Lack of effect of inhaled morphine on exercise-induced breathlessness in chronic obstructive pulmonary disease

A R Masood, J W Reed, S H L Thomas

Abstract

Background **– Inhaled nebulised morphine may reduce breathlessness in patients with lung disease, although the results of controlled trials are conflicting. A direct action of morphine on the lung has been postulated. This study aimed to investigate whether nebulised morphine reduced exercise-induced breathlessness in patients with chronic obstructive pulmonary disease (COPD) and to determine if this was a local pulmonary effect or occurred after systemic morphine absorption.**

Methods **– A double blind, randomised, crossover study was performed in 12 men with COPD to compare the effects of nebulised morphine (10 and 25 mg), equivalent intravenous doses (1 and 2·5 mg), and placebo. Breathlessness (visual analogue scale), ventilation, gas exchange, and exercise endurance were measured during graded bicycle exercise.**

Results **– None of the treatments altered breathlessness, ventilation, or gas exchange at rest or at any time during exercise, and exercise endurance was unaffected. At peak exercise mean (95% CI) changes from placebo in ventilation were −0·8 (−0·57 to 1·1) l/min and −0·4 (−2·8 to 2·0) l/min for the highest intravenous and nebulised doses, respectively. For breathlessness equivalent values were +2 (−5 to 9) and +1 (−9 to 11) mm. The study was of sufficient power that it is unlikely that a clinically important effect was missed.**

Conclusions **– Nebulised morphine in these doses has no effect on exercise-induced breathlessness. These findings do not support the hypothesis that intrapulmonary opiates modulate the sensation of breathlessness in patients with COPD.**

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Keywords: inhaled morphine, breathlessness, chronic obstructive pulmonary disease.

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Breathlessness is a common and distressing symptom which often persists in spite of maximum treatment directed at the underlying cardiac or respiratory disorder. A common cause in the United Kingdom is chronic obstructive pulmonary disease (COPD) which causes disabling breathlessness in many patients in spite of optimal treatment with steroids and bronchodilators. An effective symptomatic treatment for breathlessness would be of benefit in these patients. While various drugs have been shown to reduce breathlessness in the short term, evidence for long term benefit is lacking and their use is often limited by adverse effects.

It has been reported that the inhalation of morphine can reduce breathlessness in patients with cancer-associated dyspnoea.[1–3] Controlled trials of its effects on exercise-induced breathlessness or exercise endurance involving patients with COPD or healthy volunteers have given conflicting results.[4–7] Clarification of the effects of inhaled opiates is worthwhile because this form of treatment may be associated with less of the adverse effects that limit the use of systemic drugs. Positive results would also raise the possibility that endogenous intrapulmonary opiates modulate the sensation of breathlessness in man.

This study was therefore performed to test the hypothesis that inhaled morphine reduces breathlessness induced by exercise in patients with COPD as a result of a local action of the drug within the lung.

Methods

SUBJECTS

Twelve men with stable but severe COPD associated with disabling breathlessness were recruited from medical clinics in Newcastle. Inclusion criteria were: age 18–80 years, exercise tolerance and activities of daily living limited by breathlessness, and forced expiratory volume in one second (FEV_1) <1·5 l or FEV_1/forced vital capacity (FVC) ratio <50%. Patients who had experienced an exacerbation requiring antibiotics, change in oral steroid dose, or hospital admission within two months of the study were excluded. Also excluded were patients with overt cardiac disease, those in whom exercise testing was contraindicated, those with an arterial P_{CO_2} greater than 7·0 kPa within the previous two months, and those who had used systemic opiates, benzodiazepines or any other sedative agent other than alcohol within one month of the study. Each subject had at least two "dry run" exercise tests before taking part in the study to assess their exercise tolerance and to familiarise them with the equipment and procedure.

STUDY DESIGN

A double blind crossover study was performed which consisted of five separate experiments each separated by at least 48 hours. Ex-

periments were performed at the same time of day and with the same relationship to meals for each subject. The five treatments, given in random order, were placebo (intravenous and nebulised), nebulised morphine 10 mg (with intravenous placebo), nebulised morphine 25 mg (with intravenous placebo), intravenous morphine 1 mg (with nebulised placebo), and intravenous morphine 2·5 mg (with nebulised placebo). Intravenous doses were designed to give similar or greater plasma morphine levels than those after the nebulised morphine doses, assuming absorption from the inhaled route was 10% of the nebuliser dose or less.

