REVIEW ARTICLE

Concurrent Therapy (Long Acting Beta Agonists and Inhaled Corticosteroids) in the Management of Asthma

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ABSTRACT

Background: *Asthma is a clinical syndrome characterised by chronic inflammation of the lower respiratory tract in which many cells and cellular elements play a role, in particular mast cells, eosinophils, T-lymphocytes, macrophages, neutrophils and epithelial cells. Patients often require long-term anti-inflammatory and reliever drugs to achieve a normal life. This review aims to highlight role of concurrent therapy in the optimal management of asthma.*

Method: *A review of relevant literature was conducted using available medical journals and Science direct via the Internet. The key words employed were: asthma, concurrent therapy, long acting beta agonists and corticosteroids. British Thoracic Society and The National Heart, Lung and Blood Institute websites were also used in sourcing information for this review.*

Results: *Several studies support adding long acting beta agonists (LABA) to inhaled corticosteroids (ICS) than doubling the dose of ICS. This improves lung function, symptoms control and allows the dose of each drug to be adjusted to the patients' needs.*

Conclusion: *This review was able to show that concurrent use LABA and ICS in asthmatics helps in adjusting their treatment within limits hence achieving control of the condition with minimal side effects.*

KEY WORDS: Asthma; Concurrent Therapy; Corticosteroids; Long Acting Beta Agonists.

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INTRODUCTION

Asthma is one of the commonest diseases especially in the western world. It is a reversible chronic inflammatory disease of the airways with various cells and cellular elements interacting in the pathogenesis. These cells are primarily the mast cells, eosinophils, T-lymphocytes, macrophages, neutrophils and epithelial cells[1,2]. This distinguishes it from diseases with predominantly irreversible airway narrowing thus emphasizing the intermittent nature of asthma rather than the persistence of the underlying inflammation, with potentially inappropriate implications for treatment.

There is an increase in prevalence in children and young adults in the western world and despite this increase in prevalence, deaths are now uncommon. The disease affects over 10 per cent of children and about 5 per cent of adults[3]. Male to female ratio increases steadily from birth to teenage from which the trend reverses with females overriding males[4].

The symptoms and bronchial hyper-responsiveness seen in asthma are due to the inflammatory nature of the disease. It manifests in the form of recurrent episodes of breathlessness, cough, chest tightness and wheeze. These symptoms are often worse at night with a resultant fall in the peak expiratory flow (PEF) in the early hours of the morning hence referred to as the 'morning dip'.

Atopy may be present in the family in a significant number of patients as there is a clear genetic susceptibility[5]. Factors implicated in the aetiology include environmental factors as well as diet, maternal smoking, viral infections at infancy, low birth weight, immunologic, sedentary life style and gastro-oesophageal reflux[5,6].

Delay in diagnosis is not uncommon and any unusual features or suggestion of upper airway obstruction requires further investigations. Diagnosis is clinical on the basis of symptoms of wheezing, dyspnoea, and cough, and by objective evidence of variable airflow obstruction. In a small number of patients, methacholine or histamine challenge test can be valuable. The clinical diagnosis can be confirmed by changes in the lung function tests[5]. Investigations may include full blood counts, urea and creatinine, C-reactive protein, sputum microscopy and culture, arterial blood gases, and chest x-ray (to exclude infection, pneumothorax, pneumomediastinum, pulmonary collapse or eosinophilic pneumonia).

Pathophysiology

Understanding the pathophysiology of asthma has greatly influenced asthma pharmacotherapy. The basic pathophysiological mechanisms depend on the inflammatory mediators (histamine, prostaglandins and leukotrienes) and also chemokines and cytokines[7]. Mast cells are important initiators of the acute

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bronchoconstrictor response to allergen and probably other indirect stimuli such as exercise and hyperventilation. This produces a prolonged increase in microvascular permeability, up-regulation of adhesion molecules, attraction and activation of eosinophils and augmentation of epithelial and fibroblast proliferation. Histamine acts through its H1 receptor while prostaglandin D2 contracts the airways by interacting with thromboxane receptors. This is the basis behind bronchial smooth muscle contraction, mucus secretion and microvascular leakages, attracting other inflammatory cells[7,8]. T-lymphocytes play a vital role through the release of specific cytokines and thus promote recruitment and survival of eosinophils. They express a distinctive pattern of cytokines, the TH cells (TH1 and TH2). There is an imbalance of the TH cells with TH2 more than TH1. The balance is determined by locally released cytokines such as IL-12 favouring TH1 cell expression and IL-14 favouring TH2.

