PAPERS AND SHORT REPORTS

Dihydrocodeine for breathlessness in "pink puffers"

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Abstract

Eighteen patients with severe breathlessness due to chronic airflow obstruction completed a randomised placebo controlled double blind cross over trial of the effect of dihydrocodeine 15 mg on breathlessness, disability, and exercise tolerance. There were three periods of one week each. During the first two weeks patients were instructed to take dihydrocodeine 15 mg or placebo 30 minutes before exercise as required up to three times daily. During the third week patients received either dihydrocodeine or placebo on alternate days. During the weekly dihydrocodeine period patients were more mobile (pedometer distance increased by 16·8%) and less breathless (daily visual analogue score of breathlessness reduced by 17·8%). This benefit was confirmed by treadmill testing at the end of each treatment period, when maximum distance walked was 16·5% higher and breathlessness 11·8% less after dihydrocodeine compared with placebo. Similar benefit in breathlessness occurred during alternate day treatment. No adverse effects were encountered.

Dihydrocodeine 15 mg 30 minutes before exercise offers appreciable benefit to patients with severe breathlessness due to chronic airflow obstruction.

Introduction

Breathlessness and reduction in exercise tolerance are the major complaints of patients suffering from chronic airflow obstruction. At present prescribed treatment is aimed at improving lung function with bronchodilators and steroids. This provides only slight benefit[1] and there is therefore a real need for treatment aimed at improving the breathlessness itself.

The sensation and mechanisms of breathlessness are not fully understood; however, an imbalance between a demand for ventilation and an inability of the respiratory system to satisfy that demand appears to be important. Many of the factors concerned in this balance may be altered by drugs, in particular by opiates. Morphine, for example, reduces the ventilatory response to carbon dioxide,[2] hypoxia,[3] inspiratory flow resistive loading,[4] and exercise.[5] Morphine also reduces oxygen consumption at rest and on exercise in normal subjects[5] and may in addition alter the central perception of breathlessness. We have previously shown that 45 minutes after a single dose of dihydrocodeine 1 mg/kg[6] breathlessness was reduced by 20% and exercise tolerance increased by 18% with a reduction of ventilation and oxygen consumption. In a double blind cross over trial[7] comparing dihydrocodeine 90 mg and 180 mg daily with placebo five of the 16 patients who entered the study had to withdraw owing to nausea or vomiting or both and most of the remaining patients suffered from constipation and drowsiness. For the group as a whole any potential benefit from the drug was more than offset by the adverse effects. There were, however, several patients in the trial who appeared to benefit from treatment, with a reduction in breathlessness and an increase in exercise tolerance. In further pilot laboratory studies we found that lower doses of dihydrocodeine were also effective.

In this study we assess the value of lower dose dihydrocodeine in the long term treatment of breathlessness.

Patients and methods

Nineteen patients entered the study. All had severe breathlessness (MRC dyspnoea grade $\geqslant 3$) and severe airflow obstruction (forced expiratory volume in one second (FEV_1) $\leqslant 1{\cdot}2$ l) and normal or low arterial carbon dioxide tensions ($Paco_2 \leqslant 5{\cdot}3$ kPa ($\leqslant 39{\cdot}8$ mm Hg)). All the patients were in a stable condition and none had recently been admitted to hospital. No patient was taking sedative drugs, and patients continued to take their usual treatment of inhaled bronchodilators and steroids throughout.

Drug regimen—The patients received dihydrocodeine 15 mg or matched placebo over two consecutive one week periods in a randomised double blind cross over design. During a third week patients received on alternate days dihydrocodeine 15 mg or matched placebo double blind. Throughout the study patients were given the same instructions to take a tablet 30 minutes before exercise, up to a maximum of three tablets daily. The patients noted the number of tablets taken each day, and at the end of each treatment period

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tablets were counted. Twice before the trial (practice and baseline) and at the end of each treatment period the patients attended hospital for assessment.

