Effect of adenosine infusion on oxygen induced carbon dioxide retention in severe chronic obstructive pulmonary disease

T L Griffiths, S S D Fernando, K B Saunders

Abstract

Background – In normal subjects intravenous adenosine infusion has been shown to stimulate ventilation with a consequent fall in arterial partial pressure of carbon dioxide (Paco₂), probably by an action on the carotid bodies. The objective of this study was to determine whether the increase in Paco₂ seen when patients with ventilatory failure secondary to chronic obstructive pulmonary disease (COPD) are given a high concentration of oxygen to breathe might be ameliorated by an intravenous infusion of adenosine.

Methods – Eight subjects with chronic stable ventilatory failure secondary to COPD were studied. Their mean (SE) forced expiratory volume in one second (FEV₁) was 0.63 (0.12) l with forced vital capacity (FVC) of 1.63 (0.21) l. They received continuous intravenous infusions of saline and adenosine in random order, double blind. The infusions were administered for two minutes at 20 μg/kg/min, increasing in increments of 20 μg/kg/min every two minutes to a maximum infusion rate of 80 μg/kg/min adenosine (or an equivalent saline infusion rate), or until side effects supervened. The infusions were continued at that rate for five minutes, after which the fractional inspired oxygen (FiO₂) was raised to 0.50 during a further 20 minutes of the infusion at that rate. Haemoglobin oxygen saturation (SaO₂) and transcutaneous PCO₂ (PtcCO₂) were monitored throughout the procedure. Spirometric tests were performed before and after each infusion.

Results – Adenosine infusion was accompanied by a fall in PtcCO₂ from a mean (SE) of 7.29 (0.42) kPa to 6.95 (0.48) kPa; mean difference −0.34 (95% confidence interval, −0.56 to −0.11) kPa. During saline infusion oxygen administration resulted in an increase in transcutaneous PtcCO₂ from 7.35 (0.34) kPa to 7.88 (0.28) kPa; mean difference 0.53 (95% CI 0.20 to 0.85) kPa. PtcCO₂ did not rise above baseline levels when oxygen was administered during the adenosine infusion. A small fall in FVC was seen following adenosine infusion.

Conclusions – The increase in PtcCO₂ seen when patients with stable ventilatory failure secondary to severe COPD are given a high concentration of oxygen to breathe is counteracted by a continuous intravenous infusion of adenosine.

Keywords: adenosine, respiration, carbon dioxide, chronic obstructive pulmonary disease.

Adenosine is known to stimulate breathing in normal humans. This is likely to be mediated by an action on the carotid bodies and may relate to an effect on hypoxic chemosensitivity. However, the effect of this nucleoside on breathing in patients with chronic obstructive pulmonary disease (COPD) has not been reported. A common problem in the management of such patients (particularly during acute exacerbations) is an increase in the arterial carbon dioxide tension (Paco₂) following administration of oxygen. Part of the mechanism for this may be a reduction in alveolar ventilation as a result of reduced hypoxic ventilatory drive. The postulated action of adenosine on the peripheral chemoreceptors might facilitate the maintenance of peripheral chemoreceptor drive to breathe in patients with severe COPD who require an oxygen enriched inspirate. A study was therefore designed to determine whether, in patients with ventilatory failure secondary to COPD, deterioration of carbon dioxide retention resulting from breathing a high concentration of oxygen might be avoided by a concurrent intravenous infusion of adenosine. As the effect of infused adenosine in patients with COPD has not previously been reported, patients with stable chronic disease and carbon dioxide retention were studied rather than acutely ill patients. The observations made were the clinically important end points of arterial haemoglobin oxygen saturation monitored by pulse oximetry and Pco₂ which was monitored transcutaneously. Invasive ventilatory monitoring which might have altered respiratory responses and arterial blood sampling were avoided in this study.

Methods

SUBJECTS

After giving written informed consent, eight patients (two women) with a history of stable COPD took part in the study which was approved by the local research ethics committee. Mean (SE) forced expiratory volume in one second (FEV₁) was 0.63 (0.12) l (26 (4)% predicted). Percentage increase in FEV₁ following 200 μg inhaled salbutamol was 10 (3)%.
All had evidence of respiratory failure with arterial oxygen saturation (Sao₂) of 81 (5)%.

Transcutaneous carbon dioxide tension (PtcpO₂) was 7.46 (0.41) kPa breathing room air. Methylxanthines (which are specific antagonists at adenosine cell surface receptors) were withdrawn 24 hours before testing in those patients receiving these drugs. Xanthine-containing beverages such as coffee, tea, and cola were also withheld for 12 hours before testing. Other treatment such as inhaled β agonists, anticholinergics, and steroids were continued as usual. No subject was taking CNS depressant drugs.

