

# To Study the Efficacy and Safety of Doxophylline and Theophylline in Bronchial Asthma

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## ABSTRACT

**Background:** Asthma is a non communicable chronic disease prevalent all over the world. Two commonly used methylxanthines, theophylline and doxophylline were compared in the study in stable asthmatic patients at recommended doses by various spirometric lung function tests with forced expiratory volume at second one (FEV1) between 50 to 80% of predicted FEV1.

**Materials and Methods:** A total of 100 patients were divided in two groups. Group I was administered 300 mg theophylline twice a day and Group II was administered doxophylline 400 mg twice a day orally for six weeks. Spirometric variables symptom score, and adverse effects were recorded at the baseline level and after six weeks of therapy. Data was compared and analysed statistically.

**Results:** The spirometric values of forced expiratory volume in 1 second (FEV1), forced vital capacity (FVC), and FEV1/FVC showed a statistically significant improvement over base line with the use of both theophylline as well as doxophylline, but were not statistically different from each other. There was a statistically significant improvement in peak expiratory flow rate (PEFR) after six weeks of treatment with doxophylline compared to theophylline. It was found that the doxophylline has a better safety profile as compared to theophylline. Adverse events occurred in a greater proportion of patients in the theophylline group.

**Conclusion:** In the study it was concluded that both theophylline and doxophylline improved the lung function tests and symptoms in patients of mild Bronchial Asthma, but doxophylline has a better profile in terms of safety.

**Keywords:** Lung function tests, Methylxanthines, Moderate asthma

## INTRODUCTION

Bronchial asthma is an important health issue, especially in developing countries like India. In the year 2004, India accounted for 277 Disability Adjusted Life Years lost per 1,00,000 population and 57,000 deaths [1]. As of 2011, 235-300 million people worldwide were affected by asthma leading to approximately 250,000 deaths per year [2]. Asthma is thought to be caused by a combination of genetic and environmental factors [3]. These factors influence how severe asthma is and how well it responds to medication [4]. Allergic asthma is more sensitive for various indoor allergens exposed in early infancy and childhood which can be the important cause for the increased prevalence of bronchial asthma in early life [5]. So primary preventive measures should be taken in early life to decrease the incidence of asthma caused by various indoor allergens (wheeze 13.8%, nocturnal cough 32.3%, atopy 20.0%) [6].

The most effective treatment for asthma is identifying triggers, such as smoke, pets, or aspirin and eliminating exposure to them. Medical treatments used depend on the severity of illness and the frequency of symptoms [7]. Methylxanthines are widely used in the treatment of asthma due its ability to inhibit phosphodiesterase (PDE) causing bronchodilatation [8]. Methylxanthines also have anti inflammatory, immunomodulatory and bronchoprotective effects in addition to bronchodilation. These drugs require therapeutic drug monitoring because of narrow margin of safety requiring strict monitoring of its blood levels [9]. Methylxanthines were found to have no added significant effect over inhaled beta-agonists. According to latest guidelines methylxanthines have restricted role in the management of asthma exacerbations in view of their poor safety profile in comparison to short acting beta agonistic agents [10].

Theophylline, a PDE inhibitor has been used in asthma for its anti-inflammatory effect in the concentration range of 5- 20 µg/ml but with a variety of side effects above >20 µg/ml. A new methylxanthine derivative Doxophylline with similar efficacy but has significantly less side effects, may immensely benefit the patients [11].

Studies in both animals as well as in human adults have shown doxophylline to be safe and effective. This better safety profile of doxophylline is better explained by its decreased affinity towards A1 and A2 adenosine receptors [11].

This study was conducted to compares doxophylline with theophylline in bronchial asthma for its efficacy and safety.

