Original Research Paper

Volume-9 | Issue-3 | March-2019 | PRINT ISSN - 2249-555X

Pulmonary Medicine

NOVEL STRATEGY APPROACH OF DOXOFYLLINE AND ACEBROPHYLLINE FOR THE MANAGEMENT OF RESPIRATORY DISEASES

Dr. Kamlesh Kumar Pandey MBBS, DNB, Chest Physician at INSPIRE CHEST CLINIC, Borivali, Mumbai

Dr.Vipul Kalley MD, Consulting Chest Physician and Interventional Pulmonologist

Mamta Dhamija* ProAdWise Communications Pvt. Ltd., Mumbai, Senior Manager- Medical Affairs, ProAdWise Communications Pvt. Ltd. *Corresponding Author

ABSTRACT Among the several diseases, asthma, bronchospastic asthma and COPD (chronic obstructive pulmonary disease) are categorized to be a chronic inflammatory disorder of the airways across the globe. As per the Global Asthma Report 2018, more than 339 million people worldwide are affected with this syndrome and prevalence is still rising. Doxofylline is a xanthine derivative which is used in the treatment of asthma, produces stable serum concentrations, hence plasma monitoring is required only in patients with hepatic insufficiency and intolerance to xanthine drugs. Acebrophylline is a novel bronchodilator which has anti-inflammatory and mucoregulating effect. It is effective in patients with acute or chronic bronchitis, chronic obstructive or asthma-like bronchitis and recurrence of chronic bronchitis and also reduces the frequency of episodes of bronchial resistance and reduces the need for β2-agonists and improves indexes of ventilatory function. The present review article is intended to give comprehensive information and to study the efficacy and safety of the doxofylline and acebrophylline for the treatment of respiratory diseases.

KEYWORDS : Doxofylline, Acebrophylline, Asthma, Chronic Obstruction Pulmonary Disease. (3-4 keywords only)

INTRODUCTION:

Asthma, bronchospastic asthma and Chronic Obstructive Pulmonary Disease (COPD) are major health problem in worldwide population. These are indicated as different diseases with similar epidemiological features as well as pathophysiological mechanisms.[1] Asthma is a very common disease in worldwide population, in which almost 1 in 10 children and 1 in 12 adults are affected. According to Global Asthma Report 2018, 339 million people are affected worldwide.[2] Asthma is a chronic inflammatory disease characterized by bronchial hyper-reactivity (BHR) which is mainly responsible for mucus overproduction, airway narrowing and airway wall remodelling by reacting to non-specific stimuli (such as exercise and cold air) on smooth muscle cells in people with asthma.[3] Pulmonary disease with spasm called as bronchoconstriction or bronchospasm, results from contraction of bronchial smooth muscle induced by myriad possible stimuli, including intrinsic factors, stress, cold air, allergens and exercise.[4]

COPD is a chronic respiratory disease characterized by progressive and irreversible airway obstruction and is one of the major cause of morbidity and mortality worldwide.[1] The most commonly encountered risk factor for COPD, which is the fourth leading cause of death, is **Cigarette smoking**, although in most countries, air pollution resulting from the burning of wood and other biomasses fuels has also been considered as a COPD risk factor.[5] According to GINA (Global Initiative for Asthma) 2018**, the GOAL of treatment in ASTHMA is to:** achieve, total control and to reduce inflammation. **The GOAL of treatment in COPD is to:** prevent exacerbations, reduce symptoms and decrease mortality. Methylxanthines are included in the category of controller drugs in the GINA guidelines.[6]

Clinicians commonly use various pharmacological treatments in the management of COPD, asthma and bronchospasm to relieve symptoms, improve quality of life, enhance exercise tolerance, prevent and treat exacerbations. The main strategy to be considered in the pharmacological treatment of COPD, asthma and bronchospasm are bronchodilators; short-acting bronchodilators (β_2-agonist and anti-cholinergics) are given as first-line treatment and long-acting bronchodilators can be given in more symptomatic patients with greater functional impact.[7] Doxofylline and Acebrophylline have been widely used as an inexpensive oral treatment of asthma, bronchospasm and COPD.[8] Previously, these drugs known to have long clinical effectiveness to bronchodilation, however these drugs also showed to have anti-inflammatory actions.[9] Doxofylline and Acebrophylline have been developed with the expectation that such drugs would have greater potency than theophylline, but with an improved side effect profile.

