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Oral diamorphine: lack of effect on dyspnoea and exercise tolerance in the "pink puffer" syndrome

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ABSTRACT: The aim of this study was to assess the effects of diamorphine on breathlessness and exercise tolerance in patients with severe chronic airflow obstruction and normal arterial carbon dioxide tension (Pco_2) levels ("pink puffer" syndrome).

In this double-blind, cross-over, randomized study we examined both acute and chronic effects of single and multiple doses of oral diamorphine in 14 "pink puffer" patients. Their mean resting forced expiratory volume in one second (FEV_1) was 36% predicted normal, mean arterial oxygen tension (Pao_2) was 9.2 kPa and mean $Paco_2$ was 5.2 kPa. Ten patients took either diamorphine 2.5 or 5 mg or placebo elixir 6 hourly for 2 weeks, recording on a diary card dyspnoea, sleepiness and well-being on a visual analogue scale (VAS). The final treatment was given 30 min before measuring spirometry, arterial blood gases, plasma morphine levels, 6 min walking distances, time walked on treadmill and self-assessment of dyspnoea on a VAS scale after exercise. On two further days, eight patients took two doses, 4 h apart, of either diamorphine 7.5 mg or placebo elixir. Spirometry, 6 min walking distance with a VAS score for dyspnoea were measured before and at 1 h after each dose. Morphine levels and blood gases were also measured.

Whether given in single or repeated doses, oral diamorphine had no significant effect on exercise tolerance and breathlessness when compared with placebo. Diamorphine 2.5–7.5 mg produced neither sleepiness nor a deterioration in blood gases. However, plasma levels associated with analgesic efficacy were not achieved with these doses. Thus, as given in this study, oral diamorphine is unlikely to have therapeutic potential in the treatment of dyspnoea in the "pink puffer" syndrome.

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Breathlessness is a disabling symptom for patients with the "pink puffer" syndrome [1]. These patients have severe, irreversible airflow obstruction. They maintain a near normal arterial oxygen tension (Pao_2) with a low arterial carbon dioxide tension ($Paco_2$) at the expense of distressing dyspnoea. Since the cause of these symptoms is irremediable, attention has focused on alleviating the sensation of dyspnoea. A number of agents have previously been investigated but only modest improvements in exercise tolerance and in dyspnoea have been achieved [2–9]. However, opiates are known to reduce ventilatory responses both to carbon dioxide and to hypoxia [10–13], to inspiratory loading [14], and to exercise [11]. Dihydrocodeine can slightly reduce dyspnoea in the "pink puffer" syndrome [3, 5, 6]; oxygen consumption decreases at rest and on exercise but there is a small increase in resting $Paco_2$ levels and troublesome nausea and vomiting after multiple dosing [5, 6]. Recently, the effects of single doses of oral and nebulized morphine on exercise tolerance have been evaluated in the laboratory [8, 9]. The effect of diamorphine, a drug used frequently to treat the dyspnoea caused by pulmonary oedema, pulmonary emboli and malignant lung disease, is unknown.

The aim of the present study was to assess the value of oral diamorphine in the management of patients in the terminal stages of chronic airflow obstruction with normal $Paco_2$ levels. The effect on dyspnoea and exercise tolerance in particular was examined.

Methods

Patients

Eighteen patients (7 female and 11 male) with a mean age of 66 yrs (range 49–79 yrs) were entered into the study (table 1). Five patients were current smokers and 13 were ex-smokers. All had chronic bronchitis associated with severe, but stable, chronic airflow obstruction. The mean forced expiratory volume in one second (FEV_1) was 32% of predicted normal (range 52–21%). No patient had secondary polycythaemia (mean haemoglobin 14.1 $g \cdot dl^{-1}$). The mean resting Pao_2 was 9.0 kPa (range 7.1–10.9 kPa) and mean $Paco_2$ was 5.1 kPa (range 3.4–6.5 kPa). Patients continued their regular medication throughout the study. Written, informed consent was given by each patient and the study was approved by the Lewisham and North Southwark Health Authority Ethics Committee.

monitored by a Multicap capnometer (Datex, Helsinki) and arterial oxygen saturation (Sao_2) was measured by a Satlite pulse oximeter (Datex, Helsinki). At completion of each type of exercise, dyspnoea was assessed from none to extreme on a 10 cm visual analogue scale (VAS).

