Thorax 1989;**44**:292–297

Peripheral nerve function in patients with chronic bronchitis receiving almitrine or placebo

MARTIN B ALLEN, KEITH PROWSE

From the Department of Respiratory Physiology, City General Hospital, Stoke on Trent

ABSTRACT A double blind prospective study of the effect of almitrine bismesylate and placebo on peripheral-nerve function was carried out in 12 patients with chronic bronchitis and arterial hypoxaemia (mean (SD) FEV_1 % predicted 38 (16), arterial oxygen tension (Pao_2) 7·56 (0·76) kPa). Of the seven patients who took placebo, none developed symptoms or signs of peripheral neuropathy. One patient who had abnormal lower limb sensory nerve conduction initially showed improvement of sensory conduction but deterioration in motor conduction during the 12 month study period. Two further patients developed some slowing of motor conduction velocities in their right lateral popliteal nerve. Five patients received almitrine and all showed an improvement in Pao_2 (mean from 7·0 to 7·9 kPa). None had symptoms or signs of peripheral neuropathy on entry to the study; one patient had evidence of impaired nerve conduction on electrophysiological testing. Three patients developed symptoms and signs of peripheral neuropathy during the 12 months of the study and a fourth developed peripheral neuropathy at 18 months, having continued to receive almitrine. Studies of nerve physiology showed abnormalities in the lower limbs of all four patients. Recovery was poor, possibly because of the long half life of almitrine. The studies suggest that almitrine may precipitate peripheral neuropathy in patients with chronic obstructive pulmonary disease. Patients should be warned of this potential complication so that the drug can be stopped as soon as symptoms develop.

Introduction

Almitrine bismesylate is a respiratory stimulant, which increases arterial oxygen tension in patients who are hypoxaemic from chronic bronchitis.[1] It appears to act peripherally via the carotid body[2] to increase ventilation[3] or to redress pulmonary ventilation-perfusion imbalance.[4] After extensive investigation in Europe there have been sporadic reports of peripheral neuropathy from several countries, including Britain.[5-7]

Symptoms of peripheral neuropathy are said to be relatively common in patients with chronic bronchitis and emphysema, with 40% of 146 unselected patients experiencing sensory symptoms in one study.[8] Subclinical peripheral neuropathy, as determined by studies of nerve electrophysiology, is even more common, an incidence of 60–87% being reported.[9-11] In hypoxaemic patients taking either almitrine or placebo two groups of workers have found no difference in the incidence of peripheral neuropathy, either clinically or on electrophysiological testing, suggesting that hypoxaemia rather than almitrine may be the important factor in peripheral neuropathy.[12,13]

Patients who develop peripheral neuropathy while taking almitrine may have an underlying abnormality of peripheral nerve function as determined by electrophysiological studies, which predisposes them to neuropathy regardless of treatment. Alternatively, almitrine may act directly as a neurotoxin, especially if patients already have impaired neurological function. We have investigated the relation between peripheral neuropathy and almitrine treatment in patients with chronic obstructive lung disease.

Methods

Twelve patients with stable chronic bronchitis and daytime hypoxaemia (FEV_1 < 70% predicted, Pao_2 < 8·6 kPa) were enrolled in the study. Clinical details are shown in table 1. All gave informed consent and the study was approved by the North Staffordshire ethical committee. If the variation in Pao_2 during

Address for reprint requests: Dr Martin Allen, Department of Respiratory Medicine, Killingbeck Hospital, Leeds LS14 6UQ.

Accepted 26 January 1989

Table 1 *Details of the patients*

Patient No	Age (y)	Sex	Baseline FEV_1 (% pred)	Baseline HbCO (%)	Baseline PaO_2 (kPa)*	Baseline $PaCO_2$ (kPa)*	After treatment PaO_2 (kPa)	After treatment $PaCO_2$ (kPa)	Plasma almitrine (ng/ml)
(*a*) PLACEBO GROUP									
A	54	F	18	2·7	7·45	5·05	7·37	4·79	
B	62	F	68	0·9	8·25	4·52	8·6	5·85	
C	59	M	49	2·1	8·6	5·05	8·1	5·45	
D	63	M	30	2·3	7·78	5·52	7·45	5·59	
E	52	M	22	3·2	7·45	5·45	7·58	5·05	
F	58	M	55	1·3	8·1	4·52	6·65	4·66	
G	70	M	41	0·8	7·98	4·66	8·91	5·05	
Mean	59·7	2F 5M	41	1·9	7·94	4·96	7·82	5·19	
SD	5·6		17	0·9	0·47	0·41	0·78	0·44	
(*b*) ALMITRINE GROUP									
1	57	M	19	5·1	7·25	5·65	7·84	5·98	482
2	58	M	38·5	2·4	6·98	6·38	8·1	5·32	787·6
3	56	F	23·4	5·4	5·78	6·98	6·65	6·12	474·7
4	64	M	36	1·4	6·75	5·38	7·98	5·05	537·2
5	48	F	58·5	1·1	8·32	4·92	8·91	4·79	294·7
Mean	56·6		35·1	3·08	7·03	5·8	7·9†	5·45	512·2
SD	5·1		13·8	1·8	0·8	0·76	0·8	0·52	158·8

