



CHRONOTHERAPY OF CHRONIC OBSTRUCTIVE PULMONARY DISEASE WITH ONCE DAILY SUSTAINED RELEASE THEOPHYLLINE VS THRICE DAILY STANDARD THEOPHYLLINE PREPARATION – AN OPEN LABEL STUDY.

Dr. M. Malathi*

Assistant Professor, Institute of Pharmacology, Madurai Medical College
*Corresponding Author

Dr. R. Prabhakaran

MD, Professor & Head of the department, Department of Pulmonology, Madurai Medical College.

Dr. Arivudai Nambi

MD, Associate professor, Department of Pulmonology, Madurai Medical College

Dr. Bharathi Babu

MD, Associate professor, Department of Pulmonology, Madurai Medical College

ABSTRACT

Chronic Obstructive Pulmonary Disease (COPD) is a long-term, progressive respiratory condition characterized by airflow limitation in the lungs. There is a circadian variation in FEV1 in stable COPD peaking at 4:00 pm and dipping at around 4:00 am. In patients who experience morning symptoms, the most common morning symptoms were coughing, shortness of breath, and sputum production. Research has indicated that patients who experience morning symptoms are at higher risk for exacerbations and are more likely to use their rescue inhaler. The diurnal variation in symptom severity has been observed during COPD exacerbations, with elevated risk for intubation during early morning hours in the emergency department. Concentration related side effects dictate that serum concentration of Theophylline has to be maintained with in a narrow therapeutic range. Frequent dosing – Limits its use and compliance. Sustained release overcomes frequent dosing and decrease side effects. Study was planned to compare the serum theophylline levels and clinical efficacy of once daily sustained release theophylline with standard dose on diurnal variation in chronic obstructive pulmonary disease. To determine, whether patients with COPD who are taking Theophylline thrice daily per day will be safely switched over to once daily dosage. To confirm whether the therapeutic concentration is maintained. Evening dose theophylline is superior to morning dose in COPD in achieving clinical efficacy. Thrice daily dose does not achieve desired therapeutic level in all patients, sustained release had better therapeutic concentration but at same toxicity was more like palpitations compliance was better in sustained release tablets.

KEYWORDS : COPD, Theophylline, Serum concentration, efficacy, sustained release

1. INTRODUCTION:

In India 2nd highest cause of death killing 1 million Indians – “global burden of disease study 2018 is COPD with Prevalence of 3.49% in India. Chronic Obstructive Pulmonary Disease (COPD) is a long-term, progressive respiratory condition characterized by airflow limitation in the lungs. This limitation is typically not fully reversible and is often associated with symptoms like coughing, shortness of breath, wheezing, and chest tightness. The two primary conditions that fall under COPD are chronic bronchitis and emphysema. Chronic bronchitis involves long-term inflammation of the bronchial tubes, leading to excessive mucus production, while emphysema involves damage to the air sacs in the lungs, reducing their elasticity and impairing airflow. Risk factors for COPD include smoking (the leading cause), exposure to air pollutants (such as second hand smoke, chemicals, or fumes), genetic factors, and respiratory infections. Management and treatment of COPD usually involve: Lifestyle Changes: Quitting smoking is critical in slowing the progression of COPD. Avoiding exposure to pollutants and maintaining a healthy lifestyle, including regular exercise and a balanced diet, are also important. Medications: Bronchodilators, inhaled corticosteroids, and other medications are often prescribed to improve symptoms and lung function. Pulmonary Rehabilitation: This involves exercise training, education, and counseling to help individuals manage COPD symptoms and improve their quality of life. Oxygen Therapy: In advanced stages, supplemental oxygen may be necessary to help with breathing. COPD is a chronic condition that requires ongoing management and monitoring. Early diagnosis, along with proper treatment and lifestyle modifications, can significantly improve the quality of life for individuals with COPD and slow down its progression. Regular follow-ups with healthcare providers are crucial for adjusting treatments and managing exacerbations. role of theophylline in copd is Third-line agent But First-line agent for

