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Research Article

Comparative Study of Efficacy and Adverse Effect Profile of Theophylline and Etofylline Combination Verses Doxofylline in Patients with COPD

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Abstract: Chronic obstructive pulmonary disease (COPD), caused by chronic inflammation and destruction of the airways and lung parenchyma is usually associated with tobacco smoking or prolonged exposure to other noxious particles and gases. It is a major health problem characterized by progressive airflow obstruction that is sometimes partially reversible. Methylxanthines like theophylline have been used in combination for bronchodilation in COPD since many years. Doxofylline, a novel methylxanthine is claimed to be therapeutically similar but with better safety. This study was designed to compare the efficacy and safety of theophylline and etophylline fixed dose combination with doxofylline at doses commonly used in patients with stable COPD. The study was conducted in the department of Pulmonology. 204 patients were divided into two groups and randomly assigned to a 21 day oral treatment. Group I was administered theophylline 69 mg + etofylline 231mg (Deriphylline Retard 300 mg) once a day and group II was administered doxofylline 400 mg twice a day. Efficacy was measured objectively using spirometric parameters like FEV1 (Forced expiratory volume at the end of 1 second), FVC (Forced vital capacity) and % FEV. Adverse effects were subjectively recorded weekly. Statistical analysis showed no significant difference with respect to spirometric variables and symptom score in the two groups. But significant difference with respect to side effects was observed. Palpitation was the most common adverse effect followed by tremor, insomnia and dyspepsia. CONCLUSION: Though doxofylline has better safety profile, it has no advantage over theophylline and etofylline in terms of efficacy.
Keywords: Methylxanthines, Spirometry, Phosphodiesterase inhibitors, Deriphylline.

INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is a major cause of morbidity and mortality throughout the world. The prevalence and burden of COPD are projected to increase in the coming decades due to continued exposure to COPD risk factors and the changing age structure of the world's population. In India, it is recognised as a major health problem requiring management from the primary health care level onwards [1].

COPD is a disease state characterized by progressive airflow limitation which is not fully reversible and is associated with an abnormal inflammatory response of the lung to offending noxious particles and gases [2]. At one time, COPD was more common in men, but because of the higher risk of exposure to indoor air pollution in low-income countries, the disease now affects men and women almost equally. It is estimated that COPD becomes the third leading cause of death worldwide by 2030 [3].

Risk factors for COPD include tobacco smoking, indoor air pollution (from biomass fuel), outdoor pollution, occupational dusts and chemicals [4]. Low birth weight and respiratory infections during one's childhood also have the potency to increase the risk for developing COPD [5]. Characteristic symptoms of COPD include progressive dyspnoea, chronic cough with sputum production [6].

The diagnosis of COPD, classification of its severity and disease progression can be assessed and monitored by a simple non invasive method called spirometry. The ratio of forced expiratory volume in 1 second (FEV1) to functional vital capacity (FVC) reflects the rate of lung emptying. Presence of obstructive ventilatory defect (COPD) is defined as a value of FEV1/FVC < 0.7. Classification of obstructive disease can be made according to the Global Strategy for the Diagnosis, Management and Prevention of chronic obstructive lung disease (GOLD) [2] using the measured FEV1as percentage of the predicted FEV1 to classify COPD patients.

Classification of obstructive disease according to the Global Strategy for the Diagnosis, Management and Prevention of chronic obstructive lung disease (GOLD)

Sl. No	Gold Stage	Spirometric Analysis
1	GOLD I	FEV1 ≥ 80 % of the predicted
2	GOLD II	50% ≤ FEV1< 80% predicted
3	GOLD III	30% ≤ FEV1< 50% predicted
4	GOLD IV	FEV1 < 30% predicted or FEV1 < 50% and respiratory failure

The treatment of COPD is aimed at preventing disease progression, relieving symptoms, improving the quality of life, treating the exacerbations and to improve survival [7]. Along with drug therapy, patient education, cessation of smoking, good nutritional support and regular self directed exercises are recommended. The recommended choice of treatment in Gold staging I and II are short acting beta 2 agonist or anticholinergics. Alternative choices are methylxanthines alone or in combination with long acting beta 2 agonists or anticholinergics. For many years, theophylline (1, 3 dimethyl xanthine) and etofylline (7-2-hydroxyethyl theophylline), a theophylline derivative have been used in the treatment of COPD. Use of these drugs though has diminished in the recent years due to availability of other effective bronchodilators like long acting inhaled beta 2 agonists, they are still an effective and inexpensive drugs for oral administration.

