PAPERS AND SHORT REPORTS

Drug treatment of breathlessness: contrasting effects of diazepam and promethazine in pink puffers

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Abstract

Fifteen out of 18 "pink and puffing" patients completed a double-blind, placebo-controlled cross-over trial of diazepam and promethazine for breathlessness and reduced exercise tolerance. Dosages were 25 mg and 125 mg daily, respectively, and each course lasted two weeks. Patients with psychiatric or other major medical histories were excluded.

Of the three patients who did not complete the trial, one died during an exacerbation of breathlessness while taking diazepam, one was withdrawn because of mild hypercapnia while taking placebo, and one suffered intolerable drowsiness while taking diazepam. Of the remaining 15 patients, six needed a reduction in dosage because of drowsiness: one of these was taking promethazine and five diazepam. Diazepam had no effect on breathlessness and noticeably reduced exercise tolerance. Promethazine reduced breathlessness and improved exercise tolerance without altering lung function.

From these results diazepam is contraindicated for breathlessness and reduced exercise tolerance in fixed airways obstruction, but promethazine may be beneficial.

Introduction

Breathlessness and limitation of exercise tolerance in patients with chronic bronchitis and emphysema are variable and do not correlate well with abnormalities of lung function¹ or with the pathological findings at necropsy.² Among patients with fixed airways obstruction the "pink and puffing" type maintain a low or normal arterial carbon dioxide pressure (P_{aCO_2}) and a nearly normal oxygen pressure (P_{aO_2}) at the expense of extreme

breathlessness.³⁻⁵ Since attempts at improving lung function are relatively ineffective, there is a place for a safe remedy to relieve breathlessness.³⁻⁶ Preliminary studies indicated that diazepam might produce symptomatic relief of breathlessness and improvement of exercise tolerance in pink and puffing patients without altering resting blood gas values.⁷ Promethazine (a sedating antihistamine) may have an effect on exercise-induced breathlessness in normal subjects, whereas diazepam does not (R D Stark and S A Gambles, paper presented at SEPCR conference on breathlessness, Sheffield, August 1980; *Clin Sci*, in press). We have therefore conducted a randomised, double-blind placebo-controlled trial comparing the effects of diazepam and promethazine on breathlessness and exercise tolerance in 18 pink puffers. Including a second sedating drug made the trial more effectively blind.

Patients and methods

Eighteen patients (15 men) with severe chronic airways obstruction, moderate or severe breathlessness, and normal or low P_{aCO_2} entered the trial (table I). Patients with a current or past psychiatric or other major medical history were excluded. Of the nine patients aged over 65, four had retired prematurely owing to breathlessness. Of the nine patients aged under 65, seven were unable to work because of breathlessness and two were in sedentary occupations. All patients had smoked cigarettes (mean 41.6 pack-years, range 10-160 pack-years), though all had stopped smoking (mean 4.3 years before, range 6 months to 20 years), usually at the onset of breathlessness (5.1 years before, range 2-20 years). Thirteen patients had recently lost weight (mean current weight 56.4 kg, mean previous highest 62.2 kg).

Patients received diazepam 5 mg thrice daily and 10 mg (two tablets) at night, promethazine 25 mg thrice daily and 50 mg (two tablets) at night, or matched placebo over three consecutive two-week periods in a double-blind cross-over design. The treatments were given in randomised order. Any sedative drugs were withdrawn two weeks before the study. Patients were advised against driving, operating machinery, and drinking alcohol. Tablets were counted to ensure that correct dosages had been taken. Twice before the trial (practise and baseline) and at the end of each treatment period patients underwent the following investigations as day patients.

Respiratory measurements comprised peak expiratory flow rate (PEFR), forced expiratory volume in one second (FEV_1), and forced vital capacity (FVC).