The research was carried out in accordance with the declaration of Helsinki (1989) and was approved by the local ethical committee. The study was designed to give a 90% chance of detecting a 25% change in breathlessness at the $p<0·05$ level. Assuming that breathlessness could be measured with a within subject coefficient of variation of 20%, as found in other studies,[8] power calculations indicated that 12 subjects would be required.

EXPERIMENTAL PROTOCOL

An intravenous cannula was inserted for intravenous administration of morphine and placebo and for blood sampling. FEV_1 and vital capacity (VC) were measured using a Vitalograph and peak expiratory flow rate (PEFR) was measured using a Wright's peak flow meter before drug administration. Subsequently each patient received 2·5 mg nebulised salbutamol to standardise the time between the last dose of bronchodilator and the exercise test. Nebulised morphine or placebo was given over 10 minutes via a System 22 nebuliser (Medic-Aid, Pagham, Surrey, UK) driven by compressed air at a flow rate of 6 l/min. This produces particles of mass median diameter 3·1–4·9 μm (an appropriate size for bronchial drug deposition) and total pulmonary deposition of about 4–6% of the nebuliser dose.[9] Intravenous morphine or placebo was given over the final five minutes of nebulisation. Measurements of respiratory function were repeated five minutes after salbutamol and 10 minutes after the completion of administration of intravenous and nebulised morphine or placebo.

EXERCISE TEST

Subjects were seated on a braked cycle ergometer (Neuberger Lode NV, Groningen, Holland) and connected to the measuring apparatus 15 minutes after administration of morphine or placebo. Inhalation was from room air via a low deadspace (60 ml) low resistance mouthpiece. Ventilation and respiratory rate were measured using a vane anemometer (PK Morgan, Chatham, Kent, UK). Oxygen and carbon dioxide content of mixed expired gases were measured by infrared carbon dioxide and paramagnetic oxygen analysers (PK Morgan) and used to calculate oxygen consumption ($\dot{V}O_2$), carbon dioxide production ($\dot{V}CO_2$), and respiratory exchange ratio (RER). Arterial oxygen saturation (SaO_2) was measured using an ear oximeter (BTI Biox IIA, Boulder, Colorado, USA) after preparation of the ear with rubefacient cream. Blood pressure was recorded using a non-invasive automated sphygmomanometer (Infrasonde D4000B, Puritan-Bennett Corp, Los Angeles, California, USA) and heart rate (HR) was measured by electrocardiography. Breathlessness was quantified using a 10 cm horizontal linear visual analogue scale, the extremes of which were labelled "not at all breathless" (0 mm) and "extremely breathless" (100 mm). All apparatus was calibrated before each exercise test. Measurements of heart rate, expired gases, and ventilation were averaged over one minute periods. Discrete measurements of blood pressure, oxygen saturation, and breathlessness were obtained at the end of each minute.

After connection to the apparatus measurements were taken over a two minute rest period. Exercise commenced at zero workload and increased in 5 or 10 W increments every two minutes until symptom limitation. The incremental increases were chosen for each subject taking into account their exercise tolerance during their "dry runs". The intention was that, in the absence of active treatment, exercise would last for 6–10 minutes before symptom limitation occurred. Exercise was discontinued on the following grounds: symptom limitation or at the request of the subject, chest pain, persistent ST segment depression, cardiac arrhythmia, or fall in exercise blood pressure.

The principal end points of the study were ventilation and breathlessness at rest and predefined points during exercise which were at oxygen uptakes of 0·5 and 0·75 l/min, at 50% and 80% of the maximum exercise tolerance after placebo administration, at the highest equivalent workload (the highest workload that each subject consistently achieved in all five exercise tests), and at peak exercise (the highest workload achieved in each individual test). Other end points were change in exercise endurance and cardiovascular and gas exchange measurements at rest and during exercise.

