Role of Ipratropium bromide in management of Thunderstorm asthma

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Received: August 2022 Accepted: September 2022; Published: October 1, 2022.
Citation: Numan Ahmad, Kaleem Murtaza Buttar. Role of Ipratropium bromide in management of Thunderstorm asthma. World Family Medicine. 2022; 20(10): 89-96. DOI: 10.5742/MEWFM.2022.9525181

Abstract

Epidemic thunderstorm asthma has been reported to have occurred around twenty times over the past three decades in locations around the world. Thunderstorm asthma events are characterized by a significant increase in asthma presentations, which on occasion can overwhelm local medical services and result in fatalities. Thunderstorm asthma (TA) typically presents during an aeroallergen season in individuals, sensitized to perennial rye grass pollen (RGP) in Australia, in combination with meteorological factors such as thunderstorms and lightning activity. Short acting beta agonist (SABA) only treatment is sub-optimal therapy for prevention of asthma exacerbations. The combined treatment includes inhaled corticosteroids (ICS) and SABA but is found to be contentious. So the present review focuses on suitable alternative, short acting muscarinic antagonist (SAMA), Ipratropium bromide and its efficacy on the management of allergic asthma. Salbutamol induces bronchodilation rapidly but it elicits profound cardiovascular event as the side effects. Meanwhile, ipratropium also has equivalent effect of salbutamol with low side effect profile. Ipratropium also minifies the asthmatic response to grass pollen, allergen induced bronchoconstriction. Further, it also reduces allergen induced early and late asthmatic response and also inhibits the response towards histamine inhalation. In this regard, ipratropium may be considered as a suitable agent in the management of thunderstorm asthma and future trials are highly warranted.

Keywords: Thunderstorm asthma, grass pollen, rye grass, short acting beta agonist, Ipratropium bromide

Introduction

Thunderstorm Asthma (TA) is a clinical entity which causes increased bronchospasm or an asthma attack mediated by rampant changes in the environment such as alteration in wind speed, temperature and the most important factor is the thunderstorm activity in the surrounding places (1). TA is usually sporadic, but it also has the potential to affect a large number of population with an outbreak in a localized space or for a period of time referred to as epidemic thunderstorm asthma (ETSA).

The onset of bronchospasm may be sudden or may be progressive and last more than a few minutes. The most effective treatment for acute exacerbation of dyspnea is the Short-Acting Beta Agonists (SABAs) (Salbutamol) given by nebulizer or inhaler (2). With emerging evidence on the role of cholinergic signaling in allergic asthma, muscarinic antagonist efficacy in allergic asthma is of great interest. Historically, pre-treatment with short acting muscarinic antagonists (SAMA) such as ipratropium, prior to an allergen inhalation challenge produced rather equivocal data. Anticholinergics work by competing with acetylcholine for receptor sites at the vagus nerve-nerve or nerve-muscle junctions. This prevents transmission of reflexes induced by asthma stimuli (3).

Although, the exact mechanism is not well reported, TA occurs as a result of environmental exposure to airborne allergic particles such as fungal spores and pollen grains concentrated in thunderstorm downdrafts (4,5). Grass pollen is one of the vital factors for the progression of hay fever in humans and also induces asthma symptoms (6). Meanwhile, whole pollen is also responsible for causing hayfever, but the size of whole pollen is large so it lacks the ability to penetrate into the airways to cause TA (7). But in specific conditions, the whole pollen may rupture and release sub-pollen particles (SPPs) with submicron size that have the ability to pass the pharynx and penetrate into small airways. The cause of pollen rupture is not clearly depicted, but reports suggest the possible mechanisms such as mechanical friction, lightning activity within thunderstorm clouds and water-induced swelling (8).

