Eur Respir J, 1995, 8: 425–429
DOI: 10.1183/09031936.95.08030425
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European Respiratory Journal
ISSN 0903 - 1936

Effect of protriptyline, 10 mg daily, on chronic hypoxaemia in chronic obstructive pulmonary disease

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ABSTRACT: A daily dose of 20 mg of protriptyline can improve daytime arterial blood gas tensions in chronic obstructive pulmonary disease (COPD). Its usefulness is limited by anticholinergic side-effects. This study examined whether a daily dose of 10 mg of protriptyline improved daytime arterial oxygen tension (Pa_{O_2}) and quality of life in patients with stable mild or moderate hypoxaemia caused by COPD.

Twenty six patients were randomized to receive protriptyline or placebo in a double-blind parallel-group trial for 12 weeks, following a run-in period of 4 weeks, in order to assess the stability of hypoxaemia. Patients with a change in Pa_{O_2} of >0.7 kPa during the run-in were excluded. Spirometry, quality of life and dyspnoea score were measured at randomization and after 12 weeks, whilst arterial blood gas tensions were also measured 2 and 6 weeks after randomization.

No improvement in arterial blood gas tensions, spirometry values, dyspnoea score, or quality of life was found in either the protriptyline or the placebo group. The majority of patients receiving protriptyline experienced anticholinergic side-effects, which necessitated the withdrawal of the drug in one patient.

We conclude that there was no evidence that a daily dose of 10 mg of protriptyline had a significant effect on daytime arterial oxygen tension in stable mild and moderate hypoxaemia caused by COPD. Despite the low dose, anticholinergic side-effects occurred in most patients.

Eur Respir J., 1995, 8, 425–429.

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Keywords: Chronic hypoxaemia, chronic obstructive pulmonary disease, daytime oxygenation, protriptyline, quality of life

Received: March 9 1994
Accepted after revision December 18th 1994

In chronic obstructive pulmonary disease (COPD), chronic hypoxaemia is associated with organ symptoms and with the impairment of survival and quality of life [1–3]. The negative effects of hypoxaemia are alleviated by long-term oxygen therapy (LTOT), which is the treatment of choice in patients with chronic hypoxic COPD [1, 2]. Various cut-off levels for the arterial oxygen tension have been recommended [4–6]. Stable resting daytime arterial oxygen tensions of below 7.3 [4], 7.5 [5] and 8.7 [6] kPa have been regarded as indications for LTOT. LTOT is not possible in some patients, due to a lack of co-operation or a reluctance to accept this therapy. There is a need for alternative treatment in some patients, and an oral agent would be a convenient treatment alternative [7].

The stimulatory tricyclic drug, protriptyline, decreases episodic nocturnal desaturation in patients with an obstructive sleep apnoea (OSA) syndrome [8, 9]. Protriptyline has also been shown to improve night-time oxygenation in respiratory failure caused by muscular dystrophy [10] and to improve night-time and diurnal oxygenation in restrictive chest wall disease [11]. Twenty milligrams of protriptyline at bedtime has been shown to increase the diurnal arterial oxygen tension in patients with chronic hypoxaemia caused by COPD in the absence of OSA [12, 13]. The usefulness of the drug is limited by its anticholinergic side-effects, and an investigation of the effect of a lower dose has been suggested [12]. We have investigated the effect of 10 mg of protriptyline at bedtime on quality of life and daytime arterial blood gas tensions, during a period of 12 weeks, in a randomized double-blind, placebo-controlled trial in 26 COPD patients with chronic stable mild or moderate hypoxaemia.

Subjects and methods

Subjects

Twenty six patients with COPD and mild or moderate stable hypoxaemia were recruited in eight centres (table 1). The inclusion criteria were based on arterial oxygen tension (Pa_{O_2}) and the ratio of forced expiratory volume in one second/forced vital capacity (FEV_1/FVC). Patients were included if they were in a stable phase of the disease, with a resting daytime Pa_{O_2} in the range of 6.7–8.7 kPa and a FEV_1/FVC ratio less than 0.7 after bronchodilatation. Since the benefit of LTOT has been unequivocally shown in the lower part of this Pa_{O_2}

