EDITORIAL

INHALED β_2-ADRENERGIC AGONISTS IN ASTHMA : THE EVOLVING DILEMMA

K P Hui

ABSTRACT

Inhaled β_2-adrenergic agonists have been used in the treatment of asthma since the 1970's. They are extremely effective bronchodilators in all situations of bronchoconstriction, and are generally well tolerated by patients. The recent advent of long-acting β_2-adrenergic agonists will extend the clinical applications of this group of drugs. On the other hand, doubts have recently emerged on the safety of inhaled β_2-adrenergic agonists. Recent well controlled studies also examined the manners whereby inhaled β_2-adrenergic agonists are used in asthmatics, and the long term effects on lung functions. Although at least two decades have passed since the introduction of inhaled β_2-adrenergic agonists, strategies on their optimum use have only emerged from these recent findings. This review briefly discusses as the most important developments leading to the rationalisation of the way inhaled β_2-adrenergic agonists should be used in clinical asthma.

Keywords: asthma, β_2-adrenergic agonists

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INTRODUCTION

β_2-adrenergic agonists are potent relaxants of airway smooth muscles, capable of relieving bronchoconstriction rapidly when administered via the inhalation route. They quickly became established as standard drugs in the management of asthma because they provided prompt and effective symptomatic relief, and good tolerability by patients. Today, there appears to be a trend towards over reliance on and complacency about the use of inhaled β_2-adrenergic agonists. In the face of increasing sales of β_2-adrenergic agonists in many countries, disconcerting evidence is emerging about their unwanted side effects, in particular when epidemiological studies have suggested links with asthmatic deaths and near deaths. On the other hand, intense research efforts by the pharmaceutical industry have led to the development of long-acting inhaled β_2-adrenergic agonists, proclaimed as important new therapeutic advances in the treatment of asthma. This review discusses the emerging conflicting developments about the use of inhaled β_2-adrenergic agonists in asthma.

The new generation of β_2-adrenergic agonists

The first sympathomimetic drugs in the treatment of asthma were adrenal extracts used as early as 1900. Isoprenaline, a non-selective β-adrenergic agonist, was introduced in the 1940's, and the first selective β_2-adrenergic agonists - salbutamol - appeared in 1969. The efficacy of inhaled β_2-adrenergic agonists astonished both physicians and patients, and quickly became standard bronchodilator drugs used in all situations of bronchoconstriction in asthmatic patients. Many β_2-adrenergic agonists are now available, including terbutaline, fenoterol, metaproterenol, pirbuterol, rimiterol and reproterol, but none was shown to have any clear advantage over salbutamol. The duration of action of these β_2-adrenergic agonists is about four to six hours.

More recently, inhaled β_2-adrenergic agonists with much longer duration of bronchodilatation have been developed. Significant bronchodilatation remained for at least 12 hours after single doses of inhaled salmeterol[1] and formoterol[2]. Protection against nocturnal asthma throughout the night was achieved by single doses of inhaled salmeterol[3] and formoterol[4] before bedtime. Several large studies have shown that twice daily dosage regime of both drugs was at least as effective as the four times daily regime of the shorter-acting β_2-adrenergic agonists in the treatment of asthma[5-7]. Prolonged protection against exercise-induced asthma is also possible. Single doses of inhaled salmeterol and formoterol were able to protect against exercise-induced asthma in adults for at least 8 hours[8,9]. These long-acting β_2-adrenergic agonists were generally well tolerated. Short term studies have shown that the expected side effects of tremor, tachycardia, and headaches were no more frequent than the shorter acting β_2-adrenergic agonists. Post-market surveillance of patients treated with regularly inhaled salmeterol for one year has not revealed increased exacerbations of asthma compared to patients treated with inhaled salbutamol[10,11]. Longer term safety data are not yet available.

The unwanted effects of β_2-adrenergic agonists during an asthmatic attack

In the late 1960's, an increase in asthmatic deaths was noted in the United Kingdom. This was thought to be related to the overuse of isoprenaline which has significant cardiovascular side effects because of its non-selective β-adrenergic activity[12]. With the introduction of the selective β_2-adrenergic agonists, in particular salbutamol, no increase in asthmatic deaths was noted in the 1970's in the United Kingdom. However, in the early 1980's, an increase in asthmatic deaths was noticed in New Zealand, and was postulated to be related to the use of inhaled fenoterol[13]. A more recent study from Saskatchewan linked asthma deaths and near deaths to the use of the β_2-adrenergic agonists in general[14]. Although the results and implications of all these epidemiological studies are still debated, renewed interest was focused on whether inhaled β_2-adrenergic agonists are safe in the therapeutic doses commonly used in the treatment of asthma.

