge the FEV₁ increased more with placebo than aminophylline treatment (p=0.048). When analysed over the first five days post-admission, with admission FEV₁ or FVC as appropriate as a covariate, there was no significant difference in the change in FEV₁ or FVC between groups (p=0.49); this was also true for the first 24 hours (p=0.46) when all but two subjects (both in the aminophylline group) remained on study medication (Figure 2). Prior use of theophylline did not affect these results.

Arterial blood gas data were available in all subjects on admission and 2 hours later. In 70 patients both the admission and 2 hour samples were taken breathing room air (table 2).

<table>
<thead>
<tr>
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<th>Placebo n=36</th>
<th>Aminophylline n=34</th>
<th>Placebo n=36</th>
<th>Aminophylline n=34</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>pH</td>
<td>7.41 (7.40-7.42)</td>
<td>7.42 (7.40-7.44)</td>
<td>7.41 (7.40-7.42)</td>
<td>7.44 (7.43-7.45)</td>
<td>0.001</td>
</tr>
<tr>
<td>paO₂ (kPa)</td>
<td>7.46 (6.98-7.94)</td>
<td>7.67 (7.21-8.13)</td>
<td>7.54 (7.11-7.97)</td>
<td>7.77 (7.30-8.24)</td>
<td>0.97</td>
</tr>
<tr>
<td>paCO₂ (kPa)</td>
<td>5.96 (5.57-6.35)</td>
<td>5.46 (5.04-5.87)</td>
<td>5.79 (5.42-6.16)</td>
<td>4.99 (4.62-5.36)</td>
<td>0.01</td>
</tr>
</tbody>
</table>

**Table 2**: Arterial blood gas tensions breathing air before and 2 hours after treatment

Values are means (confidence intervals)

There was a significant difference in the change in arterial pH and PaCO₂ over the first two hours of treatment between the groups with the aminophylline group showing a larger increase in pH (p=0.001) and a larger fall in PaCO₂ (p=0.01) uninfluenced by prior theophylline use. The change in respiratory rate did not differ from admission to discharge between groups (23.9 (22.0-25.8) to 22.2 (20.4-24.0) in the placebo group; 24.8 (23.1-26.5) to 23.6 (22.2-25.0) in the aminophylline group) nor was the change in symptom score different (table 3).
Aminophylline Placebo

<table>
<thead>
<tr>
<th></th>
<th>Aminophylline</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fall in Borg score from admission to discharge</td>
<td>2.6 (1.7-3.5)</td>
<td>2.4 (1.6-3.2)</td>
</tr>
<tr>
<td>Fall in VAS score from admission to discharge</td>
<td>26 (16.1-35.9)</td>
<td>36.8 (27.5-36.1)</td>
</tr>
<tr>
<td>Self reported symptomatic improvement over first 24 hours of admission</td>
<td>48.6%</td>
<td>58.5%</td>
</tr>
<tr>
<td>Self reported symptomatic improvement from admission to day 5</td>
<td>87.2%</td>
<td>85.4%</td>
</tr>
<tr>
<td>Physician reported improvement with study drug from admission to discharge</td>
<td>48.1%</td>
<td>42.1%</td>
</tr>
</tbody>
</table>

Table 3: Changes in patient and physician reported symptoms during the course of hospital admission. There were no significant differences in any of these variables between the two groups. Data are expressed as mean (95% CI) unless otherwise stated.

Blinded evaluation of treatment efficacy could not distinguish placebo (helpful in 42%) from active drug (helpful in 49%) (p=0.56).

Mean length of hospital stay analysed on an intention to treat basis for all 78 patients who survived was 7.7 days (6.8-8.6); 7.1 days (5.9-8.3) in the aminophylline group compared to 8.2 days (7.0-9.4) for placebo treatment (p=0.19) (figure 3).

More aminophylline treated patients complained of nausea compared to those receiving placebo (46% vs. 22%; Chi² <0.05). In the aminophylline group 10 patients complained of palpitations and 14 of headache compared to 7 and 13 patients in the placebo group respectively (NS). The study drug was stopped in ten subjects due to possible side effects. Of these 6 were in the aminophylline group. Four patients reported severe nausea (all on day 1) but in only one case of nausea was the serum theophylline level supra-therapeutic. One patient had symptomatic sinus tachycardia (after 1 hour). In one additional patient, the drug was stopped after a seizure at 1.5 hours. The drug level was in the therapeutic range at the time of the seizure (53µmol/L) and the fit was later attributed on clinical grounds to alcohol withdrawal. In the placebo group three patients had severe nausea causing the drug to be discontinued (two on day 1 and one on day 4 who also complained of diarrhoea). The drug was stopped on day 8 in the remaining patient following a seizure; this subject also had epilepsy. Data were included for analysis in all these patients on an intention to treat basis.