Table 1. – Patient characteristics at randomization

Characteristic	Protriptyline	Placebo	p-value
Patients n	14	12	
Sex M/F	4/10	4/8	NS
Age yrs	66±9	59±7	<0.01
Pa_{O_2} kPa	7.9±0.6	7.6±0.5	NS
Pa_{CO_2} kPa	5.6±0.6	6.0±1.0	NS
FEV_1 *l*	0.6±0.2	0.7±0.2	NS
FEV_1/FVC	0.37	0.38	NS
Quality of life			
SIP scores			
Total	9±7	9±5	NS
Physical	9±8	7±4	NS
Psychosocial	6±7	5±6	NS
MACL scores			
Pleasantness/unpleasantness	3.2±0.6	3.3±0.3	NS
Activation/deactivation	3.0±0.6	3.2±0.4	NS
Calmness/tension	3.1±0.6	3.2±0.5	NS
HAD scale			
Anxiety	4±4	6±5	NS
Depression	4±3	3±3	NS

Data are presented as mean±SD. SIP: Sickness Impact Profile quality of life questionnaire; MACL: Mood Adjective Check List; HAD: Hospital Anxiety and Depression; M: male; F: female; Pa_{O_2}: arterial oxygen tension; Pa_{CO_2}: arterial carbon dioxide tension; FEV_1: forced expiratory volume in one second; FVC: forced vital capacity; NS: nonsignificant.

interval, it was considered unethical to withhold LTOT in patients with a Pa_{O_2} of <7.5 kPa in a placebo-controlled trial. Therefore, patients with a Pa_{O_2} of <7.5 kPa were included only if they were regarded as ineligible for long-term oxygen therapy (LTOT) because of current smoking or a lack of co-operation with the therapy.

The exclusion criteria were as follows: a diagnosis of bronchial asthma, obstructive sleep apnoea syndrome, restrictive thoracic or neuromuscular disease; >15% reversibility in FEV_1 following the inhalation of 0.4 mg of salbutamol; other severe concomitant disease; thyroid disease; urinary retention or prostate hypertrophy; women of childbearing age considering pregnancy. Patients with habitual snoring, daytime sleepiness, observed sleep apnoeas or morning headache were excluded. All the patients had one full night of oximetry, excluding sleep apnoeas performed less than one year before the run-in period. Patients with a change in Pa_{O_2} of >0.7 kPa during the 4 week run-in period were excluded from the trial.

The patients in the protriptyline and placebo groups were well-matched in terms of sex, arterial blood gas tensions, spirometry volumes, and quality of life scores (table 1). The patients receiving protriptyline were older than the patients receiving placebo medication (table 1). The prestudy medication, including bronchodilators and anti-inflammatory medication, was not changed during the study period (table 2).

The study was approved by the regional Ethics Committees and the Medical Products Agency.

Table 2. – Concomitant bronchodilatory and anti-inflammatory treatment

Drug	Protriptyline group n=14	Placebo group n=12
Bronchodilator therapy		
Oral $beta_2$-agonist	7	5
Inhaled $beta_2$-agonist	13	10
Methylxanthine	8	3
Ipratropium bromide	5	3
Anti-inflammatory therapy		
Oral steroid	3	0
Inhaled steroid	12	10

Study design

The study was a double-blind, parallel-group, randomized trial. Stability of hypoxaemia was assessed by two arterial blood gas tension analyses, with an interval of 4 weeks, during a stable phase of the disease (run-in period). Arterial blood gas tensions, spirometry after bronchodilatation, quality of life, and dyspnoea scores was recorded before randomization and after 12 weeks of treatment. The patients were randomized to receive one tablet of 10 mg protriptyline or placebo to take at bedtime. All medication apart from the study medication was kept constant during the trial, including the run-in period, with the exception that a course of antibiotics and oral steroid medication shorter than 14 days was permitted in the event of exacerbation of COPD after randomization.

Protocol

The patients were followed regularly at chest departments and received the optimum pharmacological therapy. They paid five visits to the departments for the trial to record the following data: Visit 1) start of the run-in period - FEV_1, FVC before and 15 min after the inhalation of 0.4 mg of salbutamol, and Pa_{O_2}; Visit 2) end of 4 week run-in period, randomization - clinical status, Pa_{O_2}, arterial carbon dioxide tension (Pa_{CO_2}), quality of life, dyspnoea score, laboratory evaluation, FEV_1, and FVC after the inhalation of 0.4 mg of salbutamol; Visit 3) 2 weeks after randomization - Pa_{O_2}, Pa_{CO}, side-effects, and dyspnoea score; Visit 4) 6 weeks after randomization - Pa_{O_2}, Pa_{CO_2}, side-effects and dyspnoea score; Visit 5) 12 weeks after randomization - as visit 2, side-effects, and serum protriptyline.

