

## Hypoxia, almitrine, and peripheral neuropathy

The chronic hypoxia seen at high altitude or induced experimentally by environmental changes has several physiological and pathological consequences. The carotid body, the principal sensor of blood oxygen tension, enlarges<sup>1</sup> and contains increased amounts of dopamine and noradrenaline.<sup>2</sup> The hypoxic drive to ventilation diminishes.<sup>3</sup> In the lung there is constriction of pulmonary arterioles in association with increased muscularisation of their walls, right ventricular hypertrophy, and a rise in pulmonary arterial pressure.<sup>4,5</sup> In patients with severe obstructive airways disease chronic hypoxaemia when severe is associated with peripheral oedema, often inappropriately termed cor pulmonale. Although the clinical features resemble cardiac failure with a raised jugular venous pressure, hepatomegaly, and gross anasarca, cardiac output is normal or even raised and right ventricular function minimally disturbed. Renal blood flow is reduced by half or more, and this seems to be a critical physiological abnormality, closely correlated with hypoxaemia and hypercapnia, particularly the latter.<sup>6,7</sup>

It was hoped that many of these features in patients with hypoxaemic chronic obstructive airways disease would be improved by oxygen therapy designed to restore arterial oxygen tension to at least 8 kPa and arterial oxygen saturation to 90% or more. The benefit so far, however, has been limited. Long term domiciliary oxygen therapy was found to require administration for at least 15 hours a day for benefit to be seen, better results requiring even longer treatment—up to 24 hours a day.<sup>8,9</sup> Survival is increased for some years with long term oxygen therapy but this fails to arrest the decline in airway function or the continuing pathological changes in small pulmonary vessels; benefit in the long term is limited.<sup>10</sup>

Attempts have been made to reverse the effects of hypoxia by pharmacological means as this would be considerably more convenient for the patient. Almitrine bismesylate, an orally administered triazine derivative, functions as a peripheral chemoreceptor agonist stimulating afferent carotid body nerves much as in hypoxaemia.<sup>11</sup> It causes an increase in minute ventilation and there may also be subtle ventilatory changes that are not detected as an increase in total ventilation, which increase gas flow to alveoli. Almitrine also causes pulmonary vasoconstriction, possibly more so in hypoxic areas of the lung. Whether

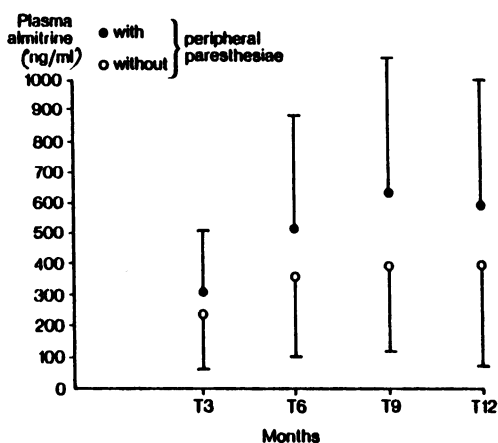
the improved arterial blood gas tensions seen with almitrine are due to an increase in minute ventilation<sup>12</sup> or to improvement in ventilation-perfusion ( $\dot{V}/\dot{Q}$ ) matching due to selective pulmonary vasoconstriction is still debated<sup>13</sup> (evidence reviewed by Tweney<sup>14</sup>).

Treatment with almitrine causes a rise in arterial oxygen tension of a magnitude similar to that produced by oxygen therapy. Studies of patients with chronic obstructive airways disease<sup>15</sup> using almitrine in a daily dose of 100–200 mg have so far shown some reduction in oedema and reduced exacerbations of illnesses requiring hospital admission. There has, however, been no effect on survival comparable to that seen with long term oxygen therapy. Breathlessness has been increased in some patients and decreased in others. Reversible peripheral neuropathy is the most important side effect. This has focused attention on the neurological manifestations of chronic hypoxaemia in patients with obstructive airways disease.