**PROCEDURE**

The study involved the intravenous administration of saline and adenosine infusions in a random order, double blind, crossover design. Subjects were seated comfortably, breathing room air. An intravenous cannula was sited in a forearm vein for the infusion of the trial solutions. Cardiac rate and Sao₂ were monitored continuously at the ear by pulse oximetry (Biox 3700e, Ohmeda, Hatfield, UK). Ptcco₂ was monitored continuously by an electrode with an operating temperature of 42°C placed on the inner aspect of the forearm (TCM 3, Radiometer, Copenhagen, Denmark). The transcutaneous electrode registered a fall in Ptcco₂ about 45 seconds after the onset of voluntary hyperventilation. Pco₂ values measured transcutaneously reflect tissue Pco₂ and tend to be systematically higher than Paco₂.\(^8\) However, in normal subjects PtcpO₂ can be used to follow changes in end tidal (and hence arterial) Pco₂. Using this method of PtcpO₂ measurement in a group of 10 normal young subjects we found that a change in inspiratory from room air to gas with inspired oxygen fraction (FtO₂) of 0.1 resulted in changes in PtcpO₂ of 0.49 (0.15) and end tidal Pco₂ of 0.48 (0.16) kPa (95% confidence intervals for the difference between the transcutaneous and tidal responses was -0.17 to 0.11 kPa, unpublished observations). Thus, this is an accurate method for following changes in Pco₂ of similar magnitude to those we report. Values of Sao₂ and PtcpO₂ were recorded at the end of each minute throughout the experiment. The electrocardiograph was monitored continuously.

When PtcpO₂ and Sao₂ had been observed to be stable for three minutes the subjects commenced a continuous intravenous infusion of either adenosine 2 mg/ml in saline solution (150 mmol/l) or placebo saline (150 mmol/l). The study drugs were loaded into syringes and delivered using a microprocessor controlled syringe driver (Harvard 22, Harvard Apparatus Ltd, Edendbridge, Kent, UK). The infusion rate was calculated to be equivalent to adenosine delivery rates of 20, 40, 60, and 80 μg/kg/min in two minute steps for both infusions. After five minutes at the 80 μg/kg/min level, additional oxygen was administered via a Venturi face mask to provide an FtO₂ of 0.5. The FtO₂ delivered by the mask was checked using a fast responding mass spectrometer sampling via a capillary tube from the anterior nares. The infusion was continued whilst breathing this high inspired oxygen concentration for 20 minutes. If unpleasant side effects such as headache, flushing, or dyspnoea were experienced the infusion rate was reduced to a level felt to be tolerable by the subject. After the 20 minutes of oxygen administration, the oxygen and infusion were discontinued and the patient rested for at least one hour. The procedure was then repeated with the second infusion. FEV₁ and FVC were measured before and at the end of each infusion with a turbine spirometer (Micro Spirometer, Micro Medicals, Rochester, UK).

**DATA ANALYSIS**

Values reported are mean (SE) with 95% confidence intervals (95% CI) for main results. Observations were analysed at three time points during the experiment – that is, at rest, at the end of the infusion alone, and at the end of the infusion + oxygen for each treatment. Analysis of variance with repeated measures – using the three time points as the repeated measures factors and saline and adenosine as the treatment factors – was used to investigate changes in Ptcco₂ with experimental time point and drug given. The Student's paired \(t\) test was used to investigate differences between the experimental observations and their respective baseline values. The paired \(t\) test was also used to determine differences between mean values of observations between the two arms of the study. A \(p\) value of <0.05 was regarded as significant.

**Results**

In three subjects the maximum infusion rate of adenosine was reduced because of side effects, primarily dyspnoea. In these subjects the final infusion rates were 70, 60, and 20 μg/kg/min. The spirometric values before and after the saline infusion showed no statistically significant changes with FEV₁ 0.62 (95% CI 0.30 to 0.94) l before and 0.60 (95% CI 0.26 to 0.94) l after the infusion and FVC 1.60 (95% CI 1.04 to 2.16) l before and 1.53 (95% CI 0.94 to 2.12) l after. FEV₁ did not change significantly with adenosine infusion, being 0.65 (95% CI 0.33 to 0.97) l before and 0.60 (95% CI 0.28 to 0.92) l after the infusion. However, there was a small but statistically significant fall in FVC following adenosine infusion from 1.67 (95% CI 1.03 to 2.31) l before to 1.57 (95% CI 0.93 to 2.21) l after the infusion (mean difference -0.10 (95% CI -0.17 to -0.03) l; \(p<0.02\)). The heart rate at rest, at the end of drug infusion, and at the end of infusion with oxygen was 85 (9), 87 (8), and 86 (7) beats/min, respectively, for saline and 86 (9), 85 (9), and 87 (7) beats/min, respectively, for adenosine. The differences between the two infusions at each point were not statistically significant.