The visits took place at the same time of the day. All patients were informed that dryness in the mouth might be expected as a side-effect of the medication, and were given written instructions on how to avoid dental complications due to dryness in the mouth.

Arterial blood gas tensions

Arterial blood gas tensions were measured before other investigations, including spirometry, and after the patient had been sitting resting for 30 min.

Quality of life

Quality of life was assessed using the Sickness Impact Profile (SIP) questionnaire [14], the Mood Adjective Check List (MACL)[15], and the Hospital Anxiety and Depression (HAD) scale [16]. SIP [17] and HAD [18] were used in versions adapted to Swedish conditions. The SIP contains 136 items, grouped into 12 categories or activities and three aggregated scores: a physical and a psychosocial dimension and a total SIP score. The result is given as a percentage of total possible dysfunction. The short form of the MACL containing 38 items, categorized into three dimensions, was used to extend the measurement of emotional status of the SIP questionnaire. The HAD was used to screen for psychiatric morbidity. The entire scale ranges 0–21 separately for the two dimensions anxiety and depression. With SIP and HAD, high scores indicate poor health, and with MACL, high scores indicate a positive emotional status.

Dyspnoea score

Dyspnoea was graded on a six step scale, ranging from 0=no dyspnoea to 6=dyspnoea at the least effort.

Laboratory evaluations

Blood samples for routine testing (haematology, biochemistry) were taken at Visits 2 and 5 and analysed locally. A blood sample for serum protriptyline determination was taken at Visit 5, serum was frozen at -20°C and all analyses of serum protriptyline were performed after the trial at the Laboratory of Neurochemistry in the Laboratory of Clinical Chemistry of the University Hospital, Lund (recommended therapeutic range in the laboratory is 270–1,000 nmol·l^{-1}).

Statistical analysis

The number of the patients in the study was calculated to detect a difference of 1 kPa in the change in Pa_{O_2} between the two treatment groups, with a power of 80% at a significance level of 5%. The analyses were performed using the Quest database programme [19]. The Mann-Whitney nonparametric test and the Wilcoxon's signed rank test were used for comparisons of unpaired and paired data at the randomization visit, and for the comparison of differences in numerical data between randomization and Visit 5, as appropriate. These comparisons were performed separately in all patients and in patients who did not have any exacerbation of COPD during the trial. A linear regression analysis was performed to test the relationship between serum protriptyline and the change in Pa_{O_2} between randomisation and Visit 5. Fisher's exact test was used to compare the number of patients with side-effects in patients treated with protriptyline and placebo. P-values of less than 0.05 were considered significant.

Results

Patients

Fourteen patients were randomized to receive protriptyline and 12 patients to receive placebo (table 1). Nineteen patients were excluded after the 4 week run-in period because of a change in Pa_{O_2} of >0.7 kPa. Two patients receiving protriptyline were withdrawn from the trial, one after 3 weeks of medication because of side-effects (dry mouth, visual disturbance, dizziness and fatigue), and one after 11 weeks due to an exacerbation of COPD necessitating in-hospital care.

Arterial blood gas tensions

The mean Pa_{O_2} increased by 0.2 kPa in the protriptyline group (fig. 1) and by 0.0 kPa in the placebo group after 12 weeks of medication (NS) (fig. 2). After exclusion of patients having an exacerbation of COPD, the mean Pa_{O_2} increased 0.2 kPa in both the protriptyline and placebo groups during the same time. In two patients receiving protriptyline and one patient receiving placebo, Pa_{O_2} increased by 1 kPa or more. The mean Pa_{CO_2} increased by 0.1 kPa in both groups during the same 12 week period (tables 2 and 3). After exclusion of patients with an exacerbation of COPD, there was no change (0.0 kPa) in Pa_{CO_2} during the same period in either the protriptyline or placebo group.

Spirometry volumes

The FEV_1 and FVC values after bronchodilatation did not change significantly in the protriptyline or placebo group when the analysis was performed in all patients (tables 1 and 3) and in patients without an exacerbation of COPD.

