

Effect of oral hypoglycemic agents on theophylline pharmacokinetics in acute exacerbation of chronic obstructive pulmonary disease patients – A randomized controlled pilot study

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ABSTRACT

Background: Chronic obstructive pulmonary disease (COPD) is a lung disease characterized by breathing difficulties due to the airflow limitation, causing blocking, and by damage of the elastic recoil of lung parenchyma, leading to hyperinflation. The main aim of this review article is to know about the hypoglycemic agents on theophylline pharmacokinetics (PKs) in COPD patients. Theophylline is the most well-known and commonly used methylxanthine. Methylxanthines are the main class of drug that is obtained from the purine base xanthine. Theophylline is one of the methylxanthine drugs used in the treatment for breathing difficulties such as COPD and asthma. **Methodology:** A randomized control study is carried out to assess the effect of oral hypoglycemic agents on theophylline PKs. A total of six blood samples (5 ml) were drawn from each participant at 0 h, ½ an h, 1st h, 3rd h, 6th h, and finally at 12th h to evaluate PK parameters such as AUC₀₋₁₂, AUC_{0-∞}, and C_{max} which are to be assayed for the two types of patients and to determine the effectiveness of the treatment given. **Results:** Theophylline PKs were studied in patients with and without diabetes. Oral hypoglycemic agents reduced the area under the concentration-time curve by 12% after the administration of hypoglycemic agents in diabetic patients and decreased metabolic clearance and volume of distribution by 16% after the administration of theophylline 150 mg. **Conclusion:** In patients receiving theophylline blood glucose levels to be monitored, if the patient is on oral hypoglycemic therapy and the dosage is to be adjusted.

KEY WORDS: Acute exacerbation, Chronic obstructive pulmonary disease, Hypoglycemic agents, Pharmacokinetics, Theophylline

INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is a lung disease characterized by breathing difficulties due to the airflow limitation, causing blocking, and by damage of the elastic recoil of lung parenchyma, leading to hyperinflation.^[1,2] The severe and prolonged infection, irritation, and temperature changes lead to exacerbation condition.

Acute exacerbation (AE) is the main cause for the development of pulmonary disease condition. The

association between AE COPD and decline in health status and lung function is well recognized.^[3,4] Around 50% of direct cost for COPD may occur.^[5]

Methylxanthines

Methylxanthines are the main class of drug that is obtained from the purine base xanthine with the degradation of purine that is produced by both plants and animals. It is found in human body tissues and fluids and in other organisms. The methylxanthine theophylline is used in the treatment of airway obstructions such as asthma and COPD.^[6,7]

It has demonstrated efficacy in attenuating three cardinal features such as follows:

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- Reversible airflow obstruction
- Hyperresponsiveness
- Airway inflammation.^[8,9]

The most relevant methylxanthine is caffeine, theobromine, and theophylline.

Theophylline

Theophylline is the most well-known and commonly used methylxanthine. Theophylline may also derive as 1, 3-dimethylxanthine. It is a methylxanthine drug used in the treatment for respiratory problems such as asthma and COPD.

At lower dose, theophylline is used as an immunomodulatory effect, anti-inflammatory, and bronchoprotective effect. At higher dose concentration, theophylline drug is used as a bronchodilator effect.^[10-12]

- Dose range in adults 5–15 µg/ml or 300–400 mg/day
- Dose range in children 5–10 µg/ml or 300 mg/day.

MATERIALS AND METHODS

The study was carried out in the Department of General Medicine in a tertiary care hospital. The sample size was calculated to be 14 with a confidence interval of 95%. The duration of the study was September 2018–February 2019. The study design was randomized controlled pilot study. A randomized control study is carried out to assess the effect of oral hypoglycemic agents on theophylline pharmacokinetics (AUC and C_{max}) in COPD patients. The study is carried out in two different groups. 5 ml of blood sample is collected.

Evaluation of PK parameters will be carried out after the morning dose. Blood samples were centrifuged at 3500 rpm for 10 min immediately after collection and transferred to glass containers, where the samples kept frozen at -20°C . PK parameters such as AUC_{0-t} , AUC_{0-max} , and C_{max} are to be assayed for the two types of patients to determine the effectiveness of the treatment given.

Study Instruments

High-performance liquid chromatography is an important analytical method commonly used to separate and quantify components of liquid samples.

Patient Selection

Inclusion criteria

The following criteria were included in the study:

1. Above 18 years of age
2. Diagnosed with AE of COPD with and without diabetes.

Exclusion criteria

The following criteria were excluded from the study:

1. Pregnant and nursing women
2. Patient with lung carcinoma
3. Palliative patients
4. Patients with coagulation disorders.