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TABLE I—Details of patients (n=18) at entry to trial

	Mean	Range
Age (years)	60.5	39-72
Weight (kg)	56.4	35-76
Forced expiratory volume in one second	0.73	0.32-1.40
Forced vital capacity	25.3	14.1-43.8
Transfer coefficient (mmol/min/kPa/l)	2.68	1.55-4.30
Arterial oxygen tension, resting (kPa)	67.2	33.3-98.8
Arterial carbon dioxide tension, resting (kPa)	0.61	0.22-1.66
MRC dyspnoea grade	9.5	6.9-11.3
	4.6	3.8-5.4
	4.0	3-5

Conversion: SI to traditional units—Transfer coefficient: 1 mmol/min/kPa/l $\approx$ 3.0 mg/min/mm/Hg/l. Arterial oxygen and carbon dioxide tensions: 1 kPa $\approx$ 7.5 mm Hg.

Psychological scores were obtained with the Morbid Anxiety Inventory⁸ and Beck Depression Inventory.⁹ Both of these self-rating scales are reliable and valid, have high correlation with expert psychiatric assessment, and are sensitive to changes in the severity of anxiety and depression with time.

Bodily symptom scores were obtained with visual analogue scales.¹⁰ Subjective assessment of breathlessness was recorded as dyspnoea grade¹¹ and with an oxygen-cost diagram.¹¹

Walking distance was measured in a 12-minute walking test.^{12 13}

Treadmill test—Patients walked to exhaustion on a treadmill at the same work rate as the maximum that had been obtained in a progressive exercise test on a bicycle ergometer before the study.¹⁴ At this maximal work rate patients stopped after one to two minutes owing to severe breathlessness (maximal time to exhaustion). This feeling was used to define the upper end of a 10 cm visual analogue scale for breathlessness (range not breathless to extremely breathless). After 30 minutes' rest patients were asked to exercise on the treadmill at 30%, 50%, and 66.6% of their prestudy maximum work load in a progressive test with two minutes at each stage. The work load was changed by a progressive increase in speed at constant gradient. Patients were asked to score breathlessness on the visual analogue scale at rest, at the end of each stage, and again every minute for four minutes of the recovery period. We have investigated repeatability in visual analogue measurements of breathlessness during a progressive exercise test and during recovery in 14 normal subjects and 12 patients with stable chronic airways obstruction on four consecutive days. After excluding the first day exponential curves fitted to breathlessness scores ($r > 0.9$ in all subjects) were not significantly different within subjects for the subsequent three days.

Progressive exercise test on bicycle ergometer (AM 368 Siemens)—Patients were seated on the bicycle for five minutes before resting values were taken. Oxygen consumption, carbon dioxide production, and minute ventilation were measured by mass spectrometry (Centronics Ltd) using the concentration of injected gas (argon) as a measure of flow.¹⁵ Heart rate was counted from an electrocardiogram, and resting and maximal exercise arterialised capillary ear-lobe blood gas tensions measured with a blood gas analyser (165 Corning Medical). External work load was increased by 100 kilopond metres/minute (kpm/min) every minute until exhaustion. The total work load to exhaustion was calculated.

The tests were performed in the same order at each attendance and at least one hour's rest was enforced between exercise tests. Throughout the trial patients performed daily measurements of PEFR and completed a daily symptom score by visual analogue scales. Measurements from the first week of each treatment period were discarded and only results from the second week of each period analysed. Statistical analysis was by a sign test comparing individual patient's results during the three treatment periods. Groups of parameters were compared using Fisher-Yates's ranking analysis. Only the results in the 15 patients who completed the trial were analysed.

Results

Table II shows the effects of the three agents on the values studied.

Compliance and side effects—Three patients did not complete the trial. One patient with the worst pulmonary function on entry (FEV₁ 0.32 l, FVC 1.55 l, Pao₂ 9.1 kPa (68.4 mm Hg), Paco₂ 4.7 kPa (35.3 mm Hg)) died after an acute exacerbation of breathlessness while receiving diazepam during the first treatment period. One patient withdrew from the trial because of intolerable drowsiness while taking diazepam. One patient was withdrawn when he was noted to be hypercapnic at the end of the first period when he had been receiving

placebo (Paco₂ 5.4 kPa (40.6 mm Hg) at the beginning of the period, 5.7 kPa (42.3 mm Hg) at the end). Although the rise in Paco₂ was only modest, we thought it unsafe to continue in this patient. During the trial many patients complained of drowsiness. While most patients continued after reassurance, in six the drowsiness was intolerable and the dosage of tablets had to be reduced in blind fashion from five to two daily. Five incidents were reported by patients that were related

