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CLINICAL EFFECTIVENESS AND SAFETY OF DOXOPHYLLINE VERSES THEOPHYLLINE PLUS ETOPHYLLINE COMBINATION IN CHRONIC AIRWAY DISEASE- A RANDOMISED, OPEN LABEL STUDY

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ABSTRACT

This study aims to compare the Safety and Efficacy of Tab.Doxophylline 200 mg bd versus Tab.Theophylline 23mg plus Etophylline 77mg combination tds in the treatment of Chronic Airway Diseases which are Chronic Obstructive Pulmonary Disease and Bronchial asthma. It was a randomized, open label, parallel group study with a sample size of 100 patients and duration of 4 weeks. Efficacy was assessed by Pulmonary function tests (FEV_1 and PEFR) and a Quality of Life Questionnaire. Patients were assessed by clinical examination and questionnaire during every visit. At the beginning and end of the study, pulmonary function tests were done. In the Doxophylline group, the change in FEV_1 and PEFR were 28.34 L/min and 46.41 L/min respectively. In the Theophylline+Etophylline group, the change in FEV_1 and PEFR were 12.9 L/min and 13.43 L/min respectively. The adverse events were found to be more in the Theophylline+ Etophylline group(30 %) compared to the Doxophylline group(20%). Dyspepsia, followed by Headache (12%) were the most frequent adverse events. There is improvement in mobility and ability to do day-to-day activities and decrease in dyspnea in Doxophylline group compared to Theophylline + Etophylline group. This may be because of the additional effect of Doxophylline on airway inflammation, mucus secretion and muco-ciliary clearance.

Key Words: Doxophylline, Theophylline + Etophylline, Chronic Airway Diseases.

INTRODUCTION

Chronic Airway Diseases include Chronic Obstructive Pulmonary Disease and Bronchial asthma. National Institute of Health defines asthma as a chronic inflammatory disorder of the airways associated with airway hyper-responsiveness and airflow obstruction that is reversible either spontaneously or with treatment [1]. According to WHO, between 100 and 150 million people around the globe suffer from asthma in 2012 and this number is rising. World-wide, deaths from this condition have reached over 180,000 annually. India has an estimated 15-20 million asthmatics [2]. A study by the Institute of Medical Education and Research across four Indian cities - Delhi, Chandigarh, Kanpur and Bangalore- reported asthma prevalence in adults at 3.47% in 2011 [3] COPD is a preventable and treatable disease state characterized by airflow limitation that is not fully reversible. The airflow limitation is usually progressive and associated with an abnormal inflammatory response of the lungs in response to noxious agents including cigarette smoke, biomass fuels and occupational agents.

Chronic Obstructive Pulmonary Disease kills more than 3 million people every year, making it the 4th largest cause of death in the world [4,5]. According to the NCMH estimates; in 2006 there were around 17 million COPD patients in India and in the next 10 years this figure is likely to reach around 22 million [6]. The prevalence of smoking in above-30-year age group was 40.9% among males and 3.9% amongst females [7]. The incidence of COPD increases with age. After 60 years, the risk of

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COPD is increased 5 fold. The growing burden of COPD is due to the rise in aging population, air pollution and the increased use of tobacco smoke [8].

Theophylline is used in Chronic Airway Disease to decrease cough, breathlessness and to improve the quality of life. However, it is associated with many cardiac and gastrointestinal adverse effects. Doxophylline is an active PDE inhibitor, but has a much lower affinity for adenosine receptors. Thus, it retains a bronchodilator effect but does not share theophylline's effects on cardiac rhythm. This might be favourable for patients with chronic respiratory disease and pre-existing arrhythmias or in those with airflow obstruction secondary to cardiac disease. Lack of drug interactions and lack of interference of constitutional factors (sex, genetics) in the metabolism makes the Doxophylline pharmacokinetics and pharmacodynamics more predictable than theophylline across the wider population and hence could be clinically more acceptable as a safer alternative in asthma and COPD.

However, data comparing the efficacy and safety of Theophylline plus Etophylline combination with Doxophylline from a large sample of patients is lacking. Therefore, this study proposes to compare the safety and efficacy of Doxophylline and Theophylline plus Etophylline combination. If Doxophylline is proved to be safer than and as efficacious as Theophylline plus Etophylline combination, it could be an alternative to Theophylline plus Etophylline combination in Chronic Airway Disease.

