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 moderate 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 i.e. 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.

Bronchial Asthma is one of the most commonest respiratory disease affecting millions of people all over the world. 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. 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.

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 NYHA class.

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, 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 min-
utes 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 the-
ophylline alone or in combination with a b2 agonist inhaler.

Exclusion criteria :
1. Clinical significant deviation from normal in physical exami-
nation, 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 ac-
tive 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.
9. Sensitivity to theophylline or theophylline like agents.
11. Oral contraceptive use was not allowed because of the pro-
pensity for these drugs to decrease theophylline clearance.
12. Lactating females.
13. Subjects using aerosol steroids will be required to discon-
tinue their use at least 1 month before the study to refrain
from them throughout the entire duration of the study.

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 dur-
ing 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-1, Day-1 : The informed consent is obtained from each
patient enrolled. Patients are selected after thorough physical
examination, ECG and relevant lab investigations. After assess-
ment 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 dos-
es 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 ad-
verse 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 ef-
cicacy 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 pulmo-
nary function tests were forced vital capacity, forced expira-
tory 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. per-
   cent 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
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).

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 the world. The rising trend of morbidity 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. 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 β2 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 mainstay in the treatment options for symptomatic relief include β2 agonists; 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 Bronchi-
Reference

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