TABLE II—Effects of three agents on values studied. Results are means

	Promethazine	Placebo	Diazepam
Daily peak expiratory flow rate (l/s)	211	201	192
Forced expiratory volume in one second (l)	0.77	0.75	0.76
Forced vital capacity (l)	2.76	2.69	2.76
Anxiety score	12.6	11.5	13.7
Depression score†	18.1	19.3	22.8
Drowsiness score	3.76	2.50	4.83*
Dyspnoea grade	3.29*	4.00	3.46
Oxygen-cost diagram	56	54	50
Daily breathlessness score (cm)	5.1	5.3	5.3
Walking distance in 12 minutes (m)	707*	675	642*
Time to exhaustion on treadmill (s)	139	129	108
Total work load on bicycle ergometer (kpm)	740	705	680
Minute ventilation, resting (l/min)	13.93	13.22	12.12
Oxygen consumption, resting (ml/min)	325	319	309
Carbon dioxide production, resting (ml/min)	285	280	269
Respiratory quotient, resting	0.86	0.88	0.87
Minute ventilation at maximum exercise (l/min)	29.17	27.14	26.26
Oxygen consumption at maximum exercise (ml/min)	801	749	703
Carbon dioxide production, maximum exercise (ml/min)	701	647	624
Respiratory quotient at maximum exercise	0.87	0.86	0.89
Arterial oxygen tension, resting (kPa)	9.4	9.4	9.1
Arterial carbon dioxide tension, resting (kPa)	4.5	4.6	4.7
Arterial oxygen tension at maximum exercise (kPa)	8.4	8.1	8.0
Arterial carbon dioxide tension at maximum exercise (kPa)	4.8	5.0	5.3*

* $p < 0.05$ compared with placebo.

† In psychiatric outpatients mean depression scores were: none/mild = 12.7;

moderate = 25.4; severe = 30.0.⁹

Conversion: SI to traditional units—Arterial oxygen and carbon dioxide tensions: 1 kPa $\approx$ 7.5 mm Hg.

to excessive drowsiness (falling down stairs; falling off motorcycle; two patients repeatedly overslept, and one was frequently late for work; one patient (engineer) was unable to continue at work in machinery instruction). Five of the six dosage reductions due to excessive drowsiness and all five drowsiness-related incidents occurred when the patients were taking diazepam. One dosage reduction occurred during the promethazine period and none during the placebo period.

Spirometry—There were no significant changes in FEV₁, FVC or PEFR.

FIG 1—Individual 12-minute walking distances and dyspnoea grades. Promethazine v placebo: $p < 0.05$. (Bars are means.)

Subjective assessment—There was a significant improvement in dyspnoea grade during the promethazine period as compared with during the placebo period (fig 1). A similar trend towards improvement was assessed by oxygen-cost diagram and daily visual analogue scores, though these did not achieve significance. Patients were significantly more drowsy when taking diazepam than when taking placebo. There was no significant difference in drowsiness between the placebo and promethazine periods or in anxiety and depression scores with any treatment.

Breathlessness—When individual breathlessness scores in each patient achieved with promethazine and diazepam were compared with those during the placebo period (sign test) there was a reduction in breathlessness after promethazine but no significant difference in breathlessness between the diazepam and placebo periods (promethazine < placebo = diazepam; $p < 0.001$) (fig 2). Alternatively, when the

FIG 2—Mean visual analogue scores of breathlessness at rest; at 33%, 50%, and 66% of each patient's maximum speed on the treadmill (two minutes at each stage); and at each minute during four minutes of recovery.

Fisher-Yates ranking analysis was applied to the mean values at each stage the p value against the null hypothesis of no difference was highly significant in favour of promethazine < placebo = diazepam ($p < 0.001$)—that is, patients were significantly less breathless when taking promethazine than when taking placebo.