In developing countries like India, one of the most commonly used methylxanthines for bronchial asthma and COPD is a combination of slow releasing formulation of etofylline and theophylline (brand name-deriphylline retard). Methylxanthines cause weak inhibition of phosphodiesterase (PDE) isoenzymes which are responsible for the metabolism of cAMP. This elevated cAMP concentration accounts for bronchodilation and cardiac stimulation. Inhibition of PDE4 in inflammatory cells decreases the release of cytokines and chemokines which in turn causes decrease in the immune cell migration and activation.

Adenosine causes constriction of bronchial smooth muscles (A_1) and histamine release from airway mast cells (A_3). At therapeutic concentrations, theophylline antagonises adenosine receptors and cause bronchodilatation (A_1). Adenosine antagonism is unlikely to account for anti-inflammatory effects of theophylline but may cause serious side effects including cardiac arrhythmias and seizures through (A_1) receptor antagonism [8].

Acetylation of histones is essential for the activation of inflammatory gene transcription. Corticosteroids thus act by recruiting histone deacetylases to the site of inflammatory gene transcription. Methylxanthines, by activation of Histone deacetylases (HDAC) and augmentation of steroid effects, bring about anti inflammatory effects which are particularly important in COPD patients [9, 10]. They improve ventilator drive, arterial oxygenation, contractility of diaphragm, mucociliary clearance and exercise tolerance. They inhibit mast cell histamine release and suppress leukocyte activation.

Doxofylline (7-1, 3-dioxalan-2-ylmethyl theophylline) is a novel xanthine bronchodilator derived from theophylline. It has remarkable bronchodilator properties. Inhibition of PDEs is similar to theophylline but it is less active as an adenosine antagonist and so has a better safety profile [11].

According to the current GOLD guidelines, the recommend dose of theophylline is 100-600 mg daily alone or as an add-on therapy in stable COPD patients [12, 13]. For doxofylline, the commonly used dose is 400 mg, twice a day [14]. Hence a comparative study was done with theophylline + etofylline combination (Deriphylline Retard) and doxofylline at the commonly used doses, for evaluating their efficacy and safety in patients with stable COPD.

MATERIALS AND METHODS

It was a randomized, prospective, parallel group and open labelled study conducted in the department of Pulmonology, Government general hospital, a tertiary care centre in Vijayawada. The study protocol was approved by the institutional ethical committee. An informed written consent was taken from all the patients included in the study. A total of 204 patients who met the inclusion and exclusion criteria were randomly divided into two groups of 102 each. One group received tablet theophylline + etofylline (deriphylline retard 300 mg) once a day and the other group received tablet doxofylline 400 mg twice a day for period of 21 days. Before starting the treatment, each patient was subjected to spirometric evaluation and the baseline readings were recorded.

Inclusion Criteria

- Patients who were diagnosed with COPD clinically and spirometrically in the department of Pulmonology, Government general hospital, Siddhartha medical college, Vijayawada.
- Patients both male and female above the age of 35 years and below the age of 65 years suffering with COPD.
- As deriphylline and doxofylline are used as single drugs, COPD patients having FEV1 above 80% predicted (Stage I) and those with

FEV1 ranging between 50-80% predicted (Stage II) only were included.

Exclusion Criteria

- Patients below the age of 35 and above the age of 65 years.
- Patients who had moderate/severe COPD or exacerbations in the last 4 weeks
- Patients on inhaled or systemic corticosteroids and oral/ parenteral beta 2 agonists at the time of screening.
- Patients with active respiratory disease other than COPD like tuberculosis, bronchial asthma, pneumonias and acute bronchitis of different aetiology, lung malignancies and other chronic miscellaneous lung disorders.
- Patients with compromised cardiac, renal and hepatic parameters.

At the time of initial visit, patients were assessed by history, clinical examination, chest X-ray and sputum examination. Data regarding smoking history and exacerbations were recorded. Objective measurements such as lung function tests that are important in diagnosing and monitoring COPD were performed.

