Chronic respiratory failure in COPD: is there a place for a respiratory stimulant?

The last decade has seen renewed interest in the use of respiratory stimulant drugs to alleviate the effects of chronic hypoxaemia in patients with chronic obstructive pulmonary disease (COPD). Factors behind this interest include the development of respiratory stimulants suitable for long term oral use,[1] awareness of the potential detrimental effects of nocturnal hypoxaemia,[2] the reluctance of some patients to consider treatment with long term domiciliary oxygen therapy (LTOT), and practical problems associated with oxygen therapy. LTOT can produce worthwhile improvements in survival in patients with COPD who have chronic ventilatory failure,[3 4] but other benefit has been difficult to show. LTOT corrects hypoxia but not hypercapnia, is both expensive and restrictive, requiring great commitment from both patient and family, and so far no definite beneficial effect on quality of life has been shown.[5] After eight to nine years any survival benefit tails off as a result of progression of airflow obstruction.[6] Treating chronic respiratory failure with an oral preparation rather than LTOT would be attractive because of its cheapness and convenience, and could be started at a much earlier stage without imposing any restriction on lifestyle. A respiratory stimulant might also be a useful adjunct to LTOT, particularly in those patients who fail to achieve a satisfactory arterial oxygen tension (PaO_2) without worsening hypercapnia.

The rationale behind giving long term respiratory stimulants to patients with COPD is, however, questionable. In patients with COPD with chronic stable ventilatory failure central respiratory drive is increased,[7–9] although it is unclear whether this high central respiratory activity is sufficient in the face of increased work of breathing from high airways resistance, hyperinflation with the inspiratory muscles operating close to their fatiguing threshold, and marked disturbances of ventilation and perfusion matching within the lung. Attempting to raise inspiratory effort further pharmacologically may allow an increase in minute ventilation only at the expense of an increase in the oxygen cost of breathing, increased carbon dioxide production by the respiratory muscles, enhanced respiratory muscle fatigue, and worsening dyspnoea.

Many drugs are capable of stimulating ventilation but most are unsuitable for clinical use because of toxic effects. Analeptics such as doxapram which cause generalised stimulation of the central nervous system have a limited role in the treatment of acute exacerbations of ventilatory failure in patients with COPD, but their use is being replaced by ventilatory support. Progestational hormones, carbonic anhydrase inhibitors, methylxanthines, tricyclic antidepressants, and almitrine bismesylate have all been advocated as treatments for chronic respiratory failure in COPD. It may be that some of these drugs, particularly agents such as almitrine bismesylate which has additional effects on modifying breathing pattern and ventilation perfusion matching, now have a place in therapeutic management. What is the current evidence to support their use?

Progestational hormones
The association between high levels of endogenous progesterone in pregnancy and the latter half of the menstrual cycle and increasing ventilation has long been recognised.

The oral synthetic derivative medroxyprogesterone acetate has similarly been shown to stimulate breathing in normal individuals[10] and in patients with respiratory disorders. It is probable that progesterone has a central action, crossing the blood-brain barrier to stimulate brain stem respiratory centres to increase alveolar ventilation,[11] an effect that persists during sleep.[12 13] Medroxyprogesterone increases minute ventilation and the ventilatory responses to both hypoxia and hypercapnia.[10] It has been used to treat patients with primary alveolar hypoventilation and those with the obstructive sleep apnoea syndrome, although results are disappointing.[14]

In 17 patients with COPD with stable chronic ventilatory failure (mean FEV_1 1·2 l, PaO_2 6·6 kPa, $PaCO_2$ 6·9 kPa) 20 mg medroxyprogesterone acetate three times a day for four weeks caused a significant reduction in mean $PaCO_2$ of 1 kPa and a rise in PaO_2 of 0·7 kPa in 10 of the 17 patients.[15] This was associated with an increase in mouth occlusion pressure, tidal volume, and alveolar ventilation. Those patients who responded could be predicted by their ability to lower arterial carbon dioxide voluntarily while awake. These findings were confirmed by Delaunois *et al* who found that 75 mg daily of medroxyprogesterone acetate for seven days increased PaO_2 and decreased $PaCO_2$ by about 1·0 kPa in nine of 15 stable hypercapnic patients with COPD.[16] In a similar study 60 mg daily of medroxyprogesterone for one month had no effect on nocturnal oxygen desaturation in 19 patients with COPD despite a mean improvement in daytime PaO_2 and a fall in $PaCO_2$ of 0·9 kPa.[13] Although in a further study Skatrud and colleagues reported less carbon dioxide retention and raised arterial PaO_2 in five patients with COPD after four weeks of medroxyprogesterone, the reduction in $PaCO_2$ persisted during sleep.[12] Medroxyprogesterone has no effect on sleep architecture but in one study the number of arousals increased.[1] Side effects with medroxyprogesterone are troublesome and include weight gain, gastrointestinal disturbance, anxiety, and there is a theoretical risk of thromboembolic events and exacerbation of hypertension and heart failure. About 10% of male patients experience loss of libido and impotence.