Aim of the present study

To compare the Safety and Efficacy of Tab.Doxophylline and Tab.Theophylline plus Etophylline combination in the treatment of Chronic Airway Disease.

Primary objectives

1. To find out which drug is more efficacious among Doxophylline and Theophylline + Etophylline combination in patients with Chronic Airway Disease.

2. To compare the improvement in Quality of life after treatment with Doxophylline and Theophylline + Etophylline combination in patients with Chronic Airway Disease.

Secondary objectives

To compare the Safety of Doxophylline Versus Theophylline plus Etophylline combination in Chronic Airway Disease by:

1. Tolerability
2. Adverse effects.

MATERIALS AND METHODS

Study design

This was a Randomized, Active controlled, Open Label, Parallel Group, Prospective Interventional Study, comparing the efficacy and safety of Doxophylline versus Theophylline + Etophylline combination in patients with Bronchial asthma and COPD. Each patient as given drugs for a period of 4 weeks. The study was conducted from February to June 2012 at the Outpatient division of the Department of TB and Chest Diseases of Sri Ramachandra Medical Collge Hospital, Sri Ramachandra Medical College and Research Institute, Porur, Chennai-600 116. The study was started after approval from the Institutional Ethics Committee. The treating physician was notified of this protocol and his consent was obtained. 100 patients suffering from Bronchial Asthma and Chronic Obstructive Pulmonary Disease were recruited.

Voluntary written Informed Consent was obtained in English and the local language (Tamil) after explaining the purpose and protocol of the study. Then the 100 patients were randomized by computerized ten block simple randomization and divided into two groups. 50 patients were given Tab.Doxophylline 200 mg bd and 50 patients were given Tab.Theophylline plus Etophylline tds. The therapy was given free of cost.

Patient's demographic data was collected. General and systemic examination was done. Baseline Total Count , Differential Count , Haemoglobin , Erythrocyte Sedimentation Rate , Chest X-ray, Pulmonary Function tests, Electrocardiography and Pulse Oximetry were done. The patients were subjected to a Questionnaire on their Quality of life. The patients were given one of the two study drugs for a period of 4 weeks. The patients were reviewed on days 14 and 28. They were assessed by clinical examination and questionnaire. Adverse effects, if any, were noted. On day 28, pulmonary function tests were done. The data was tabulated and subjected to statistical analysis.

The inclusion criteria were patients of either sex, aged 18-60 years, with Bronchial Asthma as per GINA Guidelines or patients with Chronic Obstructive Pulmonary Disease as per GOLD Guidelines. Patients on treatment with β2 agonists, Corticosteroids were also included in the study and only those willing to give Informed Consent voluntarily and who were ready to abide by the study processes were included.

Patients with Tuberculosis, Lung Abscess, Bronchiectasis, Interstitial Lung Disease, Lung Cancer, Ischemic Heart Disease and Severe Vasculitis were excluded. Patients with Hepatic or Renal Impairment, autoimmune disorders and also hypersensitivity to Methylxanthines were also excluded. Pregnant and Lactating Women and patients on Antidepressants, Antipsychotics, and Sedatives were not included in the study.

Statistical Analysis

Statistical analysis was done using SPSS Software version 15. Paired t test was used to analyse the change in continuous variables. Wilcoxon signed rank test, a non-

parametric test, was used to assess the change in Quality of life.

RESULTS

100 patients were randomized to participate in this study. The mean age of the patients was 47.54 years in the Doxophylline group and 49.58 years in the Theophylline plus Etophylline group. 52 % of patients were in the 41-60 age group for Doxophylline group and 58 % of patients were in this group in the Theophylline plus Etophylline group.

In the Doxophylline group, 50 % of the patients were male and 50 % were female. In the Theophylline plus Etophylline group, 40 % of the patients were male and 60 % were female.

In the Doxophylline group, 68 % of the patients were suffering from Bronchial asthma and 32 % were suffering from COPD. In the Theophylline plus Etophylline group, 86 % of the patients were suffering from Bronchial asthma and 14 % were suffering from COPD.

Based on GOLD and GINA criteria, the severity of illness was classified into mild, moderate, severe and very severe. In the Doxophylline group, 58 % of the patients were classified as moderate and 32 % were classified into severe. In the Theophylline plus Etophylline group, 42 % of the patients were classified into moderate and 30 % were classified into severe.