those with sleep-related breathing disorders. Improves hemoglobin saturation during sleep in COPD patients. Improves dyspnoea grading's, exercise performance, and pulmonary function. Benefits - Bronchodilator; anti-inflammatory properties, Overcomes steroid resistance by Restoring Histone deacetylase, inhibits COL1 mRNA. There is a circadian variation in FEV1 in stable COPD peaking at 4:00 pm and dipping at around 4:00 am. In patients who experience morning symptoms, the most common morning symptoms were coughing, shortness of breath, and sputum production. Research has indicated that patients who experience morning symptoms are at higher risk for exacerbations and are more likely to use their rescue inhaler. The diurnal variation in symptom severity has been observed during COPD exacerbations, with elevated risk for intubation during early morning hours in the emergency department. Concentration related side effects dictate that serum concentration of Theophylline has to be maintained with in a narrow therapeutic range. Frequent dosing – Limits its use and compliance. Sustained release overcomes frequent dosing and decrease side effects.

2. AIMS

To compare the serum theophylline levels and clinical efficacy of once daily sustained release theophylline with standard dose on diurnal variation in chronic obstructive pulmonary disease. To determine, whether patients with COPD who are taking Theophylline thrice daily per day will be safely switched over to once daily dosage. To confirm whether the therapeutic concentration is maintained. Evening dose theophylline is superior to morning dose in COPD in achieving clinical efficacy. Synchronizing theophylline concentration to circadian rhythm in COPD to increase efficacy and reduce adverse effects.

3. METHODS & MATERIALS

Therapeutic Drug Monitoring was carried out at Department of Health Research, ICMR, Multidisciplinary Research Unit, Madurai Medical College, Madurai.

Study Period

March 2020 to August 2020 - 6 months (Period of Data collection - 4 Months Period for analyzing the data - 2 Months)

Sample Size :

45 patients with COPD stage II (moderate) and stage III (severe) patients (GOLD staging) Calculated using nMaster 2.0 software

Inclusion Criteria

- Age > 18 years of either sex
- Chronic obstructive pulmonary disease stage II, and stage III patients.
- Patients willing to participate in the study and able to record PEFR by himself.

Exclusion criteria

- Patients who smokes more than 10 cigarettes per day.
- Patients with renal and liver diseases.
- Patients with H/o seizures or cardiac diseases.
- Patients on any microsomal enzyme inducers / inhibitors (Erythromycin, quinolones)
- Alcoholics
- Any psychiatric or debilitating disease.
- Pregnant and lactating females.

METHODOLOGY

45 adult patients of either gender with COPD GOLD stage II and III were selected after satisfying the inclusion and exclusion criteria. Written consent was obtained from all the patients after being informed about the nature and risks involved in the study. Demographic details of the patient was obtained. Basic biochemical investigations (CBC, LFT and RFT) and cardiac screening (ECG, ECHO) Baseline recording of Spirometry (6hrs after last adrenergic agonist) CAT score, six minute walk test was done.

The study was conducted in three phases. In first phase, the patients will be receiving Tab. Theophylline 100mg thrice daily for 21 days.

In the second phase, the same 45 patients were switched over to Tab. Theophylline 24 hour sustained release 300mg in the morning (8 AM) for 21 days. In the third phase, the same 45 patients were switched over to Tab. Theophylline 24 hour sustained release 300mg in the evening (8PM) for 21 days.

The patients were on oral/inhaled beta agonists as reliever medications throughout the study period. 5ml of blood sample was collected peak level (12 hours after the previous dose). Serum was separated and stored at - 80°C for Therapeutic Drug Monitoring until use. Trough concentrations are not useful and can lead to inappropriate dose increases; peak concentrations can be 2 to 3 times higher than trough. Therapeutic serum levels of theophylline are between 10 to 20 mcg/ml. Most adults achieve these concentrations with daily slow-release oral theophylline preparations, 200-400 mg (approximately 10 mg/Kg) twice a day.

However, when such a patient presents to the emergency room (ER) in an asthmatic attack, immediate intravenous theophylline is often given, regardless of maintenance treatment.