## MATERIALS AND METHODS

After approval from Board of Ethical committee, the study was conducted in the Government Chest Diseases Hospital Srinagar, an associated hospital of Government Medical College Srinagar with a capacity of about 300 admissions. All the stable patients in age group (15 to 60 y) labelled as bronchial asthma by the outpatient department of the hospital were enlisted and those having the FEV1 within 50% to 80% of the predicted FEV1 for their age and height and showed at least a 12% increase in FEV1, 20 minutes after inhalation of two puffs (400 microgram) of salbutamol were taken up for the study. Patients with any cardiac, hepatic, renal, metabolic disease were excluded from the study.

Patients were explained and their informed consent was taken for the study, which was followed by detailed history and clinical examination as per the proforma. All confirmed diagnosed patients were requested baseline investigations like ECG, blood sugar, CBC, Lipid profile, X-ray chest (PA) KFT, LFT and electrolytes.

The patients were asked to stop all medications for one week during which inhaled salbutamol was allowed as rescue treatment. Before doing pre-treatment Spirometry, pulse and blood pressure were recorded.

The Spirometry testing was performed according to the American Thoracic Society (ATS) guidelines. While, performing the FVC maneuver: a cough, an inspiration, a Valsalva maneuver, a leak, or an obstructed mouth piece disqualified the trial and the test was repeated. To ensure validity, each patient was asked to perform a minimum of three acceptable manoeuvres and the best reading

was noted provided the largest and the second largest FVC from the acceptable trials did not vary by >5% or 200ml, so as to ensure reliability. The largest FVC, measured from a set of three acceptable trials was taken as patient's FVC. During FVC maneuver several other measurements like FEV<sub>1</sub>, PEFR were also made.

After doing the pre-treatment spirometry patients were randomly assigned into two groups (50 patients in each group) by computer generated random numbers.

**Group I:-** received theophylline 300 mg bd orally for six weeks.

**Group II:-** received doxophylline 400 mg bd orally for six weeks.

The patients returned for clinical examination at an interval of one week during the study period. During these visits they were asked about the change in symptoms and about any adverse drug effects. The repeat (Postdrug) Spirometry was performed at the end of six weeks.

Subjective evaluation was done by asking the patient about the change in symptoms (cough and/or breathlessness). The patients were graded into the following three categories according to the change in symptomatology:

I Improved (If there was improvement in symptoms).

N. C No Change (If there was no change in symptoms).

W Worse (If there was increase in symptoms).

The objective evaluation of the effectiveness was done by estimating the improvement in the various spirometric values like FEV<sub>1</sub>, FVC, FEV<sub>1</sub>/FVC and PEFR. After six weeks of treatment, subjective assessment of asthma attack rate and salbutamol use as a rescue was asked from each patient.

Subjective assessment of the safety was done by noting the following side effects of theophylline and doxophylline from each patient; Palpitations, epigastric distress, tremors, headache, nausea, insomnia and nervousness.

## STATISTICAL ANALYSIS

The Statistical Analysis of the data was done by Student's t-test for differences of means, and the parametric data was expressed as mean  $\pm$  S.D. The nominal data was analysed by using chi-square test ( $\chi^2$ ) or Fisher's Exact test as appropriate. ( $p < 0.05$ ) was taken statistically significant otherwise non-significant. The analysis of data was performed by using statistical package SPSS version 20.0.

## RESULTS

Randomly selected 100 patients were taken for the study. The study population was divided into 5 age-groups viz.  $\leq 20$  y, 21-30 y, 31-40 y, 41-50 y & 51-60 y. The highest percentage of study population was in the age group of 51-60 y as shown in [Table/Fig-1]. Out of the 100 patients 45 were male patients and 55 were female patients (50 % in each group) as shown in [Table/Fig-2]. The [Table/Fig-3] showed that the baseline predicted values of FEV<sub>1</sub>(L), FVC(L), FEV<sub>1</sub>/FVC (L), PEFR (L/SEC) for theophylline group and for doxophylline group when compared statistically they were non-significant ( $p > 0.05$ ).