DOXOFYLLINE: A PROMISING METHYLXANTHINE

Doxofylline is a second-generation methylxanthine molecule with potent bronchodilator activity and anti-inflammatory property for relieving airway obstruction in patients with asthma or chronic obstructive pulmonary disease (COPD), with an improved therapeutic window over conventional xanthine such as theophylline.[9] It has tendency to inhibit any of the known phosphodiesterase (PDE) isoforms, thus inhibit breakdown of cyclic adenosine monophosphate (cAMP), which may contribute to the better safety profile. Phosphodiesterase-4 (PDE-4) is the enzyme responsible for metabolizing cyclic adenosine monophosphate (cAMP) and cyclic guanosine monophosphate (GMP) which further regulate immune function. Inhibition of PDE-4 leads to reductions in pro-inflammatory functions and immune cell activity. Doxofylline does not interact with histone deacetylases unlike theophylline, but is able to positively interact with β_2-adrenoceptors.[10]

Structure And Mechanism Of Action Of Doxofylline:

Doxofylline, chemically known as (7-(1,3-dioxalan-2-ylmethyl) theophylline), is a xanthine bronchodilator which differs from theophylline in that it contains a dioxalane group in position 7 **(Figure 1)**. The mechanism of action of doxofylline is related to the inhibition of phosphodiesterase activities, but in contrast it appears to have decreased affinities towards adenosine A_1 and A_2 receptors, which may account for its better safety profile.

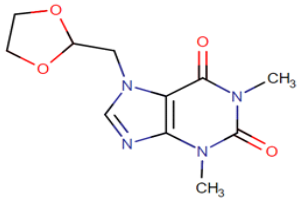

Figure 1: Doxofylline structure

Additionally, it does not interfere with calcium influx into the cells nor antagonize calcium channel blockers. As a consequence, the effective therapeutic dose of doxofylline has less cardio-stimulant effects than theophylline, such that doxofylline does not out significantly increase the cardiac frequency nor does it have arrhythmogenic effects.[9] According to experimental studies, doxofylline has been shown more potent bronchodilator with fewer side effects than theophylline.[11]

PHARMACOKINETICS OF DOXOFYLLINE:

According to the study, conducted by Bologna et al., the peak serum

doxofylline concentration in caucasian adults, after oral administration of 400 mg twice daily for 5 days, was found to be 15.21 ± 1.73 µg/mL with a mean elimination half-life of 7.01 ± 0.80 hrs. A longer half-life results in effective plasma levels even with b.i.d. dose.[12] Doxofylline was present in serum in appreciable concentrations, even after 12 h from the last oral dose. However, there was a large inter-subject variability in peak serum concentrations.[13]

Clinical Studies Of Doxofylline In The Treatment Of Respiratory Diseases:

Doxofylline have already been discussed in a number of studies investigating its efficacy and safety. The number of patients needed to treat with doxofylline 400 mg thrice a day to spare 1 dropout due to theophylline was found to be 5.[11] The number of arousals per night when patients were treated with theophylline was almost double compared with when the patients did not receive any medication, whereas doxofylline did not result in more arousals than no treatment, was documented by Sacco et al.[14] It was substantially and significantly disrupted by theophylline, whereas sleep architecture and quality remained minimally affected by doxofylline.

