Respiratory Medicine (2006) **100**, 39–45

respiratoryMEDICINE

Plant-based formulation in the management of chronic obstructive pulmonary disease: A randomized double-blind study

P.M. Murali*, S. Rajasekaran, P. Paramesh, O.R. Krishnarajasekar, S. Vasudevan, K. Nalini, S. Lakshmisubramanian, C.N. Deivanayagam

Dalmia Centre for Research and Development, B-133 & 134, Paripoorana Estates, Sundakkamuthur P.O., Coimbatore 641 010, India

Received 5 January 2005; accepted 8 April 2005

KEYWORDS
COPD;
FEV_1;
Arterial blood gas;
PaO_2;
Double-blind;
Clinical trial;
Plant-based formulation;
Herbal

Summary
Background: A randomized double-blind placebo controlled clinical study was undertaken to investigate the safety and efficacy of a plant-based formulation (DCBT1234-Lung KR), which earlier through 2 trials was found to improve FEV_1 and the quality of life of COPD patients.
Objective: The efficacy of DCBT1234-Lung KR was assessed using pulmonary function tests, arterial blood gas (ABG) analyses and the clinical symptoms of COPD in a 6-month study period against a matching placebo and a biomedical drug combination (salbutamol+theophylline+bromhexine).
Methods: One hundred and five subjects aged between 35 and 85 years with a smoking history of more than 20 pack years, showing little or no improvement in FEV_1 upon a bronchial challenge of 200 μg of inhaled salbutamol and exhibiting ABG percentage of less than 85% of oxygen saturation were taken up for the study. The study had 3 arms viz., the plant-based formulation (DCBT1234-Lung KR), placebo and salbutamol (12 mg/day) plus theophylline (300 mg/day) plus bromhexine (24 mg/day). The end point of the study was determined as an improvement of FEV_1 by 200 mL and/or increased ABG values ($>90\%$ PaO_2) and clinical symptoms like dyspnoea, wheezing, cough, expectoration, disability, and sleep disturbances.
Results: DCBT1234-Lung KR patients showed statistically significant (95% level) improvement in FEV_1 and PaO_2 in comparison with salbutamol+theophylline+bromhexine and placebo patients. Twenty-three per cent of DCBT1234-Lung KR patients, 19% of salbutamol+theophylline+bromhexine group and 12% of placebo group patients showed the desired 200 mL improvement in FEV_1 values in comparison with the other 2 arms. Improved PaO_2 was observed in 15.4% of the DCBT1234-Lung KR

*Corresponding author. Tel.: +91 422 2607987; fax: +91 422 2607688.
E-mail address: dalmiabiotechnology@vsnl.com (P.M. Murali).

0954-6111/$ - see front matter
doi:10.1016/j.rmed.2005.04.011

patients while no improvement was seen with patients in any other arms. Symptoms like dyspnoea, wheezing, cough, expectoration, disability and sleep disturbances also significantly reduced in DCBT1234-Lung KR and the biomedical group patients, but not in the placebo arm.
Conclusions: DCBT1234-Lung KR was equivalent, if not better than the present day treatment with salbutamol, theophylline and bromhexine combination in COPD patients and this was ascertained using FEV_1 and ABG values.

Introduction

COPD, which is recognized by both the American Thoracic Society and the European Respiratory Society, is a disorder that is characterized by reduced maximal expiratory flow[1] and slow forced emptying of the lungs[1]; features that do not change markedly over several months.[2,3] This limitation in airflow is only minimally reversible with bronchodilators. This is a serious respiratory disorder which primarily occurs on account of smoking.[4] The Global Burden of Diseases studies[2] has found that COPD was the 6th commonest cause of death worldwide and the prediction is it will move to the 3rd position. According to World Health Organization (WHO), this is the 4th largest killer disease already. COPD is associated with significant disability and restriction in daily activities.