Blood samples were taken via the intravenous cannula for measurement of morphine levels before administration of intravenous or nebulised drug and before and immediately after the exercise test. Plasma was separated immediately by centrifugation and samples stored frozen at −80°C until analysis for plasma levels of morphine. This was done by high pressure liquid chromatography (HPLC) using a 25 cm C18 column (Spherisorb SSODS1, Fisons, Loughborough, UK) and a fluorescence detector (Hewlett Packard 1046A, Palo Alto, California, USA) set for excitation at 210 nm and emission at 335 nm. Nalorphine was used as an internal standard. The assay has a limit of detection for morphine (as base) of approximately 1 ng/ml and coefficients of variation of 7·6% at 20 ng/ml and 5·8% at 30 ng/ml.

DATA ANALYSIS

Comparisons were made between treatments using a repeated measures analysis of variance

Table 1 Characteristics of the patients with COPD

Patient no.	*Age*	*Smoker*	*Pack years*	*FEV_1 (l)*	*FVC (l)*	*P_{O_2} (kPa)**	*P_{CO_2} (kPa)**	*Drug therapy*	*Associated conditions*
1	70	Ex	10	0·82	1·83	ND	ND	S, BDP, enalapril, bendrofluazide	Hypertension
2	59	Ex	52	0·84	2·15	8·7	4·1	S, BDP, T, quinine	
3	76	Ex	40	1·14	3·85	ND	ND	S, BDP, T, nifedipine, captopril	Hypertension
4	58	Yes	88	0·60	1·73	8·5	6·4	S, BDP	
5	68	Yes	120	0·68	1·94	11·1	4·9	S, BDP	
6	79	Ex	47	0·95	2·04	ND	ND	S, frusemide, amiloride, allopurinol	Oedema, gout
7	61	Ex	26	0·57	1·46	9·3	5·3	S, BDP, T	
8	68	Ex	48	0·40	1·45	7·2	6·6	S, IB, BDP, P, frusemide	Oedema
9	59	Ex	23	1·00	2·13	ND	ND	S	Asbestosis
10	69	Yes	67	0·83	1·44	ND	ND	S, IB, cimetidine	
11	69	Ex	26	1·21	2·92	8·6	5·5	S	
12	59	Yes	46	1·5	3·09	9·5	4·8	S, P, bendrofluazide	Hypertension

*Not during an acute exacerbation. On air.
S = salbutamol; IB = ipratropium bromide; BDP = beclomethasone dipropionate (each inhaled); T = theophylline; P = prednisolone (in stable dose); ND = not done.

Table 2 Mean (SE) plasma morphine levels following intravenous or nebulised morphine. A value of zero has been used for levels below the 1 ng/ml limit of detection in the assay

	Before exercise (ng/ml)	*After exercise (ng/ml)*
Nebulised 10 mg	2·5 (0·3)	1·7 (8·1)
Nebulised 25 mg	7·2 (2·3)	8·1 (2·3)
Intravenous 1·0 mg	10·5 (2·6)†	2·1 (1·4)
Intravenous 2·5 mg	25·0 (3·3)*†	24·3 (6·7)*†

†$p<0·05$ *v* 10 mg nebulised; *$p<0·05$ *v* 25 mg nebulised.

employing Duncan's multiple range tests and by calculating the means and 95% confidence intervals of the changes from placebo associated with each active treatment. Comparison of plasma morphine levels was by the non-parametric Wilcoxon signed rank test.

Results

Details of the patients and their clinical details are shown in table 1. All had severe exercise limitation as a result of COPD. In addition, three patients were receiving treatment for essential hypertension which in each case was controlled. One patient with prior asbestos exposure had some interstitial shadowing on the chest radiograph as well as calcified pleural plaques, and another patient had a small round lesion on the chest radiograph which was subsequently confirmed as a squamous carcinoma. All patients completed the study without serious adverse effects or intercurrent illness.

Neither inhaled nor intravenous morphine had a significant effect on FEV_1, VC, or PEFR, although small increases were seen after inhaled salbutamol in some of the patients (data not shown). Mean plasma levels of morphine taken before and after exercise were higher after 2·5 mg intravenous morphine than after 10 or 25 mg nebulised morphine. Levels following the 1 mg intravenous dose were higher than after the 10 mg nebulised dose (table 2).