Measurements at home—Peak expiratory flow rate (PEFR) was measured by the patients three times daily with a mini-Wright peak flow meter. Mobility was measured with a pedometer (Mampo Ltd). Patients were instructed to wear the pedometer attached at the waist continuously throughout the day. During weekly treatment the distance walked was recorded at the end of each week, and during alternate day treatment the distance walked was recorded each evening. Visual analogue scales were used each evening to score breathlessness, constipation, drowsiness, nausea, and anxiety.

Measurements at hospital—At the end of each treatment period FEV_1 and forced vital capacity (FVC) were measured with a dry spirometer (Vitalograph). Breathlessness and exercise tolerance were measured on a treadmill. On the day patients attended hospital they were instructed to take their routine treatment at 7 am but not to take the test treatment. On arrival at the hospital the patients took one tablet of the treatment of that period and 30 minutes later walked on a level treadmill. Its speed was progressively increased each minute from the lower speed to one producing exhaustion (1·3, 1·8, 2·5, 3·3, 4·4, 5·9, 8·0, and 10·8 km/h). At the end of each minute, while still walking, the patients were asked to score the degree of breathlessness on a 10 cm visual analogue scale ranging from not breathless to extremely breathless. Breathlessness was plotted against distance walked. The baseline distance was selected to be 75% of the distance walked on the day placebo was given. Breathlessness at that distance was compared. The total distance walked to exhaustion was calculated. The treadmill test was carried out at the same time each week. No treadmill test was carried out at the end of the third week.

Analysis—The mean peak flow for each patient during each treatment period was calculated and a mean visual analogue score for each symptom for every patient during each treatment period was also obtained. Statistical analysis was performed on individual data with a Wilcoxon matched pairs signed rank test.

Results

During the first treatment period (while taking dihydrocodeine) one patient developed a chest infection and right heart failure and was therefore withdrawn from the study. Details of the remaining 18 patients (15 men, 3 women) were: mean age 64·9±SD 9·1 years; mean weight 66·6±13·8 kg; mean FEV_1 830±260 ml; mean FVC 2080±790 ml; mean Pao_2 9·3±0·8 kPa (69·9±6·0 mm Hg); and mean $Paco_2$ 4·8±0·5 kPa (36·1±3·8 mm Hg). There was no significant difference in the mean number of tablets used during the three treatment periods (dihydrocodeine week 2·8 tablets; placebo week 2·8 tablets; alternate day treatment week 2·7 tablets).

MEASUREMENTS AT HOME

PEFR—There was no significant change in peak flow (dihydrocodeine week 185±SD 59 l/min; placebo week 187±66 l/min).

Pedometer distance (table I; fig 1)—Patients walked significantly further during the week of dihydrocodeine treatment compared with the placebo period (+16·8%). Patients walked the same distance on the dihydrocodeine days as on the placebo days during alternate day treatment.

Visual analogue scores (table I; fig 2)—Breathlessness was significantly less as assessed by daily visual analogue scores during the dihydrocodeine period as compared with the placebo period, both during the weekly (−17·8%) and on alternate day treatment (−11%).

There was no significant difference in drowsiness, nausea, constipation, or anxiety between the placebo and dihydrocodeine periods.

TABLE I—*Mobility and breathlessness (mean±SD)*

	Placebo	Dihydrocodeine	p
Alternate week treatment			
Pedometer distance (km) for one week	9·3±7·6	10·9±8·0	<0·05
Visual analogue score of breathlessness (cm). Mean daily score	5·6±2·3	4·6±2·1	0·001
Alternate day treatment			
Pedometer distance (km) per day	1·2±1·0	1·2±0·9	NS
Visual analogue score of breathlessness (cm). Mean daily score	6·4±1·8	5·7±2·2	<0·001

NS = Not significant.