The efficacy of the drugs was assessed using the following criteria: FEV_1 and PEFR. In the Doxophylline group, the mean FEV_1 was 96.18 L/min before treatment and 124.52 L/min after treatment. The change in FEV_1 was 28.34 L/min, Standard deviation was 17.32 and the p value was 0.000. In the Theophylline plus Etophylline group, the mean FEV_1 was 92.45 L/min before treatment and 105.35 L/min after treatment. The change in FEV_1 was 12.9 L/min , Standard deviation was 13.43 and the p value was 0.000.

The mean PEFR was 204.68 L/min in the Doxophylline group before treatment and 251.09 L/min after treatment. The change in PEFR was 46.41 L/min , Standard deviation was 46.31 and the p value was 0.000. The mean PEFR was 184.5 L/min before treatment and 197.92 L/min after treatment. The change in PEFR was 13.43 L/min, Standard deviation was 10.28 and the p value was 0.000.

Both the drugs were well tolerated by the patients without any major adverse event. Overall, the adverse events were found to be more in the Theophylline plus Etophylline group(30 %) compared to the Doxophylline (20%). Dyspepsia (14%), followed by Headache (12%) were the most frequent adverse events in the Theophylline plus Etophylline group. Headache (6%) and dyspepsia (4%) were the most frequent adverse events in the Doxophylline group.

The Quality of life questionnaire consisted of 5 questions. It assessed the mobility, ability to do their day to do the day to day activities and the need for nebulization of the patients. It assesses the severity of illness of the patient and whether the ongoing treatment is adequate. The change in Quality of life in the two groups was: 5.9 vs 5.2, 3.74 vs 2.65, 4.74 vs 4.15, 4.84 vs 3.32 and 3.42 vs 2.89 for the 5 questions for Doxophylline and Theophylline plus Etophylline groups respectively.

PARTICIPANT FLOW IN THE STUDY

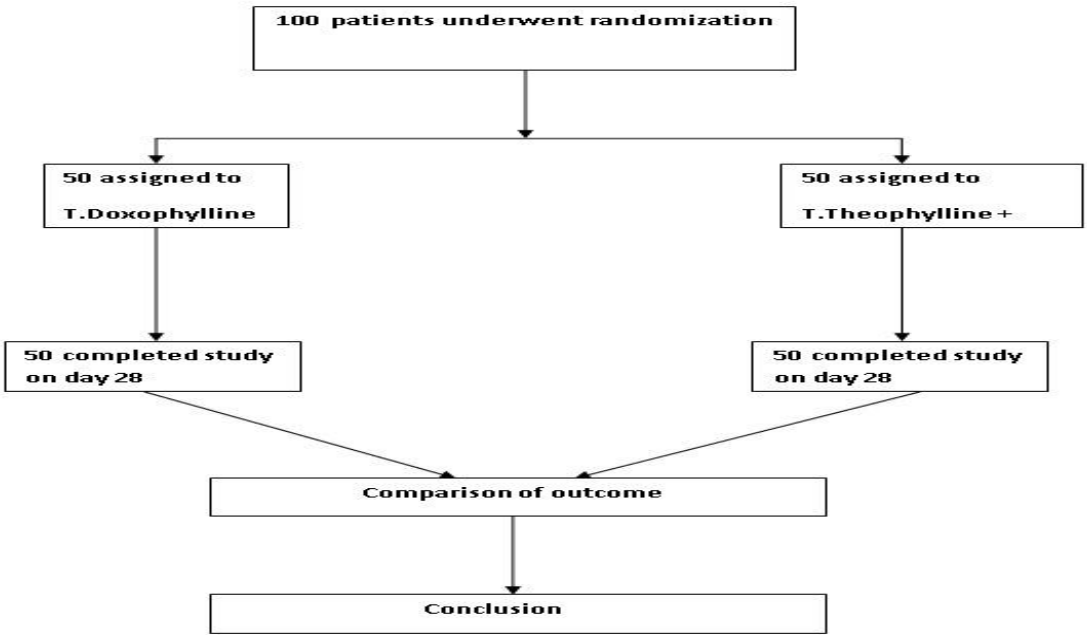

Fig. 1. Change in FEV1 from Day 1 to Day 28 in the Doxophylline group Vs Theophylline + Etophylline group.