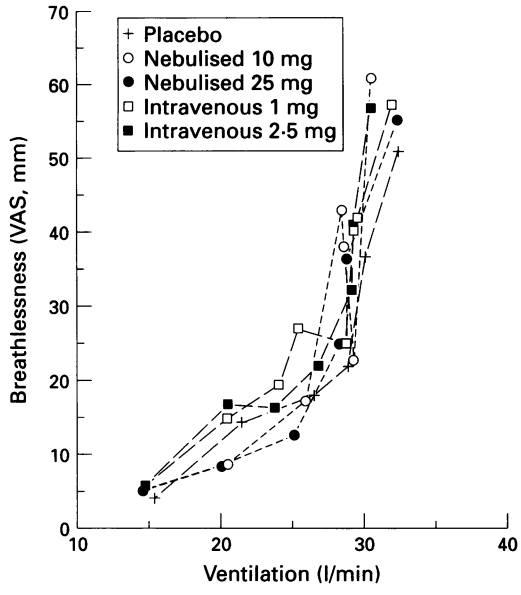
Exercise workload was increased in 10 W increments in four subjects and in 5 W increments in the remaining eight. Mean exercise duration overall was 7·9 minutes. The mean (SD) percentage changes from placebo in exercise duration after the various morphine treatments were not significantly different from zero or from each other (table 3). A mean 27% reduction in endurance after 25 mg nebulised morphine was not statistically significant and could be attributed to a single subject who exercised for a particularly short time after this treatment. No obvious intercurrent illness or other reason for this aberrant result was identified. Breathlessness occurred in all experiments and was considered by the patients to be the most important limiting factor in 51 of the 60 exercise tests. At peak exercise mean (SD) values were heart rate 110 (14) min^{-1}, respiratory frequency 35·7 (17·4) min^{-1}, $\dot{V}O_2$ 791 (235) ml/min, RER 0·89 (0·08), and Sa_{O_2} 93·7 (3·6)%. None of these variables was significantly affected by any of the morphine treatments at any point during the test.

Although small reductions in both $\dot{V}O_2$ and ventilation were observed at the predefined exercise levels with both inhaled and intravenous morphine, none of these was statistically significant and the relation between $\dot{V}O_2$ and ventilation was unaffected (data not shown). At no point during rest or exercise did any of the morphine treatments cause a significant change from placebo values in breathlessness and the relation between breathlessness and ventilation was unaffected (fig 1). For example, at peak exercise mean changes in ventilation (95% CI) from placebo were −0·7 (−3·4 to 1·8) and −0·8 (−5·7 to 1·1) l/min for the 1 mg and 2·5 mg intravenous doses and −2·1 (−4·7 to 0·4) and −0·4 (−2·8 to 2·0) l/min for the 10 mg and 25 mg nebulised doses. Equivalent values for breathlessness were +2 (−14 to 18) and +2 (−5 to 9) mm for the 1 mg and 2·5 mg intravenous doses and +6 (−5 to 16) and +1 (−9 to 11) mm for the

Table 3 Change in exercise endurance (compared with placebo) and symptom limitation with each treatment

		Morphine dose			
	Placebo	*1·0 mg iv*	*2·5 mg iv*	*10 mg nebulised*	*25 mg nebulised*
% Change in exercise endurance (95% CI)	0	−4 (−26 to 19)	−6 (−35 to 22)	−5 (−26 to 16)	−27 (−72 to 18)
Symptom limitation (n)					
Breathlessness	9	11	11	9	11
Leg pain	1	1	1	1	1
Dry mouth	2	0	0	2	0

All comparisons $p>0·05$.



Effects of nebulised and intravenous morphine on the relation between ventilation and breathlessness. Mean values for 12 patients at rest, 50% and 80% of maximum workload, $\dot{V}O_2$ values of 0·5 and 0·75 l/min, highest equivalent workload, and peak exercise.

