Research Paper

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Comparative Efficacy And Safety Of Doxofylline Versus Theophylline in Bronchial Asthma And Copd Patients

Pharmacology

KEYWORDS :

Dr. Rupali Bajrang Jadhav	Lecturer, Department of pharmacology, Dr VMGMC, Solapur (MS) 431001
Dr. Mirza Shiraz Baig	Lecturer, Department of pharmacology, GMC, Aurangabad (MS) 431001
Dr. Prakashchandra Rambhau Gade	Professor & Head, Department of pharmacology, Latur (MS) 431001
Dr. Prakash Narayan khandelwal	Associate professor, Department of pharmacology, GMC, Aurangabad (MS) 431001

ABSTRACT

The present study was conducted in the department of pharmacology at government medical college and hospital , Aurangabad to compare the efficacy and safety of doxofylline versus theophylline in the form of sustained release tablets in mild to morderate asthma and COPD patients. It was a randomized open label phase 3 clinical trial including men and women above 18 years of age attending medicine opd.The investigations carried out at start were lung function tests ie FEV1 , FVC, FEF, PEFR and ratio of FEV1/ FVC, they were repeated after 1 month of study period when patients were given theophylline and doxofylline after randomization in two groups.At the end it was found that FEV1, FEF and PEFR was significantly improved in doxofylline group than theophylline group . Considering the results obtained in the present study ,doxofylline seems to be a better alternative to theophylline in maintenance therapy for bronchial asthma and COPD.

INTRODUCTION

Allergic respiratory disorders in particular bronchial asthma are increasing in prevalence, which is a global phenomenon. The increased prevalence correlated well with demographic changes of the city like, urbanization, air pollution and environment tobacco smoke contribute more significantly.[1]

Bronchial Asthma is one of the commonest respiratory disease affecting millions of people all over the world.[2] The two obstructive airway diseases bronchial asthma and chronic obstructive diseases represent major global cause of disability and death. COPD is estimated to become the 4th most common cause of death by 2020.[3] The prevalence of bronchial asthma worldwide is around 200 million with a mortality of around 0.2 million/year. Though the prevalence is more in the developed countries, the developing countries have a higher total burden of the diseases due to differences in population.[4]

Doxofylline is a novel xanthine bronchodilator which differs from theophylline in that it contains a dioxalane group in position-7. Similarly to theophylline its mechanism of action is related to the inhibition of phosphodiesterase activities, but in contrast it appears to have decreased affinity towards adenosine A1 and A2 receptors, which may account for its better safety profile. The bronchodilating effect of doxofylline have been demonstrated in clinical trials involving patients of either bronchial asthma or chronic obstructive pulmonary disease. In contrast to other bronchodilators, experimental and clinical studies have shown that the drug is devoid of stimulatory effects. This may be of importance because the arrhythmogenic actions of bronchodilators may have negative impact on the survival of patients with respiratory diseases.

The unique cardiovascular tolerability profile of doxofylline makes it unnecessary to monitor the serum levels of the drug for the determination of its upper limit of its therapeutic range. The effects of oral doxofylline on pulmonary lung function tests in patients with New York Heart association (NYHA) functional class 2 to chronic heart failure and COPD was examined in 20 patients under optimized therapy with digitalis, ACE inhibitors and diuretics. After 10 days FEV1 increased by 18%, FVC by 7% and FEV1/FVC by 15%. 85% of patients exhibited an improvement in NHYA class.**5**

The drug therapy for bronchial asthma and COPD consisting of drugs like b2 agonist, xanthine derivatives, corticosteroids and anticholinergics, is established. However considering the potency, adverse effects, cost effectiveness , and duration of therapy which may be long lasting, there is a need of a novel agent that not only provides therapeutic response but also is important in maintenance therapy. It should be free from adverse effects and cost effective.

Considering the above mentioned background and the studies, the present study was planned to evaluate the safety and efficacy of doxofylline versus theophylline as maintenance therapy in patients of bronchial asthma and COPD.

AIMS AND OBJECTIVES

The present study was conducted in the Department of Pharmacology at Government Medical College and Hospital, Aurangabad with the following aims and objectives:

1. To evaluate the safety and efficacy of doxofylline in bronchial asthma and COPD patients.
2. To evaluate the safety and efficacy of theophylline in bronchial asthma and COPD patients.
3. To compare the safety and efficacy of doxofylline and theophylline in bronchial asthma and COPD patients.

