



Research Article

Acebrophylline Is A Better Choice Of Drug Over Theophylline For Patients With Asthma, COPD And Bronchitis Patients

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ABSTRACT

The use of pharmacological treatment for COPD has increased over the past few decades and paints a positive image. In COPD, methylxanthines are frequently utilised. Theophylline is a well-known bronchodilator and anti-inflammatory drug, whilst Acebrophylline is a more recent addition in modern respiratory treatment, both are utilised as supplemental therapies for stable COPD patients using LAMA (long-acting muscarinic antagonists). Acebrophylline has anti-inflammatory properties and regulates airway mucus. The drug's strategy for treating obstructive airway disease incorporates numerous points of attack. Theophylline-7 acetic acid, whose carrier role elevates blood levels of Ambroxol, stimulates surfactant formation quickly and intensively. The molecule includes Ambroxol, which promotes several processes in the creation of pulmonary surfactants. Ciliary clearance is significantly improved as a result of the mucus' reduced viscosity and adhesivity. Acebrophylline also exerts an anti-inflammatory effect by diverting phosphatidylcholine toward the manufacture of surfactants, which prevents it from being used for the production of inflammatory mediators like leukotrienes.

INTRODUCTION

The term "COPD" refers to chronic obstructive pulmonary disease. COPD, a chronic lung disease, provides results in ongoing airflow limitation and breathing issues. Since COPD is a progressive disorder, it usually becomes worse with time. The two primary types of COPD are chronic bronchitis and emphysema, and many COPD patient

sufferers have both of these conditions at the same time(1). The bronchial tubes (airways) in the lungs are inflamed and irritated in chronic bronchitis. This inflammation causes a chronic cough and more mucus to be produced. The lung's air sacs (alveoli), which are important for exchanging oxygen and carbon dioxide, are damaged and destroyed in emphysema. Airflow in the lungs is

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hampered and lung function is compromised as a result of this injury. For a Longer period, inhaling hazardous chemicals, mostly cigarette smoke, is the main cause of COPD(1,2). Additional risk factors include genetic disorders such as alpha-1 antitrypsin deficiency, air pollution, and occupational exposure to chemicals and dust. Shortness of breath, wheezing, a persistent cough that produces mucus or not, tightness of the chest, and respiratory infection and inflammation. An individual's quality of life may be significantly impacted if these symptoms continue to deteriorate over time(3). Despite the fact that COPD is a chronic and advancing condition, effective therapy can help reduce symptoms, halt disease progression, and enhance total lung function. Bronchodilator drugs to assist in expanding the airways, inhaled corticosteroids to decrease inflammation, pulmonary rehabilitation programs, supplemental oxygen therapy, and lifestyle changes including quitting smoking and avoiding respiratory irritants are some of the treatment options for COPD(4).

Bronchodilators are the most commonly used medicines for managing COPD and Asthma. According to recent studies, Acebrophyllin can be a better choice over Theophylline to control these respiratory issues because of its safety profile. Acebrophyllin shows fewer side effects than Theophylline. BIBO HEALTH (Hilt Brands India Pvt Ltd) has Acebrophylline sustained release medication (Bronkite AB SR 200) for prolonged reduction of Asthma and COPD in respiratory care treatment.

Bronchial Asthma

Asthma, sometimes referred to as bronchial asthma, is a long-term respiratory illness marked by inflammation and restriction of the airways. Many people are impacted by lung illness. When a person has asthma, their airways swell up and become too sensitive to a number of triggers, such as respiratory infections, exercise, cold weather,

stress, allergens pollen grains, dust particles, and other foreign substances. Breathing becomes challenging when exposed to these triggers because the muscles around the airways tighten and constrict(5,6).

Chemical and Physical properties of Acebrophylline

Acebrophylline is a chemical compound that consists mainly of Ambroxol and Theophylline-7-Acetate. Theophylline-7-Acetate content carboxylic group which was bonded with Ambroxol amino group in a stoichiometric ratio of 38.7% acid and 61.3% base. In this, Ambroxol shows a high plasma administration level compared to Theophylline-7-Acetate. Acebrophylline shows a 45% improvement in lung health when compare with Ambroxol alone(4).

