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Review article

Bromhexine: A Comprehensive Review

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ABSTRACT

Natural molecules have been a boon in the field of medical science and therapeutics. With the progress of latest technology and advancement in synthetic chemistry and computational biology, it has now become possible to precisely decide the best possible fit inhibitor molecule for the pathologically important target molecules in the human body. In recent history, many naturally occurring molecules have been derivatized to improve the inhibitory potential. Bromhexine is one such molecule that has been derivatized from the naturally occurring molecule vasicine. Vasicine is obtained from *Adhatodavasica,* a very well known herb for respiratory and other inflammatory diseases. The present review describes the importance and uses of bromhexine in the area of therapeutics with a light on its mechanism of action and its use in several diseases such as asthma and chronic bronchitis.

Introduction

Bromhexine, a benzylamine derived cardiac depressant of vasicine, is a quinazoline alkaloid obtained from the plant *Adhatoda vasica*. It was developed in the research laboratory of Boehringer Ingelheim in the late 1950s as an active ingredient for pharmaceutical use. It was introduced in 1963 under the trademark of Bisolvon® and is chemically known as N-cyclohexly-N-methyl-(2-amino-3, 5-dibromobenzyl) ammonium chloride. [1] The chemical structure of bromhexine is represented in figure 1.

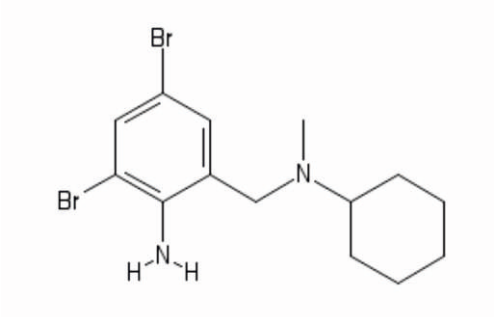

Figure 1 represents the Chemical Structure of Bromhexine.

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It is also known by the synonym as Bromhexine Hydrochloride. Bromhexine is majorly used as a mucolytic agent for curing respiratory disorders correlated with excessive or viscid mucus. It is used as a secretolytic expectorant for the effective treatment of cough with phlegm. [2, 3] In addition, bromhexine also has antioxidant properties. It is mainly associated with upper as well as lower respiratory tract infections [4] such as broncho-pneumonia [5], bronchiectasis [6], acute and chronic bronchitis [7], sinusitis [8], mixed respiratory conditions [9] & diseases like allergic asthma [10] and obstructive airway diseases whose course is complicated by infections. [11] This compound is accepted well as it has a low level of toxicity. [12] It is generally well tolerated and can also be given to children of different ages.

2. Physical Properties

Bromhexine exists as a white crystalline powder in solid state and is insoluble in water but shows little solubility in alcohol. It is also slightly soluble in chloroform and methylene chloride. [13]

3. Mechanism of action

Bromhexine's intentional use is to support the body's activities associated for clearing mucus from the respiratory tract. The mechanism of action is based on phlegm degradation, thereby easing coughs. [3] It helps in enhancing the production of serous mucus in the respiratory tract and helps in the production of thinner and less viscous phlegm. This produces a secretomotoric effect by helping the cilia in expectoring the phlegm out of the lungs. Due to this reason, it is often regarded as an important component of cough syrups. [14]

Bromhexine begins to act on the mucus at the formative stages in the glands inside the mucus-secreting cells. [12] Through oral administration in patients, the onset of action of bromhexine begins

after 30 minutes. Its complete effect is visualized by an increased production of respiratory tract fluid after 2-3 days of the commencement of treatment. Following oral administration, bromhexine has been shown to increase the volume of sputum and to decrease the viscosity of bronchial secretions in chronic bronchitis patients. [15-17] The drug induces the hydrolytic depolymerization of mucous protein fibers of high molecular weight and stimulates the activity of the ciliated epithelium. [18-19] It has been shown to reduce the viscosity of bronchial secretions in both animals [2] and men. [20]