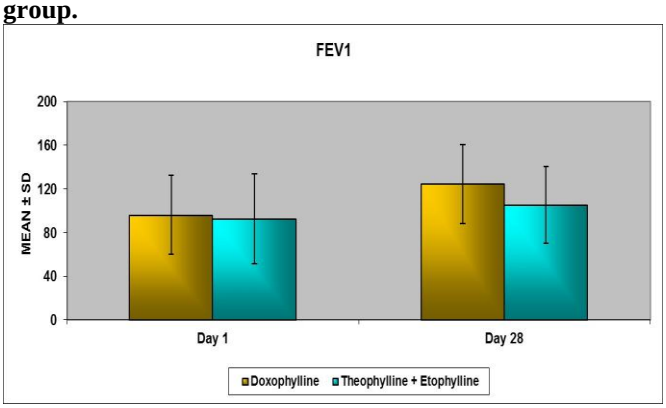

Fig. 2. Change in PEFR from Day 1 to Day 28 in the Doxophylline group Vs Theophylline + Etophylline group.

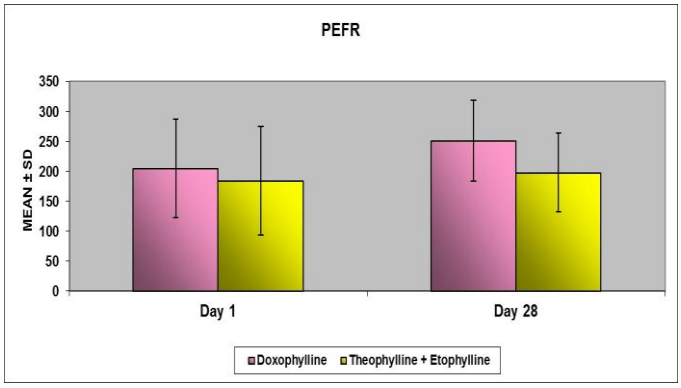

Fig. 3. Change in QOL from day 1 to day 28 in Doxophylline versus Theophylline + Etophylline combination

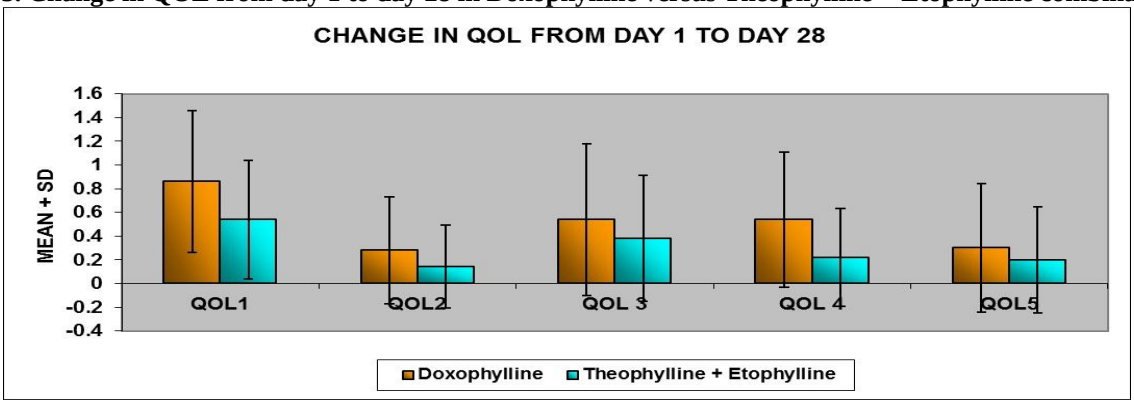

Table 1. Safety profile of Doxophylline versus Theophylline + Etophylline combination

Adverse effects	Doxophylline	Percentage	Theophylline + Etophylline	Percentage
Headache	3	6	6	12
Dyspepsia	2	4	7	14
Vomiting	1	2	0	0
Insomnia	1	2	1	2
Rashes	1	2	0	0
Tremor	1	2	0	0
Irritability	1	2	0	0
Tachycardia	0	0	1	2

DISCUSSION

The Guidelines for the treatment of Bronchial asthma and COPD aim to ensure stepwise approach to treatment based on the disease severity with more of a focus towards decreasing symptoms and/or preventing disease progression [9]. Bronchodilators, Inhaled Corticosteroids and other anti-inflammatory agents form the basis of treatment of bronchial asthma and COPD. The drugs used for the two conditions are similar, but the goals and targets of therapy are different. In our study, out of the 100 patients recruited, the baseline characteristics like age, gender are similar. The patients were on baseline treatment of long acting β_2 agonists, inhaled corticosteroids or a combination of both. Additionally, it is well recognized that not all patients achieve good control of asthma and COPD despite a high dose of β_2 agonists, long acting inhaled corticosteroids or a combination of both. In such patients, there is a need for add-on therapy with other drugs.