There is an evidence provided study conducted by Goldstein et al.,[11] that doxofylline 400 mg t.i.d. is an effective treatment for relieving airway obstruction, in patients with chronic asthma and displays a better safety profile with respect to theophylline 250 mg t.i.d. with a favorable risk-to-benefit ratio. In patients with mild bronchial asthma, whereby both doxofylline 400 mg twice a day and theophylline 300 mg twice a day improved lung function and symptoms, but where doxofylline had a better safety profile has also been documented.[13,15]

According to the Indian study, conducted by Nagawaram et al., theophylline and doxofylline were compared in patients of COPD, at doses recommended and commonly used in clinical practice, showed that both drugs significantly improved spirometric values and symptoms, cough, shortness of breath and nocturnal severity of symptoms. The use of theophylline in this study was limiting, because of the fact, of the high incidence of side effects, especially gastric distress (33% in theophylline group and 15% in doxofylline group) and CNS stimulation.[16]

One of the study conducted by Cazzola et al.,[17] published in the journal European Respiratory review in 2018, the data obtained from 998 COPD patients (47.94% treated with doxofylline, 24.82% treated with theophylline, 21.71% treated with aminophylline and 5.53% treated with bamiphylline) were selected from 14 studies published between 1987 and 2016.

Doxofylline appeared to be superior to bamiphylline (significantly better efficacy and comparable safety), aminophylline (comparable efficacy and significantly better safety) and theophylline (comparable efficacy and significantly better safety), when coupling relative effects for efficacy and safety, as shown by the efficacy/safety analysis reported in **Figure 2a**. The combined efficacy/safety SUCRA analysis (surface under the cumulative ranking curve) further confirmed the superiority of doxofylline over aminophylline, bamiphylline and theophylline as represented in **Figure 2b**.[17]

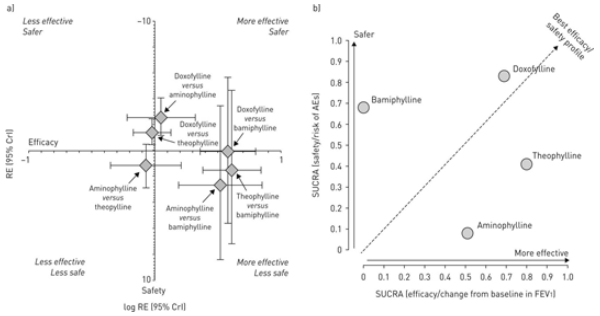

Figure 2: Summary findings regarding the efficacy/safety profile across xanthines in chronic obstructive pulmonary disease patients. a) Combined plot of the change from baseline in forced expiratory volume in 1 s (FEV1) and the risk of adverse events (AEs) of specific xanthine comparisons. b) Combined efficacy/safety SUCRA (surface under the cumulative ranking curve) analysis of specific xanthines. RE: relative effect; CrI: credible interval.[17]

Doxofylline, as indicated by the SUCRA analysis, was the most effective xanthine with regard to the impact on therapeutic efficacy (SUCRA value 0.71), followed by aminophylline (SUCRA value 0.49) and theophylline (SUCRA value 0.31).

When treating patients with ischemic heart disease, doxofylline does not increase myocardial oxygen demand, which is important, particularly relevant for patients with COPD since many such patients suffer from cardiovascular co-morbidities.[18] Doxofylline has been documented with various pharmacological effects such as anti-inflammatory and bronchodilator activities.[19]

Doxofylline produces more stable serum concentrations than theophylline. There is no supporting document of an association between doxofylline levels and incidence of adverse events.[11] There is no need for continued or repeated blood level monitoring with either low dose or high dose of doxofylline, which is well defined advantage of doxofylline over the theophylline.[9] Hence, routine monitoring of blood serum level is not justified, except patients with hepatic insufficiency and/or history of intolerance to xanthines. Doxofylline does not increase the acid or pepsin which resulting in the occurrence of fewer GI side effects**.** Hence, doxofylline has a superior gastric tolerability than theophylline.[9,13] Thus, the administration of drug is safe and cost-effective with diminutive side effects.[19]