MATERIAL AND METHODS

Nature of study :

A randomized open label phase – III clinical trial to evaluate and compare efficacy of doxofylline in treatment of bronchial asthma and COPD.

Source of patients :

Men and women above 18 years of age attending the Medicine OPD of Government Medical College and Hospital, Aurangabad.

Inclusion criteria :

1. Adults, 18 years of age and above.
2. Health status – non-smokers for at least 8 months before entering the study, in good physical conditions with more

than one year history of chronic intrinsic hyperactive airway disease (asthma).
3. Willing to undergo procedures in the protocol.
4. Willing to undergo a chest X-ray if required.
5. On screening, subjects must have had a baseline FEV1 value within 50 to 80% of the predicted FEV1 value of their age and sex.
6. On screening subjects must have had baseline FEV1 30 minutes after administration of a standard dose (2 puffs 180 ug) of salbutamol or ipratropium reversibility in smokers.
7. Subjects may have demonstrated, by verbal history a period of atleast 1 month of acceptable clinical control of their bronchial asthma in the preceding 3 months using oral theophylline alone or in combination with a b2 agonist inhaler.

Exclusion criteria :
1. Clinical significant deviation from normal in physical examination, laboratory parameters ,ECG, or chest x-ray.
2. Clinically significant cardiovascular diseases, including a history of congestive cardiac failure, angina pectoris within previous 1 year.
3. Convulsive disorders.
4. Clinical significant gastro-intestinal diseases including active peptic ulcers within preceding 1 year.
5. Renal diseases, hepatic diseases, hematologic diseases and insulin dependent diabetes mellitus.
6. Non-reversible COPD.
7. Known infection with human immunodeficiency virus.
8. Presence of any acute illness.
9. Sensitivity to theophylline or theophylline like agents.
10. History of alcohol, marijuana, barbiturate a polydrug abuse.
11. Oral contraceptive use was not allowed because of the propensity for these drugs to decrease theophylline clearance.
12. Lactating females.
13. Subjects using aerosol steroids will be required to discontinue their use at least 1 month before the study to refrain from them throughout the entire duration of the study.
14. Smokers.

Study population:
1. Men and women over 18 years of age diagnosed as patients of bronchial asthma and COPD were included in the study.
2. Patients were randomly allocated into 2 groups – Group-A (Doxofylline) and Group-B (Theophylline) on basis of a computerized randomization.

Study Duration:
The study was done in 1 month for every patient in which there were 4 visits of each patient at the end of 7 days/ 1 week during which visit they were given drugs and instructions about the drug and encouraged to come for the next follow-up visit.

Drugs used:
1. Tab.Theophylline (sustained release preparation) Dose – 200 mg
2. Tab : Doxofylline sustained release tablets.

The investigations required to be done at each visit are lung function test by spirometry that is the efficacy parameters.

1. FEV1, change in the FEV1 values from baseline values.
2. The secondary efficacy variable are FVC, FEF, PEFR and FEV1/FVC.

Study design :
Visit-I, Day-1 : The informed consent is obtained from each patient enrolled. Patients are selected after thorough physical examination, ECG and relevant lab investigations. After assessment of compliance with inclusion and exclusion criteria each patient entering the study is allotted in Group-A or

Group-B.
The patient is asked to withdraw the earlier drug and provided with enough drugs for the first administration period of 7 days. The first dose must be taken on the evening of day 1, then 2 doses on each day till day-7.

Visit-2, Day-8 : The patient is instructed to come for follow-up on day-8 for visit-2, vital signs and physical examination is done. Patients will be supplied with the drug quantity necessary for the 2nd week with the same drug and dosage schedule.

Visit-3 – Day-15 : The patients will be examined and drugs are supplied new for the next 14 days (up to day 28) and instructed to report at day 29.

Visit-4 – Day-29 : As per schedule when the patients come for follow-up, then the safety assessment and enquiry about any adverse effects suffered by the patients. All the investigations done at baseline are repeated.

Parameters for evaluations
The primary parameters for the evaluation of the study drug efficacy will be the following.