Spirometric Evaluation

Spirometer was invented in 1846 by John Hutchinson [15]. It measures the airflow in and out of lungs. Patients were asked to blow into a tube attached to the spirometer with a nose clip on their nose. A computerised sensor calculates and gives the results in a graph. The graph shows the results which demonstrate the patient's air flow rates and the volume of air that can be forced out of the lungs. The same spirometer was used throughout the study period.

Statistical Analysis

The data were analyzed statistically using Students t test and Chi square test. A p value < 0.05 was considered to be significant.

RESULTS

Out of the total study population of 204, 128 (62.7%) were males and 76 (37.2%) were females.102 patients each were randomly allotted into two groups (Group 1 on theophylline + etofylline combination and group 2 on doxofylline). Due to non compliance with the treatment and failure to come for subsequent follow-ups only 86 out of the 102 (82%) patients from theophylline + etofylline group and 94 out of 102 (92%) patients from doxofylline group completed the study. Sex wise distribution showed no significant difference in both the study groups (p value 0.98623) as shown in table 1. Most of the patients in the study group belonged to age group of 41 to 45 as shown in the Fig. 2.

Table 1: Sex wise distribution

	Theophylline + Etofylline Group		Doxofylline Group
Males	55		60
Females	31		34
Total	86		94
Chi^2 Test	Chi^2 value:0.0003	p Value: 0.986	Inference: Not significant

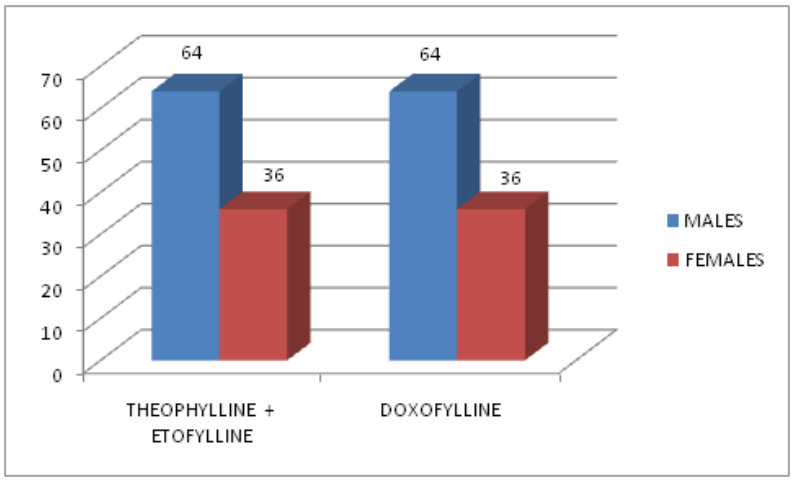

Fig. 1: Sex distribution in theophylline + etofylline and doxofylline groups (figures in percentages)

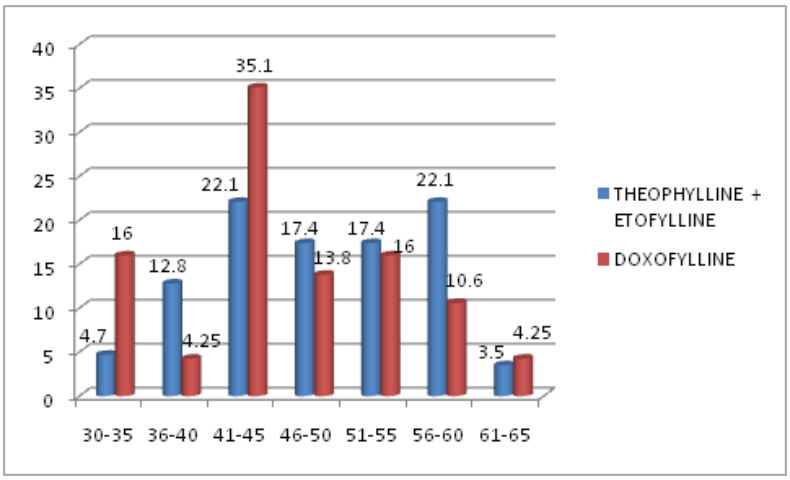

Fig. 2: Age wise distribution of patients in both the groups (figures in percentages)

Out of the total study population, 108 were smokers. Habit of smoking was present in 52(60.5 %) of patients receiving theophylline + etofylline and 56 (59.6%) of patients receiving doxofylline as shown in the table 2. In terms of pack years, 23 (21.29%) patients smoked for < 5 packs, 51 (47.22%) smoked for 5-10 pack years and 34(3.48%) smoked for 10-15 pack years. Difference between distribution of patients who smoke in both the study populations was not significant (p value 0.9030). All the patients of both the groups with the habit of smoking were males (100%).