Acebrophylline action

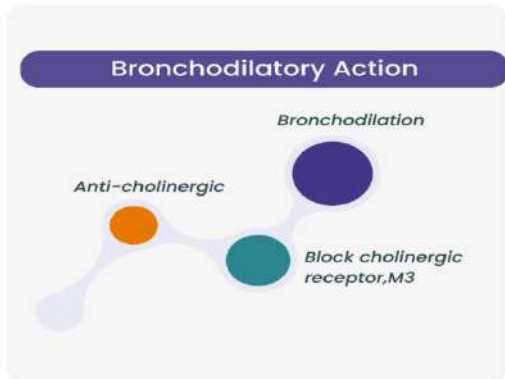
- a. Act as synthesis and release of pulmonary surfactant
- b. Mucoregulator activity
- c. Mucosecretory activity
- d. Mucokinetic action on mucociliary clearance
- e. Also have anti-inflammatory action.

Mechanism action of Acebrophylline

1 Bronchodilatory Action

Acebrophylline acts as an anti-cholinergic receptor. Its main act is the M3 receptor-blocking action. M3 receptor is a Gi type of G-protein coupled receptor. When Acebrophylline binds to the Gi-type receptor, GDP is converted to GTP, and the alpha, beta, and gamma subunit get to detach from the receptors. Followed by alpha-GTP binding to the adenylyl cyclase. Also, decrease the form of cyclic AMP. There for release of the ca^{2+} ion this case the bronchial smooth muscle construction. In this process, Acebrophylline binds to the AC process and blocks the cyclic AMP process also blocks the release of ca^{2+} ion, and in the same situation k^{+} ion gets released in the bronchial smooth mussel which causes the

bronchodilatory action Which effect releases the mucus to outside(7,8).



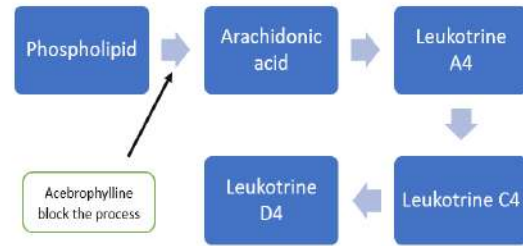
Pic: 1 Bronchodilatory Mechanism of Action

2 Anti-Allergic Action

It also blocks the leukotriene receptor producing Allergy block the LTD4 and LTC4 receptor to the production of allergic substances. Acebrophylline binds to the phospholipid layer and blocks the production of arachidonic acid. Also, block the Phospholipase A2 which is used to convert phospholipid to Arachidonic acid(9–11).



Pic: 2 Anti-Allergic Mechanism of Action



Pic: 3 Mechanism of Action How to block leukotriene receptor to prevent allergic reaction Release and synthesis of pulmonary surfactant

After five days of treatment with acebrophylline, the levels of total phospholipids and phosphatidylcholine in BAL were compared between the treated group and the control group to determine the generation of surfactant in the rat. Approximately 18 hours after the last dosage, there was a noticeable rise in the surfactant phospholipid matrix that was more pronounced in the treated group (16111 mcg/mL) than in the controls (1393.6 mcg/mL). Acebrophylline impact on the absorption of tagged surfactant precursors in rat lung slices was examined to see how much the tissue was stimulated to create surfactant in order to analyse the mechanism by which the medication increases pulmonary surfactant production and release(4).

Mucoregulating action

The mucoregulating action of Acebrophylline was shown in two phases of action direct and indirect-acting process

1 Direct Action

Animal studies have demonstrated that the Acebrophylline component Ambroxol can restore the normal viscosity of aberrant bronchial discharge. This is accomplished through its capacity to "regulate" and "balance" bronchial secretions at the glandular level rather than through any direct impact on mucus that has already been released. In fact, following therapy with this substance, mucosal cysts may transform back into healthy glandular acini, and the serous

glands may become more active in producing mucus. Thus, Acebrophylline encourages the production of mucus secretions that are of "higher quality"(12,13).