Study periods. The study was double-blind, randomized and cross-over with no wash-out intervals. During each of three 2 week periods patients took either placebo or diamorphine 2.5 or 5 mg as 5 ml of oral linctus every 6 h. They completed daily diary cards, indicating on a 10 cm VAS scale, dyspnoea, drowsiness and feeling of well-being, as well as number of times awoken at night by dyspnoea.

Study days. At the end of each 2 week period the patients attended the clinic for spirometry, arterial blood gases and venous morphine levels. This was followed by a 6 min walk and a treadmill walk. On each study day, the final dose of the linctus was given in the clinic 20 min before the first blood sample was taken. The volume of linctus remaining in the bottle was measured.

Table 1. – Demographic details of 18 stable patients with "pink puffer" syndrome

Pt. No.		Sex	Age yr	Weight kg	FEV_1 *l*	FEV_1 % pred	Slow VC *l*	Arterial blood gases kPa Pao_2	$Paco_2$	Hb $g \cdot dl^{-1}$	Drugs
1	+	M	70	52	0.55	28	1.50	8.2	6.5	12.7	S,P,D
2	+s	F	72	70	0.60	40	1.55	-	-	15.2	S,D
3	**	M	79	81	0.75	44	1.45	10.9	5.2	15.0	S,I,D,B
4	**	F	65	71	1.20	52	1.60	9.8	5.2	14.2	S,I,D
5	**	M	74	56	0.60	27	1.20	9.1	5.3	14.0	S,I,B
6		M	72	58	0.75	28	1.95	10.6	3.4	11.8	D,P
7	**+	F	52	58	0.60	21	1.70	8.5	4.8	14.4	S,B
8		M	56	62	0.80	25	2.05	8.5	4.6	16.9	S,I,B
9	+s	F	71	67	0.50	24	1.40	8.2	4.6	13.7	S,I,D,P
10	+	F	67	87	0.70	37	1.80	-	-	15.6	S,I,D
11	s	M	61	70	0.80	29	3.00	8.5	5.5	16.9	S,I
12	**+	F	52	72	0.90	31	1.60	8.9	4.9	10.4	S,I,D,P
13		M	72	70	0.60	27	1.40	7.1	6.0	16.1	S,D,B
14	**	M	49	63	1.20	30	3.80	9.5	4.4	15.2	S
15	*	M	75	58	1.00	40	3.10	8.9	5.4	12.8	S,I
16	*	M	73	67	0.90	35	3.10	10.3	5.4	11.6	S
17	s*	F	72	55	0.55	31	1.20	9.0	5.5	14.5	S,I,B,A
18	s*	M	60	62	0.90	24	2.50	7.9	5.0	13.4	S,I,A

+: withdrew from study; s: current smokers; *: patient in second part of study; **: patient in both parts of study; S: salbutamol; I: ipratropium: D: diuretic; P: prednisone; A: aminophylline; B: beclomethasone; FEV_1 forced expiratory volume in one second: VC: vital capacity; Pao_2 and $Paco_2$: arterial oxygen and carbon dioxide tension, respectively; Hb: haemoglobin.

First study

"Run-in" day. On the "run-in" day, all patients were interviewed, examined and weighed. Their spirometry was recorded. Then venous blood was withdrawn for haemoglobin and haematocrit and arterial blood for Pao_2 and $Paco_2$. Subsequently, each patient performed a practice 6 min walk and a practice treadmill walk at the lowest speed available. Distance walked and length of time on treadmill were both recorded. During the treadmill exercise period end-expiratory carbon dioxide tension (Pco_2) was

Second study

Six months later ten patients (table 1) attended for two further study days, two weeks apart. They received 5 ml elixir which contained either placebo or 7.5 ml diamorphine in a randomized cross-over, double-blind

fashion. On each day, patients arrived in the clinic at 0900 h and were given inhaled salbutamol 600 μg and ipratropium bromide 240 μg *via* a volumatic spacing device. At 30 and 40 min, respectively, patients performed spirometry and a 6 min "baseline" walk, recording dyspnoea as a VAS score. Then they took the study linctus. Venous and arterial blood was taken 20 and 70 min later for morphine levels and blood gases, respectively. The same dose of elixir and inhaled bronchodilators were given at 5 h and spirometry repeated 30 min later. Fifty minutes after each dose of elixir patients performed their 6 min walks.