Table 2: Distribution of smokers in the study population

History of smoking	Theophylline + Etofylline	Doxofylline
Smokers	52 (60.5 %)	56 (59.6%)
Non smokers	34 (39.5 %)	38 (40.4%)
Chi ^{2} value	0.0148	
p Value : 0.903 (>0.05)	Inference: Not significant	

Improvement in the symptoms of COPD like relief of breathlessness and cough, improvement in exercise tolerance were enquired in the two groups. In the theophylline + etofylline group 55.8% of the study population had improvement in the symptoms as shown in the Fig. 3. Improvement of symptoms was maximum in the age group of 41-45(68%) followed by 51-55 age group (60 %).

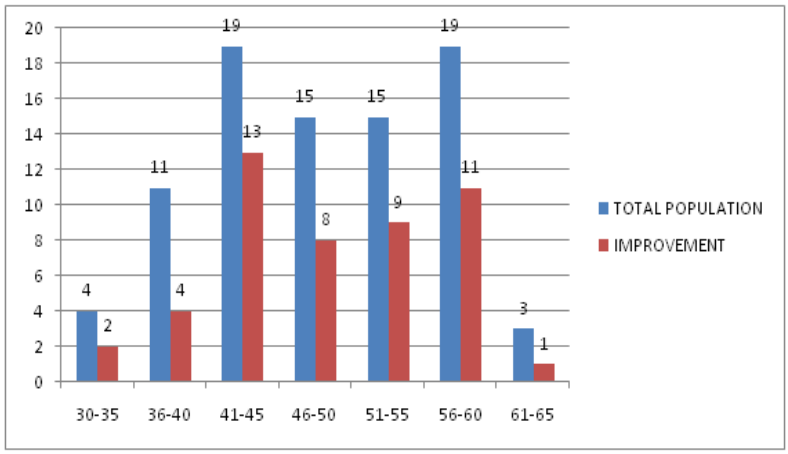

Fig. 3: Improvement of symptoms in theophylline + etofylline group (figures in numbers)

In case of doxofylline group, 60.6% (57 people) had improvement in the symptoms as seen in the Fig. 4. Maximum improvement was observed in the age group of 41-45 (72%) followed by age group between 31-35(67%).

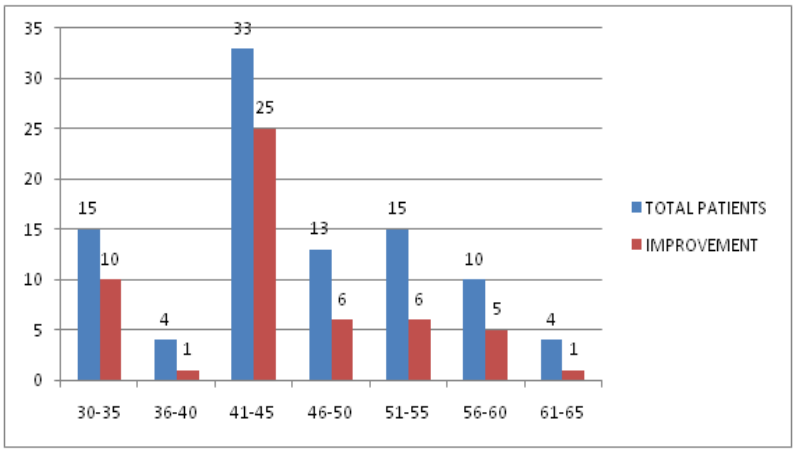

Fig. 4: Improvement of symptoms in doxofylline group (figures in numbers)

All the patients underwent spirometric evaluation before the initiation of therapy. Patients with forced expiratory volume in the first second (FEV1) above 80% of the normal were included in spirometry stage 1 and those with FEV1 between 50 to 80 % were included in spirometry stage 2.

During follow-up, all the patients were enquired about improvement or relief of symptoms and development of any adverse effects. On weekly assessment of spirometric analysis, improvement in lung parameters in both the groups, more in doxofylline group was observed as shown in table 3.