Acebrophyllin: Novel Bronchodilator And Anti-inflammatory Agent

Acebrophylline is a novel bronchodilator with mucosecretolyic and anti-inflammatory agent which is used in the treatment of asthma, bronchospasm and COPD. It is widely prescribed oral bronchodilator. On a clinical level, acebrophylline is therapeutically effective in patients suffering from acute or chronic bronchitis, chronic obstructive pulmonary disease and asthma. It works by reducing the episodes of bronchial obstruction, dosage of β_2-agonists and improves ventilatory function.[20,21]

Structure And Mechanism Of Action Of Acebrophylline:

Acebrophylline is chemically 4-[(2-amino-3,5-dibromophenyl) methylamino] cyclohexan-1-ol;2-(1,3-dimethyl-2,6-dioxopurin-7-yl) acetic acid (**Figure 3**).

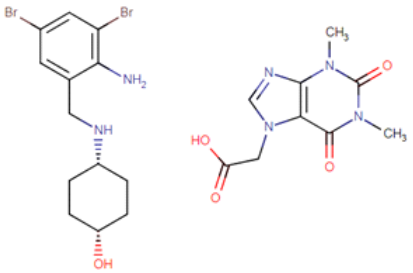

Figure 3: Acebrophylline Structure

Acebrophylline, which contains Ambroxol and Theophylline-7-Acetate, modifies mucus secretion by lowering viscosity of 'gel' phase, increasing 'sol' phase and increases mucociliary clearance by augmenting ciliary motility. It inhibits intracellular phosphodiesterase and facilitates bronchial muscles relaxation by increasing cAMP levels. It selectively inhibits phospholipase A and phosphatidyl choline, leukotrienes and tumor necrosis factor-alpha. Inhibition of such pro-inflammatory mediators causes significant reduction of the airway inflammation and obstruction in chronic stages. Acebrophylline may be useful in the treatment of this disease due to its anti-inflammatory effect. It has minimal side effects like palpitations and tachycardia, unlike other xanthine derivatives including theophylline.[22,23,24]

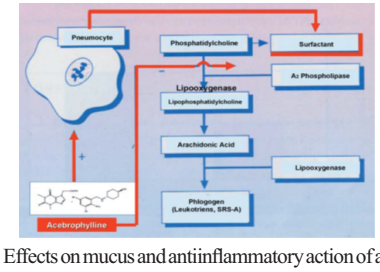

Figure 4: Effects on mucus and antiinflammatory action of acebrophylline.21 (Modified from G Cocco, GIMT (Suppl 1); 1992: 103-107)

PHARMACOKINETICS OF ACEBROPHYLLINE:

The two components of the molecule Acebrophylline - ambroxol and theophylline-7 acetic acid, when given in healthy volunteers, are released in the stomach and absorbed there and in the intestine, achieving optimal concentrations of ambroxol and very low levels of theophylline-7 acetic acid. Ambroxol reaches its peak in serum (mean Cmax 0.369 mcg/mL) at 2 hrs and theophylline- 7 acetic acid after 1 hr (mean Cmax 0.008 mcg/mL). Thus it shows that the latter is either poorly absorbed or metabolised very fast and is eliminated in a fairly short time.[25]

The excellent tolerability of the acebrophylline is its pulmonary tropism.[26] Acebrophylline has low plasma levels which confirms that there should be no interference with any other theophylline-based drug that might be used simultaneously. Acebrophylline need only be taken twice a day due to its excellent tissue diffusion, stability in an acid environment and fairly long half-life.[21]

Clinical Studies Of Acebrophylline In The Treatment Of Respiratory Diseases:

Several clinical trials were conducted for Acebrophylline in adults to show the efficacy and safety of the drug which are listed in the Table 1. Acebrophylline has significantly decreased the amount of sputum, increased in FEV_1 and vital capacity (VC) and reduced airway obstruction. Most of the studies have also revealed that acebrophylline is more active than ambroxol, as a result of more effective mucoregulation. Moreover, acebrophylline significantly reduced the frequency of bronchospastic attack and better choice over theophylline.[21]