Carbonic anhydrase inhibitors
Acetazolamide and the longer acting dichlorphenamide are reversible inhibitors of the enzyme carbonic anhydrase. They have complex actions on cerebral blood flow and cerebrospinal fluid dynamics, but their ventilatory stimulant action probably arises from inhibition of renal tubular hydrogen ion excretion with increased urinary bicarbonate excretion producing a metabolic acidosis which, in turn, stimulates both peripheral and medullary chemoreceptors.[9] Acetazolamide causes an increase in tidal volume and a parallel shift to the left of the ventilatory response to hypercapnia.[9 17] Producing a metabolic acidosis may have theoretical advantages in shifting the oxygen dissociation curve to the right to increase tissue oxygen delivery, but could be dangerous in acute exacerbations of ventilatory failure.

Clinical trials with carbonic anhydrase inhibitors have given disappointing results. Acetazolamide given in a dose of 250 mg twice daily for 10 days improved blood

gas tensions in only six of 15 patients with COPD with chronic stable carbon dioxide retention, despite an increase in plasma and cerebrospinal fluid hydrogen ion concentration.[9] In those who did respond PaO_2 increased from a mean of 6·8 to 8·5 kPa and $PaCO_2$ fell from 6·8 to 5·4 kPa. These patients, however, had less severe airflow obstruction and in this comparative study acetazolamide was a less effective ventilatory stimulant than medroxy-progesterone acetate. Any ventilatory stimulant effect produced by carbonic anhydrase inhibitors is short lived and early studies showed that side effects of headache, depression, paraesthesiae, hypokalaemia, and gastro-intestinal upset outweighed any benefit produced.[18 19] Long term treatment with acetazolamide is also not recommended because of the risk of agranulocytosis which needs monitoring with regular blood counts.

Theophyllines

Although aminophylline has been used for many years as a respiratory stimulant to treat Cheyne-Stokes respiration,[20] the effects of theophyllines on ventilation are controversial. Acute administration of intravenous aminophylline has been shown to increase minute ventilation and the hypoxic ventilatory response without changing the hypercapnic ventilatory response in normal subjects.[21] Sanders *et al* found an increase in resting minute ventilation after intravenous aminophylline but no change in the slopes of the hypercapnic and hypoxic ventilatory responses when measured at resting $PaCO_2$ levels.[22] Two recent studies have shown that oral theophylline, in a dose sufficient to attain therapeutic plasma levels and cause unpleasant side effects, had no effect on hypoxic or hypercapnic ventilatory responses, pulmonary function, or respiratory muscle strength in normal subjects.[23 24] Resting ventilation was increased in one study[23] but was unchanged in the other.[24] It is thought that any increase in ventilation produced by theophyllines occurs secondary to inhibition of central neurotransmitters, such as adenosine, which tonically inhibit ventilation.[25] Any respiratory stimulant effect is not prolonged, however, and long term treatment of COPD patients with oral theophyllines brings about only minor, if any, improvement in gas exchange.[26] Both intravenous aminophylline and oral theophylline have no effect on improving overnight oxygenation in patients with COPD.[27 28] The rationale for prescribing theophyllines to patients with COPD is primarily for their bronchodilator action, but even then their use is controversial.[29 30] Caution must be exercised when using theophyllines as increasing age, smoking, hypoxia, and hepatic congestion will all delay drug clearance and predispose to toxicity.[31]