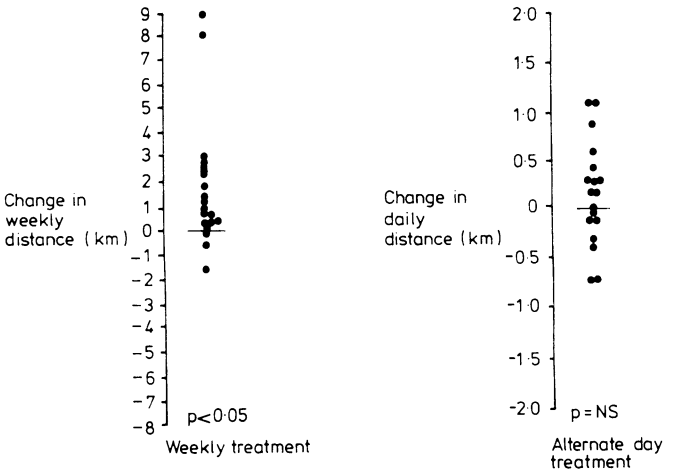

FIG 1—Change in distance walked (measured by pedometer) after dihydrocodeine as compared with after placebo.

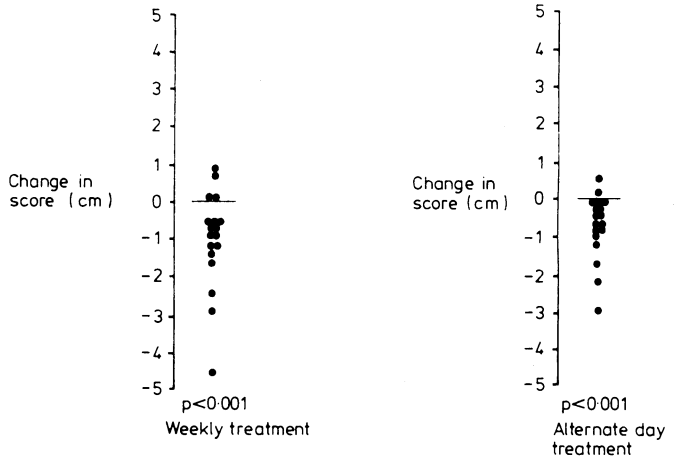

FIG 2—Change in breathlessness score (visual analogue scales) after dihydrocodeine as compared with after placebo.

WEEKLY MEASUREMENTS AT HOSPITAL

Spirometry—There was no significant change in FEV_1 or FVC (dihydrocodeine week FEV_1 770±SD 260 ml, FVC 2040±560 ml; placebo week FEV_1 800±250 ml, FVC 2070±560 ml).

Breathlessness and exercise tolerance (table II; fig 3)—Patients walked significantly further on the treadmill 30 minutes after dihydrocodeine as compared with placebo (+16·5%). Patients were significantly less breathless after dihydrocodeine than after placebo at 75% of the distance walked on the placebo day as measured by visual analogue scales (−11·8%).

Discussion

To date there has been no effective practical treatment for the breathlessness of chronic airflow obstruction. The initial promise of diazepam[8] has not been confirmed[9] and it cannot be recommended in the treatment of this group of patients. Promethazine[9] caused a slight reduction in breathlessness and improvement in exercise tolerance, but the effect was small and many of the patients complained of drowsiness. Portable oxygen[10] has been shown to be beneficial but it is cumbersome

and inconvenient. In our study dihydrocodeine 15 mg used regularly up to three times daily before exercise offered appreciable benefit to normocapnic patients with chronic airflow obstruction without reported side effects.

The third treatment period, when patients took either dihydrocodeine or placebo on alternate days, was included in the study for three reasons: firstly, because we were concerned that patients might develop tolerance to the dihydrocodeine so that increasing doses might be required to obtain the same clinical effect; secondly, in order to minimise side effects; and, lastly, because patients' appreciation of breathlessness might be modified by memory so that they might notice a day to day change but not a week to week change. The results, however, showed no evidence of tolerance, side effects, or difficulty in appreciating changes in breathlessness, and so there are no important conclusions from that part of the study. There was, however, some discrepancy in the mobility measurements. This may have been due to the fact that during weekly treatment the pedometer distance was read by the investigator whereas during the alternate day treatment the patients read their pedometer distance each evening themselves, which may be less reliable.