Table 1: Clinical trials of acebrophylline in patients with respiratory disease

Author	Size	Outcome
Milvio *et al.*[21,27]	Randomized, Double-blinded study (n = 41, age 30-80 years): Acebrophylline vs ambroxol (both at 100 mg b.i.d.) for 20 days	There was significant decrease in the amount of sputum in both groups; Viscosity greatly reduced specially in the patients given acebrophylline. Acebrophylline increased FEV_1 by about 16%, significantly more than ambroxol, although two treatments relieved clinical symptoms similarly.
Fracchia *et al.*[21,28]	Controlled trial (n = 38, mean age 64.8 years); acebrophylline 100 mg b.i.d. and ambroxol 30 mg t.i.d.	Acebrophylline showed a statistically significant increase in FEV_1 and VC and a reduction of airway resistance after 14 days of treatment. **(Figure 5)**
Sumit T *et al.*[20,21]	Randomized trial (n = 40); Acebrophylline 100 mg twice vs. sustained release (SR) theophylline 300 mg once daily	Acebrophylline and sustained release theophylline are comparable in respect of improvement of spirometric parameters and symptomatic benefit of COPD patients. The researchers concluded that acebrophylline is safer than SR theophylline in respect of cardiovascular and central nervous system related side effects.
Saravanakumar *et al.*[21,29]	Open label, single centre randomized comparative trial (n = 100, age 18-50 years); Acebrophylline 100 mg twice vs theophylline 100 mg twice for 4 weeks.	Sputum quantity and cough intensity was reduced in Acebrophylline group than Theophylline. In acebrophylline group all parameters improved remarkably than theophylline group. Side effects were more among theophylline than Acebrophylline. Acebrophylline is better choice for mild persistent asthma than theophylline.

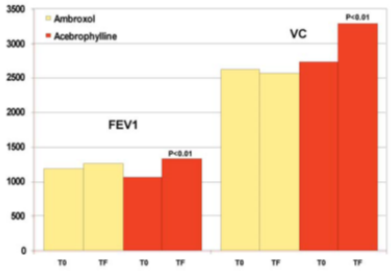

Figure 5: Changes in FEV_1 and VC induced by acebrophylline and ambroxol in patients with reversible obstruction from airway disease.[21]

Several studies in adults have confirmed that acebrophylline is well tolerated and is having less adverse reactions. Acebrophylline has been more effective than ambroxol, achieving more marked improvement, though not significant, in the visco-elasticity of mucus, making it more fluid, thus easing expectoration. Patients treated with acebrophylline showed significant improvements in measures of respiratory function.[21,30] Cardiovascular related complaints, regarding the side effects e.g. tremor, tachycardia, pain chest and palpitation were not found in patients treated with acebrophylline. The incidence of cardiovascular and CNS side- effects are reduced with acebrophylline may be due to the fact that ambroxol present in it attains higher concentration in blood than its xanthine derivative which is associated with untoward side-effects.[21]

COMBINATION THERAPIES:

Patients having persistent symptoms and inadequate control of their respiratory disorders, for them, combining different classes of bronchodilators into a single therapy is an option. Using multiple drugs in combination may lower doses of individual agents, simplify medication regimens, decrease adverse effects and improve compliance. There is some evidence pharmacologically, that combining drugs of distinct mechanisms is favorable. Xanthines appear to hold promise in significantly improving adverse effect profiles, spirometric measures, and medication compliance over currently available drugs. The use of these agents in double combinations with each other or with alternative respiratory medications may optimize outcomes while minimizing dose-related toxicities. Doxofylline (7-(1,3-dioxalan-2-ylmethyl) theophylline), a 1,3,7-tri-substituted xanthine derivative has been proved as good therapeutic molecule, in pharma. Moreover, doxofylline has largely been administered as an add-on therapy to maintenance drugs and has been shown to significantly improve spirometric parameters and decrease the need for rescue β_2 - agonists in respiratory diseases including asthma and COPD.[9,31]