RESULTS

Figure 1 represents the age, gender, body mass index, alcoholic, smoker, and duration of diabetes mellitus in both the groups of patients. The age group in Group A is found to be 42 ± 1.6 and in Group B, it is found to be 51 ± 2.4 . In Group A, six male patients were included in the study and in Group B, eight male patients were included in the study. No alcoholic patients were present in both the groups. There are three smoker patients in both the groups.

Table 1 shows that the plasma concentration of the given drug in both the groups in time interval from 0 h, 30 min, 1 h, 2 h, 4 h, 6 h, 12 h, and 24 h when compared to A group the peak plasma concentration was attained in B group.

Figure 2 shows that the plasma concentration of the given drug in both the groups in time interval from 0 h, 30 min, 1 h, 2 h, 4 h, 6 h, 12 h, and 24 h when compared to A group the peak plasma concentration was attained in B group.

Figure 3 represents the PK properties of the drug in both groups. The parameters involved are T_{max} , C_{max} , $AUC_{0-\infty}$, and AUC_{0-t} .

* $P < 0.05$ which is statistically significant.

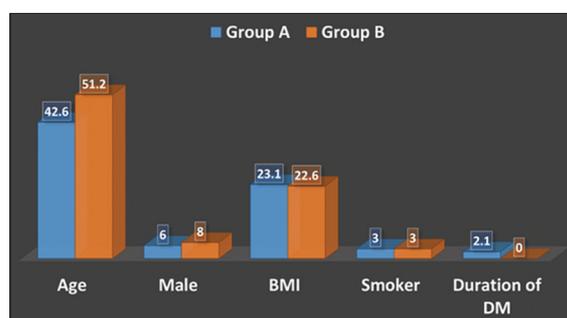


Figure 1: Baseline parameters

Table 1: Plasma concentration (µg/ml)

Time	Group A	Group B
0 h	0	0
30 min	516±13.4	560±12.6
1 h	1236±14.2	1532±16.2
2 h	2468±13.2	3097±13.6
4 h	1764±12.6	2052±13.2
6 h	610±13.8	837.6±12.1
12 h	49±12.8	136.2±17.1
24 h	17±12.6	28.1±14.8

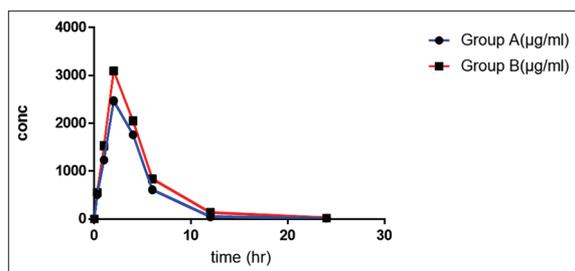


Figure 2: Plasma concentration of the drug

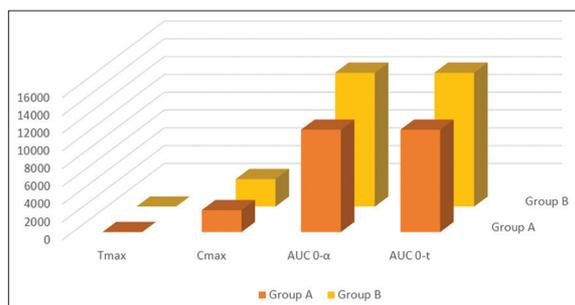


Figure 3: Pharmacokinetic parameters

DISCUSSION

COPD is characterized by airflow limitation causing breathing difficulties. This study is based on the effect of theophylline drug in COPD patients with and without diabetes that is the patients were categorized into two groups. The effect of the theophylline drug action was observed by performing the PK parameters. The patient using theophylline drug alone and the patient using theophylline drug along with the oral hypoglycemic drugs such as metformin and sitagliptin were included in this study to achieve the target drug action.

Theophylline is one of the most common and first-line drugs preferred for breathing difficulties. It acts as a bronchodilator effect. The drug theophylline at various doses acts as various mechanisms of drug action.

In this study, it was clearly observed the effect of theophylline drug alone and with the combination of oral hypoglycemic drugs. The effect of theophylline drug was reduced when it is consumed along with the oral hypoglycemic drugs. The PK parameters of those drugs were reduced and varied in their concentration with the concurrent administration of both drugs.

CONCLUSION

AUC and steady-state concentration vary and reduced by the effect of metformin and other oral hypoglycemic agents. Time of administration must be varied to achieve the target steady-state and peak plasma concentration.

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