10 mg and 25 mg nebulised doses. The 95% confidence intervals indicated that the study had sufficient power to detect reductions in ventilation of 2–6 l/min and in breathlessness of 8–18 mm depending on the treatment and exercise level. A reduction in ventilation at 50% maximal exercise was observed after the highest intravenous morphine dose. However, although the 95% confidence intervals of this change excluded zero, the change was not significant by analysis of variance and no significant effects were observed with this dose at other times during exercise.

Neither intravenous nor nebulised morphine caused any important adverse effects. Three of the 60 experiments were associated with light headedness, one involving placebo and two involving low dose inhaled morphine. A bitter taste was noted by one subject after low dose and two subjects after high dose nebulised morphine, but the other 10 subjects did not notice any taste differences.

Discussion

Various treatments have been used to try to alleviate breathlessness in patients with chronic lung disease but none has proved very useful. Benzodiazepines sometimes reduce breathlessness in the short term,[10] but benefit was not maintained during chronic therapy which frequently causes unacceptable drowsiness[11,12] and mild hypercapnia.[13] The phenothiazine promethazine reduced breathlessness and improved exercise tolerance slightly in one study[14] but not in another.[15] The opiates dihydrocodeine and morphine, given orally, have reduced breathlessness,[16,17] although other studies have failed to document benefit after buprenorphine,[16] codeine,[15] diamorphine,[18] or dextromethorphan,[19] and the high morphine doses needed to reduce breathlessness in one study caused disinhibited speech and drowsiness.[17] Thus, a clinically useful and safe treatment for the symptom of breathlessness remains elusive.

Nebulised morphine has been used for several years to relieve dyspnoea caused by cancer and there are several reports claiming benefit.[1–3] Although these were based on uncontrolled observations, a double blind controlled clinical trial performed in patients with chronic lung disease did demonstrate a 35% improvement in exercise endurance after 5 mg nebulised morphine.[4] It was suggested that this improvement might be due to a reduction in breathlessness, although this was not measured directly. The effect was unlikely to be caused by systemic absorption of the nebulised dose because delivery to the respiratory tract would be only a fraction of the 5 mg nebuliser dose, and other studies have indicated that the systemic doses required to affect ventilation or breathlessness in an average adult range from 5 to 50 mg.[20–24] Two other studies have failed to detect an effect on exercise endurance after up to 10 mg nebulised morphine in patients with chronic lung disease.[5,6] In one of these a trend towards increased exercise endurance was noted for 10 mg morphine but was not statistically significant and not associated with a reduction in breathlessness.[5] In the other study[6] 10 mg morphine had no effects but 4 mg of the more potent metabolite morphine-6-glucuronide (M6G) increased exercise endurance by 22% without significantly affecting six minute walking distance, maximum $\dot{V}O_2$, or ventilation. Effects on breathlessness were not reported. These findings suggest that to reduce breathlessness or increase exercise endurance higher doses of inhaled morphine, more potent opiates, or those which persist in the lung for longer may be needed.

A preliminary study in healthy volunteers did not demonstrate an effect of up to 25 mg nebulised morphine on breathlessness or ventilation,[7] neither were adverse effects on ventilation or lung function observed. The latter was an important observation as, in theory, inhaled morphine might provoke pulmonary histamine release and bronchospasm. The possibility remained that the regimen would only reduce pathological breathlessness so it was logical to perform a controlled trial in the same type of patients as those used in the study by Young *et al*,[4] recruiting those whose breathlessness was sufficiently severe that symptomatic treatment would be considered if it was available.

The main objective of the study was to establish if nebulised morphine affected breathlessness and the breathlessness-ventilation relationship during exercise. A graded rather than steady state exercise protocol was chosen so that measurements of breathlessness could be made over a range of ventilation and $\dot{V}O_2$ levels. This is not possible using a steady state exercise protocol, although the latter is probably a closer reflection of the type of exercise usually undertaken by patients with COPD. If a reduction in breathlessness had been observed, it would have been appropriate to carry out a steady state exercise or six minute walk

tests to establish if it was associated with a useful clinical improvement.