Environmental factors associated with the development of TA

• Aeroallergen Exposure

In the presence of water, grass pollen ruptures to release the large quantity of tiny (0.5-2.5 µm) starch granule particles with extensive presence of allergen. These ruptured starch grains are populated in the air during TA epidemics. Studies show that ryegrass pollen (starch granules) have the ability to provoke asthma like symptoms during breathing challenge tests (9). Generally, the size of ryegrass pollen grains are in the range of >35 µmdiameter and when they come into contact with the storm moisture they rupture to 3µm respirable granules (10).

• Air pollution

During thunderstorms, the level of gaseous pollutants and ozone factors are increased. But there is a lack of credible evidence of these factors in the progression of asthma in TA (11).

• Agricultural activity

Harvesting Alternaria (a genus of Deuteromycetes fungi) or Cladorsporium (a common mould) species during thunderstorm events is associated with the release of increased levels of fragmented airborne spores from these species. The evolution of new agricultural practices such as synchronized monoculture planting leads to the release of increased level of grass pollen from fodder and grain crops during the spring season with high concentrations of aeroallergens (12).

Incidence of Thunderstorm asthma

ETSA events are not only limited to Australia. There has been a global incidence with 26 reported events, but they are not responsible for large asthma exacerbations as occurred in Australia. Meanwhile, there are certain exceptions such as the 1994 London epidemic, 2013 Iran epidemic, and 2016 Saudi Arabia epidemic. In industrialized countries, the prevalence of atopic conditions is mainly due to the increased air pollutants in the atmospheric conditions (13).The occurrence of thunderstorms is higher in countries with temperate climates such as Europe or the Middle East, as well as in Australia with subtropical environments (14). TA presentations are also observed in countries like Mexico, (15) USA, (16) and Greece, (17) but till date no specific events have been documented (Table 1).

Australia has the majority of TA events with 10 episodes and among these 7 have occurred in Melbourne, precisely in the south-eastern state of Victoria which has a temperate climate. The majority of the Australian ETSA episodes have occurred during the Spring season which has high concentration airborne grass pollens. The clinical data based on the Australian ETSA event reveals that the majority of the patients were affected with allergic rhinitis (AR), meanwhile known asthma was present in 40% of the cases (18). A previous report shows that in Australian ETSA episodes the most prominent trigger allergen of TA was rye grass pollen (RGP) (Loliumperenne) (19). This pollen has a characteristic feature of < 2.5 µm diameter with ultrafine allergen-coated starch particles and can be released through osmotic shock mechanism, and is further respirable through small airways (10). The other reported mechanism responsible for TA was the outflow of colder air as a result of downdraught from the thunderstorm and this might lead to collection of pollen grains and particles and accumulates as a shallow band of air at the ground surface level (5).

Table 1: Global Thunderstorm Asthma Events

Date	Location	Allergen Trigger(s)
6–7 July1983	Birmingham, UK	Fungal spores
20–21 June 1984	Nottingham, UK	Fungal spores
11 November1984	Melbourne, Australia	Not specified
November1987	Melbourne, Australia	Not specified
22 Jul 1989	Leicester, UK	Fungal spores
November1989	Melbourne, Australia	Grass pollen
1–5 November1990	Tamworth, Australia	Grass pollen
24 Jun 1994	London, UK	Grass pollen
1 Dec1996	Kuwait City, Kuwait	Not identified
30–31 October1997	WaggaWagga, Australia	Grass pollen
27 October1998	Newcastle, Australia	Grass pollen
31 July–1 August 2000	Calgary, Canada	Fungal spores
29–31, Jul 2002	Cambridge, UK	Fungal spores
November 2002	Al-Ahsa, Saudi Arabia	Not identified
20 November 2003	Melbourne, Australia	Grass pollen
4 June 2004	Naples, Italy	Weed pollen
24 June 2005	South-East England, UK	Not identified
27–28 May, 2010	Barletta, Italy	Olive tree pollen
25 November, 2010	Melbourne, Australia	Grass pollen
8 November, 2011	Melbourne, Australia	Grass pollen
2 November, 2013	Ahvaz, Iran	Not identified
26 Oct, 2014	Canberra, Australia	Grass pollen
21 November, 2016	Melbourne and Geelong, Australia	Grass pollen
11 September, 2018	Yuling, China	Plant pollen