Early childhood infection encourages predominantly TH1-mediated response, lack of which may favour TH2-cell expression thus atopy[7-9].

Different drugs employed in the management of asthma act at different cellular levels. It has been shown that ICS and LABA interact at a receptor level with resultant synergistic effect.

ICS increase β2-adrenergic receptor transcription in the human lung and increase the synthesis of respiratory mucosal β2-receptors at clinical doses. Inhaled LABA also prime the inactive glucocorticoid receptor through a phosphorylation mechanism, rendering the receptor more sensitive to steroid-dependent activation[10,11].

Figure 1 describes interaction of the inflammatory cells, inflammatory mediators and reflex neural mechanisms in asthma; it also highlights areas where steroids and β2-agonists act.

LITERATURE REVIEW

The term concurrent therapy here denotes use of ICS and LABA via two separate inhaler devices in the management of asthma. It is well established that the core treatment for mild to moderately severe asthma is the use of ICS and LABA; this is in consonance with both National and International asthma guidelines[5,12,13].

The National guideline on the management of asthma, jointly produced by the BTS (British thoracic society) and Scottish Intercollegiate Guideline Network in April 2004, underscored the importance of adding LABA and ICS (Table I).

The BTS and GINA (global initiatives for asthma) guidelines, recommends a stepwise approach to pharmacological therapy[12] with the aim to accomplishing the goals of therapy with the least possible medication. The approach is that as asthma severity increases, the dose of ICS is stepped up and other classes of drugs are added, particularly LABA. These bodies advocate guided self-management and further encourage patient education and training to achieve success[13].

Consequently, in the United States of America, the National Asthma Education and Prevention Program (NAEPP) recommend the use of low- to medium-dose ICS with LABA for moderate persistent asthma rather than using high-dose ICS or adding LTRAs or theophyllines to the ICS[14].

The importance of establishing a partnership between patients and health care professional(s) cannot be over emphasized. This is a view for the patient to effectively achieve control of his own condition[15,16]. PEF should be used as part of the written action plan in guided self-management. This has been shown to strengthen clinician-patient communication and increases patient awareness of his disease status, as further motivated by Cochrane evidence-based of 25 studies[17].

The administration of LABA and ICS using separate inhalers allows the dose of each drug to be adjusted to the patients' needs and this is said to offer the potential for more effective implementation of guided self-management asthma plan[19,20].

The National Heart, Lung and Blood Institutes' definition of symptom severity is often used as a guiding principle in evaluating the benefits of treatment in asthmatics[18] as shown in Table II.

LONG ACTING BETA AGONISTS (LABA)

Sympathomimetic amines, to which belong β2-adrenoceptor agonists, are basically the catecholamines (adrenaline, noradrenaline, dopamine) and non-catecholamines (salbutamol, terbutaline, salmeterol, formoterol). The selective β2-agonists employed in the management of asthma are either short (salbutamol, terbutaline) or long (salmeterol, formoterol) acting. The LABA have a slow onset of action but longer plasma half-life of up to about 12 hours as compared to the SABA that has a plasma half-life of about 3-6 hours. The exception to this is formoterol, which has a rapid onset of action that is comparable to the SABA but the same duration of action as salmeterol; it is licensed for used for short-term symptom relief[21]. The tachyphylaxis seen with the SABA[22] does not apply to the LABA[23,24]. The different preparations of LABA include salmeterol, formoterol and oral bambuterol (a pro-drug of terbutaline) (Table III).

INHALED CORTICOSTEROIDS (ICS)

The advent of ICS has revolutionized the treatment of asthma in its entirety and is now regarded as the cornerstone of treatment for asthma.

They are highly lipophilic and rapidly enter cells of the airways, improving lung function, and reducing symptoms and exacerbations. These combined attributes of high topical potency and low systemic bioavailability confer a high benefit:risk ratio. This is notwithstanding the fact that about 80 to 90 per cent of a dose from a metered dose inhaler is swallowed[25,26], and are metabolised by first-pass metabolism in the liver.

Beclomethasone dipropionate (BDP), budesonide (BUD) and fluticasone (FP) are the mainstay of prophylactic therapy and also being used as preventer drugs to achieve the overall treatment objectives. Beclomethasone and budesonide are of equal potency but fluticasone is twice as potent as the two hence half the dose of fluticasone gives the same therapeutic benefit[27].

Low-dose corticosteroids confer lots of benefits to the patient with little side effects, whereas unwanted effects becomes manifest with high doses. Table IV shows the different ICS preparations and inhaler devices available.