Analysis of variance showed a significant effect of experimental time point on Sao₂ (\(p<0.0001\)). There was, however, no significant effect of the drugs on this relationship with...
Adenosine infusion in COPD

Figure 1 Mean haemoglobin oxygen saturation plotted during saline (○) and adenosine (□) infusions. The addition of oxygen at PtO₂ 0.50 to the inspirate is shown by the shaded bar. The adenosine and equivalent saline infusion rates are given at two minute intervals.

Figure 2 Mean transcutaneous Pco₂ plotted during saline (○) and adenosine (□) infusions. The addition of oxygen at PtO₂ 0.50 to the inspirate is shown by the shaded bar. The adenosine and equivalent saline infusion rates are given at two minute intervals.

Sao₂ rising significantly above baseline during elevation of the Fio₂ on both treatments. The Sao₂ at two minute intervals throughout the experiment is shown in fig 1. There was a significant effect of experimental time point on PtcCo₂ (p<0.001) with a significant treatment effect (p<0.01). The PtcCo₂ at two minute intervals throughout the experiment is shown in fig 2.

Mean PtcCo₂ at rest was 7.35 (95% CI 6.56 to 8.14) kPa for saline and 7.30 (95% CI 6.33 to 8.26) kPa for adenosine (mean difference between treatments 0.05 (95% CI -0.35 to 0.43) kPa; not significant), during acute infusion it was 7.35 (95% CI 6.56 to 8.14) kPa for saline and 6.95 (95% CI 5.89 to 8.01) kPa for adenosine (mean difference between treatments 0.40 (95% CI -0.03 to 0.83) kPa; p<0.06), and during infusion + oxygen it was 7.89 (95% CI 7.24 to 8.54) kPa for saline and 7.15 (95% CI 6.01 to 8.29) kPa for adenosine (mean difference between treatments 0.74 (95% CI 0.12 to 1.36) kPa; p<0.05). During saline infusion the rise in PtcCo₂ during hyperoxia was seen in seven of the eight subjects. During adenosine infusion a fall in PtcCo₂ was seen in seven subjects with a subsequent rise in PtcCo₂ in six subjects under hyperoxic conditions.

The mean changes from baseline to end of infusion and from baseline to infusion + oxygen, together with the differences between these responses on the two drugs, are shown in table 1. During the saline arm of the study there was, overall, a significant rise in PtcCo₂ which was greater than that seen with adenosine. In contrast, PtcCo₂ fell significantly during the lone adenosine infusion, this fall being greater than the change seen with saline. Although the rise in PtcCo₂ seen with the addition of oxygen to the inspirate during the saline infusion was twice as great as when oxygen was added during the adenosine infusion, the mean difference between treatments of 0.33 (95% CI -0.04 to 0.70) kPa just failed to achieve statistical significance (p = 0.06).

The stability of mean PtcCo₂ during the placebo saline infusion (95% confidence interval for the difference between rest and saline infusion -0.15 to 0.15 kPa) suggests that there was no systematic drift of PtcCo₂ sensing over that time period.

Discussion

We were interested to determine whether intravenous infusion of adenosine would ameliorate the increase seen in Pco₂ when patients with ventilatory failure secondary to COPD are given a high concentration of oxygen to breathe. Our findings suggest, firstly, that intravenous infusion of adenosine whilst breathing room air is accompanied by a fall in Pco₂ and, secondly, that when a hyperoxic inspirate is administered to patients with ventilatory failure concomitant intravenous adenosine infusion prevents a rise in Pco₂ above baseline levels in spite of a small but significant reduction in dynamic lung volumes. Significant effects of adenosine on Sao₂ were not encountered in our patients.

With infusion of adenosine both FEV₁ and FVC fell slightly (FVC significantly so), suggesting that intravenous adenosine may have a small effect on airway calibre in patients with COPD. This is in keeping with the observation that intravenous bolus doses of adenosine can provoke bronchospasm in patients with COPD. Interestingly, inhaled adenosine causes bronchoconstriction in asthmatic patients but intravenous infusion of up to 50 μg/kg/min does not alter their airway conductance. Thus, the effect we have found may reflect a susceptibility of the bronchial smooth muscle in patients with COPD to the bronchoconstrictor effects of adenosine. Whilst adenosine infusion was not accompanied by detrimental changes in Sao₂ in our subjects, the finding of reduced spirometric values suggests that adenosine infusion should be used with caution in patients with very severe airflow limitation.