CONCLUSION:

Asthma and COPD are still not fully curable, not treated enough, not identified enough and the therapy is still designing. Doxofylline is a novel xanthine drug with similar efficacy to theophylline in the treatment of respiratory disease. Several clinical data showed that safety doxofylline is superior to theophylline due to less side effects. On the other hand, acebrophylline is a novel drug with broncholdilating, anti-inflammatory and mucoregulating effect. The cost effectiveness, efficacy and favorable tolerability profile of acebrophylline are reflected in recommending it as an add-on drug. Acebrophylline is safer in respect of cardiovascular and central nervous system related side effects than theophylline.

It has been observed in many studies, that drug combination has better therapeutic outcomes than single drug treatment always. By reviewed therapeutic effects and results of clinical trials of doxofylline and acebrophylline, to combine doxofylline 400 mg with acebrophylline 100 mg in a single dose to cure COPD, bronchial asthma and pulmonary disease with spastic bronchial asthma; is a good strategy to overcome the major problem in worldwide population and it is more beneficial than a single drug therapy. Thus, the subsequent understanding over the molecular and physiological behaviour of this combination will be helpful in further research.

REFERENCES:

1) Alshabanat, A., Zafari, Z., Albanyan, O., Dairi, M., & FitzGerald, J. M. (2015). Asthma and COPD overlap syndrome (ACOS): a systematic review and meta-analysis. PloS one, 10(9), e0136065.
2) Global Asthma Report 2018, https://www.researchgate.net/publication/3 29424076_ The_Global_Asthma_Report_2018
3) Lambrecht, BN., & Hammad, H. (2015). The immunology of asthma. Nature immunology, 16(1), 45.
4) Woods, BD., & Sladen, RN. (2009). Perioperative considerations for the patient with asthma and bronchospasm. British journal of anaesthesia, 103(suppl_1), i57-i65.
5) GOLD (Global Initiative for Chronic Obstructive Lung Disease) - global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease,