Exercise tolerance—Patients walked a significantly greater distance in 12 minutes when taking promethazine and significantly less when taking diazepam than when taking placebo. This trend was paralleled in other measures of exercise tolerance (time to exhaustion on treadmill; total work load on bicycle ergometer; maximal ventilation) but did not achieve statistical significance. There were no significant changes with any treatment in resting ventilation, alveolar-arterial gas exchange, arterial desaturation, or metabolic gas exchange. Resting blood gas tensions and maximal exercise P_{aO_2} were unchanged but maximal exercise P_{aCO_2} was significantly higher during the diazepam period than during the placebo or promethazine period.

Discussion

Breathlessness is a major symptom of chronic lung disease and is often more distressing than the limitation of exercise tolerance. This is particularly so in pink and puffing patients with fixed airways obstruction, who maintain nearly normal blood gas tensions for many years at the cost of persistent breathlessness. Treatment aimed at improving lung function is largely ineffective and we therefore aimed for symptomatic relief of breathlessness. Attempts at symptomatic improvement with carbimazole¹⁶ and β_1 blockade¹⁷ were unsuccessful, and we were therefore encouraged by the preliminary work of Mitchell-Heggs *et al.*,⁷ which suggested that diazepam in the doses used in our study might reduce breathlessness and improve exercise tolerance in four pink and puffing patients.

Stark and Gambles (SEPCR conference on breathlessness, Sheffield, August 1980), who used similar methods to ours for assessing breathlessness by visual analogue scale in normal subjects exercising on a treadmill, reported that promethazine 25 mg in a single oral dose may reduce breathlessness but that oral diazepam 10 mg was ineffective. In our study diazepam caused a significant deterioration in exercise tolerance and had no effect on breathlessness at fixed work loads when compared with placebo. This is contrary to the findings of Mitchell-Heggs *et al.*,⁷ who reported a "striking reduction in dyspnoea and improvement in exercise tolerance." Two of their patients had early dementia, however, and one was depressed. Any improvement of breathlessness in a group of psychologically disturbed patients treated with an anxiolytic drug must be interpreted with caution. We deliberately excluded patients with a history of psychiatric illness. Mitchell-Heggs *et al.* also compared diazepam with placebo in an uncontrolled manner. It is impossible to blind the sedative effect of diazepam against placebo alone and we included a second sedating drug to make the trial effectively double-blind. In addition to reducing exercise tolerance, considerable morbidity was associated with diazepam. The only death during the study occurred when the patient with the worst pulmonary function was taking diazepam. Although the patient was tachypnoeic immediately before death, we cannot exclude the possibility that an inappropriate reduction in respiratory drive contributed to death. The use of diazepam in airways obstruction should be limited strictly to those few patients with extreme anxiety and low P_{aCO_2} .

We found a small but significant reduction in breathlessness and improvement in exercise tolerance with promethazine when compared with placebo. This was achieved without significant alteration of lung function or resting and exercise blood gas tensions. While we cannot completely exclude a small change in lung function, these results tend to confirm the suggestion that promethazine reduces the feeling of breathlessness. Many patients did complain of drowsiness while taking promethazine but this did not achieve statistical significance over the whole group, and only one dosage reduction was made during a promethazine period. Further investigation will find the dosage of promethazine that offers the maximum benefit with the least side effects, and other antihistamines must be studied.

We conclude that promethazine is beneficial for breathlessness and exercise tolerance in pink and puffing patients with fixed airways obstruction and does not alter lung function; but these benefits are slight and must be weighed against the disadvantages of drowsiness, which may be a problem in some patients. Diazepam failed to produce any benefit and, indeed, may be positively harmful and is contraindicated in patients with airways obstruction unless there is severe anxiety and a low P_{aCO_2} .

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SHORT REPORTS

Addiction to tranlycypromine

Psychiatrists recognise that patients taking tranlycypromine may develop psychological dependence and often have difficulty weaning them off even small doses of the drug. Some patients become addicted with a pronounced tendency to increase the dose. Neither Martindale¹ nor Goodman and Gilman² note the addictive properties of tranlycypromine. Since 1965 three cases of addiction have been reported.³⁻⁵ We describe four others.