COPD comprises 2 related diseases, chronic bronchitis and emphysema, one rarely occurring without a degree of the other. The pathological basis of chronic bronchitis is mucus hypersecretion secondary to hypertrophy of the glandular elements of the bronchial mucosa. Emphysema is a condition, where there is permanent destructive enlargement of the airspaces distal to the terminal bronchioles without obvious fibrosis.[5] Patients with COPD have features of both conditions, although one may be more prominent than the other.[5]

COPD is a major problem in countries like India mainly affecting the lower strata and the industrial workers. As of now, most of the concurrent medications fail to effectively stop the disease progress and moreover may be accompanied by systemic side effects when administered as a maintenance dose. These drugs can contribute to side effects like tremors, palpitation, seizures and Cushingod features.[6]

Two pilot studies carried out earlier by this group found that the plant-based formulation, DCBT1234-Lung KR, improved the patients' quality of life. They also tolerated the drug very well without any side effects.[7] The 1st pilot study was a double-blind randomized placebo controlled clinical trial, with 30 patients, 15 in each arm. The objective of the trial was to observe improvement of clinical symptoms on the usage of DCBT1234-Lung KR in comparison to placebo for a week. The absence of clinical symptoms like dyspnoea, wheezing, cough, expectoration, disability and sleep disturbances were scored as 0 and 1, 2, or 3 corresponding to mild, moderate and severe. Patients administered with DCBT1234-Lung KR showed improvement in the clinical symptoms studied. The 2nd study was an open trial with 30 patients for a period of 12 weeks with the primary objective of recording any improvement of 200 mL in FEV_1 values and/or attainment of 90% PaO_2 in arterial blood gas (ABG) values. Patients administered with DCBT1234-Lung KR showed statistically significant improvement over the placebo group. Both the trials were approved by the ethics committee of the respective hospitals and patients signed the consent form.

The present study was designed with a structured protocol with the primary objective of observing improvement in pulmonary function and ABG in patients administered with DCBT1234-Lumg KR in comparison with a placebo and a biomedical arm for a period of 24 weeks.

Methods

The hospital ethics committee had earlier approved a 2-week run in period without any medication to the volunteers of the trial to be inducted into the study. Volunteers, between 35 and 85 years of age having COPD with moderate and stable symptoms for the previous 1 year, maintained on drugs such as salbutamol, theophylline, bromhexine, prednisolone, inhaled corticosteroids such as ipratropium bromide singly or in combination, without requiring hospitalization, with a smoking history of 20 pack years, showing little ($<10\%$) or no improvement in FEV_1 on the baseline recordings (15 min after the administration of 200 μg, 2 puffs of inhaled salbutamol with a gap of 5 min between puffs), ABG percentage of less than 85% of oxygen saturation were included in the study conducted at the Government Hospital for Thoracic Medicine (GHTM), Chennai, India.

Absence for occupation-related lung diseases or nasal allergy, chest radiographs to confirm COPD and to rule out bronchial asthma and other lung diseases, patients suffering from concurrent systemic diseases, which would include cardiopulmonary and other diseases such as tuberculosis, pulmonary eosinophilia, cancer, congestive failure, hepatic dysfunction, neurological disorders and diarrhoeal disorders were excluded from the trial. Fully treated pulmonary tuberculosis was not an exclusion criterion and patients showing less than 10 g% haemoglobin level and exhibiting short seasonal changes of less than 4 weeks duration were also excluded from the study.

Study design

The 24-week study was a double-blind randomized placebo controlled clinical trial with 3 arms; DCBT1234-Lung KR, a biomedical and a placebo arm. The hospital ethics committee had approved the protocol. The primary objective was to observe improvement of 200 mL in FEV_1 and/or improved oxygen tension in the blood ($PaO_2 \geqslant 90\%$) and with a secondary objective to observe improvement in clinical symptoms in patients.

Study medication

The biomedical arm contained salbutamol (12 mg/day) plus theophylline (300 mg/day) plus bromhexine (24 mg/day), DCBT1234-Lung KR with the plant-based formulation and the placebo containing lactose filled in identical capsules of uniform color and shape and packed in uniform strips. The combination of salbutamol+theophylline+bromhexine is the standard medication prescribed for the treatment of COPD in this hospital and oral corticosteroids are given whenever the patient's condition deteriorates. Each generic biomedical drug was filled in capsules with each capsule containing 4 mg equivalent of salbutamol plus 100 mg equivalent of theophylline and 8 mg equivalent of bromhexine. Lactose was used in placebo and as a filler to arrive at uniform weight for the other 2 drugs.