Since the rationale for this common therapeutic approach has been challenged, the current study was undertaken. The results were evaluated at a significance level of p-value of less than 0.05 and with 95% confidence intervals.

4.RESULTS

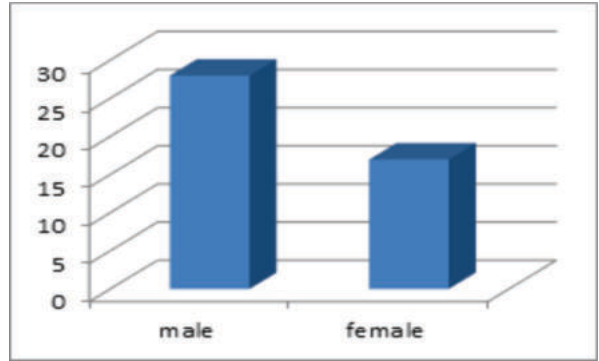


Figure No 1 Age Distribution

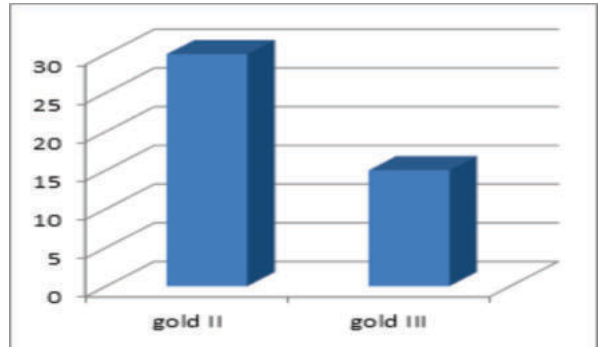


Figure No 2 Disease Category

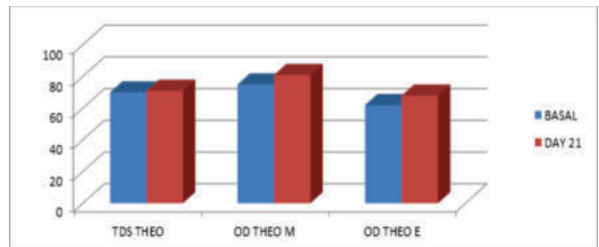


Figure 3 Comparison Of Fev1 Basal And Day 21

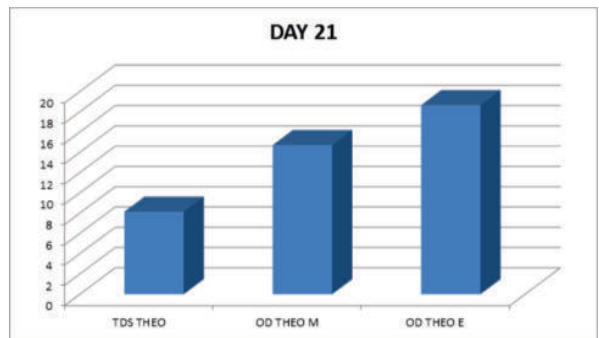


Figure No 4 Serum Concentration At 21 Days

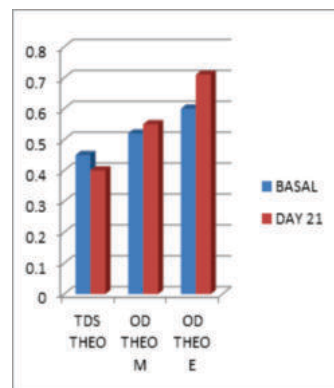


Figure 5 Comparison Of Fev1/fvc Basal And Day 21

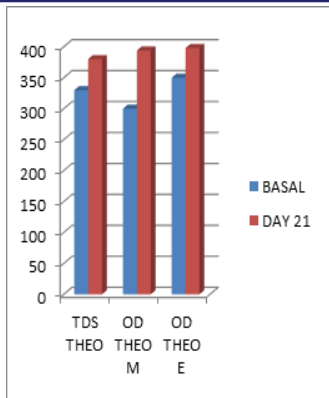


Figure 6 Comparison Of Perf Basal And Day 21 Between Three Groups

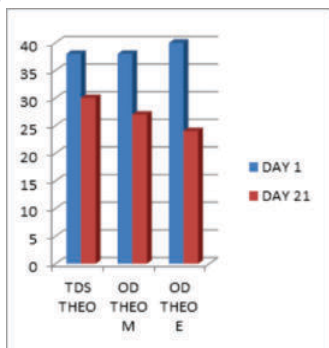


Figure No 7 Comparison Of Cat Score Between Three Groups

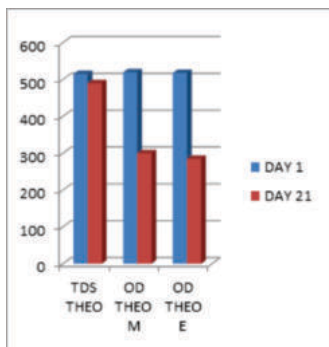


Figure No 8 Comparison Of 6 Mins Walk Test Between Three Groups Day 1 And Day 21

5. DISCUSSION AND CONCLUSION

Theophylline is a medication primarily used to treat respiratory conditions like asthma and chronic obstructive pulmonary disease (COPD). It's a type of bronchodilator that helps relax the air passages in the lungs, making it easier to breathe. Theophylline works by relaxing the smooth muscles in the airways and also has effects on the immune cells and inflammatory mediators in the respiratory system. It's available in various forms like tablets, capsules, and extended-release formulations. However, it's important to use theophylline under medical supervision as it can have side effects and interact with other medications. Theophylline, while effective for respiratory conditions, can also cause several side effects, especially when the levels in the blood become too high. Some common side effects include: Nausea and Vomiting, Headaches, Insomnia or Restlessness, Increased Heart Rate, Tremors, Gastrointestinal Issues, Increased Urination, Dizziness or Lightheadedness, Rash or Skin Irritation. In rare cases, theophylline can cause more severe side effects like seizures, irregular heartbeat, or signs of an allergic reaction such as rash, itching, swelling, severe dizziness, or trouble breathing. Chronotherapy refers to the

