



Short review

Can bronchial asthma with an highly prevalent airway (and systemic) vagal tone be considered an independent asthma phenotype? Possible role of anticholinergics



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ABSTRACT

Recently, we studied occurrence and role of non-respiratory symptoms (n-RSs) before a worsening of asthma symptoms. Some n-RSs such as anxiety, reflux, heartburn, abdominal pain, which appeared within 3 h before the onset of an asthma attack, are the likely result of an imbalance between sympathetic/parasympathetic systems with an increase in cholinergic tone. Therefore, it is likely that some of these n-RSs induced by the increased cholinergic tone might be present related with specific parasympathetic-associated respiratory symptoms such as those elicited by airway narrowing.

It is likely that, at least in some categories of asthmatics, an increased cholinergic tone, rather than other well-known factors, might play a prevalent role in triggering bronchospasm. If this is the case, it is possible to speculate that the use of anticholinergic agents (mainly those with long-acting activity) in patients suffering from asthma should be more beneficial in individuals characterized by a higher degree of cholinergic tone that, consequently might be the ideal target for the use of long-acting anticholinergics and, possibly, represent a novel asthma phenotype. The presence of parasympathetic-associated n-RSs might help the physician to identify this type of patients, although this might be followed by a more detailed assessment.

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1. Introduction

In a recent article, we studied occurrence and role of non-respiratory symptoms (n-RSs) before or during a worsening of asthma symptoms since only very few data on n-RSs are present in literature [1–3]. In fact, the “classic” view of asthma diagnosis primarily based on respiratory symptoms (RSs) implies that airway obstruction is virtually disconnected from other organs or systems. Conversely, it has been widely recognized that, at least in part, airways homeostasis is under the control of sympathetic and parasympathetic systems [4–7]. Obviously, autonomic nervous system plays an important role also in controlling, at the same time,

the function of several other organs. Five hundred and ten out of 806 (63.3%) asthmatic patients enrolled in our study reported at least one n-RS that generally appeared within 3 h before an asthma attack. Anxiety, headache, palpitations and itching were the most common n-RS with percentages up to 20%. N-RSs were significantly more frequent in asthmatics suffering from persistent moderate/severe disease in comparison to those with intermittent/persistent mild asthma.

Potential link between most common n-RSs and asthma through an increased cholinergic tone.

Behavioural symptoms such as anxiety and, to a lesser extent, excitement or depression, represented the most common n-RSs in our study and are common in asthmatics [1,8–13]. It is well documented that psychological stress may enhance bronchial hyperreactivity through several mechanisms such as mast cell activation and mediator release, inflammation and imbalance of the autonomic system [14,15]. In particular, a significant relationship was

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found between psychosocial stress and stimulation of the cholinergic system [16,17]. It has been postulated that an increased cholinergic tone is responsible for the increased airway resistance and that the vagal-mediated responses induced by psychosocial stress are fast in their onset (after 1–2 min following the stimulus) [18–21]. Interestingly, there is evidence that ipratropium bromide is able to prevent airway obstruction induced by emotional stimuli [17].

Asthma is associated with several comorbidities [22]. Abnormalities of gastrointestinal peristalsis are relatively common in asthmatics, especially children, also in the absence of a clear history of food allergy [23,24]. Vomiting as a dominant or presenting symptom of asthma has been also described [25,26]. In fact, previous studies have demonstrated an increase in airway hyper-responsiveness and a high prevalence of asthma among patients with irritable bowel syndrome [27,28]. A close relationship between asthma exacerbations and gastrointestinal symptoms such as abdominal cramps and pain with the urge to defecate has been also shown [29–31]. This defecation-related asthma tends to be severe and occurs suddenly.

Asthma induced by gastro-esophageal reflux (GER) is still a controversial issue especially for the difficulties to explain the exact mechanism of inducing bronchial hyperreactivity by esophageal acid [32]. In recent years a possible association between airway narrowing, GER and cholinergic tone has been postulated [33,34]. Acid stimulation of the distal esophagus induced by stomach acid results in increased cholinergic tone and a concomitant bronchoconstriction in asthmatics irrespective of their reflux state [35,36]. This finding further strengthens the hypothesis that GER may trigger asthma-like symptoms through a cholinergic mediated esophago-bronchial reflex [35,36].

Bronchial asthma with an highly prevalent airway (and systemic) cholinergic tone: a new independent asthma phenotype ?

Some n-RSs that we have observed in our study are the consequence of an imbalance between sympathetic/parasympathetic systems with a prevalence of cholinergic tone. As a consequence, it is likely that some symptoms induced by cholinergic hyperactivity/hyperactivation (e.g. dry mouth, sweating, heartburn, abdominal pain) or associated to this condition (e.g. psychological stress) could be present together with parasympathetic-associated RSs such as those elicited by airway narrowing [1].