All patients admitted to the trial were dewormed, as outpatients, by administering a tablet albendazole 400 mg, before the commencement of the trial. Only 1 patient from 1 family was enrolled to the trial. Patients were instructed to avoid the use of all drugs, by themselves, for any ailment. They were advised to consult the treating physician for any symptom or complaint. The physician made a careful record of all the details of the complaints and dispensed any essential medication.

Patients were advised to visit the hospital daily during the 1st week. Subsequently, they visited every month for follow up and collection of medication. The patients were instructed to take 3 capsules every day, 1 each after breakfast, lunch and dinner.

Patients were directed to bring at each visit the drug container supplied during the previous attendance, along with any unconsumed capsules. The physician interrogated the patient regarding the regularity of drug intake and also recorded the number of unconsumed capsules in the container if any. A new container with drugs (for the next month) was issued each month. The investigating centre provided direct access facility for the patient all round the clock for any emergency.

Before signing the consent form, information and details of the trial were given to each patient and were informed of the option to withdraw from the study at any time without assigning any reason. The principal investigator could withdraw any patient from the trial if the patient showed any deterioration of vital signs of kidney function or elevated liver or cardiac enzymes. Monthly review meetings between the investigators, physicians and the trial coordinators were conducted to monitor the progress and compliance of the trial.

Study visits

Comprehensive assessment comprising history, clinical assessment, laboratory investigations and lung function tests were recorded before the medication dispensation. Clinical assessment was done daily in the 1st week and at monthly intervals thereafter. The laboratory investigations were performed on the 7th day, 3rd month, and at the end of the 6th month. Lung function tests were recorded twice a day in the 1st week and then monthly thereafter. ABG values were recorded every month.

Examinations

Clinical assessment included dyspnoea, wheezing, cough, expectoration, disability and sleep disturbances were recorded daily in the 1st week and subsequently every month. They were assessed individually as absent, mild, moderate and severe with scores of 0, 1, 2 and 3. Lung function tests were recorded twice a day (at 11 a.m. and 5 p.m.) in the 1st week. Subsequently, it was done every month at the outpatient department of the hospital. ABG (PaO_2) was analyzed every month.

Spirometry was done using Transfer Test C model lung function machine (P.K. Morgan, UK) and ABG analysis was carried out in model 1312 Instrumentation Laboratory machine (USA).

Statistical and other analyses

Scores of 0, 1, 2 and 3 were used in clinical symptoms such as dyspnoea, wheezing, cough, expectoration, disability and sleep disturbances that were assessed as absent, mild, moderate and severe, respectively. The mean values of baseline in comparison to the values on completion of the study for each of the arms for the above parameters were computed and standard deviation determined. The Mann–Whitney test was performed to find any variations in the baseline and if found, inter-group comparisons were done using the Bonferrroni's test to identify the significantly different groups. Pulmonary function values are expressed as mean $\pm$ standard deviation (SD). The paired '*t*' test was used to analyze the improvement of clinical symptoms, FEV_1 and PaO_2 in the patients before and after the trial within the group and analysis of variance (ANOVA) was used to study variations between the groups. A "*P*" value of <0.05 is considered as statistically significant.

Composition of DCBT1234-Lung KR

The composition of the plant-based formulation, DCBT1234-Lung KR is listed in Table 1.

Results

Recruitment of patients took 8 months. Out of 135 patients recruited in this study, 105 patients completed the 6-month study with 32 patients in the biomedical arm, 39 patients in DCBT1234-Lung KR arm and 34 patients in placebo arm. During the course of the trial, 6 patients in DCBT1234-Lung KR arm, 13 patients in the biomedical arm and 11 patients in the placebo arm were lost to follow up.