It is well recognized that chronic obstructive bronchitis is characterized by inflammatory and obliterative changes in the small airways of the lung. According to Cogo et al, there is a large body of evidence that Theophylline is valuable in decreasing inflammation of airways at concentrations which are therapeutically significant [10]. Theophylline is effective in attenuating

antigen mediated early and late hyper-responsiveness of the airways and in improving the muco-ciliary clearance in COPD patients [11].

Our study proves that the addition of methylxanthines improves the FEV_1 and PEFR in Pulmonary function tests. The therapeutic dose of Doxophylline is from 400 mg bd to 400 mg tds and is associated with 13-33% improvement in FEV_1. However, this dose is associated with a lot of adverse events like headache, dyspepsia and rashes. In our study, we used a sub-therapeutic dose of 200 mg bd Doxophylline to decrease the side effects. The mean FEV_1 was 96.18 L/min before Doxophylline treatment and 124.52 L/min after treatment. The change in FEV_1 was 28.34 L/min . The mean PEFR was 204.68 L/min in the Doxophylline group before treatment and 251.09 L/min after treatment. The change in PEFR was 46.41 L/min .This is very similar to 400 mg bd of Doxophylline. Since Doxophylline has a possible direct anti-inflammatory effect, protective effect against Platelet Activating Factor induced airway inflammation, inhibitory effect on Histamine and Leukotriene release, these may contribute to the regression of inflammatory changes during treatment.

In our study, we observed that in the Theophylline+Etophylline treated group, the mean FEV_1 was 92.45 L/min before treatment and 105.35 L/min after treatment and the change in FEV_1 was 12.9L/min. The mean PEFR was 184.5 L/min before treatment and 197.92 L/min after treatment and the change in PEFR was 13.43 L/min.

The molecular mechanism of bronchodilatation is inhibition of Phosphodiesterase 3 and 4, but the anti-inflammatory effect may be due to histone deacetylase (HDAC2) activation, resulting in switching off of activated inflammatory genes [12]. Through this mechanism, theophylline also reverses corticosteroid resistance and this may be of particular value in severe asthma and COPD where HDAC2 activity is markedly reduced. Other proposed mechanisms of action of Theophylline are Adenosine receptor antagonism (A_1, A_{2A}, A_{2B} receptors), inhibition of nuclear factor κB (decreases nuclear translocation), inhibition of phosphoinositide3-kinase δ, increases IL-10 secretion, increases apoptosis of inflammatory cells and decreases poly (ADP-ribose) polymerase-1 (inhibits cell death).

According to Bagnato et al, Doxophylline has less side effects compared to Theophylline+Etophylline combination and the efficacy and tolerability of Doxophylline is high [13]. Our study confirmed that Doxophylline is a safer alternative to the classical xanthine derivatives. Due to its favourable profile, most notably because of no reports of fatal events no major arrhythmias in patients treated with the drug, the therapeutic range of the compound was considerably wider with respect to Theophylline. Therefore, plasma monitoring is recommended only in patients with hepatic insufficiency and intolerability to xanthine alkaloids.

The Quality of life questionnaire shows that there is improvement in mobility and ability to do day-to-day activities and decrease in dyspnea in Doxophylline group compared to Theophylline + Etophylline group. This may be because of the additional effect of Doxophylline on airway inflammation, mucus secretion [14] and muco-ciliary clearance.

CONCLUSION

This study has demonstrated that Doxophylline has more efficacy than the widely used Theophylline + Etophylline combination in patients with chronic airway disease. Doxophylline also displays less adverse effects and better tolerability than Theophylline + Etophylline combination. The improvement in Quality of life is also more in the Doxophylline group than the Theophylline + Etophylline group.

To conclude, Doxophylline is more efficacious and has a better safety profile than Theophylline + Etophylline combination for the treatment of Bronchial asthma and COPD.

LIMITATIONS OF THE STUDY

The study was of a short duration and four weeks therapy may not be adequate for some cases of bronchial asthma and COPD. The study was an open label study leading to bias and the sample size was small and was conducted at a single site. A larger multicentric study with a bigger sample size, with double blinding and longer duration could give a better picture of the nature of the new drug, Doxophylline and the results could be extrapolated to a wider population.

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