Another important effect of adenosine infusion which might affect oxygen delivery is an increased heart rate which has been described in normal subjects. We, however, did not detect any significant difference in heart rate between saline and adenosine infusions in our patients with COPD, which may reflect the relatively low infusion rate used in the present study. We monitored changes in Pco₂ transcutaneously. Transcutaneous monitoring has
been successfully used by previous investigators to follow changes in P CO2 during adenosine infusion.13,14 Heating the electrode produces local hyperaemia and this may be why infusion of adenosine does not alter the relationship between end tidal P CO2 and transcutaneous P CO2 in normal subjects.14 As measurement of transcutaneous oxygen tension may be affected by adenosine under hypoxic conditions,14 oxygen saturation was used to follow oxygenation.

The mechanism of the effect of adenosine infusion on Ptcco2 has not been addressed in this study. However, in normal subjects infusion of adenosine up to 80 μg/kg/min does not affect either oxygen uptake or carbon dioxide production but is accompanied by a fall in estimated Paco2,6 which implies an increase in alveolar ventilation. In the present study the lack of improvement in SaO2 with adenosine infusion argues against a favourable change in the ventilation/perfusion relationships of the lung. Thus, increased alveolar ventilation may be the explanation for the effect of adenosine on Ptcco2 found in this study. In normal subjects a reduction in the ratio of dead space ventilation to total ventilation is seen with adenosine.13 Such an alteration might be particularly important in patients with COPD.

In normal subjects the stimulation of breathing by adenosine1-3 may be mediated by carotid body stimulation.24 Our findings are consistent with a similar effect in patients with COPD, the Ptcco2 being maintained below baseline even when a hyperoxic gas mixture is breathed. Thus, it is possible that by supplying exogenous adenosine, carotid body discharge may be maintained even under hyperoxic conditions when the peripheral chemoreceptors are normally silenced.15-17

Carbon dioxide retention is an important complication of oxygen therapy in patients with ventilatory failure secondary to COPD. To our knowledge, this is the first description of adenosine being used to ameliorate oxygen induced hypercapnia. The changes in Ptcco2 we report are small and thus the effect of adenosine in this group of patients is of little clinical importance per se. However, the results do suggest that it is possible to attenuate the physiological response to hyperoxia in severe COPD. We have shown the short term action of adenosine in patients with stable ventilatory failure, but the importance of the bronchochstriction we observed and whether tachyphylaxis to the effects of adenosine might occur during prolonged infusion merit further investigation. It is a matter of conjecture whether a similar beneficial effect on PaCO2 would be seen if adenosine were to be used in conjunction with oxygen treatment during acute on chronic exacerbations of COPD when the drive to breathe may already be high.

In conclusion, we have found that a continuous intravenous infusion of adenosine results in a fall in Ptcco2 and counteracts the rise in Ptcco2 seen in patients with ventilatory failure secondary to COPD when breathing an oxygen rich inspire. A small reduction in dynamic lung volumes is also seen during adenosine infusion in these patients.

This study was supported by a project grant from the British Lung Foundation (BLF).

Table 1 Changes in transcutaneous carbon dioxide tension (Ptcco2) during saline and adenosine infusions with and without the addition of oxygen to the inspire (Ppo2 0.50)

<table>
<thead>
<tr>
<th></th>
<th>Saline infusion (95% CI)</th>
<th>Adenosine infusion (95% CI)</th>
<th>Difference between infusions (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre-infusion Ptcco2 (kPa)</td>
<td>7.35 (6.56 to 8.14)</td>
<td>7.30 (6.33 to 8.26)</td>
<td>0.05 (0.33 to 0.43)</td>
</tr>
<tr>
<td>Change in Ptcco2 from rest to end infusion (kPa)</td>
<td>0.00 (–0.15 to 0.15)</td>
<td>–0.34 (–0.57 to –0.11)**</td>
<td>0.34 (0.03 to 0.65)**</td>
</tr>
<tr>
<td>Change in Ptcco2 from rest to end infusion + O2 (kPa)</td>
<td>0.53 (0.22 to 0.84)**</td>
<td>–0.14 (–0.48 to 0.20)</td>
<td>0.66 (0.26 to 1.06)**</td>
</tr>
</tbody>
</table>

*p<0.05; **p<0.01.

References

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