Table I. Steps on the Management of Asthma (Bts)

STEP	TREATMENT
STEP 1: Mild intermittent asthma	Inhaled short acting β2-agonists as required.
STEP 2: Regular preventer therapy	Add inhaled steroids 200-800mcg/day*. - 400mcg is an appropriate starting dose for many patients. - start at dose of inhaled steroid appropriate To severity of disease.
STEP 3: Add-on therapy	1. Add inhaled long acting β2-agonist (LABA) 2. Assess control of asthma: - good response to LABA- continue LABA. - benefit from LABA but still inadequate- continue LABA and increase inhaled steroid dose to 800mcg/day*(if not already on this dose). - no response to LABA- stop LABA and increase inhaled steroid to 800mcg/day* If control still inadequate, institute trial of other therapies eg leukotriene receptor Antagonist or SR theophylline.
STEP 4: Persistent poor control	Consider trials of: - increasing inhale corticosteroids up to 2000mcg/day*. - addition of a forth drug eg leukotriene receptor antagonist, SR theophylline, β2-agonist tablet.
STEP 5: Continuous or frequent use of oral Steroids	Use daily steroid tablet in lowest dose providing adequate control. Maintain high dose inhaled steroid at 800mcg/day*. Consider other treatments to minimise the use of steroids tablets. Refer patient for specialist care.

*BDP or its equivalent
(BRITISH THORACIC SOCIETY, APRIL 2004-Internet source).

Table II. Definition of asthma symptom severity (NHLBI)

	Symptoms	Night-time symptoms	PEF
Severe persistent	Continuous: limited physical activity	Frequent	?60% predicted variability > 30%
Moderate persistent	Daily: use ?2-agonist daily Attacks affect activity	>1 time a week	>60% to <80% predicted variability >30%
Mild persistent	?1 time a week but <1 time a day	>2 times a month	?80% predicted variability:20-30%
Mild intermittent	<1 time a week asymptomatic and normal PEF between attacks	? 2 time a month	?80% predicted variability <20%

(NHLBI, 1997)

Table III. preparations of long-acting beta agonists

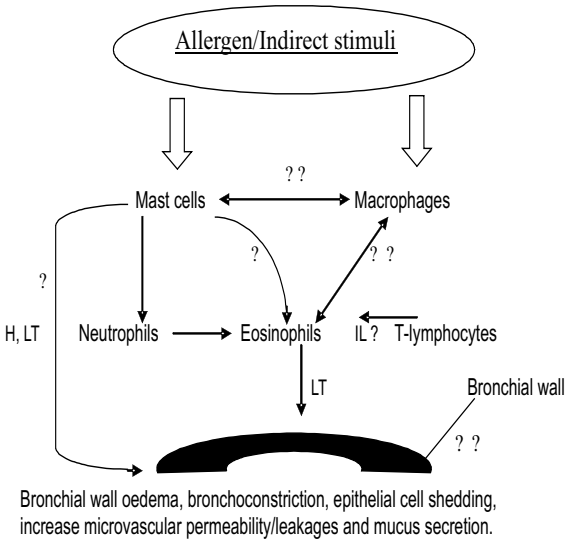
Drug	Brand name	Inhalers	
		Breath actuated inhaler (BAI)	Metered dose inhaler (MDI)
Bambuterol	Bambec® (oral tablet)	-	-
Formoterol	Foradil®	Inhaler & caps*	-
	Oxis®	Turbohaler†	-
Salmeterol	Serevent®	Accuhaler†	-
		Diskshaler & disks*	Mdi and Volumatic

† bai with integral drug
* bai device and drug
(modified from mims april 2004)

Table IV. Preparations of Inhaled Corticosteroids

DRUG	BRAND NAME	INHALERS	
		Breath actuated inhaler (BAI)	Metered Dose Inhaler (MDI)
? Beclomethasone	•Aerobec®	Autohaler†	
	•Asmabec®	Asmabec clickhaler†	
	•Beclazone®	Easi-breathe†	MDI
	•Becloforte®		MDI
	•Becodisks®	Diskhaler & becodisk*	
	•Becotide®		MDI
	•Filair®		MDI
	•Qvar®	Autohaler†	MDI
	•Pulvin al-Beclomethasone®	Pulvinal†	
? Budesonide	•Pulmicort®	Turbohaler†	MDI
? Fluticasone	•Flixotide®	Accuhaler†	MDI
		Diskhaler & disks*	&EVOHALER
? Mometasone	•Asmanex®	Twisthaler†	

† Bai with integral drug
* Bai device and drug
(MIMS, APRIL 2004)



LT= leukotrienes
H = histamine
IL = interleukins,
? ? = sites of action of steroids (?) and β2-agonists (?).