Indirectly, the results of our study confirm the assumption that cholinergic pathway is a determinant bronchoconstrictor at least in a group of asthmatic patients. In fact, some n-RSs that precede the appearance of an asthma attack are clearly the expression of an increased cholinergic tone. In other words, it is likely that, in some individuals, a prevalence of cholinergic tone might play a significant role in determining airway narrowing, although, more in general, it must be highlighted that cholinergic contractile tone is increased by airway inflammation associated with asthma [4].

On the basis of these considerations, we suggest that attention should be focused on considering the role of parasympathetic system as trigger of bronchial obstruction in asthmatics who report the usual onset of cholinergic-related n-RSs before an asthma attack.

It is likely that, in some categories of asthmatics (we still do not know if they could be considered a specific phenotype), an increased cholinergic tone could play a prevalent role in triggering bronchospasm in comparison to other well known factors such as inhalation of allergens/air pollutants, virus infections, exercise etc. Consequently, we could postulate that blocking muscarinic impulse transmission at the airway smooth muscle might be more beneficial to control airway obstruction and mucus secretions in these asthmatics.

Can anticholinergics play a role in bronchial asthma with an

increased cholinergic tone?

As a consequence of this background, theoretically, the use of an anticholinergic agent (mainly the recent compounds with a long-acting bronchodilator profile) in patients suffering from asthma should be more useful in those individuals characterized by an increased cholinergic activity [37,38]. Unfortunately, until today only Peters et al. have suggested that a higher cholinergic tone is a predictor of a positive clinical response to an anticholinergic agent (tiotropium) in asthmatics [39]. In effect, these authors were able to document that patients with lower resting heart rate (that is an expression of higher cholinergic tone) displayed a better response to tiotropium than salmeterol [39].

Very few other contributions underlie the role of increased vagal airway tone as a basis for using anticholinergic agents to treat patients suffering from asthma [5]. The majority of studies that have explored the effectiveness of tiotropium in asthma have been carried out in individuals with a higher degree of severity or in individuals uncontrolled despite ICS/LABA [40–44]. On the contrary, only few studies have used tiotropium in patients suffering from mild/moderate asthma.

Two short-term studies have been carried out in patients with moderate asthma and reported non-inferiority between tiotropium and a LABA, both used as an add-on therapy to low-dose to medium-dose inhaled corticosteroids [45,46]. A recent series of pivotal phase III studies have investigated tolerability and efficacy of tiotropium as add-on to maintenance treatment of adults [47,48], adolescents [49,50] and children [51] suffering from moderate asthma not controlled by low-medium ICS. Finally, Kerstjens et al. [52] carried out a large trial assessing the safety and efficacy of tiotropium (5 µg or 2.5 µg/die) in patients with moderate asthma who were symptomatic despite treatment with medium-dose inhaled corticosteroids. Addition of once-daily tiotropium significantly improved lung function and asthma control compared with placebo, was similar to salmeterol in efficacy and tolerability.

Considering the known role of cholinergic tone in bronchial homeostasis we are not surprised that tiotropium is more effective than placebo and not inferior to salmeterol also in moderate asthma as maintenance therapy. Unfortunately, none of these studies also evaluated the cholinergic tone (even with a simple method as the measurement of resting heart rate) in tiotropium-responder patients. Since the degree of cholinergic tone is likely to be different among asthmatics, it is impossible to rule out that the efficacy of tiotropium might be higher in patients with an increased degree of this baseline characteristic.

Because of concerns about the safety of LABA use in patients with asthma (they may increase the risk of hospitalization and asthma-related death) [53], the possible increased responsiveness to anticholinergics should be usefully evaluated. Recently, Chung [54] has highlighted the need for a better definition of subgroups of patients with moderate asthma, who could benefit from the use of tiotropium or salmeterol. Furthermore, Hamelmann et al. [50] stated “To date, features that can be used to predict responses to LABAs versus long-acting anticholinergic bronchodilators have not been reported but, if identified, might be of benefit in helping to inform treatment decisions. ... Further prospective trials in adolescents with poorly controlled asthma might help to identify predictors of response to the different step-up options, including tiotropium”. These points of view strongly fit very well with our hypothesis that an increased cholinergic tone in asthma could be considered a “marker” of a “cholinergic phenotype” with a better response to anticholinergics.