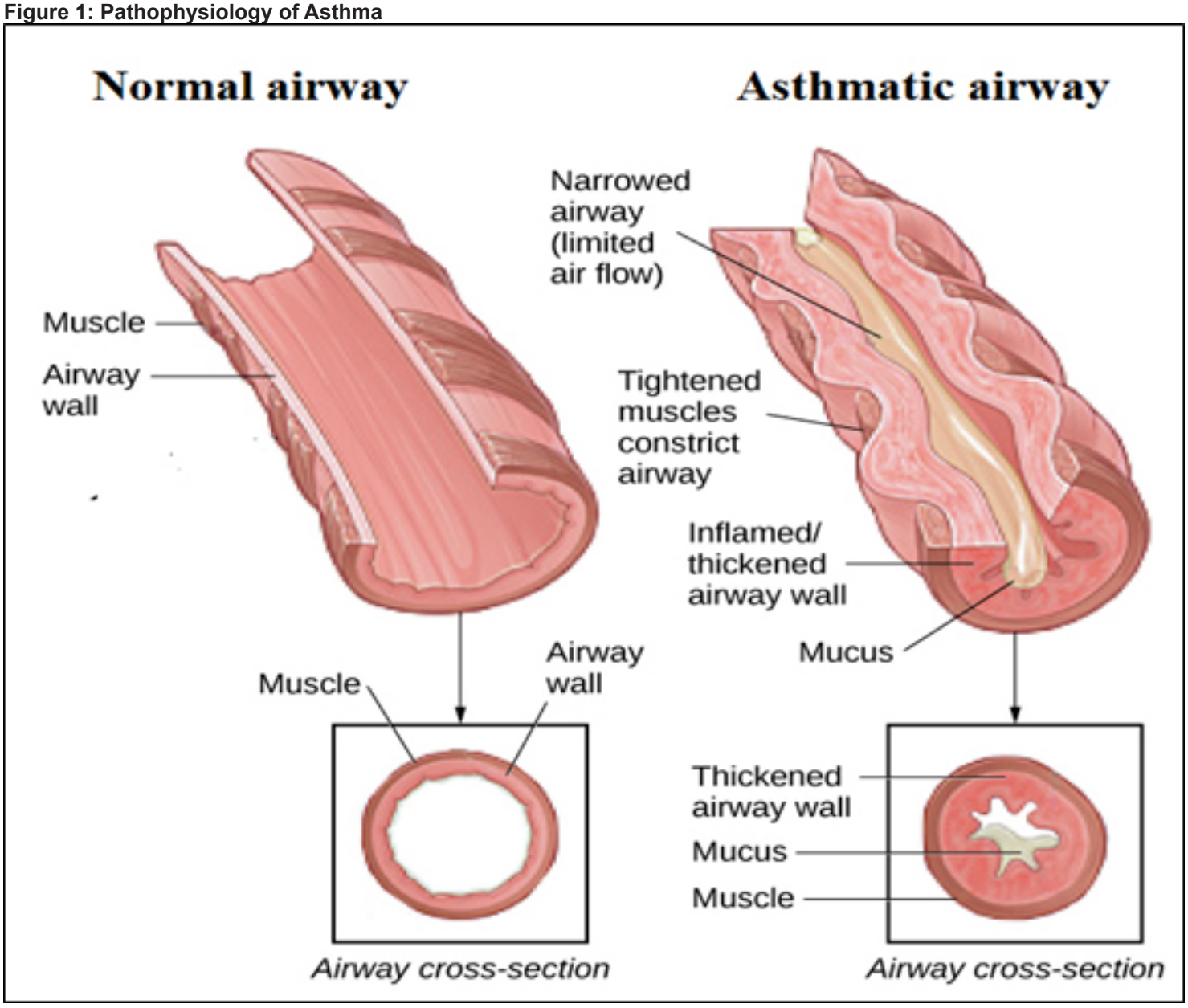
The first event of ETSA in Melbourne was reported during November 1984 (20), following a UK episode in July 1983 . Further, there were two quick events in 1987 and 1989 respectively, with the former reported to have second mortality due to TA (19). All seven ETSA episodes in Melbourne were recorded during the peak RGP season particularly in late Spring especially during November , which is considered a thunderstorm prone month. Meanwhile, the 2016 Melbourne ETSA event was larger in size in terms of severity and magnitude and thus raises the concerns over environmental conditions, health services and patient related factors contributing towards this event (21). During this event, the storm generated rye grass pollen from agricultural land and further bursts of tiny particles into the lungs of the residents. Further, the emergency department was presented with more than 14,000 admissions with the symptoms of TA. Meanwhile, within a span of time mortality was observed in seven men and three women aged between 18 and 57 years. Thus this event was considered as one of the worst events globally till date. The detailed sequence of TA events worldwide is depicted in Table 1.