revised. (2006). http://www.goldcopd.org. pp. 1–100.
6) GINA (Global Initiative for Asthma) – global strategy for asthma management and prevention, revised. (2018). http://www.ginasthma.org. pp. 1–162.
7) Morales, OMG., Rojas-Reyes, MX., & Dennis, RJ. (2017). Oral xanthine derivatives (theophylline and doxofylline) for patients with stable chronic obstructive pulmonary disease (COPD). Cochrane Database of Systematic Reviews, (8).
8) Barnes, PJ. (2003). Theophylline: new perspectives for an old drug. Am J Respir Crit Care Med, 167, 813-8.
9) Page, CP. (2010). Doxofylline: a "novofylline". Pulmonary pharmacology & therapeutics, 23(4), 231-234.
10) Cazzola, M., Calzetta, L., Rogliani, P., Page, C., Matera MG. (2018). Impact of doxofylline in COPD: A pairwise meta-analysis. Pulmonary Pharmacology & Therapeutics, Volume 51, Pages 1-9.
11) Goldstein, MF., Chervinsky, P. (2002). Efficacy and safety of doxofylline compared to theophylline in chronic reversible asthma - a double-blind randomised placebo-controlled multicentre clinical trial. Med Sci Monit, 8, 297-304.
12) Bologna, E., Laganà, A., Terracino, D, Bolignari P., Biffignandi P. (1990) Oral and intravenous pharmacokinetic profiles of doxofylline in patients with chronic bronchitis. J Int Med Res; 18: 282-288.
13) Matera, MG., Page, C., Cazzola, M. (2017). Doxofylline is not just another theophylline! International Journal of Chronic Obstructive Pulmonary Disease, Volume 12, Pages 3487—3493.
14) Sacco, C., Barthiroli, A., Gross, E., Donner, CF. (1995).The effects of doxofylline vs theophylline on sleep architecture in COPD patients. Monaldi Arch Chest Dis., 50(2), 98–103.
15) Margay, SM., Farhat, S., Kaur, S., Teli, HA. (2015). To study the efficacy and safety of doxophylline and theophylline in bronchial asthma. J Clin Diagn Res.,9(4), FC05–FC08.
16) Nagawaram, PR., Kanchanpally, V. (2016). Comparative study of theophylline and doxofylline in the treatment of stable chronic obstructive pulmonary disease. Int J Basic Clin Pharmacol. 5(2), 251–256.
17) Cazzola, M., Calzetta, L., Barnes, PJ., Criner, GJ., Martinez, FJ., Papi, A., Matera, MG. (2018). Efficacy and safety profile of xanthines in COPD: a network meta-analysis. European Respiratory Review, 27, 180010.
18) Dini, FL., Cogo, R. (2001). Doxofylline: a new generation xanthine bronchodilator devoid of major cardiovascular adverse effects. Curr Med Res Opin., 16(4), 258–268.
19) van Mastbergen, J., Jolas, T., Allegra, L., Page, CP. (2012). The mechanism of action of doxofylline is unrelated to HDAC inhibition, PDE inhibition or adenosine receptor antagonism. Pulm. Pharmacol. Ther., 25, 55–61.
20) Kuriachan, S., Amberkar, MBV., Mohan, MK., Shahul, HA., & Kishore, MK. (2015). Acebrophylline-induced angioedema. Indian journal of pharmacology, 47(2), 219.
21) Pozzi, E. (2007). Acebrophylline: an airway mucoregulator and anti-inflammatory agent. Monaldi Arch Chest Dis, 67, 2, 106-115.
22) Giovanni, A. (1995). Acebrophylline in the treatment of chronic obstructive pulmonary disease. Current Therapeutic Research., 56(2), 169–75.
23) Tapadar, SR., Das, M., Chaudhuri, AD., Basak, S., and Mahapatra ABS. (2014). The Effect of Acebrophylline vs Sustained Release Theophylline in Patients of COPD - A Comparative Study. J Clin Diagn Res. Sep, 8(9), MC11–MC14.
24) Sharma, A., Adiga, S., Chogtu, B., Mohapatra, AK., and Magazine, R. (2014). Comparing the Efficacy and Influence on the Quality of Life of Three Classes of Drugs Used in Bronchial Asthma - A Prospective Study. Journal of Clinical and Diagnostic Research. Sep, Vol-8(9), HC13-HC15.
25) Sved, S., Gilveray, IJ., Beaudoin, N. (1981). The assay and absorption kinetics of oral theophylline-7 acetic acid in the human. Biopharm Drug Disposit. 2, 177-84.
26) Mezzetti, M., Colombo L. (1990). A pharmacokinetic study on pulmonary tropism of ambroxol in patients under thoracic surgery. J Emerg Surg Int Care. 13 (3),179-85.
27) Milvio. C., Borellini. P., Benazzi, et al. (1985). Clinical effects of ambroxol theophylline-acetate. Giorn Ist Ric Clin Ter. 4, 77-80.
28) Fracchia, C., Della, T. M., Zanotti, E., et al. (1987). Evaluation of acebrophylline activity (P3011): controlled study of ambroxol. Rass Pat App Resp, 1, 177-181.
29) Saravanakumar, C., Vijayalakshmi, D., Parameswari, D. (2014). Theophylline and Acebrophylline in Mild Bronchial Asthma: A Comparative Study of Efficacy and Safety. Int J Pharm Bio Sci, 5(2), 214-22.
30) Goldgrub, N., Soares, V. R. X., Hamaoui, A., Zavattini, G., & Poli, A. (1992). Therapeutic activity and tolerability profile of acebrophylline. Advances In Therapy, 9(2), 107-115.
31) Mak, G., and Hanania, NA. (2012). New bronchodilators. Current Opinion in Pharmacology. 12, 238-245.