2 Indirect Action

The viscosity of bronchial secretions is decreased by promoting the formation of alveolar surfactants. Regarding a potential physico-chemical interaction between phospholipids and mucus. Bronchial phospholipids seem to have a role in how mucus develops its fibrillary structure. Secreted mucus must pass through two layers in order to produce the supraciliary colloidal "gel": the so-called "sol" and the layer of phospholipids, or inter-sol-gel; this requires a physicochemical interaction between the mucus and the surfactant molecules. This interaction may lead to the development of mucus particles that are emulsified and have a decreased meuco-viscosity(14).

Treatment of Acebrophylline

Treatment for respiratory conditions that as bronchial asthma and chronic obstructive pulmonary disease use a medication called Acebrophylline. It is a xanthine derivative with broncho-dilatory and mucoregulator properties. It functions as a bronchodilator to widen the airways and further increase airflow by unwinding the smooth muscles in the airways. It also has anti-inflammatory qualities that reduce airway irritation and may prevent the formation of inflammatory mediators. The mucoregulator properties of Acebrophylline may be used to control the production of mucus in the airways. It could make respiratory secretions less viscous, which would make expectoration and mucus clearance more effective. Patients with respiratory conditions who use Acebrophylline breathe easier, less cough frequently, and have fewer total exacerbations. It could help with symptoms including wheezing, breathing problems, and chest heaviness(15).

The effects of acebrophylline on sputum production, FEV vital capacity (VC), and airway 1 blockage were all significantly positive. Additionally, the majority of research has shown that acebrophylline is more active than Ambroxol because of its more efficient mucoregulator. Additionally, acebrophylline significantly decreased the number of bronchospastic attacks and was a superior option to theophylline. Acebrophylline is well tolerated and has fewer side responses, according to several trials in adults. The viscous-elasticity of mucus has improved more noticeably with acebrophylline than with Ambroxol, but not significantly, making it more fluid and reducing the need for expectoration. Patients receiving acebrophylline showed significant improvements in tests of respiratory function. Patients receiving acebrophylline did not report any cardiovascular problems, such as tremors, tachycardia, chest discomfort, or palpitations. The fact that acebrophylline has a lower frequency of cardiovascular and CNS adverse effects may be because it has a greater blood concentration of the Ambroxol it contains than its xanthine derivative, which is linked to unfavourable side effects(3,16,17).

Role of Theophylline in Respiratory Care

Since the 1930s, asthma patients have been treated with theophylline, a potent methylxanthine with properties comparable to coffee in chemical structure. Methylxanthines are found in a variety of plants, including *Theobroma cacao*, *Thea sinensis*, and *Coffea arabica* (coffee) (cocoa, chocolate). It also shows the effect on the CNS(5). Theophylline is a methylxanthine class of drug. For a very long period, it was used to cure respiratory diseases such as Asthma and COPD. Theophylline assists in widening and opening the airways by relaxing the smooth muscles in them. This bronchodilator action improves airflow and makes it easier for patients to breathe. Theophylline also has additional mechanisms of



action, including the ability to reduce inflammation and boost respiratory drive. Oral administration of theophylline tablets or capsules is typical. It enters the bloodstream, where the liver processes it. Since theophylline has a constrained therapeutic range in the blood, it's crucial to regularly check blood levels to ensure they stay within this range. This is because theophylline may have harmful consequences when administered in either excessively low or large amounts(18).

Consistent adverse effects (side effects) of theophylline medication include headaches, tachycardia, nausea, drowsiness, vomiting, and fast heartbeat. In larger dosages or if blood levels are excessively high, it might result in more serious side effects, including heart palpitations, arrhythmias, seizures, and even life-threatening outcomes. When using theophylline, it's important to adhere to the doctor's recommendations and have your blood levels tested frequently(1).