Pathophysiology of asthma

Asthma is a chronic airway inflammatory disease, with symptoms ranging from wheezing, dyspnea, cough, and chest tightness along with expiratory airway obstruction. Globally, around 334 million individuals suffer from asthma (22).

The asthma exacerbation encompasses an early and late phase. The sensitized IgE antibodies released from plasma cells are responsible for early phase as a result of environmental triggers. IgE antibodies then bind to high-affinity mast cells and basophils (23). During inhalation of pollutants, the mast cells degranulate which leads to the release of cytokines and also the other inflammatory mediators such as histamine, prostaglandins, and leukotrienes. These mediators bind to the smooth muscle receptors and cause airway constriction (23). Th2 lymphocytes trigger the release of interleukins such as IL-4, IL-5, IL-13 and GM-CSF which also mediates the inflammatory process during asthma. Further, the mast cells are also responsible for the recruitment of acute phase reactants to the inflamed site(24). Thus inflammation along with bronchoconstriction develops intermittent airflow obstruction and elevates the breathing workload (Figure 1).

Figure 1: Pathophysiology of Asthma



Airway hyperresponsiveness (AHR) is a hallmark feature of asthma as a result of exaggerated bronchoconstrictor response due to a wide range of external stimuli. AHR is mediated by the release of acetylcholine (Ach) from airway neuronal and epithelial (non-neuronal) cells. Ach binds to muscarinic receptors located in the airways and leads to smooth muscle contraction and mucus production (25).

Role of bronchodilators in the management of asthma

Widely used pharmacotherapies for acute asthma are short acting beta agonist (SABA) e.g. Salbutamol, oral prednisone, short acting bronchodilators such as ipratropium and long-acting beta agonist/inhaled glucocorticoids (LABA/ICS); (e.g., budesonide-formoterol).

Short acting Beta2 Agonist (SABA)

SABA (Salbutamol, Turbutaline, Albuterol, Levalbuterol) bind to the beta2-receptors and cause airway smooth muscles to relax which leads to bronchodilation (26). SABAs are the frequently used therapeutic strategy for fast and acute relief of asthmatic events. Common side effects of SABA are tremors, tachycardia, and palpitations. Frequent use of SABAs must be restricted since it might be associated with resistance and thus deteriorates asthma control.

Long acting Beta Agonist (LABA)

LABAs (e.g. salmeterol and formoterol) are the drug of choice for long term management of asthma with marked bronchospasm since 1990s (27). The principal action of β2-agonists is to relax airway smooth muscle by stimulating β2-adrenergic receptors. This increases the intracellular messenger cyclic AMP that is responsible for the control of smooth muscle tone (28). Thus, activation of the β2-adrenergic receptor results directly in bronchodilation.