1. The primary efficacy variable is FEV1 ie change in the FEV1 value from the baseline value.
2. The secondary efficacy variables derived from the pulmonary function tests were forced vital capacity, forced expiratory volume at the end of 1st second, forced expiratory flow . FEF : 25-75% and peak expiratory flow rate. These variables will be assessed a manner similar to that for FEV1, i.e. percent change from baseline will be calculated and analysed.

Statistical analysis :
1. Chi-square test
2. Paired 't' test and Unpaired 't' test.

OBSERVATIONS AND RESULTS

TABLE – 11

COMPARATIVE LUNG FUNCTIONS IN DOXOFYLLINE GROUP AT BASELINE AND AT THE END OF 4 WEEKS (MEAN VALUES)

Parameters	Doxofylline group		
	Baseline	AT 4 weeks	'p' Value
FEV_1	0.84 ± 0.61	1.47 ± 0.68	1.98
FVC	1.77 ± 1.21	2.10 ± 0.88	0.06
FEF	4.07 ± 13.8	1.64 ± 1.14	0.32
PEFR	1.19 ± 0.85	2.22 ± 1.18	4.03
FEV_1/ FVC	47.77 ± 25.55	67.66 ± 33.5	0.02

'p' is < 0.05 then statistically significant.

'p' is > 0.05 then statistically not significant.

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TABLE – 12

COMPARATIVE LUNG FUNCTIONS IN THEOPHYLLINE GROUP AT BASELINE AND AT THE END OF 4 WEEKS (MEAN VALUES)

Parameters	Theophylline group		
	Baseline	AT 4 weeks	'p' Value
FEV_1	0.82 ± 0.53	1.26 ± 0.64	0.008*
FVC	1.58 ± 0.84	2.95 ± 0.96	0.091
FEF	5.38 ± 19.3	1.20 ± 0.79	0.22
PEFR	2.11 ± 5.4	1.90 ± 0.93	0.82
FEV_1/ FVC	49.4 ± 29.9	61.51 ± 28.2	0.07

* Note :

'p' value is < 0.05 then statistically significant.

'p' is > 0.05 then statistically not significant.

TABLE – 13

EFFECT OF THEOPHYLLINE AND DOXOFYLLINE ON LUNG FUNCTION TESTS AFTER 4 WEEKS

Parameters	'p' Value
Forced Expiratory Volume in L/S	0.027*
Forced Vital Capacity in L/S	0.551
Forced Expiratory flow in L/S	0.008*
Peak Expiratory flow rate in L/S	0.008*
Ratio of FEV_1/FVC	0.115

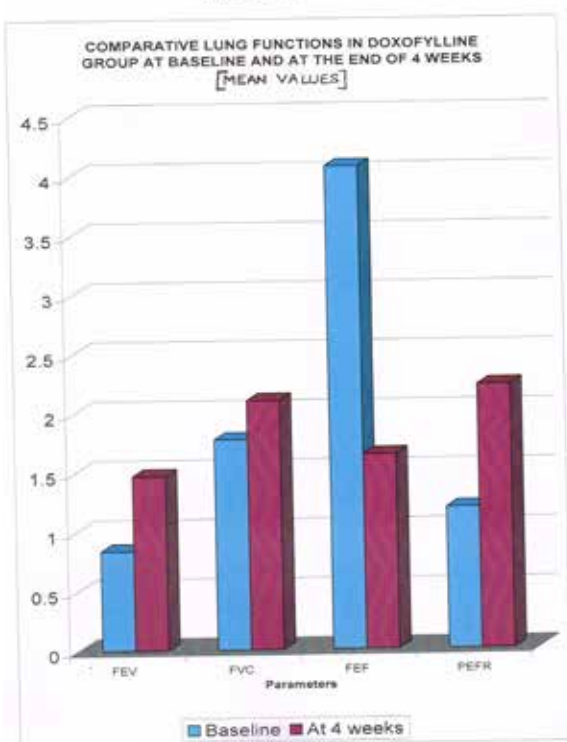
Note :

'p' value is < 0.05 then statistically significant.