Tricyclic antidepressants

Protriptyline, a non-sedating tricyclic antidepressant, decreases time spent in rapid eye movement (REM) sleep[32] when most severe falls in nocturnal oxygen saturation (SaO_2) occur.[2] It may also preferentially increase activity in the pharyngeal muscles during sleep to reduce upper airway resistance.[33] Protriptyline has no stimulatory effect on ventilation during wakefulness.[34] In 16 stable patients with COPD (mean FEV_1 1·0 l, PaO_2 7·8 kPa, $PaCO_2$ 6·5 kPa) 20 mg protriptyline at night for 10 weeks increased PaO_2 by a mean of 0·9 kPa and decreased $PaCO_2$ by 0·3 kPa compared with a two week run in placebo period.[35] Sleep architecture did not alter apart from the expected decrease in REM sleep time with an associated improvement in nocturnal oxygen desaturation. Eleven of the 16 patients reported a subjective improvement in sleep quality. In a double blind placebo controlled crossover trial 10 mg of protriptyline at night for six weeks decreased total REM sleep time from 16% to 9% and produced a small improvement in total sleep time spent with an SaO_2 below 90% in 17 patients with more severe airflow obstruction and hypoxia (median FEV_1 0·6 l, PaO_2 6·9 kPa, $PaCO_2$ 6·4 kPa).[36] This was associated with a fall in daytime $PaCO_2$ of about 1 kPa, a small but non-significant rise in daytime PaO_2, and a small increase in maximal inspiratory pressure and six minute walking distance. Measures of breathlessness were unchanged, although an improvement in well being (assessed by the General Health Questionnaire) was recorded, presumably because of the antidepressant properties of protriptyline. Unfortunately dose dependent anticholinergic side effects such as dry mouth, urinary retention, blurred vision, and constipation are common with protriptyline; in the study by Carroll *et al* [36] all 17 patients noted side effects and five said they would be reluctant to continue treatment on a long term basis.

Almitrine bismesylate

Almitrine bismesylate is a piperazine derivative which is well absorbed orally but has a long half life of several weeks. It differs importantly from other respiratory stimulants in that it increases ventilation through a stimulatory action on the carotid and aortic body chemoreceptors[37] with no effect on the central nervous system. Almitrine improves arterial blood gas tensions in patients with COPD but its mode of action is uncertain and probably involves several mechanisms. Minute ventilation increases but improvement in blood gas tensions is often greater than would be expected from the observed increase in ventilation.[38 39] Other mechanisms include an alteration in breathing pattern causing subtle changes in alveolar ventilation,[40] and a direct vasoconstrictor action on small pulmonary blood vessels redistributing blood flow to areas with better ventilation.[39 41 42]

Several studies have examined the effect of almitrine bismesylate in hypoxic patients with COPD for periods of up to a year. The largest of these, the Vectarion International Multicentre Study (VIMS), examined the effect of 50–100 mg almitrine twice daily, the dose being titrated against initial improvement in PaO_2, or placebo in 701 patients with stable hypoxic COPD (mean FEV_1 0·87 l, PaO_2 7·6 kPa, $PaCO_2$ 6·0 kPa).[43] After 12 months of treatment PaO_2 had increased in the actively treated patients by about 1 kPa with a third achieving a rise of 2 kPa; mean PaO_2 in the almitrine treated group at 12 months was 8·5 kPa. The corresponding fall in $PaCO_2$ was much smaller but was still significant with a mean $PaCO_2$ at 12 months of 5·7 kPa. There were no significant changes in blood gas tensions during the study period in the placebo treated patients. In the group treated with almitrine 25% did not show any improvement in blood gas tensions, defined as an increase in PaO_2 of less than 0·7 kPa. It was not possible to predict "good responders" from "non-responders" from baseline physiological and clinical measurements, although "good responders" tended to have less severe disease and be less hypercapnic. The almitrine treated group experienced a reduction in secondary polycythaemia, a decrease in the number of hospital admissions, a small but significant improvement in FEV_1, but no change in six minute walking distance. Quality of life was not assessed. Unfortunately the improvement in blood gas tensions was achieved at the expense of a large number of drug side effects, namely increased dyspnoea, gastrointestinal disturbance, malaise, weight loss, and peripheral neuropathy. In total 40% of

the actively treated group withdrew from the study compared with 25% of the controls. Side effects correlated with drug plasma levels, which were often well above the therapeutic range of 200–300 ng/ml due to the unexpectedly long half life.

Eighty nine patients from the VIMS study continued treatment for two years with significant improvement in blood gas tensions being maintained.[44] Again withdrawals were high with 29 of 43 almitrine treated and 22 of 46 placebo treated patients failing to complete the full two years of treatment. No difference was seen in survival between the placebo and almitrine treated groups. Survival at two years was 82% in the actively treated patients and 86% in those taking placebo. Survival after two years was better than that observed in the treated groups in the NOTT and MRC LTOT trials where rates were 78% and 77% respectively.[3] [4] Patients in the almitrine study were, however, less hypoxic, and not all were hypercapnic or had experienced episodes of oedema. To determine any beneficial effect on survival patients with more severe arterial hypoxia need to be studied for longer periods.