Tab: 1 Role of Theophylline versus Acebrophylline

Sl.no	Activity	Acebrophylline	Theophylline
1	Class of drug	A xanthine derivative drug	A methyl Xanthin derivative
2	MOA (Mechanism of action)	It acts as a bronchodilator and an anti-inflammatory and is hypothesized to have a dual mechanism of action. It eases the smooth muscles of the airways, which might lessen mucus production and inflammation of the airways.	It relaxes the smooth muscles in the airways, which primarily work as a bronchodilator. Although less so than corticosteroids, it also has some anti-inflammatory properties.
4	Clinical use	Most often, this medication is used to treat COPD and bronchial asthma. It could improve airflow while reducing swelling and mucus production.	For many years, individuals with COPD and asthma have used it to relieve bronchospasm and improve breathing. However, their use has lately decreased due to the availability of newer medications with fewer side effects.
5	Route of administration	is typically ingested orally as pills or capsules	It can be given intravenously in some circumstances or taken orally as pills or capsules.
6	Metabolism and monitoring	acebrophylline is processed in the liver, regular blood level monitoring is not necessary.	Because it is processed in the liver, it requires routine blood level monitoring to maintain therapeutic levels and prevent toxicity.
7	Side effects	It is often well accepted, and any adverse effects, such as gastrointestinal issues, headaches, dizziness, and skin rashes, are typically moderate and temporary.	Its side effects are more diverse and may include nausea, tremors, migraines, digestive issues, and an increased heart rate. Significant adverse effects including arrhythmias or convulsions might occur with high dosages.

A New Bronchodilator and Anti-Inflammatory Agent: Acebrophylline

A new bronchodilator with mucosecretory and anti-inflammatory properties, Acebrophylline is used to treat asthma, bronchospasm, and COPD. Oral bronchodilators are frequently recommended.

On a clinical level, Acebrophylline is therapeutically effective in patients suffering from acute or chronic bronchitis, chronic obstructive pulmonary disease, and asthma. It functions by lowering the frequency of bronchial obstruction



episodes, increasing the amount of beta-agonists, and enhancing ventilatory function(15,19).

Tab: 2 Advantage of Acebrophylline over Theophylline

Sl.no	Characteristic	Acebrophylline	Theophylline
1	action	Show dual action	Show signal action
2	Bronchodilator effect	present	present
3	Mucolytic effect	present	Absent
4	CNS side effect	Absent	Present (tremor)
5	CVS side effect	Less severe	Severe (chest pain, tachycardia, and insomnia)
6	Safety profile	More likely use due to better safety profile	Less likely use due to narrow safety profile
7	Generation of drug	New generation	Old generation

Pharmacokinetics study of Acebrophylline

When 200 mg of oral Acebrophylline is administered to healthy volunteers, the two molecules that make up the compound Ambroxol and Theophylline-7 acetic acid are released in the stomach and absorbed there as well as in the intestine, where they reach their peak concentrations of Ambroxol and very low levels of Theophylline-7 acetic acid. Theophylline-7 acetic acid (mean C_{max} 0.008 mcg/mL) and Ambroxol (mean C_{max} 0.369 mcg/mL) both peak after one hour. As a result, it appears that the latter is either poorly absorbed or metabolized quickly and removed quickly. Due to its low blood levels, it is unlikely to have the undesirable effects that theophylline had in humans, whose therapeutic window corresponds to much greater plasma concentrations (10–20 mcg/mL). Acebrophylline good tolerability is also due in part to its pulmonary tropism. Another assurance that there shouldn't be any interaction with any other theophylline-based medications that may be administered concurrently comes from the low plasma levels of the xanthine derivative. Acebrophylline only has to be taken twice a day due to its stability in an acidic environment, good tissue diffusion, and relatively long half-life(20,21).