*Difference in pretreatment PaO_2 and $PaCO_2$ between the two groups: $p < 0.05$.
†Difference between pretreatment and post-treatment PaO_2 in the almitrine group: < 0.01.
HbCO—carboxyhaemaglobin; PaO_2—arterial oxygen tension; $PaCO_2$—arterial carbon dioxide tension.

a three week stabilisation period was less than 0·67 kPa patients were randomised to receive in a double blind manner almitrine bismesylate 50 mg twice daily or placebo for 12 months. Patients attended at three monthly intervals to return unused tablets and collect a fresh supply. At the start and end and at each visit a full neurological examination was undertaken by one person (MBA), and spirometry and arterial blood gas analysis were performed. Venous blood was taken for a biochemical profile, which included measurement of γ glutamyl transferase activity and glucose concentration, mean corpuscular volume and haemoglobin and carboxyhaemoglobin concentrations, and almitrine concentration.

After 12 months the code was broken and patients who had received almitrine were given the option to continue almitrine if they thought that their symptoms had improved and they agreed to further follow up. All patients were seen three months after cessation of treatment to assess the effect of stopping the trial drug and after another three months if they had developed peripheral neuropathy.

Spirometry was performed with a dry wedge spirometer (Vitalograph), blood gas tensions were determined with a Corning blood gas analyser and carboxyhaemoglobin with a CO-oximeter, biochemical measurements were made on a multichannel analyser, and haematological investigations were done with a Coulter counter. Any patient who developed symptoms or signs of peripheral neuropathy was investigated further—with a full drug and alcohol history, clinical examination, chest radiography, and the following blood tests: autoimmune screen, antinuclear factor, blood glucose and vitamin B_{12} concentrations, erythrocyte sedimentation rate, and serological tests to exclude syphilis.

Electrophysiological studies of peripheral nerves were undertaken during the three week stabilisation period and after 12 months' treatment (or earlier if peripheral neuropathy developed), a Medelec MS92 machine and standard techniques being used.[14] The studies were performed and interpreted by one person, who was unconnected with the trial. Sensory nerve action potential onset latencies of both ulnar and median nerves were obtained by orthodromic stimulation with ring electrodes and recording with surface electrodes at the wrist. Both sural nerves were stimulated antidromically with recordings made lateral to the Achilles tendon for determination of conduction velocities and amplitudes. Ulnar and median nerves (between the wrist and the elbow) and the lateral popliteal nerves (between the fibular head and lateral malleolus) on both sides were stimulated supramaximally, with surface recordings over the appropriate muscle to obtain maximal motor conduction velocities. Normal values for a population aged over 40 years were based on our own laboratory data and agree with published results.[15] In the lower limb motor conduction velocities below 40 m/s and sensory conduction velocities below 30 m/s were taken as abnormal.

Results for blood gas analyses are expressed as means with standard deviations in parentheses. Paired and unpaired *t* tests were used to make comparisons within and between groups, $p < 0.05$ being taken as significant.

Results

CLINICAL FINDINGS

Five patients were randomised to receive almitrine and seven placebo. Those receiving almitrine tended to be younger and to have lower Pao_2 and FEV_1 values and higher carboxyhaemaglobin concentrations and arterial carbon dioxide tensions ($Paco_2$) than the placebo treated group. The pretreatment Pao_2 (7·0 and 7·9 kPa) and $Paco_2$ (5·8 and 5·0 kPa) differed significantly between the two groups (table 1).