Anon in 1971 postulated an increase in the lysosomal activity which was associated with bromhexine. [15] There were significant improvements in the pulmonary function besides an ease in expectoration, in bronchitis patients. Several other pharmacological effects of bromhexine have also been posited such as an increment of secretion from exocrine glands (eg, tear production) and an upsurge in pulmonary surfactant production. [17-18] Bromhexine also has clinical efficacy to increase sputum concentrations in combination with various antibiotics such as oxytetracycline, erythromycin, ampicillin and amoxicillin. [13, 16, 17, 21] However, some of these effects reported (exocrine stimulation and increased sputum concentrations etc.) have not yet been confirmed in the studies. [22-24]

It has been suggested that, Ambroxol (NA-872) which is a metabolite of bromhexine, can also contribute to an increased secretion from exocrine glands during bromhexine administration. [25-26] Asthmatic and chronic bronchitis patients have sputum comprising of fibre systems characterized with mucoproteins and mucopolysaccharides. The nuclei of cells lining the mucosal wall of the bronchial track disintegrate leading to the formation of purulent fibres of deoxyribonucleic acid. This leads to the formation of sputum viscosity due to an increase in the mucopolysaccharide and DNA fibre systems. Although, antibiotics effectively decrease the DNA contribution, it has been seen under the microscope that bromhexine helps in breaking down the mucopolysaccharide fragments and thus cause a reduction in sputum viscosity. Therefore, it is now more easily removed through coughing. Bromhexine therapy often amends the sputum immunoglobulins and causes changes in the secretory granules of bronchial and nasal mucosa glands as seen through electron microscopic studies. [1] Although there is a decline in the sputum volume, its viscosity remains low until the bromhexine treatment is maintained. This causes an increased response to bronchodilator drugs by our body. It is preferable in some cough medication as it does not include any sedatives which can otherwise make the users feel drowsy. [27]

4. Use of Bromhexine in pathological conditions

4.1 Asthma

Various studies have been performed to analyse the therapeutic applications for bromhexine for Asthma. Forty seven patients, who were experiencing symptoms of respiratory disease such as, the production of mucopurulent sputum were given a dosage of 8 mg of bromhexine thrice daily for one week in a double blind controlled crossover clinical study. An increase in the ventilatory capacity leading to significant clinical improvement was seen in a greater number of patients than those who were administered placebo. However, there was a difference in the results in different parts of the trial which was carried out in winters and summers. [28] On the other hand, in another double blind crossover technique, thirty four patients were given the oral treatment with two drugs and placebo for three consecutive times with a gap of 12 days. These people suffered from chronic asthma and persistent mucoid expectoration. There was no significant enhancement in the sputum viscosity, clinical state, PEF or airway resistance. Though, patients' own preference regarding bromhexine as a mucolytic agent increased by 0.1%. [29]

Similarly in another study of a double blind therapeutic regimen, fourteen patients received oral or intravenous treatment of bromhexine or placebo in conjunction with the regular standard therapy for acute severe asthma. There was no prominent recovery seen for bromhexine group of patients. [30] In the next decade, twenty children in the range of ages from 3 to 14 years were nebulized with 2 ml of saline or bromhexine (2 mg/ml) for two weeks. They had been suffering from bronchial asthma in combination with chronic sinusitis. Both treatments had shown compelling improvements but saline nebulization was more significant than bromhexine. [31] Hence, it can be seen that although there are several studies related to asthma that have been performed with bromhexine, some have shown positive effects while the others have shown nil effect.

4.2 Chronic Bronchitis

Similar to asthma, in the case of chronic bronchitis, either types of reports were available in which positive or none effects were seen. Bromhexine has been shown to change the sputum characteristics *in vitro* but, it has produced varying results in several clinical trials. [32] Here is a brief scenario highlighting both the positive and nil effects observed by the bromhexine therapy in chronic bronchitis patients.