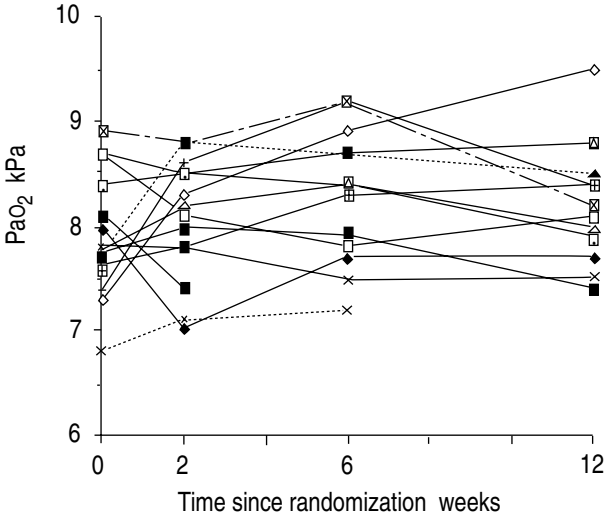

Fig. 1. – Arterial oxygen tension (Pa_{O_2}) after 0, 2, 6 and 12 weeks of treatment with 10 mg of protriptyline at bedtime (n=14). The Pa_{O_2} values of patients without an exacerbation of COPD are connected by unbroken lines, and the values of patients with an exacerbation of COPD are connected by dotted or dashed/dotted lines. COPD: chronic obstructive pulmonary disease.

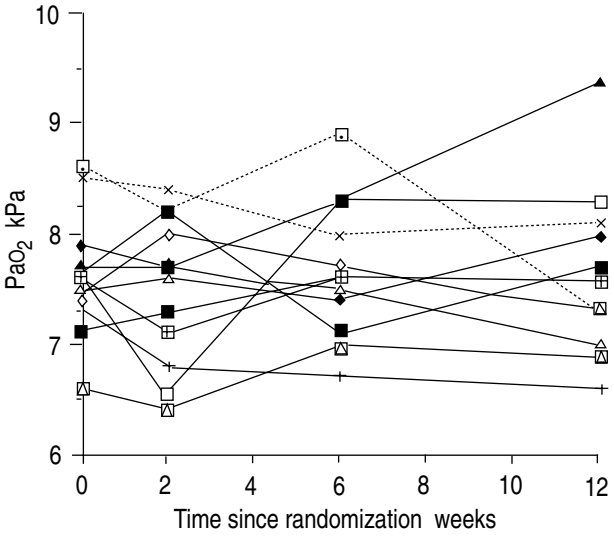

Fig. 2. – Arterial oxygen tension (Pao_2) after 0, 2, 6 and 12 weeks treatment with placebo (n=12). The Pao_2 values of patients with an exacerbation of COPD are connected by unbroken lines, and the values of patients with an exacerbation of COPD are connected by dotted lines.

Quality of life

There were no significant differences in the quality of life questionnaire scores between randomization and Visit 5 in either of the two treatment groups, irrespective of whether all patients (tables 1 and 3) or patients without an exacerbation of COPD were included in the analysis.

Dyspnoea score

Neither protriptyline nor placebo had any impact on the dyspnoea score.

Table 3. – Patient characteristics after 12 weeks of treatment with protriptyline or placebo

Characteristic	Protriptyline	Placebo	p-value
Patients n	12	12	
Pao_2 kPa	8.2±0.6	7.6±0.8	NS
$Paco_2$ kPa	5.7±0.7	6.2±0.9	NS
FEV_1 *l*	0.7±0.3	0.7±0.3	NS
FEV_1/FVC	0.34	0.39	NS
Quality of life			
SIP scores			
Total	7±4	8±4	NS
Physical	6±6	5±4	NS
Psychosocial	4±3	4±5	NS
MACL scores			
Pleasantness/unpleasantness	3.4±0.4	3.3±0.4	NS
Activation/deactivation	3.2±0.5	3.2±0.4	NS
Calmness/tension	3.2±0.7	3.2±0.6	NS
HAD score			
Anxiety	4±4	5±5	NS
Depression	3±3	3±2	NS

Data as presented as mean±SD. For abbreviations see legend to table 1.

Laboratory evaluations

There was no significant impact by protriptyline or placebo on routine laboratory evaluations. The mean serum protriptyline value was 738 nmol·l^{-1} at Visit 5 (range 0–2,900 nmol·l^{-1}). A tendency towards a positive correlation was seen between serum protriptyline and the change in Pao_2 between randomization and visit five (r=0.55; p=0.08).

Exacerbations of COPD

Three patients in the protriptyline group and two patients in the placebo group experienced exacerbations of COPD during the trial (NS).