All seven patients who received placebo completed the study; none developed evidence of generalised peripheral neuropathy. One patient (A) developed weakness, paraesthesia, and nocturnal discomfort in both hands with a positive Tinel's sign, suggesting bilateral median nerve entrapment in the carpal tunnel (table 2*a*).

Of the five patients who received almitrine, four completed the study; only patient 4 continued beyond 12 months. Four patients developed symptoms and signs of peripheral neuropathy (table 2*b*). Patient 2 was withdrawn after nine months' treatment because of severe neuropathy. This began with painful paraesthesia over the great toes of both feet and spread over a month to the mid tarsal region. The discomfort was constant and severe, interfering with sleep and normal daily activities. At the nine month visit changes in sensitivity to light touch and pinprick over the feet were found, and both ankle reflexes were absent; no motor deficit was detected. Patients 1 and 3 developed symptoms of peripheral neuropathy insidiously between the nine and the 12 month visits. Both complained of "walking on cotton wool" but had no painful paraesthesia. Sensory changes were present in both feet and ankle reflexes were absent.

Patient 4 had normal baseline blood glucose concentrations but developed mild diabetes mellitus after nine months' almitrine treatment. Dietary advice was effective and fasting and random blood glucose con-

Table 2 *Neurological symptoms and signs after treatment**

Patient No	*Duration of treatment (months)*	*Symptoms*	*Signs*		
(*a*) PLACEBO GROUP					
A	12	Paraesthesia in both hands with weakness and nocturnal discomfort at 9 months	Minimal weakness of abductor pollicis brevis; positive Tinel's sign bilaterally	R	A—normal K—normal
B	12	Nil	Nil	R	A—normal K—normal
C	12	Nil	Nil	R	A—normal K—normal
D	12	Nil	Nil	R	A—normal K—normal
E	12	Nil	Nil	R	A—normal K—normal
F	12	Nil	Nil	R	A—normal K—normal
G	12	Nil	Nil	R	A—normal K—normal
(*b*) ALMITRINE GROUP					
1	12	7 wk persistent paraesthesia in both feet	LT ↓ to both ankles PP ↓ over R mid tarsal region PS Absent in R great toe V Absent in feet	R	A—absent K—normal
2	9	4 wk progressive painful paraesthesia	LT, PP ↓ over mid tarsal region V Absent in feet	R	A—absent K—normal
3	12	5 wk progressive numbness in both feet	LT ↓ to mid tarsal level PP ↓ to calf on R and ankle L V Absent at R, reduced at L ankle	R	A—absent K—normal
4	18	4 wk persistent ache in both feet	LT, PP Little objective change V Absent at R ankle and L toe	R	A—absent K—normal
5	12	Nil	Nil	R	A—normal K—normal

*No one in either group had any neurological symptoms or signs before receiving almitrine or placebo.
LT—light touch; PP—pin prick; PS—joint position; V—vibration; R—reflexes; A—ankles; K—knees.

centrations returned to within the normal range. After 12 months' treatment his respiratory symptoms were improved and clinical neurological examination showed nothing abnormal, so he continued to take almitrine. After 18 months' treatment, however, he developed painful paraesthesiae over the tarsal region of both feet over four weeks. Neurological examination showed no sensory loss but ankle reflexes were absent. Six months after stopping treatment he had few neurological symptoms but both ankle reflexes were still absent. Only patient 5 did not develop peripheral neuropathy. She was an obese woman (90 kg), was younger and less hypoxaemic than the other patients, and had the lowest mean almitrine concentration.

In the four patients with neuropathy no other cause was apparent. All denied alcohol abuse and had normal γ glutamyl transferase activity and mean corpuscular volume. There was no family history of neurological disease and all the additional investigations gave normal results. After stopping almitrine treatment they had no deterioration in their respiratory symptoms. Clinical neurological examination three and six months later showed only slight improvement in the peripheral neuropathy, which for patient 1 continued to be painful and limit activity.

NEUROPHYSIOLOGICAL STUDIES

In the placebo group only patient A showed any abnormalities in the initial electrophysiological studies (absent right sural nerve action potential, slowed conduction velocity in left sural nerve). Patients D and G had borderline normal conduction velocities in one or both lateral popliteal nerves (table 3*a*).