In the trials of long term oxygen, treatment was found to improve neuropsychiatric manifestations, such as depression, quality of life, and emotional behaviour marginally.<sup>16</sup> Patients with hypoxaemic bronchitis were found to have a much greater range of neuropsychological abnormality than matched controls but overt peripheral nerve disorder was not observed (reviewed by Grant and Heaton.<sup>17</sup>) The first papers on peripheral nerve function in patients with chronic obstructive airways disease reported physiological disturbance of peripheral nerve function in up to 60% of patients, though there was little clinical evidence of this.<sup>18–20</sup> The disorder was considered to be “subclinical.” When peripheral neuropathy was first reported in a small number of bronchitic patients taking almitrine by Chedru *et al*<sup>21</sup> and Gherardi *et al*<sup>22</sup> the neurological disturbances were attributed to the drug.

Further studies with almitrine showed that the onset of neuropathy was usually insidious and of mostly a distal sensory neuropathy affecting the lower limbs in particular, with histological and electrophysiological evidence of axonopathy.<sup>22</sup> Although the first reports suggested that peripheral nerve pathology might be associated with almitrine with or without additional effects from other respiratory drugs, electrophysiological studies soon began to show that patients with hypoxaemic chronic bronchitis had a similar incidence of such changes whether treated with almitrine or not.<sup>23–27</sup> Electrophysiological changes are seen more often than abnormal neurological symp-

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Plasma almitrine concentrations from patients in the active group of Vectarian International Multicentre Study. Patients complaining of paraesthesiae had higher plasma almitrine concentrations than those without such symptoms. From Voisin *et al*<sup>15</sup>; reproduced by courtesy of the *Bulletin Européen de Physiopathologie Respiratoire*.

toms and signs.<sup>28</sup> With almitrine the clinical manifestations for some reason are more apparent. There are problems with standardisation of electrophysiological measurements and much disagreement between neurophysiologists (see review by Jarratt<sup>29</sup>). The clear implications are that caution needs to be exercised in comparisons of the incidence of electrophysiological abnormalities in patients with hypoxaemic chronic obstructive lung disease.

Prospective studies on the relation of almitrine to peripheral neuropathy have been published recently.<sup>30</sup> Lerebours *et al*<sup>31</sup> studied 110 patients with chronic bronchitis and hypoxaemia, 22 receiving almitrine (50 mg twice daily) and 78 acting as control subjects. At the start of the study 64% of the control subjects and 55% of patients receiving almitrine had at least one neurophysiological abnormality. After six and 12 months of almitrine treatment there was no change in any of the clinical or physiological measures studied. In another long term placebo controlled, double blind multicentre study of almitrine treatment in patients with hypoxaemia and chronic bronchitis<sup>15</sup> 50 of 344 patients in the treated group (14.5%) recorded paraesthesiae compared with only eight of 357 (2.2%) in the control group ( $p < 0.001$ ). The dose of almitrine in this study varied from 100 to 200 mg daily. Some patients accumulated plasma concentrations well above the optimal therapeutic concentration of 200–300 ng/ml. Raised plasma almitrine concentrations were related to the incidence of symptoms (figure).

In this issue Allen and Prowse<sup>32</sup> record the results of a careful double blind prospective study of 12 patients

with chronic bronchitis. None of the seven patients receiving placebo developed clinically manifest peripheral neuropathy and electrophysiological measurements did not show deterioration. Of the five receiving almitrine (50 mg twice daily for nine to 18 months), four developed clinical features of peripheral neuropathy and in two there was increased electrophysiological abnormality. Slow improvement followed cessation of treatment. Their study suggests that patients developing the first symptoms of paraesthesiae should have the drug stopped and that recovery may then be expected.

Hypoxaemia appears to be the principal aetiological factor for peripheral neuropathy, in addition to almitrine; but concurrent features, such as age, alcoholism, tobacco smoking, and taking other drugs, may contribute. It is intriguing to speculate how almitrine, whose effects mimic many of the other physiological aspects of hypoxia, might augment neurological conditions caused by hypoxia. Recent work by Ward and colleagues<sup>33</sup> suggests that local hypoxia is important in the aetiology of peripheral neuropathy in diabetes mellitus. There are many similarities between the neurological features of the two conditions. Endothelial proliferation of the vasa nervorum has been found in sural nerve biopsy specimens from patients with diabetes mellitus and similar changes have now been shown in peripheral nerves<sup>34</sup> from patients with chronic bronchitis and hypoxaemia. This is of particular interest for studies in small pulmonary vessels, where we have found gross endothelial proliferation.<sup>10</sup> Disturbance of endothelial growth factors by hypoxia might be a common denominator of vascular endothelial and smooth muscle changes in several parts of the body.