Side-effects

Twelve patients receiving protriptyline and six patients receiving placebo reported side-effects (p=0.06; NS). The most common side-effect was dryness in the mouth, reported by eight patients in the protriptyline group and three patients in the placebo group (NS).

Discussion

We found no significant benefit from 10 mg of protriptyline daily on daytime arterial oxygenation or quality of life in COPD patients with mild or moderate chronic hypoxaemia. A daily dose of protriptyline, 10 mg, had no effect on the $Paco_2$ level after 12 weeks of treatment. The lack of effect was equally obvious after exclusion of patients who experienced an exacerbation of COPD during the study period. The number of patients included in the trial was small, but there was no indication that the lack of effect by protriptyline was a statistical type II error, *i.e.* that the lack of observed effect was the result of the small number of patients. However, some effect of protriptyline in some patients with a Pao_2 of <8.0 kPa cannot be excluded from this small trial. Even so, if 10 mg of protriptyline daily has an appreciable effect on hypoxaemia, it appears to be limited to a subpopulation of patients. In the nine patients with this degree of hypoxaemia, Pao_2 increased by >1 kPa in three patients after 2, 6 or 12 weeks of protriptyline medication, whilst only one patient receiving placebo experienced an increase in Pao_2 of this magnitude (fig. 1).

The majority of patients receiving protriptyline observed anticholinergic side-effects, but there was no significant difference in the number of side-effects in patients receiving protriptyline and placebo. The high incidence of dryness in the mouth might be partly explained by the information given to all patients on how to avoid dental complications due to dryness in the mouth. The majority of the patients receiving protriptyline experienced some other anticholinergic side-effect in addition to dryness in the mouth.

Protriptyline has been reported to decrease daytime $Paco_2$ in patients with chronic airflow limitation and chronic hypercapnia whilst in a stable state [20]. We did not observe any reduction in $Paco_2$ with the same dose of protriptyline, but most of our patients were not hypercapnic.

The reason why our results differ from those of previous investigations could be the low dose of protriptyline. The fact that a tendency towards a correlation was seen between serum protriptyline and the rise in Pa_{O_2} indicates that the reason for the lack of effect might be that the dose of protriptyline was too small. On the other hand, a higher dose might have induced more side-effects and a lower compliance with the medication. Ten milligrams of protriptyline daily did not increase daytime oxygenation significantly in one 6 week trial [20]. The reason could also be that our patients were carefully selected as having stable hypoxaemia assessed during a 4 week period. Variations in Pa_{O_2} over time and an improvement during follow-up are common in hypoxaemic COPD [1, 21]. During an exacerbation of COPD, hypoxaemia is often accompanied by hypercapnia [22]. If protriptyline medication is started when a patient is not in a stable state, an improvement in both hypoxaemia and hypercapnia might be expected. The fact that five of our patients had an exacerbation of COPD during the trial did not explain the lack of effect, which was equally disappointing after exclusion of these patients from the analyses. Yet another possible explanation is the fact that the majority of our patients received bronchodilatory and anti-inflammatory treatment, which might limit the impact of protriptyline on arterial blood gas tensions.

LTOT is not possible in all patients with symptomatic chronic hypoxaemia and there is a need for alternative treatments. Earlier reports have shown a moderate effect by protriptyline on hypoxaemia from various causes [10–13]. A recent report found no long-term effect by protriptyline on the daytime arterial blood gas tensions in COPD [23]. Our study is the first randomized, controlled trial of protriptyline on patients with COPD and strictly verified stable hypoxaemia. Unfortunately, it revealed little or no effect of protriptyline, 10 mg daily, on hypoxaemia, and no effect on dyspnoea and quality of life. From our results, we cannot conclude that a higher dose of protriptyline would be equally ineffective. However, the high incidence of protriptyline-induced anticholinergic side-effects observed during the 12 week treatment period of our trial suggests that the tolerability of higher doses might be quite limited. Our results indicate that protriptyline has little value in the treatment of mild and moderate stable hypoxaemia caused by COPD.

Acknowledgements: The authors gratefully acknowledge the assistance of the nurses involved in the trial (M. Kennemar, Karlskrona; E. Fröström;, Göteborg; G. Jönsson, Halmstad; V. Eklund, Örebro; L. Markusson. Östersund; A. Ali, Gävle; C. Salomonsson, Stockholm) and the advice given by M. Sullivan, concerning the measurement of quality of life. They also thank A. Odén, and N-G. Pehrsson, for advice on the statistical evaluation.

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