During the 12 month study period nerve conduction studies in patient A confirmed median nerve entrapment; motor conduction in the left lateral popliteal nerve was now borderline normal, but the right sural nerve action potential was found easily and conduction velocity of the left sural nerve was now normal. Motor conduction in patient G was unchanged but velocity in the right lateral popliteal nerve of patient D was further reduced. Patients C and F showed some reduction in lower limb motor conduction velocities, although only the right lateral popliteal nerve of patient F was clearly abnormal (table 3*a*).

In the patients who received almitrine the initial neurophysiological studies showed abnormality only in patient 1 (slow sensory conduction velocities in the sural nerves, borderline normal conduction in the lateral popliteal nerves). Patient 2 had borderline normal conduction velocities in the right sural nerve prior to treatment.

At the end of the study patient 1 had abnormal motor conduction velocity in the left leg and loss of the right sural action potential (table 3*b*). Patient 2, studied after nine months' treatment, showed reduced motor conduction velocities in both legs, although sural nerve conduction velocity was improved. In patient 3 no action potential could be detected from the left sural nerve and there was some reduction in both lower limb motor conduction velocities. Patient 4 had no changes in the 12 month study, but at 18 months lower limb muscle denervation was present on the concentric needle electromyogram in keeping with axonal neuropathy. For patient 5 the only abnormality was the absence of any sensory action potential from the right sural nerve.

ARTERIAL BLOOD GAS CHANGES

In the placebo treated group there were no significant changes in arterial blood gases during the study. In the almitrine treated group all five patients showed an increase in Pa_{O_2} ($p < 0{\cdot}01$) with a mean rise of 0·88 (0·26) kPa. Mean Pa_{CO_2} and hydrogen ion concentrations were unchanged (table 1).

Discussion

The main finding of this prospective study is the high

Table 3 *Lower limb neurophysiological measurements: sensory and motor conduction velocities* before and after treatment*

Patient No		*Sensory (m/s)*		*Motor (m/s)*	
		Before	*After*	*Before*	*After*
(*a*)	PLACEBO GROUP				
A	L	25	34	47	41
	R	—	36	48	44
B	L	42	45	46	49
	R	39	39	49	52
C	L	38	48	56	41
	R	37	47	60	41
D	L	33	52	43	42
	R	33	45	41	37
E	L	39	45	57	49
	R	37	47	53	48
F	L	35	49	51	43
	R	38	52	44	38
G	L	37	43	45	43
	R	37	38	40	42
(*b*)	ALMITRINE GROUP				
1	L	23	36	40	30
	R	25	—	41	38
2	L	33	38	46	37
	R	31	39	45	37
3	L	38	—	47	41
	R	37	41	49	42
4†	L	35	40	46	42
	R	42	47	48	43
5	L	37	53	48	48
	R	33	—	48	49

*Lower limit of motor conduction velocities 40 m/s, sensory conduction velocities 30 m/s.[15] — indicates absence of action potential.
†Denervation evident from muscle sample at 18 months.

incidence of both clinical and electrophysiological abnormalities in the peripheral nerves of patients receiving almitrine. Only two of the 12 patients had electrophysiological evidence of neuropathy on entry into the study, a considerably lower proportion than the 60–87% reported in some French and North American studies of hypoxaemic patients with chronic bronchitis.[11 16 17]

No patient who received placebo showed clinical evidence of peripheral neuropathy, though patient A developed the carpal tunnel syndrome. Electrophysiological studies of nerve function before treatment in this group showed a sensory nerve abnormality in one patient only (patient A), though two other patients had borderline normal lower limb motor conduction. Over the 12 months two patients showed a reduction in motor conduction velocities below the normal values in the right lateral popliteal nerves. No lower limb sensory nerve abnormalities developed during the study (patient A showed an improvement in sural nerve function). Upper limb nerve studies gave normal results before and after the 12 month period in all patients except the one who developed the carpal tunnel syndrome.

None of the patients in the almitrine group had clinical evidence of peripheral neuropathy at the start of the study; three developed symptoms and signs of peripheral neuropathy during the study and a fourth after 18 months' almitrine treatment. In one patient this was of sufficient severity to warrant withdrawal from the study at nine months.

In the five patients receiving almitrine the results of nerve conduction studies were abnormal in only one patient and borderline in a second at the start of the study. After almitrine treatment neurophysiological studies gave abnormal results in all five patients, although not until 18 months in patient 4. In patient 5, who did not have clinical neuropathy, only the right sural nerve action potential was lost and the significance of this is not clear.