Case reports

Case 1—A 33-year-old woman was admitted after prolonged abuse of Parstelin (tranlycypromine 10 mg, trifluoperazine 1 mg), culminating in an overdose of 40 tablets. Though initially lucid, 24 hours later she became hallucinated, confused, agitated, and aggressive. Over the next eight days she returned to normal. She had first suffered from depression at the age of 15, and had since had continuous psychiatric treatment. Personality disorder and depression were diagnosed. At the age of 25 Parstelin was started and before long she was taking 30 tablets daily. On at least two occasions she developed severe thrombocytopenic purpura due to the Parstelin abuse. All attempts at withdrawal from the drug were only temporarily successful.

Case 2—A 34-year-old schoolteacher was admitted complaining of addiction to Parstelin. He was taking 15 tablets daily, but had had some difficulty obtaining the drug, getting prescriptions from many different doctors. He had a history of three previous admissions for anxiety, depression, and alcoholism. On abstaining from Parstelin he suffered headaches, diarrhoea, and weakness and felt unable to cope with work. He also abused chlordiazepoxide, taking about 100 mg daily. While abusing Parstelin he did not drink alcohol. In hospital, on withdrawal, he complained of anxiety and depression. After discharge he immediately resumed Parstelin, taking up to 20 tablets daily.

Case 3—A 65-year-old man was admitted taking up to 30 Parstelin tablets daily. He had been taking Parstelin and chlordiazepoxide for 10 years and obtained prescriptions from many doctors. He stated that he felt well only when taking Parstelin. He had had treatment for alcoholism but since abusing Parstelin he had abstained from alcohol, stopped smoking, and worked effectively. After withdrawal from Parstelin and chlordiazepoxide he became tense, pacing around the ward all day. He was discharged drug free but soon resumed the Parstelin.

Case 4—A 39-year-old shopkeeper was admitted for depression and Parstelin abuse. He had obtained Parstelin and diazepam from numerous doctors and pharmacists. He took up to 20 Parstelin and 10 diazepam tablets daily, and without them felt unable to work. He was a shy, conscientious, obsessional man and had been a very heavy drinker. After admission and withdrawal from Parstelin he became restless and anxious and complained of generalised aches for 10 days, despite treatment with chlordiazepoxide and chlorpromazine. He showed no other withdrawal symptoms.

Comment

Addiction to tranlycypromine is not widely recognised and each of our patients received many prescriptions with relative ease. The addictive properties of tranlycypromine are not surprising in view of its close structural relation to amphetamine⁶ and its powerful effect in suppressing rapid-eye-movement sleep.⁴ All our patients showed a notably increased tolerance to tranlycypromine and three also showed abuse and increased tolerance of benzodiazepines. On abrupt withdrawal of Parstelin our first patient became hallucinated

and confused. This was probably a withdrawal state, as in the case of Ben-Arie and George,³ but intoxication could not be completely ruled out.

We wish to emphasise that tranlycypromine should be used with great care in dependence-prone patients, and doctors should be wary of requests for prescriptions of the drug. Withdrawal from high dosage of tranlycypromine should be gradual because of the danger of withdrawal psychosis.

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Damage to the tricuspid valve with a Swann-Ganz catheter

We report a case of damage to the tricuspid valve during preoperative insertion of a Swann-Ganz catheter. The lesion was discovered by visual inspection during the operation, which suggests that the incidence of undetected damage and its complications¹⁻³ might be greater than previously thought.

Case report

A 59-year-old woman with a history of rheumatic heart disease was admitted for elective aortic and mitral valve replacement and insertion of a tricuspid ring. Two months previously cardiac catheterisation had shown mixed mitral valve disease, predominantly stenosis and aortic insufficiency. The murmur of tricuspid incompetence could also be heard. Chest x-ray examination showed an enlarged left ventricle, right ventricle, and left atrium.

A pulmonary artery catheter was inserted for measurement of filling pressures and thermodilution cardiac outputs during the operation. A triple-lumen 7 FG flow-directed Swann-Ganz catheter (Instrumentation Laboratories) was inserted via the right cephalic vein in the antecubital fossa using a Cordis introducer. A cut-down had previously been performed on the right basilic vein, and the catheter was inserted at the right cephalic vein after failure to enter the chest using the left cephalic vein.

The catheter entered the chest easily, and as soon as it was in the superior vena cava the balloon was inflated and the pressure at the catheter tip