SALBUTAMOL USE (PUFFS/DAY) and ASTHMA ATTACK RATE (NO./DAY) showed nonsignificant result when compared statistically at the baseline level between two treatment groups as shown in [Table/Fig-4]. The comparison of FEV<sub>1</sub> at baseline and at six weeks after treatment for theophylline and doxyphylline group individually was highly significant ( $< 0.001$ ) as shown in [Table/Fig-5].

The comparison of FVC (L) at baseline and at six weeks after treatment for theophylline and doxyphylline group individually was highly significant ( $< 0.001$ ) as shown in [Table/Fig-6].

The comparison of FEV/FVC (%) at baseline and at six weeks after treatment for theophylline and doxyphylline group individually was highly significant ( $< 0.001$ ) as shown in [Table/Fig-7].

Age (Years)	GROUP		Total Number (%)
	Theophylline Number (%)	Doxophylline Number (%)	
$\leq 20$	8(16%)	6(12%)	14(14%)
21-30	4(8%)	0 (0%)	4(4%)
31-40	4(8%)	8(16%)	12(12%)
41-50	9(18%)	12 (24%)	21(21%)
51-60	25(50%)	24(48%)	49(49%)
TOTAL	50	50	100

**[Table/Fig-1]:** Distribution of age in the study population

Chi-square test,  $p=0.194$  (not significant)

Sex	GROUP		Total Number (%)
	Theophylline Number (%)	Doxophylline Number (%)	
MALE	23(46%)	22(44%)	45(45%)
FEMALE	27(54%)	28(56%)	55(55%)
TOTAL	50	50	100

**[Table/Fig-2]:** Distribution of sex in the study population

Chi-square test,  $p=0.841$  (not significant)

Spirometric Variables	Theophylline Mean $\pm$ SD	Doxophylline Mean $\pm$ SD	p-value (unpaired t-test)
Baseline FEV <sub>1</sub> (L)	1.76 $\pm$ 0.57	1.75 $\pm$ 0.62	$> 0.05$ *
% Predicted FEV <sub>1</sub>	68.05 $\pm$ 11.18	68.66 $\pm$ 11.44	$> 0.05$ *
Baseline FVC	2.87 $\pm$ 0.83	2.77 $\pm$ 0.78	$> 0.05$ *
FEV <sub>1</sub> /FVC	61.54 $\pm$ 7.77	63.62 $\pm$ 8.69	$> 0.05$ *
Baseline PEFR	3.51 $\pm$ 1.49	3.81 $\pm$ 2.04	$> 0.05$ *
Baseline AAR (no. Per day)	1.68 $\pm$ 0.47	1.80 $\pm$ 0.40	$> 0.05$ *
Baseline salbutamol use (puffs per day)	3.36 $\pm$ 0.94	3.60 $\pm$ 0.81	$> 0.05$ *

**[Table/Fig-3]:** Comparison of baseline spirometric variables among the treatment groups

\*- Non Significant

Spirometric Variables	Theophylline Mean $\pm$ SD	Doxophylline Mean $\pm$ SD	p-value (unpaired t-test)
Change in FEV <sub>1</sub> (l)	0.29 $\pm$ 0.19	0.32 $\pm$ 0.14	$> 0.05$ *
% PRECDICTED change in FEV <sub>1</sub>	17.48 $\pm$ 18.69	18.14 $\pm$ 3.23	$> 0.05$ *
Change in FVC	0.14 $\pm$ 0.15	0.13 $\pm$ 0.14	$> 0.05$ *
FEV <sub>1</sub> /FVC	6.84 $\pm$ 11.88	6.78 $\pm$ 2.62	$> 0.05$ *
Change in PEFR (l/sec)	0.77 $\pm$ 0.43	1.12 $\pm$ 0.73	0.004 ( $< 0.05$ )* *
% Change in PEFR (l/sec)	22.32 $\pm$ 8.51	30.72 $\pm$ 14.75	0.001***
Change in salbutamol use (puffs/day)	-1.36 $\pm$ 0.94	-1.76 $\pm$ 0.66	0.016 ( $< 0.05$ ) **
Change in AAR (no./day)	-0.68 $\pm$ 0.47	-0.88 $\pm$ 0.33	0.016 ( $< 0.05$ )**