Why patients with chronic bronchitis develop peripheral neuropathy is unknown. A relationship may exist between the duration of the hypoxaemia, its severity, and symptoms of neuropathy,[10 18] although this has been questioned.[8 9] Hypoxaemia producing impairment of axonal transport mechanisms in long nerve fibres has been suggested,[19 20] and this may explain why only lower limb abnormalities were detected before and after the study (if we exclude the patient with the carpal tunnel syndrome).

Poor nutrition leading to vitamin deficiencies has been suggested as a factor, although the evidence for this is poor.[9] Hydrocyanic acid and carbon monoxide from tobacco smoke may be important.[11 16] Our patients did not claim to have reduced their tobacco consumption before entering the study, so smoking seems unlikely, given their carboxyhaemoglobin concentrations, to have been the cause of their neuropathy.[21] People who smoke are more likely to have a high intake of alcohol, a well recognised neurotoxin.[22] National variations in the amount of alcohol ingested may explain differences in the reported incidence of peripheral neuropathy between countries. All of our patients, however, denied alcohol abuse, and had normal γ glutamyl transferase activity and mean corpuscular volumes, making alcohol an unlikely cause of the peripheral neuropathy. Drugs used in the management of patients with chronic bronchitis are rarely associated with the development of neuropathy[23 24] and a detailed drug history was unhelpful. The additional investigations we carried out failed to identify any cause for the neuropathy.

Only one other study has addressed the importance of underlying neuropathy in patients with chronic bronchitis taking almitrine. Lerebours *et al* enrolled 22 patients with chronic bronchitis and emphysema in an open study of almitrine 50 mg twice daily. At the time of publication 13 had completed one year's treatment; none had developed either clinical or electrophysiological neuropathy.[25] Unfortunately changes in arterial blood gas tensions and blood almitrine concentrations were not given and lower limb sensory potentials, which are probably more sensitive in detecting early changes, were not measured.

From the small number of patients we studied we cannot say for certain that the peripheral neuropathy was caused directly by almitrine, but almitrine seems likely to have acted as the precipitating agent in patients predisposed to the condition, perhaps by hypoxaemia. Peripheral neuropathy, however, has been reported in six patients who were taking almitrine combined with raubasin for "chronic cerebrovascular insufficiency" and who had no evidence of chronic respiratory disease and presumably were not hypoxaemic.[26] Interestingly, the four patients who developed peripheral neuropathy had relatively high mean blood almitrine concentrations and the neuropathy developed earliest in the man with the highest concentration. This suggests that the blood concentration of almitrine achieved with treatment, especially if it continues to rise, may be relevant to the development of neuropathy.

Our initial clinical examination did not identify which patients might be at risk of developing neuropathy and neurophysiological studies identified a pre-existing abnormality in only one of the four patients receiving almitrine who developed peripheral neuropathy. Detailed nerve conduction studies are time consuming for both patient and operator and are not available in many hospitals. There seems to be no strong indication for undertaking these as a routine before starting treatment with almitrine.

Almitrine appears to be effective in partially correcting the hypoxaemia of severe chronic bronchitis and is potentially an important therapeutic option. Patients should be questioned and examined for evidence of neuropathy before starting almitrine and if lower limb paraesthesia develops the drug should be stopped immediately. Rapid resolution of the symptoms is unlikely to occur because of the long half life of almitrine.[27] Maintaining blood almitrine concentrations below 400 ng/ml may prevent the development of neuropathy and the results of studies using regimens designed to achieve this are awaited.

We wish to thank Dr C P Chandrasekera for performing and interpreting the nerve conduction studies and Servier Laboratories for providing the almitrine and analysing the serum concentrations and for giving financial support.

References

1 Arnaud F, Bertrand A, Charpin J, *et al.* Almitrine bismesylate in long term treatment of patients with chronic bronchitis at the stage of chronic respiratory insufficiency. A multicentre double-blind placebo controlled study. *Clin Respir Physiol* 1982;**18**(suppl 4): 373–82.

2 De Backer W, Vermeire P, Bogaert E, Janssens E, Van Maele R. Almitrine has no effect on gas exchange after bilateral carotid body resection in severe chronic airflow obstruction. *Clin Respir Physiol* 1985;**21**: 427–32.

3 Stradling JR, Nicholl CG, Cover D, *et al.* Pattern of breathing and gas exchange following oral almitrine bismesylate in patients with chronic obstructive pulmonary disease. *Eur J Respir Dis* 1983;**64**(suppl 126);255–64.