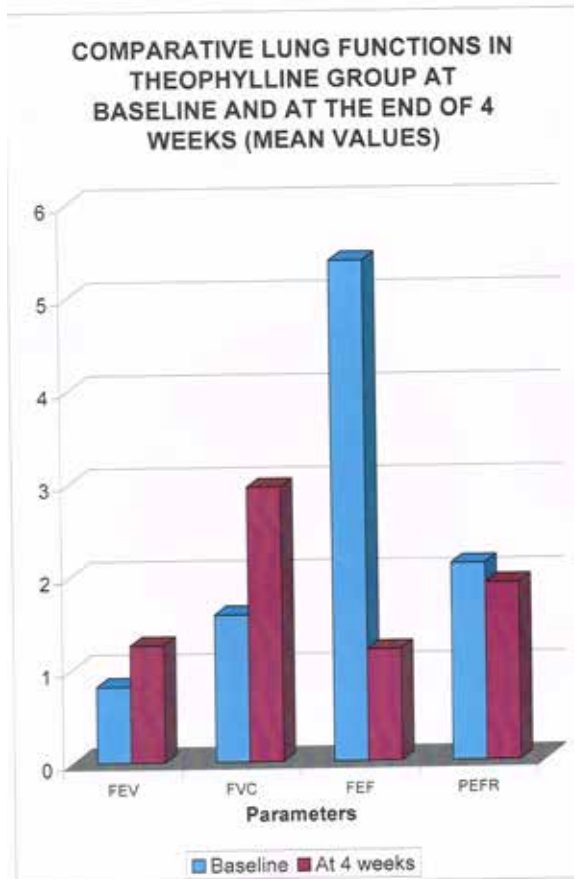
'p' is > 0.05 then statistically not significant.

GRAPH -1

GRAPH-2



GRAPH - 2



Results :

Sixty eight Patients (n=68) of bronchial asthma and COPD completed the study. A comparative evaluation of doxofylline and theophylline on pulmonary lung functions using spirometry was done. The result obtained before and after therapy showed that:

The mean values of FEV1 in doxofylline group was increased (1.47 ± 0.68) as compared to baseline values (0.84 ± 0.61) which was statistically not significant ($p < 0.05$). In theophylline group the mean values of FEV1 at baseline were (0.82 ± 0.53) which was statistically (p is <0.05) increased to (1.26 ± 0.64) Further in the doxofylline group mean values of FVC at baseline were (1.77 ± 1.21) which increased to (2.10 ± 0.88) the increase was not statistically significant (p value is > 0.05). Similarly in theophylline group mean values of FVC at baseline were(1.58 ± 0.84) which increased to mean values (2.95 ± 0.96) which is not statistically significant (p value is > 0.05) Also in the doxofylline group it was found that mean values of FEF decreased to (1.64 ± 1.14) from baseline values of (4.07 ± 13.8) which is statistically not significant (p value is > 0.05)

Likewise in theophylline group mean values of FEF at baseline were (5.38 ± 19.3) which decreased to (1.20 ± 0.79) this was statistically not significant (p value is > 0.05) Similarly in doxofylline group mean values of PEFR at baseline were (1.19 ± 0.85) which increased to mean values of (2.22 ± 1.18) which was not statistically significant (p value is > 0.05) .

In theophylline group mean values of PEFR at baseline were (2.11 ± 5.4) which decreased to mean values(1.90 ± 0.93) which is statistically not significant (p value is < 0.05) .

In the doxofylline group mean values of ratio of FEV1/FVC at

baseline were (47.77 ± 25.55) which increased to (67.66 ± 33.5) which is statistically not significant (p value is > 0.05) .

It was also found that in theophylline group mean values of FEV1/FVC at baseline were (49.4 ± 29.9) which increased to (61.51 ± 28.2) which is statistically not significant (p value is > 0.05) .

Intergroup comparison .

1. FEV1 in doxofylline and theophylline group at the end of the study:

The mean values in doxofylline group (1.47 ± 0.68) when compared to mean values in theophylline group (1.26 ± 0.64) show that doxofylline is better than theophylline (p value < 0.05).

2. FVC in doxofylline and theophylline group at the end of the study:

The mean values in doxofylline group (2.10 ± 0.88) when compared to mean values in theophylline group (2.95 ± 0.96) , the difference was not statistically significant (p value < 0.05).

3. FEF in doxofylline and theophylline group at the end of the study:

The mean values in doxofylline group (1.64 ± 1.14) when compared to mean values in theophylline group (1.20 ± 0.79) , the values were statistically significant in doxofylline group (p value < 0.05).