At 6 weeks post-discharge, 28 had experienced a further exacerbation requiring treatment or hospitalisation of whom 9 patients had died. Neither mortality nor further exacerbation were related to the initial treatment allocation nor did spirometry or health status differ between treatments in those assessed at 6 weeks.
Discussion
This is the first adequately powered trial to study whether adding intravenous aminophylline to conventional treatment benefits exacerbating COPD patients, either acutely or post-discharge. We found no evidence of any clinical or physiological benefit during the hospital stay nor did the use of intravenous aminophylline shorten hospitalisation significantly or influence subsequent progress.

Our patient groups were well matched at admission. All received identical medical treatment and trial treatment was blinded to the investigator by the use of dummy theophylline levels in those receiving placebo. The magnitude of change in lung function was similar to that we have reported previously during the recovery from an exacerbation (2). The lack of any statistical or clinically significant difference in FEV₁ between treatment arms, either early or late in the course of the illness is in keeping with the data from Rice et al who studied similar patients and it suggests that aminophylline is not providing additional bronchodilatation beyond that achieved with high dose nebulised therapies. Although an effect on more peripheral airways has been proposed as the mechanism of pulmonary deflation with theophylline treatment in stable disease (16), we saw no difference in FVC between our treatment groups and the post-bronchodilator FVC showed smaller changes with theophylline than with placebo.

Prior theophylline use might have confounded these effects but this was equally distributed between the treatment limbs and the theophylline level was almost undetectable 24 hours after admission in those receiving placebo. Restriction of the analysis to the 61 patients who were theophylline naïve did not change the spirometric outcomes. However, a different picture was seen with the early changes in arterial blood gas tensions where aminophylline- treated patients breathing air had lower CO₂ tensions and a slightly higher pH at 12 hours compared with those randomised to placebo, a change that was more obvious in those who were theophylline naive. This is in keeping with the known effect of aminophylline as a ventilatory stimulant, probably due to increases in central nervous system hypoxaemia (17;18). However, these changes were clinically unimportant in our patients who were selected as having non-acidotic exacerbations. Whether this effect would benefit patients with hypercapnic respiratory failure remains to be tested, although current evidence would suggest that the use of aminophylline would best be seen as an adjunct to non-invasive ventilatory support (19).

The change in the patients’ breathlessness, whether assessed by the Borg or visual analogue scale and the rate of resolution of symptoms, was uninfluenced by aminophylline treatment. Treatment was continued for approximately 30-50 hours with no sign of a clinical or physiological difference in favour of active therapy emerging as therapy progressed. The decision to stop treatment, made by clinicians unaware of the treatment allocation, was similar in each group and the clinical evaluation of the success of the therapy was likewise randomly distributed. This latter helps explain the individual clinician’s belief in the value of this therapy, as it is possible to attribute benefit to treatment when improvement has been spontaneous. Similar concerns also affect the perception of side effects with withdrawal due to potential theophylline-related toxicity in the placebo treated patients being as common as in those who received the active drug.
The theophylline concentration achieved during active treatment was below the midpoint of the therapeutic range, although in no case was it sub-therapeutic. It is possible that a higher concentration might have improved lung function, but only at the risk of greater toxicity. The relatively ‘low’ toxicity in our study may reflect our careful monitoring of theophylline use, but despite this, several patients developed nausea and the risk of uncontrolled aminophylline treatment has been well-documented elsewhere (8).

In conclusion, our data demonstrate that the addition of intravenous aminophylline to nebulised bronchodilators and oral corticosteroids in the management of non-acidotic COPD patients cannot be recommended, as it confers no clear benefit and potentially increases both the risk of side-effects and the complexity of management.

Conflict of interest statement
All authors declare that the answer to the questions on your competing interest form (http://bmj.com/cgi/content/full/317/7154/291/DC1) are all No and therefore have nothing to declare.

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Authors Contributions
ND, PW and FD assessed the patients and collected the data, ND conducting all the final reviews. ND undertook the data analysis and wrote the manuscript together with PMAC and LD who originally developed the study protocol.
References


CONSORT diagram indicating progress of patients throughout the clinical trial.

320 screened

188 not eligible
- Not COPD 35
- pH<7.30 25
- Not COPD exacerbation 23
- Already on iv aminophylline 23
- Assisted discharge 20
- Consolidation on CXR 15
- No smoking history 10
- Previous thoracic surgery 9
- Confused 7
- Others 21

132 eligible

52 declined consent

39 Aminophylline

39 completed study to discharge

29 Followed up after discharge

4 died before follow up
6 refused

41 placebo

39 completed study to discharge

30 Followed up after discharge

5 died before follow up
4 refused

2 died (neither while on study Drug)

Figure 1
CONSORT diagram indicating progress of patients throughout the clinical trial.
Figure 2a

Forced expiratory volume in one second (litres)

Days from admission

6046 on 6 June 2015. Downloaded from http://thorax.bmj.com on November 1, 2023 by guest. Protected by copyright.
Figure 2b

Mean and 95% confidence intervals of the post-bronchodilator FEV1 (a) and FVC (b) data during the trial with aminophylline treatment indicated by crosses and placebo as closed circles.
Figure 3

Kaplan-Meier plot of the proportion of patients remaining in hospital in the two treatment groups. Symbols as in figure 2.