practice of timing medication administration to coincide with the body's natural rhythms or biological cycles, such as the sleep-wake cycle or the body's internal clock (circadian rhythm). This approach aims to optimize the effectiveness of treatment while minimizing side effects by syncing drug delivery with the body's natural physiological patterns. By considering the body's natural rhythms and the specific properties of medications, chronotherapy seeks to enhance treatment outcomes and reduce side effects. However, it's crucial to consult healthcare professionals before altering the timing of medication administration, as individual responses to timing can vary, and not all medications are suitable for chronotherapy adjustments. The role of theophylline in COPD is as a Third-line agent. But as a First-line agent for those with sleep-related breathing disorders, it improves hemoglobin saturation during sleep in COPD patients, improves dyspnoea grading, exercise performance, and pulmonary function. Benefits include: Bronchodilator; anti-inflammatory properties, Overcomes steroid resistance by restoring histone de-acetylase, inhibits COL1 mRNA. There is a circadian variation in FEV1 in stable COPD, peaking at 4:00 pm and dipping at around 4:00 am. In patients who experience morning symptoms, the most common morning symptoms were coughing, shortness of breath, and sputum production. Research has indicated that patients who experience morning symptoms are at higher risk for exacerbations and are more likely to use their rescue inhaler. The diurnal variation in symptom severity has been observed during COPD exacerbations, with elevated risk for intubation during early morning hours in the emergency department. Concentration-related side effects dictate that serum concentration of Theophylline has to be maintained within a narrow therapeutic range. Frequent dosing – Limits its use and compliance. Sustained release overcomes frequent dosing and decreases side effects.

Thrice daily dose does not achieve desired therapeutic level in all patients, sustained release had better therapeutic concentration but at same toxicity was more like palpitations. Compliance was better in sustained release tablets. Limitation of the study we could have excluded patients who had taken parenteral theophylline the day before our sample collection.

Conflict Of Interest: Nil

Ethical Clearance Obtained

Funding

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