Breathlessness was measured using the well established visual analogue scale method which is both sensitive[25] and reproducible.[26-28] Inhaled morphine was delivered using a nebuliser with well documented output characteristics. This was expected to deliver at least as high a proportion of the nebuliser dose to the lungs as that used in the study by Young *et al.*[4] To ensure adequate delivery and to test for possible dose-response effects, the morphine nebuliser doses used in this study were up to five times higher than those previously employed.[4] Subjects were exercised starting 15 minutes after morphine administration. This interval appeared to be suitable because it was the same as that used in the previous study and is sufficiently long for peak plasma morphine levels to be obtained after nebulisation.[29 30]

The experiments were designed so that it could be established if effects on breathlessness were the result of pulmonary or central morphine actions. Using the System 22 Acorn nebuliser 10–15% of the dose is inhaled and about 5% deposited in the lungs.[9] It was estimated that the systemic absorption of a nebuliser dose would be 10% or less, an estimate supported by the recent measurement of nebulised morphine bioavailability of 4–8%.[31] Using these figures the highest nebulised dose of morphine used in these studies would deliver a systemic dose of less than 2·5 mg, which was the highest intravenous dose. Plasma morphine levels taken before and after the exercise test support this estimate. If this nebulised dose had reduced breathlessness while the highest intravenous dose did not, this would be firm evidence that the effect was local rather than systemic.

The results showed no effect of inhaled or intravenous morphine on the principal end points of ventilation or breathlessness during exercise, nor were changes in heart rate and gas exchange detected. The reproducibility of results in these studies was not quite as good as in previous reports, perhaps because of day to day variation in the patients' clinical condition as reflected by their exercise tolerance. Nevertheless, at peak exercise the study had the power to detect as significant reductions of 7–11% for ventilation and 12–28% for breathlessness following administration of placebo. While the study may have missed smaller reductions in breathlessness than these, it is unlikely that these would be of much clinical value.

The results do not support the hypothesis that inhaled morphine has an intrapulmonary action and are consistent with the recent studies which failed to detect an effect with up to 10 mg nebulised morphine in similar patients.[5 6] Our findings indicate that doses up to 25 mg are ineffective, although higher doses still may merit further assessment. The negative results are also consistent with the observation that intravenous naloxone does not affect breathlessness or exercise endurance in patients with COPD.[32] This suggests that endogenous opiates, either central or pulmonary, are not important in modulating breathlessness during exercise in these patients. The result is also consistent with the finding that anaesthesia of the airways, which is presumably associated with non-specific blockade of intrapulmonary neurones, does not reduce breathlessness in patients with interstitial lung disease.[33]

The possibility remains that nebulised morphine may reduce breathlessness if given in still higher doses or to other patient groups. Further studies using higher doses, more potent opiates or those which, because of their physical properties, persist within the lung for longer, would be worthwhile.