Blood gas values were not monitored during this study. In our previous study[7] there was a small but significant rise in $PaCO_2$ after dihydrocodeine 60 mg three times a day. In no patient, however, did the $PaCO_2$ rise above 5·3 kPa (39·8 mm Hg) and there was no change in $PaCO_2$. Hence for normocapnic patients in a stable clinical condition it seems unlikely that dihydrocodeine 15 mg will precipitate respiratory failure. This may not apply during infective exacerbations, and in such cases dihydrocodeine should undoubtedly be discontinued.

From our study we cannot say that dihydrocodeine will either be effective or safe for other groups of patients with breathlessness. We have done some preliminary studies using buprenorphine in patients with restrictive lung disease and found no benefit, and side effects were a considerable problem. Stark *et al*[12] recently showed that codeine does not reduce breathlessness in normal subjects. Further studies using different drugs in different forms of breathlessness are needed to define further the role of opiates in breathlessness.

The method of action of dihydrocodeine in improving breathlessness in our patients remains speculative. Probably the drug acts by reducing ventilation secondary to a reduction in oxygen consumption. This has been demonstrated by Santiago *et al*[5] using morphine in normal volunteers and by Woodcock *et al* with dihydrocodeine in patients with chronic airflow obstruction. The lack of demonstrable change in oxygen consumption or ventilation may explain the failure of codeine to affect breathlessness in the study of Stark *et al*.

Bronchodilators and steroids remain the mainstay of treatment for chronic airflow obstruction, but in normocapnic patients who are severely disabled by breathlessness dihydrocodeine 15 mg before exercise offers some benefit without side effects.

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TABLE II—*Results of treadmill exercise test 30 minutes after dihydrocodeine or placebo (mean ± SD)*

	Placebo	Dihydrocodeine	p (paired *t* test)
Treadmill distance to exhaustion	213 ± 127	249 ± 139	<0·01
Breathlessness (cm)	7·6 ± 1·9	6·7 ± 2·3	<0·001

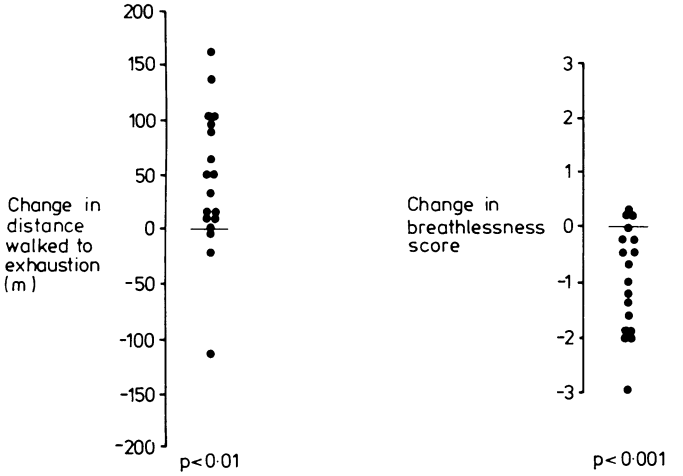

FIG 3—Change in distance walked to exhaustion and breathlessness score at 75% of treadmill distance on placebo day. (Dihydrocodeine compared with placebo.)

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SMALLAGE grows naturally in dry and marshy ground; but if it be sown in gardens, it there prospers very well. It abides green all the Winter, and seeds in August.

It is an herb of Mercury. Smallage is hotter, drier, and much more medicinal than parsley, for it much more opens obstructions of the liver and spleen, rarefies thick phlegm, and cleanses it and the blood withal. It provokes urine and women's courses, and is singularly good against the yellow jaundice, tertian and quartan agues, if the juice thereof be taken, but especially made up into a syrup. The juice also put to honey of roses, and barley-water, is very good to gargle the mouth and throat of those that have sores and ulcers in them, and will quickly heal them. The same lotion also cleanses and heals all other foul ulcers and cankers elsewhere, if they be washed therewith. The seed is especially used to break and expel wind, to kill worms, and to help a stinking breath. The root is effectual to all the purposes aforesaid, and is held to be stronger in operation than the herb, but especially to open obstructions, and to rid away any ague, if the juice thereof be taken in wine, or the decoction thereof in wine used. (Nicholas Culpeper (1616-54) *The Complete Herbal*, 1850.)