Table 2 outlines the medical history and the baseline demographic data of the patients. All patients were male. The mean weight, body mass index (weight in kg/height in m^2) and haematological parameters for all the 3 arms were similar. Placebo arm had higher PFT values than the other 2 arms. However, the Mann–Whitney test indicated that all the 3 arms had similar baseline values including FEV_1. The mean predicted FEV_1 values, FEV_1/FVC ratio and the ABG values were also similar in all the 3 arms. Good compliance ($>90\%$) with the medication dispensed in all the 3 arms were recorded when empty blisters and unconsumed capsules were counted.

Signs and symptoms

Signs and symptoms of the patients in the study were analyzed individually and only the baseline (initial) and 6th month (final) values of each symptom are represented in Table 3. DCBT1234-Lung KR group patients exhibited improvement in all the clinical symptoms studied while the biomedical drug did not control dyspnoea and disability.

Pulmonary function tests

The mean baseline FEV_1 values of all the 3 arms were similar ($P = 0.39$). Mean FEV_1 values of the baseline and the end of the trial showed statistically significant improvement ($P<0.05$; 95% significance) in DCBT1234-Lung KR arm, but not in the biomedical and placebo arms (Table 3). Twenty-four per cent of DCBT1234-Lung KR patients, 19% of biomedical drug patients and 12% of placebo patients showed 200 mL improvement in FEV_1 values at the end of the trial (Table 4). The mean values of PaO_2 presented in Table 3 showed DCBT1234-Lung KR group exhibited statistically significant ($P\leqslant0.05$) improvement at the end of the trial whereas the biomedical and placebo group patients failed to demonstrate the improvement. It was also noticed that except 6 patients in the DCBT1234-Lung KR arm, none in the other arms exhibited the desired improvement to more than 90% oxygen saturation in blood (Table 4).

Table 1 Composition of DCBT1234-Lung KR.

Botanical names	English names	Quantity of a.i. (per capsule)
Bryonia alba	Bryonia	75–80 μg of cucurbitacins
Cephaelis ipecacuanha	Ipecac	100–110 μg of emetine
Drosera peltata	Sun-dew	90–100 μg of plumbagin
Lactose and other excipients	—	q.s.

Table 2 Demographic and baseline information of the patients.

Characteristic	DCBT1234-LungKR ($n = 39$)	Salbutamol+theophyline +bromohexine ($n = 32$)	Placebo ($n = 34$)
Mean age (years)	52	53	53
Range (years)	(35–74)	(35–81)	(38–80)
Mean weight (kg)	48.18 ± 6.85	49.56 ± 6.93	50.76 ± 7.02
Mean BMI	18.87 ± 4.29	19.24 ± 4.32	19.53 ± 4.35
Mean eosinophil count (cells/cm m)	250.3 ± 15.60	260 ± 15.87	200 ± 14.14
Mean Hb (g%)	10.6 ± 3.21	10.3 ± 3.15	10.6 ± 3.20
Smoking history (in pack years)	21.46 ± 4.57	22.47 ± 4.66	23.81 ± 4.81
Mean FEV_1* (L/s)	1.32 ± 0.61	1.22 ± 0.60	1.46 ± 0.66
Mean FEV_1 (predicted) (L/s)	2.81 ± 0.61	2.80 ± 0.47	2.78 ± 0.51
Mean FVC† (L)	2.06 ± 0.71	1.90 ± 0.64	2.15 ± 0.59
Mean FEF (25–75%)‡ (L/s)	1.12 ± 0.82	1.01 ± 0.94	1.36 ± 1.23
Mean PEFR¶ (L/min)	280.60 ± 95.17	270.30 ± 114.67	311.40 ± 116.89
FEV_1/FVC ratio	0.63 ± 0.15	0.63 ± 0.15	0.64 ± 0.15

±Standard deviation (SD).
*FEV_1 = forced expiratory volume in 1 s.
†FVC = forced vital capacity.
‡FEF = forced expiratory flow.
¶PEFR = peak expiratory flow rate.