4.2.1 Positive effects of bromhexine for chronic bronchitis studies

Hamilton *et al.* reported that, when 16 mg bromhexine was administered orally for three times daily for 11 days in twenty five patients in a double blind clinical trial, it resulted in a prominent increment in sputum volume along with a reduction in the viscosity of sputum. No change in the ventilatory capacity or in the respiratory state of the patients was visualized. There was a change in the yield values with no possible side effects seen amongst patients. [20] In agreement to Hamilton, Seventy-five patients diagnosed with chronic bronchitis were administered a daily dosage of 24 mg bromhexine and a placebo. Sixty one patients produced suitable results for evaluation. Out of these, a significant group felt better after consumption of bromhexine and showed fewer side effects as compared to the placebo group. [33]

It has been seen that intra-alveolar haemorrhage and sustained intermittent positive pressure ventilation therapy leads to an increase in the viscosity of bronchial secretions in chest injuries. To stop this kind of injuries an appropriate mucolytic drug can be used to break the mucopolysaccharide complex along with the moistening of inhaled air. When bromhexine was used 12 mg daily along with ventilation therapy in a patient with chronic bronchitis, it showed significant results. [14] In yet another controlled double blind cross over clinical study of twenty one patients suffering from severe chronic bronchitis, 24 mg or 48 mg bromhexine was significantly correlated with a placebo for 14 weeks daily. Sodium fluorescein was utilized as a drug marker. Sufficient data was obtained from eighteen patients with no change or enhancement in the ventilatory capacity or sputum properties. No side effects were

observed in these patients. [34] As put forward by Lal and Bhalla, forty one patients with chronic bronchitis were given 16 mg bromhexine or placebo thrice daily for 3 weeks along with 500 mg oxytetracycline twice daily. These patients also had symptoms of irreversible airways obstruction. Thirty six patients showed reduction in stickiness of phlegm whereas five patients had developed influenza. There was no significant change in other respiratory illnesses such as cough, sputum volume and ease of breathing. [35]

As reported by Aylward, bromhexine was compared with S-carboxymethylcysteine in a clinical study in patients having mucoid sputum for 10 days. Both the drugs were given orally as syrup formulations thrice daily as 750 mg for S-carboxymethylcysteine and 16 mg for bromhexine. There was a prominent change in cough severity, consistency of sputum and expectoration ease. However, bromhexine didn't show any overall benefits in the respiratory states and thus was not prefered by clinicians. One person had also shown side effects of severe nausea after receiving bromhexine. [36] Armstrong posited that there were beneficial results after consuming bromhexine (Bisolvon) which was used for the treatment of chronic bronchitis. There were prominent amendments in the sputum volume, consistency, peak expiratory flow rate and ascultatory findings. This proved that bromhexine was effective for most people with thick sputum. [37] In a double cross blind clinical trial, thirty patients were randomized for 36 mg of bromhexine and 45 mg of ambroxol (metabolite VIII of bromhexine). Several parameters of mean bronchial flow resistance, arterial blood gases, forced expiratory volume, static lung volumes and laboratory results were analyzed. However, bromhexine didn't cause a change in any of the lung parameters. [38]

