

## Inflammation *versus* Bronchospasm: Do Bronchodilators have a Role in Bronchial Asthma?

Inhaled corticosteroids (ICS) constitute the cornerstone of management of most forms of asthma. This is primarily attributed to their anti-inflammatory effects on the airways. On the other hand, the role of bronchodilators in the management of asthma continues to remain as secondary or supportive. But bronchodilators are widely prescribed in preference to the ICS, especially so in the primary care settings. Of course, short-acting beta-agonists (SABAs) for mild or occasional asthma episodes (i.e. Global Initiative for Asthma [GINA] Step 1 therapy), and combination of inhaled corticosteroids with long-acting beta-agonists (LABAs) are recommended in most asthma-guidelines for the maintenance treatment of stable asthma.<sup>1,2</sup>

There has been a major shift in our concepts about the pathogenesis of bronchial asthma over the last century, thus changing our approach to its management.<sup>3</sup> In the past, the episodic airways-obstruction of asthma was thought to occur due to spasmodic contraction of airway-smooth muscles (i.e. bronchospasm) in response to an allergic response mostly following an inhalational exposure. The concept had prevailed for over a century. Therefore, bronchodilators and expectorants were most commonly used for the treatment. Even earlier for several centuries when the causes and mechanism of asthma were not known, herbal therapy (with '*datura*' and '*ephedra*') for relief of cough and breathlessness of asthma contained bronchodilatory ingredients.<sup>4</sup> Similarly, 'black coffee' with a high content of theobromine (with bronchodilatory effect) was described for the treatment of asthma.<sup>5</sup> It was only around the 19<sup>th</sup> Century that bronchodilator drugs (atropine and ephedrine compounds) were isolated from these herbs. Therapy with their derivatives constituted the mainstay of treatment of asthma till the 1970s and 1980s.

Towards the end of the 20<sup>th</sup> Century, it was established through different studies that airway inflammation was the primary pathological mechanism of asthma.<sup>6,7</sup> A complex inflammatory cascade that ensues following stimulation by different triggers, such as inhalation of an allergen, respiratory tract infection, exercise, cold air and other stresses result in the release of a large number of cells and mediators involved in the inflammatory circuit.<sup>6-8</sup> A number of patho-physiological changes which take place in the airways (i.e., mucosal oedema, increased inflammatory exudation and mucus plugging, bronchial hyper-responsiveness (BHR), and bronchial smooth muscle spasm) are responsible for clinical symptoms and signs of asthma.

Recognition of airway-inflammation was the game-changer for the management of asthma. The focus of treatment changed from oral bronchodilators to the use of anti-inflammatory medications. The availability of ICS alleviated the fear of side-effects of oral or parenteral corticosteroids, the most commonly employed anti-inflammatory drug. In spite of the poor compliance with inhalation therapy and other difficulties associated with the use of inhalers, a large number of products appeared in the market. In due course of time, oral therapy with bronchodilators was either abandoned or significantly reduced all over the world, including in India.

There are three different kinds of bronchodilators used for the management of asthma and chronic obstructive pulmonary disease (COPD): (i) beta-agonists and other sympathomimetic agents; (ii) anti-cholinergic or parasympathomimetic agents and (iii) theophyllines. Of them, sympathomimetic agents and theophyllines are widely available as oral drugs. Most sympathomimetic agents are also available in inhalational form, which is the preferred mode of administration in asthma as well as in COPD.

A large number of patients in this country continue to use oral bronchodilators because of their cheaper costs, ease and convenience of use. Moreover, there are several misgivings and inhibitions with the use of inhalers. Inhalational therapy is considered as a stigma as well as addictive, especially in case of children.

Do bronchodilators currently have a role in the treatment of asthma? Beta-agonists have a long history of use in asthma with a good efficacy and safety profile. Short-acting beta-agonist, such as isoprenaline was the first to come in the modern armamentarium of anti-asthma drugs. Over-dependence resulted in misuse, resulting in markedly increased death rates in patients relying on their unregulated use in several Western countries.<sup>9</sup> For a long time thereafter, the drug went into disrepute. Selective beta-2 agonists, such as salbutamol, terbutaline and fenoterol remained popular for several years until increased deaths were again reported with the use of high-dose fenoterol.<sup>9</sup>

Today, the use of LABAs along with ICS is the cornerstone of management of asthma. Their use is undoubtedly recommended for maintenance treatment of asthma as per the most recent and widely followed GINA guidelines.<sup>1</sup> On the other hand, the inhaled anti-cholinergic drugs and oral theophyllines are reserved as add-on therapy for stage III, IV and V

(i.e., poorly controlled and uncontrolled) asthma. Similar recommendations are also made in most other international and the Indian Asthma Guidelines.<sup>2</sup>

Should other bronchodilators, such as inhaled anticholinergic agents and/or oral theophyllines be added to routine management of stable asthma? Based on several clinical trials, their place at present is reserved as add-on therapy for severe forms and/or acute exacerbations.<sup>1</sup> However, one can anticipate benefits of adding small dosages of additional bronchodilators in routine management for stable asthma, such as reduction in dosages and of side-effects of ICS and inhaled beta-agonists, with oral bronchodilators. In addition, there is convenience of use and lowering of costs with this approach.

There is at least some experimental evidence to suggest that theophyllines may be useful for the maintenance treatment of asthma. In a novel experiment in an asthma model (i.e., ovalbumin-sensitized guinea-pigs), repeated administration of inhaled aminophylline was shown to have anti-inflammatory effect manifested by suppression of the eosinophilic infiltration and airway hypersensitivity to acetyl choline.<sup>10</sup> High concentrations of aminophylline also inhibited the production of oxygen radicals. In another experiment, theophylline was shown to inhibit capsaicin-induced cough in guinea-pigs, under both normal and disease conditions.<sup>11</sup> In a recent study, however no significant difference was seen in therapeutic effect and safety in patients with moderate to severe persistent asthma treated with fluticasone aerosol combined with theophylline compared to the use of salmeterol/fluticasone aerosol.<sup>12</sup>

There are several clinical reports as well, on the use of theophylline preparations for asthma treatment. Theophylline in combination with ICS fluticasone and beta-agonist salmeterol is reported to provide greater protection against asthma exacerbations.<sup>13</sup> Low dose theophylline is frequently recommended to reverse corticosteroid resistance, particularly in patients with severe asthma and COPD. It is also shown to have mild anti-inflammatory effects. There have been several attempts to find improved derivatives of theophyllines for effective asthma management. But the progress in oral bronchodilator therapy has been slow and unremarkable. A number of novel phospho-di-esterase (PDE) inhibitors, natural phytotherapeutics and chloride channel modulators are now being developed.<sup>14</sup>

At present, one can only hope that an effective alternative will be available sooner than later. Similarly, the newer molecules amongst beta-agonists and anticholinergics are likely to add further impetus to asthma management with bronchodilators in future. Meanwhile, our understanding of asthma-pathogenesis has considerably improved with our knowledge about the presence of structural remodelling in early asthma.<sup>15</sup>

We are back to the origin of asthma in the airway wall with a possibly increased role of bronchodilators and targeted treatments in its management.

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