Table 3: Weekly analysis of spirometric parameters in both the study groups

Spirometric Parameter	Day	Theophylline + Etofylline Group (n= 86) Mean ± SD	Doxofylline Group (n= 94) Mean ± SD
FEV1	0	1.119 ± 0.266	1.252± 0.37
	7	1.137± 0.268	1.269± 0.373
	14	1.150± 0.268	1.28± 0.372
	21	1.155± 0.266	1.287± 0.37
% of FEV1 Predicted	0	67.83± 8.53	68.56±8.51
	7	68.96± 8.66	69.55± 8.38
	14	69.78± 8.77	70.2± 8.18
	21	70.26±8.57	70.63±8.198
FVC	0	1.67±0.426	1.92 ± 0.62
	7	1.68±0.42	1.92±0.62
	14	1.69±0.425	1.93±0.62
	21	1.695±0.423	1.94±0.62

Values of FEV1 and %FEV1 in both the deriphylline and doxofylline groups were documented and analysed using paired t test as in the table 4 and 5 respectively.

Table 3: Analysis of changes in FEV1 and % FEV1 within deriphylline group

Theophylline + Etofylline Group	FEV1		% FEV1	
Statistical Analysis	Before	After	Before	After
Mean	1.1191	1.1552	67.83	70.26
Standard Deviation	0.2661	0.266	8.53	8.57
Paired t Statistic	14.455		13.432	
p Value	<0.0001		<0.0001	

Table 5: Analysis of changes in FEV1 and % FEV1 within doxofylline group

Doxofylline Group	FEV1		% FEV1	
Statistical Analysis	Before	After	Before	After
Mean	1.2525	1.2871	68.56	70.63
Standard Deviation	0.3072	0.3078	8.51	8.19
Paired t Statistic	26.452		22.191	
p Value	<0.0001		<0.0001	

In both groups the improvements observed were significant statistically from baseline to the end of the study with respect to FEV1 and %FEV1. Mean improvements in FEV1, %FEV1 and FVC were compared between the two study groups using unpaired t test as shown in the table 6.

Table 6: Mean improvement in FEV1, %FEV1 and FVC compared between the groups

	Mean improvement in FEV1 from baseline to 21days	Mean improvement in % FEV1 from baseline to 21days	Mean improvement in FVC from baseline to 21days
Theophylline + Etofylline	0.0356	2.43	0.019
Doxofylline	0.0345	2.06	0.023
Unpaired t statistic	0.4098	1.84	1.2
p value	0.341	0.333	0.11
Inference	Not significant	Not significant	Not significant

The adverse effects associated with the drugs used by the patients were enquired about. Most common adverse effect developed in the study population was palpitations (91%) in theophylline + etofylline group and (58%) in doxofylline group followed by tremors, headache and insomnia. All the side effects were significantly high in theophylline + etofylline group except for dyspepsia.

Table 6: adverse effects observed in both the groups and their comparison

Sl. No.	Adverse effects	Theophylline (n=86)		Doxofylline (n=94)		p value
		Patients	%	Patients	%	
1.	Palpitations	78	91	58	61	< 0.0001
2.	Tremors	62	72	34	36	< 0.0001
3.	Headache	28	33	11	11	0.0006
4.	Insomnia	52	60	38	40	0.0072
5.	Dizziness	28	33	8	9	<0.0001
6.	Dyspepsia	38	44	30	32	0.089
7.	Pruritis	22	26	8	9	0.0021
8.	Nausea	9	10	2	2	0.019

Most commonly found adverse effect in the patients on theophylline + etofylline was palpitations (91%), followed by tremors (72%) and insomnia (60%). Adverse effect seen in doxofylline group were palpitations (60%) which was most common, followed by insomnia(40%) and tremors(36%).Both the study groups experienced dyspepsia(44% in theophylline + etofylline group and 30% in doxofylline group) which was treated by adding antacids to the therapy. Adverse effects observed were mild in nature and none of them necessitated hospital admission. Cases with palpitations and tremors were reassured and those with headache and dyspepsia were treated with analgesics and proton pump inhibitors respectively.