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1 Ahmedzai S. Respiratory distress in the terminally ill patient. *Respir Dis Practice* 1988;Oct/Nov, 20–9.
2 Farncombe M, Chater S. Case studies outlining use of nebulised morphine for patients with end-stage chronic lung and cardiac disease. *J Pain Symptom Management* 1993;**8**:221–5.
3 Tooms A, McKenzie A, Grey H. Nebulised morphine. *Lancet* 1993;**342**:1123–4.
4 Young JH, Daviskas E, Keena VA. Effect of low dose nebulised morphine on exercise endurance in patients with chronic lung disease. *Thorax* 1989;**44**:387–90.
5 Beauford W, Saylor TT, Stansbury DW, Avalon K, Light RW. Effects of nebulised morphine sulfate on exercise tolerance of the ventilatory limited COPD patient. *Chest* 1993;**104**:175–8.
6 Davis C, Hodder C, Love S, Shah R, Slevin M, Wedzicha J. Effect of nebulised morphine and morphine-6-glucuronide on exercise endurance in patients with chronic obstructive pulmonary disease (abstract). *Thorax* 1994;**49**:393P.
7 Masood AR, Subhan F, Reed JW, Thomas SHL. Effects of inhaled nebulised morphine on ventilation and breathlessness during exercise in healthy man. *Clin Sci* 1995;**88**: 447–52.
8 Mador MJ, Kufel TJ. Reproducibility of visual analogue scale measurements of dyspnea in patients with chronic obstructive pulmonary disease. *Am Rev Respir Dis* 1992; **145**:82–7.
9 Thomas SHL, O'Doherty MJ, Page CJ, Nunan TO. Variability in the pulmonary deposition of a nebulised aerosol in man. *Clin Sci* 1991;**81**:767–75.
10 Mitchell-Heggs P, Murphy K, Minty K, Guz A, Patterson SC, Minty PSB, *et al.* Diazepam in the treatment of dyspnoea in the 'pink puffer' syndrome. *Q J Med* 1980; **193**:9–20.
11 Woodcock AA, Gross ER, Geddes DM. Drug treatment of breathlessness: contrasting effects of diazepam and promethazine in pink puffers. *BMJ* 1981;**283**:343–6.
12 Mann GCW, Hsu K, Sproule BJ. Effect of alprazolam on exercise and dyspnoea on patients with chronic obstructive pulmonary disease. *Chest* 1986;**90**:833–6.
13 Shiveram U, Cash M, Finch P. Acute effects of alprazolam on gas exchange, work of breathing and exercise tolerance in severe emphysema (abstract). *Chest* 1987;**92**:82S.
14 Woodcock AA, Gross ER, Gellert A, Shah S, Johnson M, Geddes DM. Effects of dihydrocodeine, alcohol, and caffeine on breathlessness and exercise tolerance in patients with chronic obstructive lung disease and normal blood gases. *N Engl J Med* 1981;**305**:1611–6.
15 Rice KL, Kronenberg RS, Hedemark LL, Niewoehner DE. Effects of chronic administration of codeine and promethazine on breathlessness and exercise tolerance in patients with chronic airflow obstruction. *Br J Dis Chest* 1987;**81**:287–92.
16 Johnson MA, Woodcock AA, Geddes DM. Dihydrocodeine for breathlessness in 'pink puffers'. *BMJ* 1983;**286**:675–7.
17 Light RW, Munro JR, Sato RI, Stansbury W, Fischer C, Brown SE. Effects of oral morphine on breathlessness and exercise tolerance in patients with chronic obstructive pulmonary disease. *Am Rev Respir Dis* 1989;**139**:126–33.
18 Eiser N, Denman WT, West C, Luce P. Oral diamorphine: lack of effect on dyspnoea and exercise tolerance in the 'pink puffer' syndrome. *Eur Respir J* 1991;**4**:926–31.
19 Giron AE, Stansbury DW, Fischer CE, Light RW. Lack of effect of dextromethorphan on breathlessness and exercise performance in patients with chronic obstructive pulmonary disease (COPD). *Eur Respir J* 1991;**4**:532–5.
20 Loeschke HJ, Sewell A, Kough RH, Lambertsen C. Effect of morphine and of meperidine (Dolantin, Demerol) upon the respiratory response of normal men to low concentrations of inspired carbon dioxide. *J Pharmacol Exp Ther* 1953;**108**:376–83.
21 Orkin LR, Egge RK, Rovenstine EA. Effect of Nisentil, meperidine and morphine on respiration in man. *Anesthesiology* 1955;**16**:699–707.
22 Weil JV, McCullough RE, Kline JS, Sodal IE. Diminished ventilatory response to hypoxia and hypercapnia after morphine in normal man. *N Engl J Med* 1975;**292**:1103–6.