In Greek medicine several early remedies such as cinnamon, garlic, pepper, turpentine etc. have been replaced with the modern mucokinetic remedies of ephedrine, atropine, theophylline and bromhexine. [39] The efficacy of bromhexine therapy was observed in the treatment of eighty eight patients who were diagnosed with bronchiectasis, by administering them with 30 mg capsules of bromhexine or placebo thrice daily in conjunction with ceftazine for one week. Bromhexine produced effective results and improved the respiratory conditions of patients. [19] In a one-week, multicentric and randomised double-blind clinical study, four hundred twenty six patients with progressive coughing were tested for the efficacy and tolerability of three expectorant formulations for three times per day for 7 days. Group A were given a fixed dose concentration of 2 mg salbutamol, 100 mg guaiphenesin and 8 mg of bromhexine HCl. There was a significant improvement in the reduction of cough frequency and several sputum characteristics. Group B were administered with a combination of 100 mg guaiphenesin and 2 mg salbutamol. Group C were given a combined dosage of 8 mg bromhexine HCl and 2 mg salbutamol. Both groups B and C didn't produce effective results as compared to group A. [40] This further affirmed that the combination of salbutamol, bromhexine and guaiphenesin over bromhexine or guaiphenesin given alone, could be used effectively as a cough expectorant for alienating the cough produced.

4.2.1 Nil effects of bromhexine for chronic bronchitis studies

Langlands in 1970 reported that 8 mg Bromhexine or identical placebo tablets were administered in patients with chronic bronchitis exacerbations and those having mucoid sputum for 14 days. There was no change in the volume, yield value and viscosity of the sputum. The ventilatory capacity of the lungs remained unaffected after treatment with no shift in the ease of breathing. [41] In another study, eleven out of twenty two patients were asked to take bromhexine along with 1 g of erythromycin ethyl succinate twice daily for a period of 10 days. The other half group were administered with placebo along with the antibiotic. These people had acute exacerbations of chronic bronchitis. There was no clinical improvement seen in both these groups. [42] .

4.3 Diabetic Nephropathy

Bromhexine has also been tested for the treatment of nephropathy. Male wistar rats were given single intravenous injections of streptozotocin (40 mg/kg) for the onset of diabetes. They were treated with bromhexine at two different dose levels for the subsequent 13 months. Renal analysis of these rats along with non diabetic controls and untreated diabetic rats showed a prominent increase in the glomerular volume. It led to an increase in the thickness of the basement membrane in untreated diabetic animals. Diabetic rats treated with bromhexine showed a reduction in the glomerular volume as compared to animals that were not given bromhexine therapy. This proved that bromhexine effectively enhanced one of the changes in vitro diabetic nephropathy. [43] On the other hand, in a study performed by Marshall *et al.* in 1991, the activity of 72 mg of bromhexine daily was observed in nine insulin dependent diabetes melitus patients with normal albumin excretion in a randomised cross over double blind clinical trial. There was no change in the albumin excretion after bromhexine treatment in all the three groups tested with no change in blood pressure, blood glucose levels or creatinine clearance. Thus, they concluded that bromhexine had no effect in insulin dependent diabetes mellitus patients. [44]

4.4 Radiotherapy induced Xerostomia

Twenty five patients suffering from xerostomia after head and neck radiotherapy were given a treatment of pilocarpine and bromhexine in a randomized crossover single blind clinical trial. Initially, they were given pilocarpine for a period of 2 weeks followed by a wash out period of one week. Then, they were given bromhexine for the subsequent 2 weeks. In the second part of the clinical trial, patients were first asked to consume bromhexine and then pilocarpine for a period of 2 weeks each along with a gap of one week wash out period in between. The results were analyzed based on the saliva secretion rates of patients. Pilocarpine proved more effective in treating xerostomia as correlated with bromhexine. However, bromhexine also showed effective results alone but was more productive in reducing radiotherapy associated problems when used in combination with pilocarpine. [45]

5. Conclusion

On the basis of the above mentioned descriptive studies highlighting the role of bromhexine in various clinical conditions, it can be stated that bromhexine has been effective in most of the cases when administered to people. It has been proven to be a suitable molecule that alters the mucus properties and has been helpful in easing many clinical conditions like asthma, bronchitis, nephropathy and xerostomia. The trend of research on this

molecule has slowed down these days and it is important to analyze this molecule further by focusing on the optimization of its drug regime with dose, time intervals, frequencies and combinations with other drug to enhance its efficacy in the above stated clinical conditions along with several unexplored diseased areas.

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