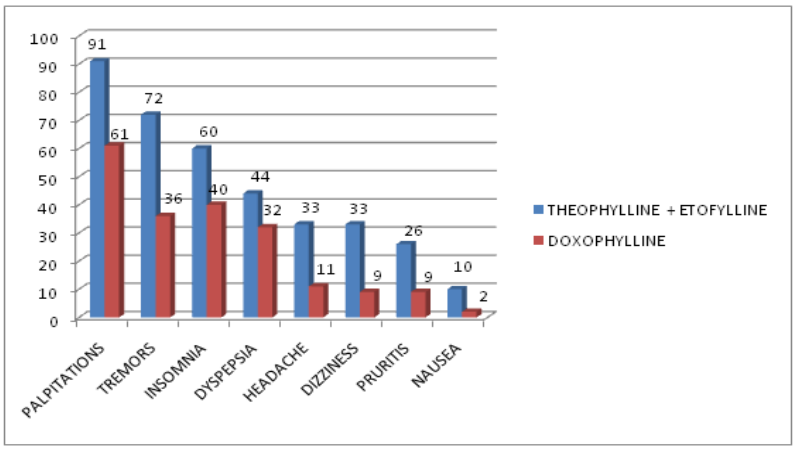

Fig. 5: Incidence of adverse effects in percentages (figures in numbers)

DISCUSSION

In developing countries like India, combination of slow releasing formulation of theophylline and etofylline (Deriphylline - Retard) is commonly used in the treatment of COPD. Low cost and efficacy of these methylxanthines could be the

reasons. Less awareness on safety profile and non availability of other oral alternatives could also contribute to the usage of these drugs. In this scenario, we tried to explore the efficacy and safety profile of theophylline and etofylline combination in comparison with doxofylline in stable cases of COPD.

Out of the total 204 patients recruited, 180 patients (86 patients on theophylline + etofylline and 94 patients on doxofylline) completed the study (percentage of drop outs was 11.8). Of these, 48 (55.8%) patients receiving theophylline + etofylline and 57 (60.0%) patients receiving doxofylline had improvement in the symptoms which was not statistically significant (p value 0.736).

With respect to spirometric variables, the COPD patients on 7^{th}, 14^{th} and 21^{st} days of treatment showed gradual improvement. This improvement within the study groups was statistically significant when compare to the pre-treatment values. Improvements seen in the spirometric parameters were compared between the two groups and analysed. Test results showed that there was no significant difference in the improvements observed in both the groups.

Patients in the doxofylline group experienced lesser adverse effects when compared to theophylline + etofylline group. This can be attributed to the lesser affinity of the drug towards the adenosine receptors. According to the previous studies done by Villani *et al*. [11] in 1997, a significant improvement in FEV1, FVC and other spirometric parameters in the beta2 responders among the COPD patients treated with doxofylline 400 mg thrice a day [6] was reported.

Also Marino O *et al*., in 1988, compared Doxofylline with theophylline SR in COPD patients and concluded that the spirometric variables had improved in both treatments [14].

Panagia *et al*., in 1987 in a parallel study on patients with chronic bronchitis, compared Theophylline (200 mg) and Doxofylline (400 mg) thrice a day and indicated an improvement in the respiratory variables [14].

In a recent study done by MD Fiaz akram *et al*. [14] in 2013 concluded that the side-effects of theophylline in the dose of 400 mg SR once daily were not of much concern and that the side-effects were not significantly different from that of Doxofylline.

But in the present study the dose of theophylline + etofylline (Deriphylline Retard) was only 300 mg once daily and still the patients showed significantly high incidence of adverse effects. As methylxanthines had no role in the treatment of acute exacerbations in COPD, theophylline is only used in the long term management of the disease.

Due to its non specific PDE inhibition and due to its action on adenosine receptors, patients on theophylline + etofylline were more prone for adverse effects. The cost of theophylline + etofylline was 1 rupee per tablet where as it was 4 rupees for a tablet of doxofylline.

CONCLUSION

Based on the results of this study, we can conclude that though theophylline + etofylline is cheaper than doxofylline, the side-effects of the former drug combination are of concern in the dose of 300 mg once a day (commonly used clinically). Also at this dose, the side-effects are significantly more when compared to doxofylline. So doxofylline can be used as an effective alternative to patients who cannot tolerate the adverse effects of theophylline. Methylxanthines are orally administered drugs used as an alternative to newer inhalational drugs in the therapy of COPD. As they also have the property of enhancing the responsiveness to corticosteroid therapy in patients with COPD, newer methylxanthines should be developed with specific PDE inhibition and less affinity towards adenosine receptors so that the adverse effects could be decreased.

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