**[Table/Fig-4]:** Comparison of change in various spirometric variables among the treatment groups

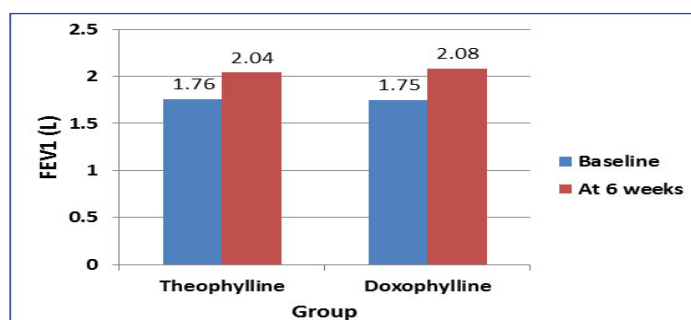
\*- Non Significant \*\*- Significant \*\*\*- Highly Significant

The comparison of PEFR (L/SEC) at baseline and at six weeks after treatment for theophylline and doxyphylline group individually was highly significant ( $< 0.001$ ) as shown in [Table/Fig-8].

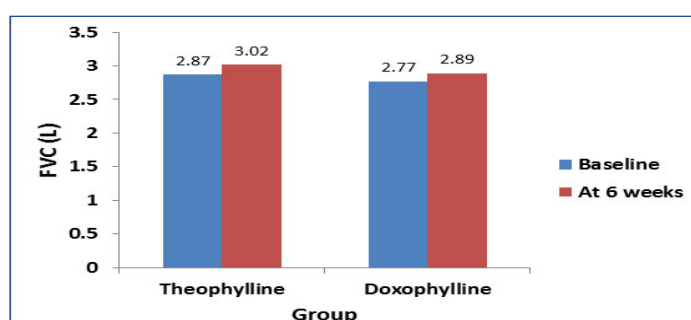
The comparison of AAR (No./day)and SALBUTAMOL USE (puffs/day) at baseline and at 6 weeks after treatment for theophylline and doxyphylline group individually was highly significant ( $< 0.001$ ) as shown in [Table/Fig-9].

The [Table/Fig-3] showed that the values of FEV1(L), FVC(L), FEV1/FVC (L) after treatment of six weeks between theophylline group and for doxophylline group when compared statistically they were non-significant ( $p>0.05$ ). But change in PEFR (L/SEC) after therapy it was significant between two groups. SALBUTAMOL USE (PUFFS/DAY) and ASTHMA ATTACK RATE (NO./DAY) showed nonsignificant result when compared statistically after six wks of therapy between two treatment groups as shown in [Table/Fig-9].

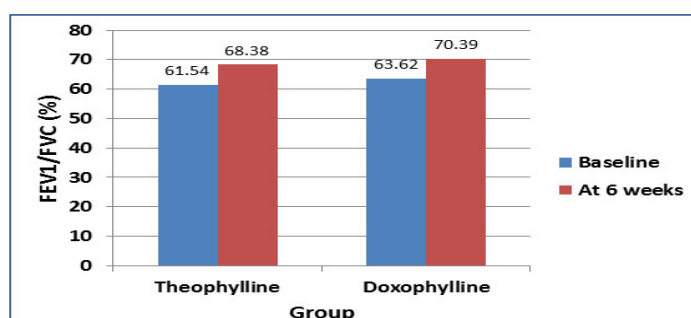
The most common side effect noted in the study was epigastric distress found in 4(8%) patients in theophylline group and 2 (4%) in doxophylline group followed by headache insomnia, nausea and nervousness. Palpitations and tremors were rare as shown in [Table/Fig-10].