4 Melot C, Naeiji R, Rothchild T, Mertens P, Mols P, Hallemans R. Improvements in ventilation-perfusion matching by almitrine in COPD. *Chest* 1983;**83**: 528–33.

5 Chedru F, Nodzenski R, Dunand JF, *et al.* Peripheral neuropathy during treatment with almitrine. *Br Med J* 1985;**290**:896.

6 Cherardi R, Louarn F, Benvenuti C, *et al.* Peripheral neuropathy in patients treated with almitrine dimesylate. *Lancet* 1985;i:1247–9.

7 Allen MB, Prowse K. Peripheral neuropathy during treatment with almitrine. *Br Med J* 1985;**290**:1288.

8 Kinsman RA, Yaroush RA, Fernandez E, Dirks JF, Schocket M, Fukuhara J. Symptoms and experiences in chronic bronchitis and empysema. *Chest* 1983;**83**:755–61.

9 Appenzeller O, Parkes RD, MacGee J. Peripheral neuropathy in chronic disease of the respiratory tract. *Am J Med* 1968;**44**:873–80.

10 Narayan M, Ferranti R. Nerve conduction impairment in patients with respiratory insufficiency and severe hypoxaemia. *Arch Phys Med Rehabil* 1978;**59**:188–92.

11 Faden A, Mendoza E, Flynn F. Subclinical neuropathy associated with chronic obstructive pulmonary disease. *Arch Neurol* 1981;**38**:639–42.

12 Suggett AJ, Jarratt JA, Proctor A, Howard P. Almitrine and peripheral neuropathy. *Lancet* 1985;ii:830–1.

13 Alani SM, Twomey JA, Peake MD. Almitrine and peripheral neuropathy. *Lancet* 1985;ii:1251.

14 Goodgold J, Eberstein A. *Electrodiagnosis of neuromuscular diseases*. 3rd ed. London: Williams and Wilkins, 1983.

15 Behse F, Buchthal F. Normal sensory conduction in the nerves of the leg in man. *J Neurol Neurosurg Psychiatry* 1971;**34**:404–14.

16 Paramelle B, Vila A, Stoebner P. Peripheral neuropathies and chronic hypoxaemia in chronic obstructive lung disease. *Eur J Respir Dis* 1986;**69**(suppl 146):715.

17 Moore N, Lerebours G, Senant J, Ozenne G, David PH, Nouvet G. Peripheral neuropathy in chronic obstructive lung disease. *Lancet* 1985;ii:1311.

18 Valli G, Barbieri S, Sergi P, Fayoumi Z, Berardinelli P. Evidence of motor neuron involvement in chronic respiratory insufficiency. *J Neurol Neurosurg Psychiatry* 1984;**47**:1117–21.

19 Cavanagh JB. The problems of neurons with long axons. *Lancet* 1984;i:1284–7.

20 Spencer PS, Sabri MI, Schaumburg HH, Moore CL. Does a defect of energy metabolism in the nerve fibre underlie axonal degeneration in polyneuropathies? *Ann Neurol* 1979;**5**:501–7.

21 Gasnault J, Moore N, Arnaud F, Rondot P. Peripheral neuropathies during hypoxaemic chronic obstructive airways disease. *Clin Respir Physiol* 1987;**23**(suppl 11):199–202.

22 Emirgil C, Sobol BJ, Heymann B, Shibutani K. Pulmonary function in alcoholics. *Am J Med* 1974;**57**:69–77.

23 Argov Z, Mastaglia FZ. Drug induced peripheral neuropathies. *Br Med J* 1979;**i**:663–6.

24 Lane RJM, Routledge PA. Drug induced neurological disorders. *Drugs* 1983;**26**:124–47.

25 Lerebours G, Senant J, Moore N, *et al.* Evolution of peripheral nerve function in hypoxaemic COPD patients taking almitrine bismesylate: a prospective study. *Clin Respir Physiol* 1987;**23**(suppl 11):203–6.

26 Louarn F, Gherardi R. Almitrine and peripheral neuropathy. *Lancet* 1985;ii:1068.

27 Campbell BD, Gordon B, Taylor A, Williams J. The biodisposition of almitrine bismesylate in man: a review. *Eur J Respir Dis* 1983;**64**(suppl 126):337–48.

28 Cotes JE. *Lung function: assessment and application in medicine*. 4th ed. Oxford: Blackwell, 1979.