The results obtained from the study days and study periods of the first study were compared by analysis of variance. For the second study paired t-tests were used to compare the effects of diamorphine 7.5 mg and placebo.

Results

Compliance and side-effects

Of the original 18 subjects entered into the studies four withdrew during their first period of the first study. Patient 1 developed a chest infection and declined to continue, patient 2 developed itching on diamorphine 2.5 mg, patient 10 was constipated on diamorphine 5 mg and patient 9 developed a headache due to cerebral metastases from an unknown primary carcinoma. Patients 3 and 4 continued the study despite constipation and vomiting while taking diamorphine 5 mg *q.d.s.*

Two patients withdrew after the first day of the second study - patient 12 developed chest pain during the interval between the studies and refused to continue, whilst the blood gases of patient 7 had deteriorated to a level unacceptable for further study (Pao_2 6.5 kPa and $Paco_2$ 5.2 kPa). Although severely nauseated on diamorphine 7.5 mg, patient 4 once more completed the protocol.

Compliance with the study medication was assessed by measuring the volume of linctus remaining at the end of each study period. Only two patients took all 56 doses of medication prescribed for each 2 week period. There was no difference in the pattern of non-compliance between the study periods. More than eight doses were missed during a two week period by nine patients; five patients omitted 8–30 doses of placebo, two omitted 17 and 19 doses of diamorphine 2.5 mg and two omitted 9 and 22 doses, respectively, of diamorphine 5 mg.

First study

The same results were obtained from the diary cards whether the whole 2 week period or only the final 7 days were compared. Figure 1 shows the mean results for the final 7 days of each study period. When compared by analysis of variance there was no statistical difference in the degree of sleepiness or well-being or in the number of puffs of bronchodilator taken by the group between any of the study periods. Nor was there any significant difference in the degree of perceived dyspnoea during any of the periods. No patient volunteered any views as to whether a particular elixir had improved their breathing.

All patients had severe airflow obstruction which was stable for the duration of the study (table 2). This was associated with hypoxaemia and normal $Paco_2$ levels. Analysis of variance revealed no significant difference between the arterial blood gases nor the alveolar-arterial oxygen tension difference ($A\text{-}aPo_2$) on any of the study days. The 6 min walking distance, the time spent walking on the treadmill and the degree of breathlessness recorded on the visual analogue scale after these exercise tests was also similar on all study days.

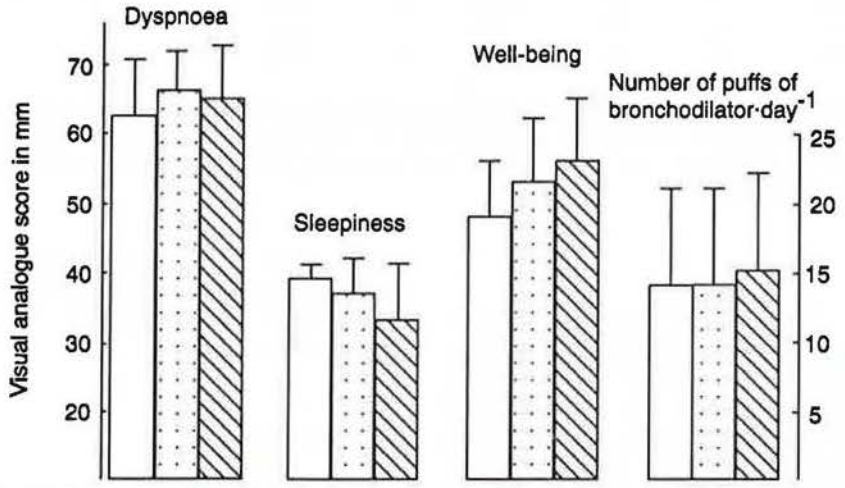

Fig. 1. – Comparison of the effects on the visual analogue scale (VAS) scores for dyspnoea, sleepiness, well-being and on number of puffs of bronchodilator·day^{-1} of diamorphine 2.5 mg *q.d.s.* (▭), diamorphine 5 mg *q.d.s.* (▨) and placebo linctus (▭) for the last 7 days of a 2 week period. The mean and standard deviation for 10 patients with the "pink puffer" syndrome are shown. By analysis of variance no significant difference was found between placebo and the two doses of diamorphine elixir for any parameter on the diary cards.