Short acting muscarinic antagonist (SAMA)

Short acting bronchodilators such as ipratropium and tiotropium, block the muscarinic effects of acetylcholine. Ipratropium bromide is economically affordable with a good safety profile and elicits smooth muscle mediated bronchodilation. Ipratropium hydrobromide which belongs

to the class of SAMA, is an isopropyl derivative of atropine with low lipid solubility and poor absorption. Ipratropium has the ability to block all muscarinic receptor subtypes with the same affinity, including neuronal M2 receptors (29). Further, due to the inhibition of a neuronal receptor, ipratropium has the potency to stimulate vagal mediated bronchoconstriction at the clinically used doses (30).

The Uptodate (53) recommends ipratropium bromide for the management of moderate to severe childhood asthma exacerbation in combination with beta-agonist. Previous RCTs, systematic reviews and meta-analyses show that 2-3 doses of inhaled ipratropium in combination with inhaled beta-agonist displayed marked reduction of hospital admission and enhances the lung function in children with moderate-to-severe asthma exacerbations as that of the inhaled beta-agonist alone.

Long acting muscaranic antagonist (LAMA)

Muscaranic antagonists (glycopyrronium, aclidinium and umeclidinium) were recommended only for the management of COPD and not for asthma, due to the involvement of vagal tone (31). Muscarinic antagonists are less effective in the management as compared to β2-agonists, since the cholinergic mediated bronchoconstriction is less as compared leukotrienes mediated constrictor effects (31). However, a previous study comparing the effect of LAMA, tiotropium and LABA, salmeterol asthmatic patients shows that both are equally effective in mediating the bronchodilator effect, exacerbations and patient reported outcomes (32).

Further, LAMAs, initially tiotropium as well as other agents such as glycopyrronium and umeclidinium are used as an add on therapy in asthmatic patients with frequent exacerbations, albeit the patients have been on inhaled corticosteroid (ICS)/LABA treatment (33).

A previous study done by Peters et al. showed the efficacy of tiotropium as add on therapy in mild to moderate asthma patients, whose disease was uncontrolled even on treatment with low-dose ICS (80 µg beclomethasone twice daily) (34). A systematic review which evaluated the efficacy and safety of LABAs, LTRAs and LAMAs (tiotropium) in pediatric asthma patients reveals that LABA as an add-on therapy to ICS improved the lung function as compared to the placebo (35).

Preventer' drugs or anti-inflammatory agents in management of asthma

Inhaled steroids (IHS)

Inhaled steroids such as beclomethasone, budesonide, ciclesonide, flunisolide, fluticasone, or mometasone are employed as a maintenance therapy among the asthma patients (36).

The recent GINA guidelines recommend the use of IHS in patients with asthmatic symptoms or SABA twice or more per month, one time or more for waking due to asthma or in patients with minimal symptoms or less risk factors associated with exacerbation (37). BTS/SIGN (2016) (38) implicates the use of IHS in patients' asthma attack for the past two years.

Oral corticosteroids

Corticosteroids mediated anti-inflammatory efficacy in asthmatic airways is rendered by blocking the release of proinflammatory mediators and also through inhibition chemotaxis of inflammatory cells to lungs. Thus, due to their efficacy with profound safety, the systemic corticosteroids are recommended in asthmatic children and adults (39).

Leukotriene inhibitors

Zafirlukast and montelukast are leukotriene inhibitors used in the management of allergic rhinitis and asthma symptoms. A previous randomized controlled trial encompassing 889 patients with uncontrolled asthma symptoms on inhaled budesonide and addition of montelukast to their regimen showed profound effect, which is also similar to the effect of doubling the dose of budesonide (40).