Safety in adults and children

Acebrophylline is well tolerated, with a low rate of adverse reactions, typically only mild

gastrointestinal upset (2.6 percent), not requiring any treatment discontinuation, except as a precaution; no abnormalities have been reported in blood chemistry. This has been demonstrated in numerous trials in adults. The outcomes in youngsters further support the drug's safety. Only 6.5% of more than 4000 children with acute bronchitis that was either catarrhal, spastic or asthma-like reported experiencing adverse events in a post-marketing study. Only 0.7% of instances required stopping therapy since the symptoms were often minor and temporary (22).

Clinical trials study

The efficacy of Acebrophylline and Ambroxol were compared in two early clinical studies. Milvio and Co et al. 41 patients between the ages of 30 and 80 who had acute asthma-like bronchitis or flare-ups of chronic types, with or without fever, increased bronchial secretion, cough, and mucus, or mucopurulent or purulent sputum, were treated in a double-blinded trial. For 20 days, patients were randomly assigned to receive either acebrophylline or Ambroxol (both at 200 mg b.i.d.). Sputum production in both groups had significantly decreased at the conclusion of the trial, and viscosity had also significantly decreased, particularly in the Acebrophylline-treated individuals. However, Acebrophylline considerably raised FEV₁ compared to Ambroxol by around 16 percent while both therapies greatly reduced clinical symptoms (23).

Similar outcomes were observed by Fracchia et al. from a controlled experiment comparing the effects of acebrophylline (200 mg bi-daily) and Ambroxol (30 mg tri-daily) in 38 patients, with a mean age of 64.8 years. The two medications produced comparable increases in mucous visco-elasticity, making it more fluid and simpler to evacuate. This led to an improvement in both subjective and objective symptoms compared to baseline, which was visible as early as the third day of therapy. However, after 14 days of therapy, only those patients receiving Acebrophylline showed a statistically significant improvement in FEV1 and VC as well as a decrease in airway resistance (24).

Combination Therapies

Combining various classes of bronchodilators into a single treatment is an option for patients with chronic symptoms and insufficient management of their respiratory illnesses. Combining several medications can reduce individual drug dosages, streamline prescription schedules, lessen side effects, and boost compliance. Pharmacological research suggests that combining medications with different mechanisms is beneficial. Compared to presently available medications, xanthine shows the potential to significantly improve side effects in rates, spirometry measurements, and medication compliance. The use of these medicines in double combinations with one another or with other respiratory drugs may maximize results while reducing toxicities due to dosage. Furthermore, it has been demonstrated that Doxofylline significantly improves spirometry parameters and reduces the requirement for rescue agonists in respiratory disorders including asthma and COPD. It has mostly been used as an add-on therapy to maintenance medicines. Numerous studies have shown that medication combinations always produce superior therapeutic results than single-agent treatments. Combining Doxofylline 400 mg with Acebrophylline 100 mg in a single dose to

treat COPD, bronchial asthma, and pulmonary disease with spastic bronchial asthma is a good strategy to address the major issue in the global population and is more beneficial than single drug therapy, according to reviews of the therapeutic effects and outcomes of clinical trials of Doxofylline and Acebrophylline (25,26).

CONCLUSION

Asthma and COPD are still not completely curable, not sufficiently treated, not sufficiently identified, and the medicine is continuously being developed. Acebrophylline is a brand-new xanthine derivative medication that treats respiratory diseases similarly to theophylline. Because Acebrophylline has fewer adverse effects than theophylline, several clinical studies have demonstrated that it is safer. However, Doxofylline a new medication, has bronchodilatory, anti-inflammatory, and mucoregulating properties. Doxofylline is suggested as an add-on medication due to its affordability, efficacy, and acceptable tolerability profile. Theophylline is more likely to have negative effects relating to the circulatory and neurological systems than acebrophylline. Bibo Health (Hilt Brands India Pvt Ltd) has an Acebrophylline sustained release tablet (Bronkite AB SR 200) which is used for the treatment of several respiratory treatments like Asthma and COPD.

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