A daily dose of almitrine bismesylate of 100–200 mg appears to be too high. Our own studies (unpublished) with lower doses have so far shown a similar improvement in arterial oxygen tension with noticeably less neurological side effects. The optimal therapeutic dose has still to be determined. A threshold phenomenon has not been observed.

The carotid body with its afferent nerve supply intact has been shown to be an essential prerequisite for the increase in arterial oxygen tension with almitrine in experimental animals<sup>35</sup> and man.<sup>12</sup> The enlargement of the carotid body, with accumulation of catecholamines, particularly dopamine, in patients and animals with chronic hypoxaemia, suggests that almitrine could exert its effects by manipulating the concentration or action of these transmitters. Are the actions of almitrine restricted to the carotid body? The enhancement of hypoxic effects on peripheral nerves suggests a possible direct effect on this tissue, perhaps through hypoxia receptors or by restriction of blood supply from endothelial proliferation. In short term

experiments no discernible effects of almitrine could be observed in chemodectomised animals<sup>35</sup> or man.<sup>12</sup> The carotid body is therefore not excluded as an important intermediary or even modulator of hypoxic neural effects. The same consideration might apply to other body tissues, including endothelium. Further studies of the interaction between hypoxia and almitrine on the carotid body and tissues such as lung, kidney, and peripheral nerves are awaited with great interest.