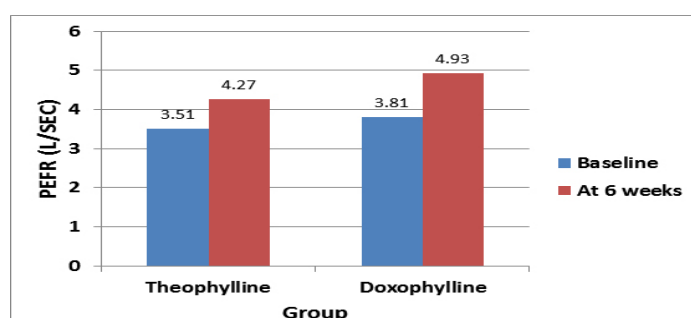
[Table/Fig-5]: Comparison of FEV1 at baseline and at 6 weeks in the two groups



[Table/Fig-6]: Comparison of FVC(L) at baseline and at 6 weeks in the two groups



[Table/Fig-7]: Comparison of FEV1/FVC (%) at baseline and at 6 weeks in the two groups



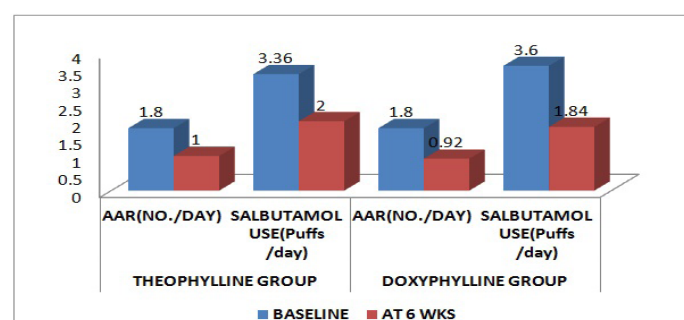
[Table/Fig-8]: Comparison of PEFR (L/SEC) at baseline and at 6 weeks in the two groups

## DISCUSSION

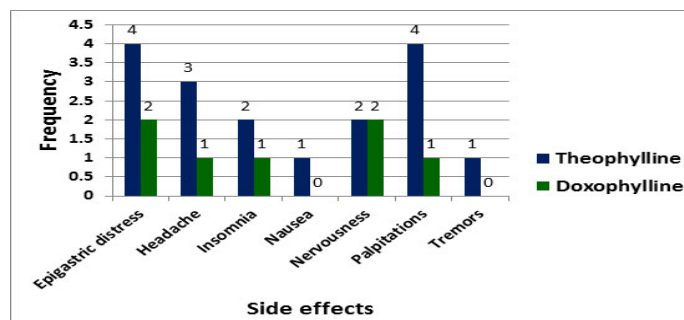
Asthma is a chronic inflammatory disease characterised by hyper responsiveness of airways to multiple stimuli, reversible airflow limitation and chronic eosinophilic infiltration of airways [12].

Methylxanthines are widely used in the treatment of asthma. Doxophylline has emerged as one such drug; studied in animals as well as in human adults and children with obstructive air way diseases have found it to be effective and safe with efficacy similar to theophylline [13].

In the present study 100 stable adult patients in age group of 15–60 y labelled as bronchial asthma having FEV1 for their age and height and showed at least 12% increase in FEV1 20 minutes after inhalation of two puffs (400 micro-grams) of salbutamol were studied. The



[Table/Fig-9]: Comparison of AAR (no./Day) and salbutamol use (puffs/day) at baseline and at 6 weeks in the two groups



[Table/Fig-10]: Side effects among patients in the two treatment groups

results of the present study demonstrated the efficacy and safety of doxophylline compared to theophylline in the management of patients with bronchial asthma.