Ipratropium bromide (IB) in the management of Asthma

Ipratropium bromide which belongs to the class of SAMA is administered through pressurized metered-dose inhaler and it is the first inhaled muscaranic antagonist for the management of bronchoconstriction (41). Ipratropium displays non-selective affinity towards the airways muscarinic receptor subtypes such as M1, M2 and M3 respectively. M1 and M3 receptor inhibition leads to bronchodilation, whilst M2 blockade leads to the vagal stimulation Ach and thus lessens the bronchodilator effect (42). Thus due to its non-selective property, its use is limited as a bronchodilator.

A systematic review analysis encompassing various randomized controlled trials was conducted to evaluate the efficacy ipratropium bromide alone, or as a combination therapy with SABA and the results showed that ipratropium bromide alone showed a significant effect as compared to SABA alone (43). Ipratropium bromide alone displayed marked improvement of spirometry compared to SABA, with a mean difference of 30ml (95% CI 0 to 60) for FEV1 and 70 ml (95% CI 10 to 140) for forced vital capacity.

Efficacy of ipratropium bromide allergic asthma

A previous study shows that ipratropium (80µg) administered through metered dose inhaler (MDI) displayed significant protection in allergen induced bronchoconstriction. They also reported that out of 12 patients, 7 of them showed marked improvement in FEV1 following allergen (44). Further, 4 patients displayed late asthmatic allergy response (LAR) and ipratropium has not shown profound inhibition of this response.

In another study, ipratropium (40µg) administered through MDI showed marked protection against allergen and histamine and it is evaluated by calculating the number of

breaths required to elicit a 20% fall in FEV1 (45). Further, a single dose of ipratropium (1mg, via MDI) showed significant inhibition in grass pollen induced asthmatic response in 6 of 10 subjects even after the increased dose of grass pollen (46). Meanwhile, contrasting reports have been published in which nebulized ipratropium (1mg) displayed no marked effects in the allergen mediated fall in FEV1 in six allergic asthmatic patients (47).

The unique clinical action of SABA and SAMA is the quick onset of bronchodilation precisely during the case of acute bronchoconstriction (48). Thus, the bronchodilator effects of ipratropium and SABA, salbutamol has been compared in various studies. Salbutamol elicits rapid bronchodilation and it is employed as a first line treatment in patients with acute symptomatic bronchospasm (41). A previous study shows that salbutamol displays higher bronchodilator effects as compared to ipratropium in asthma patients (49). However, SABA tend to elicit cardiovascular adverse effects in some patients who were unable to tolerate it (50). In such cases, ipratropium may be prescribed due to its low toxic profile. Meanwhile, frequent use ipratropium is associated with tolerance towards bronchodilator effect, however there are no substantial clinical reports evaluate this issue (51).

Clinical utility of salbutamol and ipratropium during a thunderstorm asthma event

To date there are no studies in evaluating the efficacy of salbutamol and ipratropium in thunderstorm asthma.
Recently, Anderson et al. evaluated the medication and administration profile among the thunderstorm asthma and normal patients exposed to a thunderstorm event. In this study, the median time from triage to the first dose of salbutamol administration was 40 minutes in TA patients and 34 for control patients and it was found to be non-significant (p=0.19). Further, the study also showed that, salbutamol en-route provided by ambulance paramedics was higher for TA 33/53 (62.3%) thunderstorm asthma as compared to control 3/6 (50%) control patients. Meanwhile, the medication order history revealed salbutamol has been ordered by 48.3% and ipratropium has been ordered by 24.8% of the patients respectively (52).

Conclusion

Albeit, less frequent and episodic, ETSA can cause large outbreaks which further affect healthcare services with significant fatal cases. So more research is warranted to evaluate the environmental, climate and patients related susceptibility factors to understand the disease mechanism and also various treatment strategies for the accurate management. Evidence was reported regarding the efficacy of ipratropium in allergic asthma, superior to salbutamol. Thus future trials are warranted to study the efficacy of both drugs in the management of thunderstorm asthma.

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