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## References

- Dhillon DP, Barer GR, Walsh M. The enlarged carotid body of the chronically hypoxic and chronically hypoxic and hypercapnic rat: a morphometric analysis. *Q J Exp Physiol* 1984;**64**:301-17.
- Barer GR, Pallot DJ. Changes in catecholamine content of the rat carotid body in chronic hypoxia and hypercapnia and its modification by carotid body sympathectomy. *J Physiol* 1986;**378**:69P.
- Heath D, Williams DR. *Man at high altitude*. 2nd ed. Edinburgh: Churchill-Livingstone, 1981.
- Herget J, Suggett AJ, Leach E, Barer GR. Resolution of pulmonary artery hypertension and other features induced by chronic hypoxia in rats during complete and intermittent hypoxia. *Thorax* 1978;**33**:468-73.
- Finlay M, Middleton HC, Peake MD, Howard P. Cardiac output, pulmonary hypertension, hypoxaemia and survival in patients with chronic obstructive airways disease. *Eur J Respir Dis* 1983;**64**:252-63.
- Stuart-Harris CH, MacKinnon J, Hammond JDS, Smith WD. The renal circulation in chronic pulmonary disease and pulmonary heart failure. *Q J Med* 1956;**25**:389-405.
- Aber GM, Bishop JM. Serial changes in renal function, arterial gas tensions and the acid base state in patients with chronic bronchitis and oedema. *Clin Sci* 1965;**28**:511-25.
- Medical Research Council. Domiciliary oxygen trial. *Lancet* 1981;*i*:681-5.
- Nocturnal Oxygen Therapy Trial Group (NOTT trial). Continuous or nocturnal oxygen therapy in hypoxaemic chronic obstructive lung disease. *Ann Intern Med* 1970;**93**:394-9.
- Wilkinson M, Langhorne CA, Heath D, Barer GR, Howard P. A pathophysiological study of 10 cases of hypoxic cor pulmonale. *Q J Med* 1988 (NS);**249**:65-85.
- Laubie M, Schmitt H. Longlasting hyperventilation induced by Almitrine: Evidence for a specific effect on carotid and thoracic chemoreceptors. *Eur J Pharmacol* 1980;**61**:125-36.
- De Backer W, Vermeire P, Bogaert E, Janssen E, Van Moele R. Almitrine has no effect on gas exchange after bilateral carotid body resection in severe chronic airflow obstruction. *Bull Eur Pathophysiol Respir* 1985;**21**:427-32.
- Castaing Y, Manier G, Varenne N, Guenard H. Almitrine orale et distribution des rapports  $V_A/Q$  dans les bronchopneumopathies chroniques obstructives. *Bull Eur Physiopathol Respir* 1981;**17**:917-32.
- Tweney J. Almitrine bismesylate. The current status. *Bull Eur Physiopathol Respir* 1987;**23**(suppl 11):153-63S.
- Voisin C, Howard P, Ansquer JC. Almitrine bismesylate. A long term placebo controlled double-blind study in COAD—Vectarian International Multicentre Study Group. *Bull Eur Physiopathol Respir* 1987;**23**(suppl 11):169-82S.
- Heaton RK, Grant I, McSweeney AJ, Adams KM, Petty TL. Psychological effects of continuous and nocturnal oxygen therapy in hypoxaemic chronic obstructive airways disease. *Arch Intern Med* 1983;**143**:1941-7.
- Grant I, Heaton RK. Neuropsychiatric abnormalities in advanced COPD. In: Petty TL, ed. *Chronic obstructive pulmonary disease*. 2nd ed. (*Lung biology in health and disease series*, vol 28.) New York: Dekker, 1985:355-73.
- Appenzeller P, Parks RD, MacGee J. Peripheral neuropathy in chronic disease of the respiratory tract. *Am J Med* 1968;**44**:873-80.
- Narayan M, Ferranti R. Nerve conduction impairment in patients with respiratory insufficiency and severe chronic hypoxaemia. *Arch Phys Med Rehab* 1978;**59**:188-92.
- Faden A, Mendoza E, Flynn F. Sub-clinical neuropathy associated with chronic obstructive pulmonary disease: possible pathophysiological role of smoking. *Arch Neurol* 1981;**38**:639-42.
- Chedru F, Nodzenski R, Dunand JF. Peripheral neuropathy during treatment with almitrine. *Br Med J* 1985;**290**:896.
- Gherardi R, Benvenuti C, Lejonc JL, et al. Peripheral neuropathy in patients treated with almitrine bismesylate. *Lancet* 1985;*ii*:1247-50.
- Suggett AJ, Jarratt JA, Proctor A, Howard P. Almitrine and peripheral neuropathy. *Lancet* 1985;*ii*:830.
- Alani SM, Twomey JA, Peake MD. Almitrine and peripheral neuropathy. *Lancet* 1985;*ii*:1251.
- Moore N, Lerebours C, Senant J, Ozenne G, David P, Nouvet G. Peripheral neuropathy in chronic obstructive lung disease. *Lancet* 1985;*ii*:1311.
- Lerebours C, Ozenne G, Senant J, Moore N, David P, Nouvet G. Abnormalities in the electrophysiological examination of patients with chronic obstructive lung disease: a preliminary study of the effects of almitrine. *Eur J Respir Dis* 1986;**69** (suppl 146):713-4.
- Gerard M, Leger P, Couturier JC, Robert D. Ten cases of peripheral neuropathy during treatment with Almitrine in COPD patients. *Eur J Respir Dis* 1986;**69** (suppl 146):591-6.
- Gasnault J, Moore N, Arnaud F, Rondot R. Peripheral neuropathies during hypoxaemic chronic obstructive airways disease. *Bull Eur Pathophysiol Respir* 1987;**23** (suppl 11):199-202S.
- Jarratt JA. The electrophysiological diagnosis of peripheral neuropathy. A brief review. *Bull Eur Physiopathol Respir* 1987;**23** (suppl 11):195-8S.
- Paramelle B, Vila A, Pollak P, et al. Frequence des polyneuropathies dans les bronchopneumopathies

- chroniques obstructives. *Presse Méd* 1986;15:563-7.
- 31 Lerebours G, Senant J, Moore N, *et al.* Evolution of peripheral nerve function in hypoxaemic COPD patients taking almitrine bismesylate: a prospective long term study. *Bull Eur Pathophysiol Respir* 1987;23 (suppl 11):203-6S.
- 32 Allen MB, Prowse K. Clinical and electrophysiological observations in patients with chronic bronchitis taking almitrine and placebo. *Thorax* 1989;44:292-7.
- 33 Ward JD. Diabetic neuropathy. In: Alberti KGMM, Krall LP, eds. *Diabetes annual*. No 4. Amsterdam: Elsevier (in press).
- 34 Church S, Masson EA, Boulton AJM, Woodcock A. Functional and morphological characteristics of peripheral neuropathy in chronic lung disease. *Thorax* (in press).
- 35 Dhillon DP, Barer GR. Respiratory stimulation by almitrine during acute and chronic hypoxia-hypercapnia in rats. *Bull Eur Physiopathol Respir* 1982;18:751-64.