In the present study spirometric variables FEV1, FVC, FEV1/FVC showed a significant improvement over base line with the use of both theophylline as well as doxophylline. The improvement over baseline values for FEV1, FVC and FEV1/FVC was similar in both the theophylline and doxophylline groups. The results of the present study correlated well with the previous studies conducted by Dolcetti A et al., Melillo et al., Both doxophylline and theophylline treatments significantly improved all pulmonary function parameters as compared to base line ( $p < 0.05$ ), but were not statistically different from each other [14,15]. The comparison of FEV/FVC (%) at baseline and at six weeks after treatment for theophylline and doxyphylline group individually was highly significant ( $<0.001$ ) in this present study. Marc F Goldstein and Paul Chervinsky randomly assigned 346 patients to a 12 wk oral treatment with either doxophylline or theophylline 400 mg thrice a day (high dose), doxophylline 200 mg tid (low dose), theophylline 250 mg tid (active control) or placebo. Changes in FEV1 two hours after the administration of treatments vs baseline exhibited significant statistical difference between doxophylline 400 mg tid and placebo and between theophylline and placebo [11].

In the present study there was a statistically significant improvement in PEFR at 6 weeks over baseline values in both theophylline and doxophylline groups. However, the improvement in PEFR was significantly more in the doxophylline group as compared to



theophylline group ( $p=0.004$ ). Doxophylline is significantly more efficacious in improving PEFR as compared to theophylline [16].

In the present study it was found that doxophylline 400 mg twice a day was more efficacious in reducing the asthma attack rate and the need for rescue salbutamol inhalation. Same results were obtained in the studies conducted by Marc F Goldstein, Melillo, Grossi [11,14,17,18].

Subjectively both the regimens were well tolerated as no case warranted the withdrawal of treatment. In the present study it was found that doxophylline has a better safety profile as compared to theophylline. Adverse events occurred in a greater proportion of patients in the theophylline group. The results of the study in terms of safety profile correlated with the various previous studies as done by Shukla, Grossi, Cirillo, Bierman [16,18-20].

The limitations of the methylxanthines are the gastrointestinal side effects and tachycardia. Doxophylline is known to cause less of these side effects than theophylline because of more specificity and less of interference with calcium channels in cardiac cells. Moreover, it does not affect sleep rhythm, gastric secretions, heart rate and rhythm and CNS functioning [21]. The fact that serum toxicity levels overlap therapeutic levels explains the high incidence of toxic side effects. The risk of such adverse events can be reduced by monitoring the drug's plasma levels and reducing the dose accordingly [22]. Doxophylline produces stable serum concentrations; hence plasma monitoring is required only in patients with hepatic insufficiency and intolerance to xanthine drugs [23].

Cravanzolac et al., in a study showed that the use of theophylline is associated with the occurrence of side effects i.e. nausea, vomiting, epigastric pain, insomnia, anxiety, restlessness, tachycardia and extrasystoles [24].

Cipri et al., conducted a number of studies carried out in patients with chronic respiratory diseases that have shown that intravenous doxophylline does not exert significant cardiac chronotropic actions and cause a significant decrease in occurrence of ventricular premature beats as compared to theophylline which could be explained by its low affinity for adenosine receptors [25]. Sankar J et al., demonstrated that unlike other xanthines, doxophylline lacks any significant affinity for adenosine receptors and does not produce stimulant effects [23].

Sacco C et al., studied in obstructive pulmonary disease patients with nocturnal hypoxemia that use of doxophylline as a respiratory stimulant does not produce any alternation in the sleep architecture unlike theophylline [26].

## CONCLUSION

The spirometric values of FEV<sub>1</sub>, FVC, and FEV<sub>1</sub>/FVC showed a statistically significant improvement over base line with the use of both theophylline as well as doxophylline, but were not statistically different from each other. There was a statistically significant improvement in PEFR after six weeks of treatment with doxophylline compared to theophylline. It was found that doxophylline 400

mg bd was statistically significant in reducing the asthma attack rate and the need for rescue salbutamol inhalation. It was found that the doxophylline has a better safety profile as compared to theophylline.

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