Table 2. – Study 1 (n=10); comparison of effects of diamorphine 2.5 and 5 mg with that of placebo on measurements

Measurement	Placebo	Diamorphine 2.5 mg	Diamorphine 5 mg	
FEV_1 *l*	0.8±0.1	0.8±0.1	0.8±-0.1	NS
Pao_2 kPa	9.0±0.6	8.6±0.4	9.7±0.4	NS
$Paco_2$ kPa	5.2±0.2	5.4±0.3	5.0±0.2	NS
A-aPo_2	4.5±0.5	4.7±0.4	4.1±0.3	NS
Walking distance m	216±40	221±35	226±34	NS
VAS dyspnoea score cm for walk	6.5±0.7	7.0±0.7	7.0±0.8	NS
Time on treadmill s	165±68	104±19	156±47	NS
VAS dyspnoea score cm for treadmill	6.5±1.0	6.6±0.6	5.8±1.0	NS
O_2 saturation %	89±2	90±2	89±2	NS
O_2 saturation rest-exercise %	-3±1	-2±1	-4±2	NS
End-tidal Pco_2 exercise kPa	31±2	33±2	34±3	NS

Mean±SEM. NS: no significant difference, calculated from an analysis of variance; A-aPo_2: alveolar-arterial oxygen tension difference; VAS: visual analogue score; Pco_2: carbon dioxide tension. For further abbreviations see legend to table 1.

Second study

Paired t-tests (table 3) showed that for the group as a whole, mean baseline walking distances and VAS dyspnoea scores were similar on the two study days and, within individuals, walking distances were reproducible. However, in some patients baseline VAS scores were less repeatable (fig. 2). The effects of placebo and diamorphine on 6 min walking distance and on the VAS dyspnoea score were compared after each dose of elixir. Although there was a trend for both walking distances and VAS scores to improve and the blood gases to deteriorate on diamorphine, there was no statistical difference between the effects of placebo and diamorphine 7.5 mg in either FEV_1, arterial blood gases, 6 min walking distances or VAS dyspnoea scores. There was no correlation between the effects of diamorphine on walking distance and on $Paco_2$.

Venous morphine levels

In general, higher blood levels of morphine were obtained after the larger doses of diamorphine. However, no morphine was detected in 14 of 27 blood samples analysed after 2.5–7.5 mg diamorphine. Detectable levels of morphine ranged between 1.8–9.2 $ng \cdot ml^{-1}$. No statistical correlation between the plasma morphine levels and changes in either walking distance or blood gases could be made.

Table 3. – Study 2; comparison of effect of diamorphine 7.5 mg with placebo

Measurement	Placebo elixir 1 h	Placebo elixir 5 h	Diamorphine 7.5 mg 1 h	Diamorphine 7.5 mg 5 h
FEV_1 *l*	1.0±0.3	1.0±0.3	0.9±0.3	0.9±0.3
VC *l*	2.3±0.7	2.3±0.8	2.3±1.0	2.3±1.0
Pao_2 kPa	9.2±0.3	-	8.6±0.2	-
$Paco_2$ kPa	5.0±0.1	-	5.3±0.1	-
A-aPo_2 kPa	4.6±1.1	-	4.8±0.8	-
Walking distance m	263±51	249±50	272±49	270±46
VAS score cm	6.1±0.7	7.4±0.5	6.2±0.7	6.3±1

n=8; mean±SEM. Paired t-tests showed no significant difference for any parameter, comparing placebo with diamorphine elixir; mean values from 1 and 5 h data were compared for FEV_1, VC, walking distance and VAS dyspnoea score. For abbreviations see legends to tables 1 and 2.