4. PEFR in doxofylline and theophylline group at the end of the study

The mean values in doxofylline group (2.22 ± 1.18) when compared to mean values in theophylline group (1.90 ± 0.93) , was statistically significant in doxofylline group (p value > 0.05). 90

5. Ratio of FEV1/FVC in doxofylline and theophylline group at the end of the study :

The mean values in doxofylline group (67.66 ± 33.5) when compared to mean values in theophylline group (61.51 ± 28.2) were not statistically significant (p value < 0.05). The adverse effects in doxofylline group were seen in 12 patients as compared to 15 patients in theophylline group

DISCUSSION AND CONCLUSION

Bronchial asthma and COPD is a major cause of chronic morbidity and mortality throughout the world. COPD is currently 4th leading cause of death in world and further increase in prevalence and mortality of the disease can be predicted in the coming decades.**6** Morbidity and mortality due to bronchial asthma is on the rise worldwide. The rising trend of morbidity and mortality in bronchial asthma is a matter of global concern in recent years.[7] The main goals of therapy in Bronchial asthma and COPD cases are to reverse the airway obstruction and to provide symptomatic relief; to prevent or retard the progression of the disease; and to rehabilitate the individual. The drugs which are routinely used in the management of bronchial asthma and COPD are b2 agonists, methyl xanthines, anticholinergics, corticosteroids, antibiotics and mucolytics. Thus the goal of therapy in bronchial asthma and COPD is to achieve a stable, asymptomatic state with the best pulmonary function possible using the least amount of medication.**4**

Bronchodilators being the main stay in the treatment options for symptomatic relief include b2 agonist; these drugs have significant effect on the therapeutic outcome but are associated with untoward adverse effects. Similarly the Methyl xanthines which are Phosphodiesterase inhibitors in use have comparable adverse drug profile. Considering the duration of the treatment required in bronchial asthma and COPD and with due importance to the adverse drug effects the Methyl xanthines have shown promising results in the maintenance therapy of Bronchial asthma and COPD.

The Methyl xanthines act by inhibiting Phosphodiesterase-4, they relax airway smooth muscle, suppress the activation of inflammatory cells, and modulate the activity of pulmonary nerves. In addition to the short term effect on bronchomotor tone, they may find utility in reducing the protease burden associated with neutrophilic inflammation; as well as down regulating the activity of CD8 T cells and macrophages leading to slow decline in lung functions.**8,9**

If inhalation is not feasible due to any reason, like cost of medication or inability to take medication as in children and old people, oral methylxanthines can be given.[10] For maintenance therapy long acting drug like theophylline SR or doxofylline compounds are available and can be given once or twice daily.**11**

Doxofylline is a new methyl xanthine derivative recently introduced in therapy for mild to moderate asthma.**12** Sugeta et al, reported that Doxofylline decreased airway responsiveness at the dosage which does not affect the heart rate and respiratory rate with theophylline in beagles.**6**

In experimental studies doxofylline displayed a more potent bronchodilator activity and less cardiac adverse effects than theophylline.**13** Villani F et al, showed that doxofylline has an bronchodilating effect in patients responsive to inhaled □2 agonists like salbutamol.**14**

In this study safety and efficacy of doxofylline versus theophylline was compared. It was found that doxofylline was more effective in improving the lung functions particularly forced expiratory flow and peak expiratory flow rate. Doxofylline was also more effective in improving forced expiratory volume than theophylline. In comparison with theophylline, doxofylline was found to be safer as shown by the adverse drug profile of the patients.

The results of the present study are in accordance with Crescioli S et al (1991); Franzone JS (1998), Villani F et al (1997) and Sugeta A, who showed that doxofylline seemed to be better alternative in the treatment of bronchial asthma and reversible chronic airway obstruction in view of its better safety profile.**13,12,15,16**

Considering the adverse effects, the results obtained in the present study are similar to the studies by Checchini M et al (1997) who showed that the group treated with doxofylline have a better reduction in cardiac frequency in acute cardio-respiratory syndrome versus aminophylline while maintaining the same effects on the respiratory apparatus.**17,18**

In conclusion the need of patients with bronchial asthma and COPD is relief from the respiratory distress and simultaneously therapy should be cost effective with less adverse effects. Considering the results obtained in the present study and supported by the other clinical studies, doxofylline seems to be a better alternative to theophylline in maintenance therapy for bronchial Asthma and COPD.

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