Brief Communication

Stepping Down in Asthma

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ABSTRACT

Beta-2-agonists continue to find a dominant role in all the current guidelines on the management of chronic persistent bronchial asthma. However, the safety of the drugs remains doubtful. Thus, there is a case for review of the "Step up-Step down" approach in the management of chronic persistent bronchial asthma. Based on the currently available experimental and clinical data on bronchial asthma, the authors are of the opinion that chronic persistent bronchial asthma is best managed by a modified "Step I-Step II" approach.

INTRODUCTION

Several guidelines have been developed and are revised at regular intervals to update physicians on evidence based management of asthma.[1,2] The guidelines address an incremental and decrimental use of inhaled corticosteroids (ICS) along with β_2-agonists, i.e. a "Step up-Step down" approach". However, surveys in Europe[3], Asia-Pacific[4] and the United States of America[5] have revealed that control of asthma continues to be poor. It was also observed in these surveys that many physicians considered β_2-agonists as the drug of choice, prescribed ICS in low doses or delayed their introduction. We reasoned that the guidelines by themselves may not be robust for an optimal outcome. Suggestions on an alternative "Step I-Step II" approach are presented here.

BETA-2-AGONISTS IN ASTHMA

Isoproterenol pressurised metered dose inhaler (MDI) was the first inhalational drug to treat asthma. However, it soon fell into disrepute as increasing asthma deaths were reported with its increased use.[6] Latter, more selective short-acting β_2-agonists (SABAs), such as albuterol and terbutaline and, long-acting β_2-agonists (LABAs), such as formoterol and salmeterol were discovered and are in current use. The β_2-agonist controversy, however, continues. Cates and colleagues reported more adverse events with formoterol[7] and salmeterol[8] as compared to placebo. A joint meeting convened by the Food and Drug Administration (FDA) to examine the issue concluded that the risks of treatment with salmeterol or formeterol outweigh benefits when used as monotherapy in asthma and advised their use only in combination with ICS.[9]

ICS-LABA IN ASTHMA

Inhaled corticosteroids reduce airway inflammation, and thus, improve pulmonary functions, reduce bronchial hyperreactivity and deposition of collagen/tenascin in airway mucosa. Response to ICS, however, depends on the time of introduction, co-prescription of β_2-agonists and its dose. Early introduction is recommended, as delay may lead to irreversible changes in the airways pathology.[10] ICS provide a better clinical response when used with β_2-agonists.[11] A daily dose of 400-800mg of beclomethasone dipropionate (or its equivalent) is sufficient in most of patients except those with severe disease who need higher dosage.[12] Several studies including that of Woolcock *et al*,[13] have shown that addition of LABAs to ICS result in greater improvement in asthma symptoms than doubling the dose of ICS. This led to the widespread use of low dose ICS with LABAs (often in combination devices) and this has been advocated by the various asthma guidelines. Other workers including Bhagat *et al*[14] have cautioned that long term use of LABAs along with low dose ICS may lead to tolerance, possibly due to masking of the ongoing airway inflammation.

Another approach, single maintenance and reliever therapy (SMART), evolved with the use of formoterol as the LABAs component in the combination device. Several studies including the one by Humbert *et al*[15] showed that besides being convenient to patients, it led to improved control of asthma and reduced risk of exacerbations of asthma. But it needs to be noted that the SMART treated

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patients received higher doses of ICS than those in the comparator arms and that may be the reason for improved asthma outcomes. Pauwels *et al*[11] showed greater reduction in exacerbation rates by increasing the dose of budesonside from 200mg to 800 mg per day, irrespective of the use of formoterol. Others including Tukiainen *et al*[16] also noted that higher dose ICS led to improved clinical response and pulmonary functions, and decreased airway hyperreactivity and surrogate markers of inflammation. High dose of ICS also allowed discontinuation of systemic steroids.[12]

Concerns have been raised regarding the risk of adverse effects with high dose ICS but these may be prevented by rinsing the mouth with water after inhalation or with the use of a spacer device with MDI and by lowering the dose during the maintenance phase.[17]

BETA-2-AGONISTS! WHY THE FRIENDS HAVE TURNED FOES?

Beta-2-agonists are the best known as bronchodilators. However, experimental studies have shown that these drugs may be pro-inflammatory. Regular use of albuterol led to inhibition of interleukin (IL)-12 production by human monocytes and modified the development of Th-1 inflammatory pathway.[18] Terbutaline treated monocytes increased release of IL-4 and IL-5 and decreased release of interferon-gamma.[19] McGraw *et al*[20] observed increased airway hyperreactivity and gain in contractile signalling in mice on chronic β_2-agonist exposure. Callaerts-Vegh *et al*[21] showed that β_2 adrenoceptor agonists and beta-blockers may exert reciprocating effects on cellular signalling, depending on duration of exposure in murine models**.** These data suggest that the relationship between β_2-receptor activation or its blockade, airway inflammation, and airway responsiveness in asthma are complex. The effects of β_2-agonists may not be the same on their short-term and long-term use. Therefore, timely introduction of ICS in optimal doses is critical and β_2-agonists are not recommended as monotherapy in asthma.

"STEP I-STEP II" APPROACH *VERSUS* "STEP UP-STEP DOWN" APPROACH IN ASTHMA

The focus in the management of asthma has now shifted to achievement of control and prevention of severe medical crises and day-to-day disability. Guidelines here advised using objective measure of asthma control, such as, the "Asthma Control Test".[22]

A common practice, however, in the use of moderate to high dose of ICS (>500mg of beclomethasone dipropionate or its equivalent), depending on severity as an initial step and that too along with LABAs as initial step (Step 1). This is in line with suggestions made by several authors including Tukiainen *et al*.[16] Additional broncho-dilators in the form of anti-cholenergics, oral theophyllines and/or leucotrienes inhibitors may be added subsequently to achieve control.

The Global Initiative for Asthma (GINA) guidelines (2010)[5] in the "Step up-Step down" approach advocate low dose ICS at Step 2 and low dose ICS with LABAs or moderate dose ICS alone at Step 3. Higher dose ICS is recommended only at Step 4. Further, it advocates reducing the dose of ICS and continuing LABAs during "Step down" in adults.

However, continuation of LABAs and low dose of ICS during Step-down (as per GINA guidelines) may result in increased airway inflammation, that may be masked due to the former drug, and therefore, place such patients at risk of decontrol. The FDA also recommends that as far as possible, LABAs should be withdrawn first during step down.[23] The available experimental and clinical data also favours withdrawal of LABA is the approach. If the control is sustained, ICS should be tapered down to maintain the therapy on the lowest possible dose along with SABA as 'on demand' basis.

The GINA guidelines favour this approach only as a second alternative for fear of loss of control. However, any loss of control can be managed by re-introduction of LABAs along with optimal dose ICS, i.e. a reversal to "Step-I".

It is important to recognise loss of control at the earliest so that it can be managed without delay. Any loss of control is likely to be more evident in patients who step down with LABAs in contrast to those who step down with ICS and continue with LABAs who may have masking effect.

In conclusion, studies are required to examine the two strategies, i.e. stepping down initially by reducing the dose of ICS or by withdrawal of LABAs.

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