23 Bourke DL, Warley A. The steady state and rebreathing methods compared during morphine administration in humans. *J Physiol* 1989;**419**:509–17.
24 Santiago TV, Johnson J, Riley DJ, Edelman NH. Effects of morphine on ventilatory response to exercise. *J Appl Physiol* 1979;**47**:112–8.
25 Aitken RCB. Measurement of feelings using visual analogue scales. *Proc R Soc Med* 1969;**62**:989–93.
26 Stark RD, Gambles SA, Chatterjee SS. An exercise test to assess clinical dyspnoea: estimation of reproducibility and sensitivity. *Br J Dis Chest* 1982;**76**:269–78.
27 Wilson RC, Jones PW. A comparison of the visual analogue scale and modified Borg scale for the measurement of dyspnoea during exercise. *Clin Sci* 1989;**76**:277–82.
28 Muza SR, Silverman MT, Gilmore GC, Hellerstein HK, Kelsen SG. Comparison of scales used to quantitate the sense of effort to breathe in patients with chronic obstructive pulmonary disease. *Am Rev Respir Dis* 1990;**141**: 909–13.
29 Masters NJ, Bennett MA, Wedley JR. Nebulised morphine: a new delivery method for pain relief. *Practitioner* 1985; **229**:649–53.
30 Chrubasik J, Wüst H, Friedrich G, Geller E. Absorption and bioavailability of nebulised morphine. *Br J Anaesth* 1988;**61**:228–30.
31 Davis C. Symptomatic management of breathlessness. Some of the more unusual pharmacological options. In: *Research aspects of the palliation of breathlessness*. Workshop, Royal Marsden Hospital and Institute of Cancer Research, October 1993.
32 Kirsch JL, Munro JR, Stansbury DW, Fischer CE, Manfore R, Light RW. Effect of naloxone on maximal exercise performance and control of ventilation in COPD. *Chest* 1989;**96**:761–6.
33 Winning AJ, Hamilton RD, Guz A. Ventilation and breathlessness on maximal exercise in patients with interstitial lung disease after local anaesthetic aerosol inhalation. *Clin Sci* 1988;**74**:275–81.

Adventitia

"Non-tuberculous mycobacteria"

I have been concerned for many years with some logical difficulties in discourse about mycobacterial diseases[1] and have concluded that some, at least, of this continued confusion arises from the adoption in the current nomenclature of mycobacteria of the specific name *tuberculosis* for the species most commonly associated with tuberculosis in the human subject. In colloquial discourse this organism has always been called the human tubercle bacillus with clarity and propriety, and it is regrettable that in the formal terminology of the mycobacteria this was not translated into Latin as *Mycobacterium hominis*. The increasing use of such absurd terms as "non-tuberculous mycobacteria" impels me to return to this theme.

We must surely accept that "tuberculosis" currently refers to a disease, in man or other animals, characterised by granulomatous changes caused by mycobacteria, and must not confuse this disease with its own cause. A diagnosis of tuberculosis places the patient in a category with defining characteristics in two fields – morbid anatomy and aetiology. A complete diagnostic statement would include identification of the causal mycobacterium. When a diagnosis of tuberculosis (unspecified) is made in man, it is an acceptable convention that the causal organism is thought, or has been shown, to be the human tubercle bacillus. In the days when disease caused by *Mycobacterium bovis* was important in man we referred to it as bovine tuberculosis, implying with perfect clarity disease caused by the species of mycobacterium most commonly causing disease in cattle. The adoption of the name *hominis* for the species most prevalent in the human race would have been logical and convenient, and would not have implied that only the disease caused by this species is properly called tuberculosis – leaving in limbo granulomatous diseases caused in man by other species of mycobacteria – and raising interesting logical questions about the nomenclature of granulomatous diseases caused by various species of mycobacteria in other animals.

Since tuberculosis is a compound diagnostic category with morbid anatomical and aetiological defining characteristics, the argument that epidemiological considerations justified the specific name *tuberculosis* for the mycobacterium most important in man was always weak since the aetiological term in the diagnostic label is evidently the one most relevant to epidemiology. Indeed, it was always recognised that the epidemiology of the disease caused in man by *M bovis* and uncontroversially called tuberculosis was epidemiologically distinct. I see no reason why it should not be proper to speak of tuberculosis caused by any species of mycobacterium. We may properly refer to non-tuberculous mycobacterial disease if we encounter one of the rare cases of acute mycobacteriosis causing only necrotic and non-granulomatous changes; but I see no logical justification for the ghastly term "non-tuberculous mycobacteria" which seems to imply mycobacteria that do not cause tuberculoid granulomatous changes. Presumably the excuse for this clumsy usage is that it is to be understood as referring to mycobacteria other than *M tuberculosis*. We should always be prepared to use a few extra words to express our meaning clearly and logically. If the human tubercle bacillus had been called *M hominis* we could refer to what I think (but am sometimes left uncertain) is intended by "non-tuberculous mycobacteria" as "mycobacteria other than *M hominis*" without unwanted implications.

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1 Scadding JG. Nomenclature of mycobacterial disease. *Am Rev Respir Dis* 1987;**136**:1308–9.