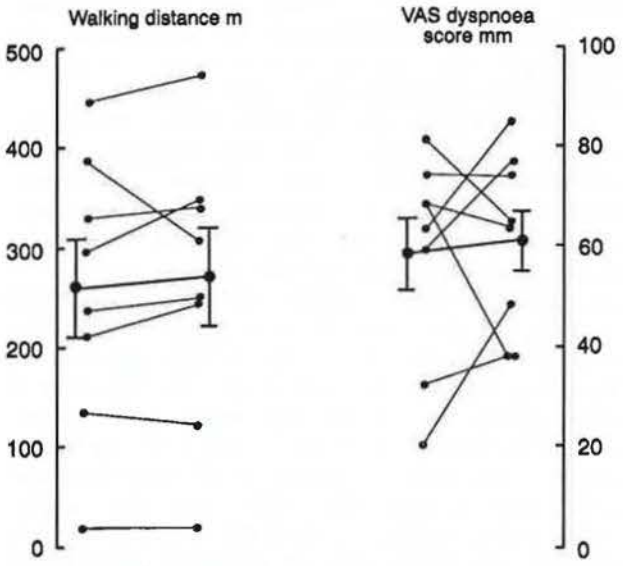

Fig. 2. – Illustration of the reproducibility of walking distances and visual analogue scale (VAS) dyspnoea scores in the eight patients in Study 2 during the baseline walks (before linctus) on the two study days. Individual and mean group data with standard deviations are shown. Paired t-tests showed no significant difference in either parameter between the two study days.

Discussion

In this study we have investigated both the acute and the chronic effects of diamorphine on exercise tolerance in a group of patients with severe, stable chronic airflow obstruction and the "pink puffer" syndrome. Exercise tolerance was assessed both by measuring the time walked on the treadmill and by recording the 6 min walking distance. The use of walking distances in the assessment of exercise tolerance has been validated previously [15, 16]. If, as in this study, two practice walks precede formal assessment, the measurement is reproducible, with an intrasubject coefficient of variation of 4% [16].

Results from a 6 min walk correlate well with those from 12 min walks [17]. Similarly, the sensitivity and reproducibility of VAS dyspnoea scores has been established by STARK and co-workers [18–23]. Since the reproducibility of the VAS score varies between patients with chronic airflow obstruction (COAD) [23], we assessed it as an integral part of our study [24] during the run-in day in Study 1 and during the baseline walks before medication in Study 2. As seen in figure 2, the reproducibility of the VAS dyspnoea score was less good than that of the 6 min walking distance.

When the effects of single doses of opiates have been studied under laboratory conditions, 18–30% improvements in exercise tolerance have been reported [4, 6, 8, 9]. Although statistically significant, these changes were relatively small. The results of clinical studies with repeated doses of opiates have been disappointing; WOODCOCK and co-workers [4] gave 30–60 mg dihydrocodeine daily for 2 weeks to patients with COAD. There was no significant improvement in breathlessness but side-effects were prominent. Our results with 2 weeks of regular diamorphine confirmed these observations.

More powerful opiates have been investigated recently. Single doses of nebulized morphine 1.7 mg produced an impressive mean increase in endurance exercise tolerance [8]. However, there were very large differences in the effect between individuals; 8 of 11 patients with COAD showed minimal, if any, change. After a single oral dose of morphine (0.8 $mg \cdot kg^{-1}$) a 15% mean increase in exercise tolerance associated with a rise in $Paco_2$ and a fall in Pao_2 was reported by LIGHT *et al.* [9]. The dose of diamorphine in the present study was smaller, 0.04–0.08 $mg \cdot kg^{-1}$ in Study 1 and 0.12 $mg \cdot kg^{-1}$ in Study 2. The results of LIGHT *et al.* [9] must be treated with some caution; their study was only single-blind and so subject to possible observer bias. In addition, the heroic dose of morphine given to the patients produced serious side-effects necessitating naloxone treatment at the end of each study. It would not be feasible to give such large doses in clinical practice.