Two recent studies, one from Europe and one carried out in several centres in the UK, have examined the effect of a lower dose of almitrine (approximately half the dose used in the VIMS study), 25–50 mg twice daily with an intermittent schedule of administration of two months treatment followed by a one month washout period to allow for the drug's long half life.[45] [46] The UK study ran for 18 months, only the first six of which were double blind and placebo controlled, all patients then taking the active drug for a further six months.[45] In view of the previous problems with peripheral neuropathy, peripheral nerve function was subject to particular scrutiny with careful clinical and electrophysiological evaluation. Eighty five patients with COPD were studied (mean FEV_1 0·89 l, PaO_2 7·8 kPa, $PaCO_2$ 5·8 kPa). After six months the improvement in baseline PaO_2 values with almitrine was 0·8–1·3 kPa, similar to that found with higher doses in the VIMS study, with again about a third of patients showing no response. $PaCO_2$ fell slightly in the patients taking almitrine but blood gas tensions did not alter in the placebo treated patients. After withdrawal of therapy blood gases slowly reverted to pretreatment levels. The sequential dosing regimen allowed plasma drug levels to stabilise within the therapeutic range and produced fewer side effects, although there was still a high drop out rate of 28% in the almitrine group and 20% in the placebo group. Dyspnoea, gastrointestinal disturbances, and paraesthesiae were recorded equally between the groups. No increase in six minute walking distance occurred with almitrine. A substantial degree of peripheral nerve dysfunction was found, with only 28 patients (38%) having a normal electromyographic study before entering the trial. The majority of abnormalities were, however, entrapment neuropathies, most of which were asymptomatic with only three (5%) having a possible generalised peripheral neuropathy. During the study period there was a slight reduction in peroneal motor conduction velocity in both the treated and control groups but no patient developed a clinical peripheral neuropathy.

The European study evaluated pulmonary haemodynamic changes during long term almitrine treatment.[46] There had been uncertainty over the long term safety of almitrine since acute increases in mean pulmonary artery pressure were observed in short term studies after both intravenous and oral administration attributed to enhanced hypoxic vasoconstriction.[38] [47] Weitzenblum and coworkers[46] treated 45 hypoxic patients with COPD

(mean FEV_1 1·04 l, PaO_2 7·6 kPa, $PaCO_2$ 5·8 kPa) with either low dose intermittent almitrine or placebo for 12 months. In the 16 patients treated with almitrine who completed the study no change in mean pulmonary artery pressure (measured both at rest and during exercise), pulmonary vascular resistance, or cardiac output occurred despite achieving therapeutic almitrine levels and a modest improvement in PaO_2 of around 0·8 kPa. No changes in blood gas tensions or pulmonary haemodynamics were recorded in 10 placebo treated patients who finished the study.

Almitrine has been shown to improve nocturnal oxygenation in patients with COPD largely by increasing PaO_2 when awake and raising the baseline SaO_2. In nine patients with COPD in ventilatory failure (mean FEV_1 0·6 l, PaO_2 6·7 kPa, $PaCO_2$ 6·5 kPa) 50 mg almitrine twice daily for 14 days improved daytime blood gas tensions and oxygenation during sleep, lowest SaO_2 rising from an average 65% to 77% without impairing sleep quality.[48] In six patients 1·5 mg/kg almitrine was more effective in improving nocturnal oxygen desaturation than 100 mg medroxyprogesterone.[1] Further studies, although again containing small numbers, have shown the effect of almitrine on nocturnal desturation to be maintained after treatment for up to a year without any changes in the quality or quantity of sleep.[49] [50] There does not, however, appear to be any additional benefit from combining almitrine with oxygen to treat nocturnal oxygen desaturation.[51] There is evidence from short term studies that, in patients with COPD on LTOT who cannot attain a satisfactory PaO_2 without excessive hypercapnia, supplemental almitrine bismesylate may be a useful additional treatment.[52] There was also evidence of a useful additive effect to LTOT from the VIMS study, although no long term studies have addressed this issue.

Conclusions

Treatment with respiratory stimulant drugs can produce sustained improvements in both daytime and nocturnal arterial blood gas tensions in some patients with COPD. However, patients in whom arterial blood gas tensions are likely to improve tend to have less severe disease with less mechanical impairment to ventilation. Other benefit has not been realised and side effects with all agents are troublesome. Almitrine bismesylate shows most promise, yet after a decade of investigation no clear place in the therapeutic management for patients with COPD has emerged. There is currently no convincing scientific evidence that any long term respiratory stimulant improves either symptoms or survival in patients with hypoxic COPD. Their use must remain experimental.

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