Comparison of the acute effects on gas exchange of nasal ventilation and doxapram in exacerbations of chronic obstructive pulmonary disease

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Abstract
Background – Nasal intermittent positive pressure ventilation (NIPPV) is useful in exacerbations of chronic obstructive pulmonary disease (COPD) complicated by ventilatory failure. The effects of NIPPV were compared with those of the respiratory stimulant doxapram on gas exchange in patients with COPD and acute ventilatory failure.

Methods – Patients admitted with acute exacerbations of COPD and type 2 respiratory failure (Pao₂ < 8 kPa and Paco₂ > 6.7 kPa) who did not improve with conventional treatment were randomised to receive either NIPPV or intravenous doxapram. Blood gas tensions were monitored for four hours.

Results – In nine patients who received NIPPV the arterial Pao₂ improved from a mean (SE) of 5.9 (0.4) kPa to a maximum of 8.1 (0.6) kPa which was maintained at four hours. Eight patients who received doxapram had a similar baseline Pao₂ of 5.6 (0.4) kPa which rose to a maximum of 7.3 (0.5) kPa but this was not maintained at four hours. The improvement in Pao₂ in patients on NIPPV was accompanied by a fall in Paco₂ but, in contrast, in those who received doxapram there was no improvement in Paco₂.

Conclusions – NIPPV may be more effective than doxapram in the management of acute ventilatory failure complicating COPD.

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Keywords: respiratory failure, NIPPV, doxapram.

The usual cause of death in patients with chronic obstructive pulmonary disease (COPD) is respiratory failure.1 Until recently the only readily available forms of ventilatory support were intravenous doxapram or mechanical ventilation via an endotracheal tube. Doxapram drives respiration, probably by stimulating peripheral chemoreceptors.2,3 This is helpful if there is suppression of central drive but, in the context of an acute exacerbation of chronic lung disease, the respiratory muscles may already be functioning at near maximal capacity. Intubation and full scale intermittent positive pressure ventilation is invasive, expensive, and it may be difficult to wean the patients off the ventilator. An effective alternative would be desirable.

Nasal intermittent positive pressure ventilation (NIPPV) has also been shown to improve arterial blood gas tensions in patients with COPD,4,5 but no comparison has been published of the effects of NIPPV and doxapram in the emergency treatment of ventilatory failure. We have therefore compared NIPPV and doxapram in a group of patients presenting to a respiratory ward with type 2 respiratory failure.

Methods

Patients

Patients were included if they had an acute exacerbation of COPD complicated by type 2 respiratory failure (Pao₂ < 8 kPa and Paco₂ > 6.7 kPa). Seventeen patients completed the study; nine (five men) of mean (SE) age 64 (2.3) years and forced expiratory volume in one second (FEV₁) 0.76 (0.02) l received NIPPV and eight (four men) of mean (SE) age 61.9 (2.7) years and FEV₁ 0.77 (0.09) l received doxapram. The study was approved by the Glasgow West ethical committee and informed consent was obtained.

Study Design

Blood gas tensions were measured on admission. Patients were then started on routine treatment with oxygen (1–3 l/min by nasal cannulae), steroids, antibiotics, and nebulised or intravenous bronchodilators. One hour later arterial blood gas tensions were repeated. If the values were static or deteriorating, the patient was randomised to receive either nasal ventilation or doxapram. Oxygen was continued at the same rate as before randomisation. NIPPV was administered via a pressure cycled machine (Ventimate, Thomas Respiratory Systems, London, UK). Ventilation pressure was set at...
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14–18 cm H₂O and oxygen enriched air was delivered using nasal pillows or a tight fitting nasal mask. Doxapram was given by intravenous infusion using the manufacturer’s protocol (4 mg/min for 15 minutes, 3 mg/min for 30 minutes, 2 mg/min for 60 minutes, and 1.5 mg/min as maintenance dose). Arterial blood gas tensions were checked hourly for the first four hours. The protocol was modified later so that if there was continued deterioration on either NIPPV or doxapram the alternative was added at four hours.

DATA ANALYSIS
Arterial blood gas tensions were compared using ANOVA, pH was converted to H⁺ concentration, compared by ANOVA, and reconverted to pH expressed as the geometric mean + 95% confidence intervals. p values of less than 0.05 were regarded as significant.

Results
At entry the baseline blood gas tensions were similar in the two groups. The changes in arterial blood gas tensions during the four hour assessment period are shown in fig 1. The mean (SE) baseline Pao₂ of 5.9 (0.4) kPa improved on NIPPV to a maximum value of 8.1 (0.6) kPa (p<0.05) which was maintained at four hours. The baseline Paco₂ of 10.1 (0.4) kPa also improved on NIPPV to 8.7 (0.6) kPa (p<0.05), and the improvement was maintained at four hours.

In patients receiving doxapram the mean (SE) baseline Pao₂ of 5.6 (0.4) kPa improved on treatment to a maximum value of 7.3 (0.5) kPa (p<0.05), but this was not maintained at four hours. The baseline Paco₂ of 10.1 (0.8) kPa did not improve on treatment. At four hours the change in Pao₂ was significantly greater in the NIPPV group than in the doxapram group.

Discussion
This study has shown that non-invasive nasal ventilation produces an immediate improvement in gas exchange in patients with ventilatory failure complicating an exacerbation of COPD, and that this improvement is maintained for at least four hours. It is possible that the fractional inspired oxygen (FIO₂) was altered by the insertion of the nasal mask circuit but the fall in Paco₂ with NIPPV suggests an improvement in ventilation.

In contrast, on doxapram an initial improvement in Pao₂ was not maintained. There are three explanations for this late deterioration. Firstly, the prescribing guidelines recommending a high initial loading dose followed by a reduction may be inappropriate. Secondly, although matched and randomised, the doxapram group may have simply

![Figure 1](image-url) Mean (SE) changes in Pao₂ and Paco₂ in patients admitted with acute respiratory failure treated with either intravenous doxapram (n=8) or nasal intermittent positive pressure ventilation (NIPPV, n=9). * p<0.05 compared with baseline. † p<0.05 NIPPV compared with doxapram.

![Figure 2](image-url) Changes in arterial pH in patients admitted with acute respiratory failure following treatment with intravenous doxapram (□, n=8) or NIPPV (○, n=9). Geometric mean and 95% confidence intervals are shown. * p<0.05 compared with baseline. † p<0.05 NIPPV compared with doxapram.
deteriorated more rapidly. Thirdly, and most likely, with the respiratory muscles already working at near capacity a stimulant may offer only temporary benefit until fatigue supervenes. In contrast, assisted ventilation may offload the respiratory muscles.

Between four and 24 hours three patients in the doxapram group died. Two further patients who deteriorated in the doxapram group were treated successfully by the addition of NIPPV. One patient in the NIPPV group received doxapram, resulting in better cooperation with the nasal ventilation. While it might have been possible to alter ventilator settings rather than add doxapram, we would suggest that the addition of doxapram might improve acceptance of NIPPV, particularly if, as here, the patient was drowsy.

Despite the lack of evidence for successful treatment of ventilatory failure using doxapram in patients with acute infective exacerbations of COPD, it is widely used for this purpose. In contrast, there is good evidence for the effectiveness of NIPPV in this situation. We have now shown in a small study that NIPPV is more effective than doxapram in these patients. We suggest that doxapram is reserved for patients who are centrally sedated or are unable to tolerate nasal ventilation.