We strongly believe that, although patients with severe or uncontrolled asthma are the main target for use of recent long-acting anticholinergics, also patients with an increased cholinergic tone, documented by the presence of cholinergic-related n-RSs, may

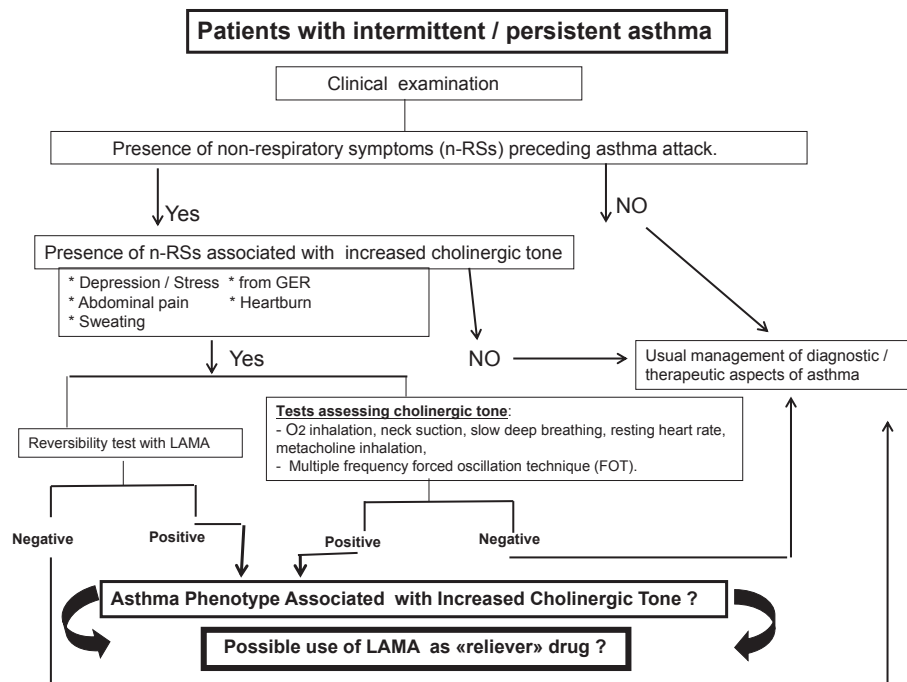


Fig. 1. Suggested flow chart to evaluate asthmatic patients with a basal increased cholinergic tone and possibly targeted for the use of long-acting anticholinergics as reliever drugs.

benefit from the use of these bronchodilators. In other words, defining in some way the occurrence of an increased cholinergic tone in the single patient, might be a better approach to choose long-acting anticholinergics in asthma regardless of asthma severity and the control of asthma symptoms. Obviously, we agree with the point of view suggesting the need for seeking a specific asthma phenotype which may be more appropriate for the treatment with anticholinergics [55].

In our opinion, the likely asthma phenotype in which anticholinergics could elicit more effective clinical efficacy is that in which asthma is associated with increased cholinergic tone. Although it is not easy to study and measure the vagal tone, there is need for non-invasive indices of vagal control to better define individuals with a higher basal cholinergic tone [56,57]. Recently, Zannin et al. reviewed several non-invasive stimuli, such as O₂ inhalation, neck suction, slow deep breathing, metacholine inhalation and multiple frequency forced oscillation technique (FOT), which can be used to study the effect of cholinergic tone on cardiovascular and bronchial systems [58]. Peters et al. have suggest to only measure resting heart rate [39].

According to our results, also a simple question exploring the presence of vagal-related n-RSs during the collection of anamnestic data could help to identify asthmatics with imbalance between sympathetic and parasympathetic systems. In any case, in addition to our first questionnaire on the presence of n-RSs, a further questionnaire that might offer a more accurate evaluation could be planned only for those subjects who reported cholinergic-related n-RSs. In Fig. 1, we suggest a possible flow-chart to select asthmatics that may benefit from the use of long-acting anticholinergics before the onset of an asthma attack. Obviously, further specific studies should be performed in a selected population of asthmatics with predominant airway cholinergic tone (assessed through the available aforementioned methods) to confirm our suggestion. Since our experience on some aspects of increased cholinergic tone at bronchial/systemic levels is limited to the onset of asthma attack, at present time we can hypothesize the use of LAMA only in this condition. Further studies should be carried out to confirm the

possibility that the efficacy of LAMA as maintenance therapy of asthma could be better in patients with increased cholinergic tone.

2. Conclusions

We hypothesize that asthmatics with a basal increase of cholinergic tone in airways constitute an ideal target for the use of anticholinergics (mainly those with a long-acting activity) and, possibly, they could represent a novel asthma phenotype. The presence of not respiratory parasympathetic-associated symptoms could help the physician to recognize this type of patients at least from a clinical point of view.

If our hypothesis will be confirmed by further studies through the specific aforementioned methods to measure cholinergic tone, the use of anticholinergics could be indicated as first-line therapy either as “reliever” or, associated with an inhaled corticosteroid, as “maintenance” treatment of those asthmatic patients belonging to the “cholinergic phenotype”.

Summary statement

An increased airway (and systemic) cholinergic tone might be a peculiar pattern in some asthmatic individuals and likely constitute an ideal target for the use of anticholinergics.

Authorship

All authors contributed equally in the writing and revision of the manuscript.

Financial disclosure/conflict of interest

All authors declare that they have no conflict of interest and that the study has been carried out without any financial support.

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