Table 3 Signs and symptoms, FEV_1 and PaO_2 of COPD patients.

Signs and symptoms	DCBT1234-Lung KR ($n = 39$)	Salbutamol+theophylline+ bromhexine ($n = 32$)	Placebo ($n = 34$)
Dyspnoea			
Baseline	2.25 ± 1.64	0.75 ± 0.50	3.00 ± 1.73
End of the trial	1.14 ± 1.35*	1.00 ± 1.41^{ns}	2.66 ± 1.15^{ns}
Wheezing			
Baseline	1.33 ± 2.14	0.25 ± 0.50	2.67 ± 2.52
End of the trial	0.00 ± 0.00*	0.00 ± 0.00^{ns}	2.33 ± 0.58^{ns}
Cough			
Baseline	1.29 ± 1.60	1.25 ± 1.26	0.50 ± 0.70
End of the trial	1.00 ± 1.41*	1.00 ± 1.41^{ns}	1.00 ± 0.90^{ns}
Expectoration			
Baseline	1.43 ± 1.90	1.20 ± 0.84	3.00 ± 2.83
End of the trial	0.57 ± 0.13*	0.85 ± 0.50^{ns}	3.00 ± 0.00^{ns}
Disability			
Baseline	1.33 ± 1.67	1.50 ± 1.85	2.29 ± 2.21
End of the trial	0.64 ± 1.21^{ns}	2.00 ± 1.92^{ns}	2.14 ± 1.67^{ns}
Disturbances in sleep			
Baseline	1.70 ± 1.16	0.80 ± 0.42	2.00 ± 0.89
End of the trial	0.08 ± 0.29*	0.20 ± 0.42^{ns}	2.36 ± 0.42^{ns}
FEV_1			
Baseline	1.32 ± 0.61	1.22 ± 0.60	1.43 ± 0.66
End of the trial	1.50 ± 0.72*	1.04 ± 0.36^{ns}	0.75 ± 0.15^{ns}
PaO_2			
Baseline	80.83 ± 16.52	82.78 ± 28.02	83.93 ± 19.57
End of the trial	92.03 ± 0.76*	81.80 ± 8.39^{ns}	84.00 ± 1.02^{ns}

*$P < 0.05$; ns—not significant.

Table 4 Number of patients showing improvement in FEV_1 and PaO_2.

Drug type	No. of patients taken for analysis	Number of patients shown >200mL improvement in FEV_1 after 6 months		Number of patients shown improvement of >90% PaO_2 after 6 months	
DCBT1234-Lung KR	39	9	23%	6	15%
Salbutamol+theophylline+bromhexine	32	6	15%	0	0%
Placebo	34	4	10%	0	0%
Total	105	19	49%	6	6%

Discussion

Several authors have expressed their reservations in using complementary and alternative medicine for the treatment of a number of diseases as they have opined that a randomized clinical trial with a matching placebo under controlled conditions without any bias is necessary to validate the efficacy of plant-based formulations.[8] In this study, with a plant-based formulation, DCBT1234-Lung KR, besides a matching placebo, we felt that it would be incisive to also add a biomedical arm to the study for comparing the efficacy of the plant-based formulation.

The demography of the patients in this study was very similar in nature. All the patients inducted were males only. The dropouts were higher in the biomedical arm and placebo arm followed by DCBT1234-Lung KR. Lowest dropouts in the DCBT1234-Lung KR arm probably suggesting that patients felt comfortable with the plant-based formulation as evinced from the results of the clinical symptoms. Most of the clinical symptoms were significantly reduced in DCBT1234-Lung KR patients.

FEV_1 is the most important spirometry test in diagnosing and monitoring improvement in COPD patients.[9] An increase of 200 mL or 15% in the FEV_1 values would be rated as a significant improvement in such patients. Though only 23% of Lung KR patients showed 200 mL improvement in FEV_1 values, the biomedical arm showed improvement only in 19% patients. A similar trend was also seen in the PaO_2 values of both the arms. Except 6 patients in DCBT1234-Lung KR arm, none in any other arm exhibited improvement in ABG value to attain 90% oxygen saturation.