Fig. 1. Schematic representation of interaction of inflammatory cells, chemical mediators and reflex neural mechanisms in asthma including sites of action of steroids and β2-agonists.

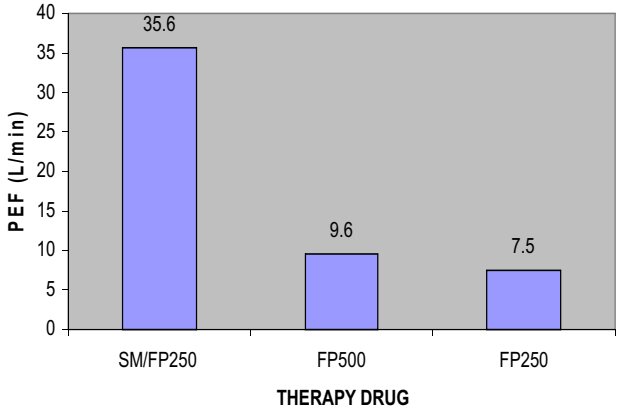


Fig. 2. Showing change in morning PEF at the end of one-week treatment with SM50/FP250, FP500 and Fp250

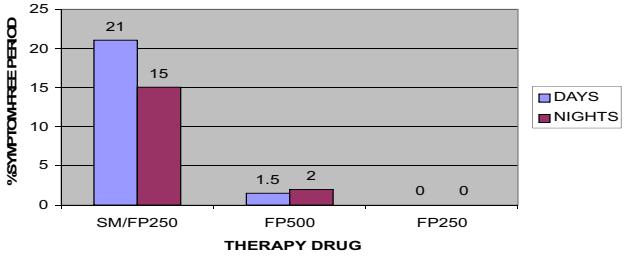


Fig. 3. Showing the baseline percentage of patients who did not experience day- or night-time symptoms over 6-month treatment period

RESULTS

The first report on the benefits of adding SM to BDP therapy was from a study conducted by Greening AP *et al* [28]. This team conducted a 6-month randomised, double-blind, parallel study involving 426 symptomatic asthmatics despite being on low-dose BDP (200mcg) bid and divided them into two groups. One group (206 patients) was on high-dose BDP (500mcg) alone but the other group (220 patients) had SM (50mcg) added to the BUD (200mcg). All groups were on twice-daily regimen of their respective medications. The outcome showed that adding SM (50mcg) to BDP (200mcg) was more effective than the high-dose of BDP alone. This was evidenced by increase in both mean morning and evening PEF in those receiving SM/BDP concurrently than those on increased dose of BDP. There wasn't any significant difference noted in terms of side effects or asthma exacerbation further supporting that use of LABA is not associated with increase risk of exacerbation.

Subsequent other studies, including meta-analysis of salmeterol, confirmed the advantages of adding salmeterol to ICS. Although some of these studies overlooked the importance of constant dose control arm, still the benefit of adding salmeterol to ICS greatly outweighed doubling the dose of ICS.

The first study that underscored the importance of using a constant dose control arm to gain additional understanding of SM/FP combination was conducted by Ind PW[29] *et al*. The superiority of SM50/FP250 over FP250 or FP500 was established from this study. The study, which involved 496 asthma subjects, was conducted over a 6-month period of treatment in a multi-centre, randomised, double-blind, parallel group in 100 hospitals across Europe and North America. The result of the study, presented in figure 2, showed a mean increase in early morning PEF within the first one week of the study with SM50/FP250 (35.6L/min), compared to FP500 (9.6L/min) and FP250 alone (7.5L/min). This further showed that those receiving SM50/FP250 showed significant reduction in diurnal variation, symptom-free days and nights, and significantly lower exacerbations.

Figure 3 represents the end of the 6-month study period with a median change from base line in percentage of symptom-free days as 21%, 1.5%, and 0% with SM50/FP250, FP500 and FP250, respectively (both p=0.002) while symptom-free nights were 15%, 2%, and 0%, respectively, (both p 0.002).

CONCLUSION

Both clinical and scientific rationale for the use of

ICS and LABA is well founded and compelling. No other single therapy or combination of other therapies has been shown to provide equal asthma control or to equally prevent the sequelae of uncontrolled asthma, including exacerbations and hospitalizations.

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