Diamorphine was selected for the present study since we commonly use it for relief of pain and dyspnoea in terminally ill patients. The dose chosen was equivalent to 5–15 mg of morphine - a realistic dose for chronic use. Whilst only three patients had constipation or vomiting, several others complained of mild nausea during the 2 week course of diamorphine 20 mg daily. Strangely, the blood levels of morphine did not approach that expected to produce a therapeutic analgesic effect (17 $ng \cdot ml^{-1}$) (Henry, personal communication). Indeed, in many cases morphine was undetectable in the blood. The reason for this is obscure; the venous samples were taken at the time when maximum serum levels were expected. The patients were observed while they took the medication. There was no reason to suspect malabsorption and no patient was taking concomitant medication expected to affect the measurement or the metabolism of the diamorphine. Since these low serum levels were unexpected, the study protocol did not include any measure of analgesia to assess the biological effect of the diamorphine given. In retrospect, this was a pity.

In conclusion, repeated doses of oral diamorphine 2.5–7.5 mg, failed either to ameliorate the distressing dyspnoea or to increase the exercise tolerance of our patients with the "pink puffer" syndrome associated with severe stable chronic airflow obstruction. On the other hand, it resulted in no increase in hypoxaemia and no additional carbon dioxide retention in these patients. For unknown reasons serum morphine levels were probably subtherapeutic; this probably accounts for the disappointing results. As given in our protocol, oral diamorphine is unlikely to contribute in the out-patient management of patients with the "pink puffer" syndrome. Results from this and other studies suggest that higher doses of oral opiates would not be any more useful since they would probably give unacceptable side-effects during chronic use.

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Diamorphine orale; absence d'effet sur la dyspnée et tolérance à l'effort dans le syndrome des "pink puffers". N. Eiser, W.T. Denman, C. West, P. Luce.

RÉSUMÉ: L'objectif de cette étude est d'apprécier les effets de la diamorphine sur la dyspnée et la tolérance à l'effort chez les patients atteints d'une obstruction sévère chronique des voies aériennes, avec des niveaux de Pco_2 artériel normaux ("syndrome pink puffer").

Dans cette étude en double anonymat, avec permutation croisée et randomisation, nous avons examiné à la fois les effets aigus et chroniques de doses uniques et multiples de diamorphine par voie orale chez 14 patients "pink puffers". Leur VEMS moyen au repos atteignait 36% des valeurs prédites, leur Pao_2 moyenne était de 9.2, et leur $Paco_2$ moyenne de 5.2 kPa. Dix patients ont pris, soit la diamorphine 2.5 ou 5 mg, soit un élixir de placebo, toutes les 6 heures pendant 2 semaines, avec enregistrement sur une carte quotidienne de la dyspnée, des insomnies, et de la sensation de bien-être sur une échelle analogique visuelle (VAS). Le traitement final a été administré 30 minutes avant la mesure de la spirométrie, des gaz du sang artériel, des niveaux plasmatiques de morphine, de la distance de marche pendant 6 minutes, du temps de marche sur un tapis roulant, et de l'appréciation personnelle de la dyspnée sur une échelle VAS après effort. Au cours de 2 jours ultérieurs, 8 patients ont pris 2 doses, séparées de 4 heures, soit de 7.5 mg de diamorphine soit d'élixir de placebo. L'on a mesuré la spirométrie, la distance de marche pendant 6 minutes, et des scores de dyspnée au moyen d'une VAS, à la fois avant et 1 heure après chaque dose. Les niveaux de morphine et des gaz du sang ont été mesurés également.

Qu'elle soit donnée en doses uniques ou répétées, la diamorphine par voie orale n'a pas d'effet significatif sur la tolérance à l'effort et la dyspnée, par comparaison avec le placebo. La diamorphine (2.5–7.5 mg) n'a produit ni insomnie, ni détérioration des gaz sanguins. Toutefois, les niveaux plasmatiques associés à une efficacité analgésique n'ont pas été atteints au moyen de ces doses. Donc, administrée comme dans cette étude, la diamorphine par voie orale n'est pas susceptible d'avoir un potentiel thérapeutique dans le traitement de la dyspnée, dans le syndrome des "pink puffers".

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