The plants used in the formulation have proven record in their usefulness in the treatment of respiratory diseases. *Bryonia alba* has been used in Homoeopathy as one of the ingredients for treatment of whooping cough and bronchitis.[10] *Drosera* has been used in the treatment of deep hoarse cough. The genus *Drosera* contains naphthoquinones considered as the main constituent with antispasmodic, demulcent, and expectorant activities. Plumbagin of *Drosera* is active against *Streptococcus*, *Staphylococcus* and *Pneumococcus* species. Its relaxing effect upon involuntary muscles helps in the symptomatic relief in respiratory illnesses.[11] Mucolytic activity and thinning of sputum by the same plant has also been recorded.[12] Another ingredient of DCBT1234-Lung KR, ipecac, contains the alkaloids, emetine and cephaeline, which has been used as an emetic, diaphoretic and expectorant since the 18th century.[13]

It is interesting to note that DCBT1234-Lung KR a multicomponent plant-based formulation is effective in the management of COPD without side effects associated with modern biomedical drugs. The investigator and his group are currently working on understanding the mechanism of action of the multicomponent formulation DCBT1234-Lung KR.

Acknowledgements

The cooperation and support of the Dalmia Brothers Private Limited, New Delhi, and Government Hospital for Thoracic Medicine, Chennai, is highly appreciated. The statistical analyses carried out by Ms. Stella of DCRD on similar lines of analysis by Mr. Kishore of Chennai is also acknowledged.

References

1. Mak V. The burden of COPD. Chronic obstructive pulmonary disease (COPD). The UK perspective. Chest Medicine online. *COPD webpage.htm*
2. Hodgkin JE, Farrell MJ, Gibson ST, et al. American Thoracic Society. Medical Section of the American Lung Association. Pulmonary rehabilitation. *Am Rev Respir Dis* 1981;**124**(5): 663–6.

3. Barnes PJ. Chronic obstructive pulmonary disease. *N Engl J Med* 2000;**343**(4):269–80.
4. Mak V. Smoking and bronchial hyperreactivity. The causes of COPD and who is at risk? Chest Medicine online. *The causes of COPD and who is at risk.htm*
5. Mak V. The definition of COPD. Chest Medicine online. *The definition of COPD.htm*
6. Iqbal A, Schloss S, George D, Isonaka S. Worldwide guidelines for chronic obstructive pulmonary disease: a comparison of diagnosis and treatment recommendations. *Respirology* 2002;**7**(3):233–9.
7. Deivanayagam CN, Sridhar CB, Rajasekaran S, et al. Promising plant-based formulation in the treatment of chronic obstructive pulmonary disease and asthma. An oral presentation in National symposium on pulmonary and critical care medicine, under the aegis of Raj Nanda Pulmonary Disease Research Trust, Escorts Hearts Institute and Research Center & Foundation for Chest, Critical Care and Sleep held at Hotel Ashoka, New Delhi, India, August 30–September 1, 2002 in *Chest Summit* 2002.
8. Linde K, Jonas WB, Melchart D, Willich S. The methodological quality of randomized controlled trials of homeopathy, herbal medicines and acupuncture. *Int J Epidemiol* 2001;**30**: 526–31.
9. Dakin JH, Kourteli EN, Winter RJD. *Making sense of lung function tests; a hands-on guide*. London: Arnold; 2003.
10. Boericke W. *Manual of homoeopathic materia medica*, 9th ed. New Delhi: Indian Books and Periodicals Publishers; 1927.
11. Didry N, Dubreuil L, Trotin F, Pinkas M. Antimicrobial activity of aerial parts of *Drosera peltata* Smith on oral bacteria. *J Ethanopharmacol* 1998;**60**(1):91–6.
12. Juniper BE, Robins RJ, Joel DM. *The carnivorous plants*. London: Academic Press; 1989.
13. Yoshimatsu K, Shimomura K. Emetic alkaloid in root culture of *Cephaelis ipecacuanha*. *Phytochemistry* 1991;**30**(2):505–7.