Clearly, the systemic effects of β_2-adrenergic agonists are less with the inhaled route compared to the oral routes. Concerns emerged recently over the systemic effects of clinically relevant doses of inhaled β_2-adrenergic agonists. A recent prospective, placebo controlled study comparing three commonly used β_2-adrenergic agonists showed that the increase in heart rate and fall

Department of Medicine
National University Hospital
Lower Kent Ridge Road
Singapore 0511

K P Hui, MRCPI, FAMS, MD
Consultant Physician

in serum potassium were larger with fenoterol than both salbutamol and terbutaline[15]. Another study showed that these cardiovascular side-effects induced by inhaled fenoterol were more pronounced during hypoxaemia[16]. This study further showed that the effects of inhaled fenoterol and hypoxaemia on the increase in heart rate and prolongation of electrographic QTc interval were additive. Induced hypokalaemia and ECG changes were not drug specific, but seemed to be class specific, as similar changes had been demonstrated for both salbutamol[17] and terbutaline[18]. The latter study showed that these effects were more pronounced in females than males. During an asthmatic attack, asthmatic patients are known to self-administer excessive doses of inhaled β_2-adrenergic agonists, thus increasing the magnitude of cardiovascular side effects because of a direct dose-effect relationship[19]. Additional factors encountered commonly in an asthmatic attack would enhance the direct cardiovascular effects of inhaled β_2-adrenergic agonists. These factors include elevated endogenous levels of catecholamines released by stress and the use of other drugs known to cause hypokalaemia (the xanthines and corticosteroids) and tachyarrhythmia (xanthines). Therefore, during an asthmatic attack, the cumulative risk of ventricular tachyarrhythmia can be considerable.

Another area of concern is whether the acute effects of the β_2-adrenergic agonists on the airways would remain unchanged with prolonged use – the tachyphylaxis effect. Several studies have shown that the magnitude of bronchodilatation did not wane with long term use of inhaled β_2-adrenergic agonists at conventional doses. More recently, the ability of inhaled β_2-adrenergic agonists to protect against bronchoconstrictor stimuli has been scrutinised. It is well known that pre-treatment with inhaled β_2-adrenergic agonists offers protection against bronchoconstriction induced by various stimuli. However, exposure to increasing doses of bronchoconstrictor stimuli would eventually lead to breakthrough bronchoconstriction despite the protection afforded by the β_2-adrenergic agonists[20]. When the nature of breakthrough bronchconstriction was studied, it was found that the slope of the FEV_1-dose response curve was steeper and the maximum fall in FEV_1 was similar. These results imply that even in the presence of β_2-adrenergic agonists, breakthrough bronchoconstriction was no less severe, and the rate of development of bronchoconstriction may be faster. Recent studies have also shown that the protection against bronchoconstrictor stimuli is reduced after regular use. The protection offered by inhaled terbutaline against bronchoconstriction induced by inhaled adenosine monophosphate was halved after seven days of treatment[21]. Similarly, the protection afforded by inhaled salmeterol against methacholine induced bronchoconstriction reduced from a 10-fold shift in dose response curve to a 2-fold shift after 8 weeks of treatment[22]. In both these studies, the acute bronchodilatation after inhalation of β_2-adrenergic agonists was unchanged. In other words, with prolonged use of inhaled β_2-adrenergic agonists, although the bronchodilatation effect may remain unchanged, there is less effective protection against provoked bronchoconstriction.

Therefore, short-comings of inhaled β_2-adrenergic agonists have been revealed by carefully controlled studies. Significant acute cardiovascular effects can be directly induced by the doses of inhaled β_2-adrenergic agonists used clinically. Long term use of inhaled β_2-adrenergic agonists can lead to reduced efficacy in the protection against induced bronchoconstriction. Exposure to larger doses of bronchoconstrictor stimuli would overcome the protection. These episodes of breakthrough bronchoconstriction are just as severe, and have a more rapid development. In an acute asthmatic attack, the cardiovascular effects of β_2-adrenergic agonists would be greater because of the higher doses used, which can be accentuated by rapidly developing hypoxaemia. Other commonly encountered factors such as stress and the use of other hypokalaemia-inducing drugs further enhance the risk of tachyarrhythmia. These confounding effects may explain, at least in part, the increases in mortality that are linked to the use of inhaled β_2-adrenergic agonists in epidemiological studies.

Long term use of β_2-adrenergic agonists

All but the mildest asthmatics need inhaled β_2-adrenergic agonists for relief of bronchoconstriction on a long term basis. Early recommendations were to use inhaled β_2-adrenergic agonists regularly in order to reduce the frequency of exacerbations and normalise lung functions[23,24]. It is undisputed that in patients with moderate to severe asthma, where inhaled β_2-adrenergic agonists were inadequate in controlling asthma, addition of inhaled corticosteroids offered great benefits[25]. Now, it is also clear that the use of inhaled β_2-adrenergic agonists alone is unable to prevent declines in lung functions in both children and adults who have mild asthma. A large, long-term study over two years in adult patients with newly diagnosed mild asthma compared treatment by inhaled terbutaline with (50 patients) or without (35 patients) inhaled budesonide. The results showed that in the group treated with inhaled terbutaline and budesonide, all assessments were better: lung functions tests, asthma symptom scores, bronchodilator use and airway hyperresponsiveness. Furthermore, patients treated with inhaled terbutaline alone as a group had a decline in FEV_1 (mean of -200 ml per year) that was about three times the rate in the group of patients treated with inhaled corticosteroid as well[26]. Similar findings in children with asthma were shown in a large randomised double-blind Dutch study over 22 months. Asthmatic children who were treated with inhaled salbutamol regularly (58 children) had reduction in lung function compared to those who were also treated with inhaled corticosteroids (58 children)[27]. Other benefits in children treated with inhaled steroids were fewer dropouts, and less bronchial hyperresponsiveness.

The manner of using inhaled β_2-adrenergic agonists is also under scrutiny. The relative benefits between on-demand use of symptom relief versus regular-interval use were examined in two recent carefully controlled studies involving a large number of patients treated over a long period of time. In a placebo controlled, double blind cross-over study, overall control of asthma was better in the majority of patients (40 out of 64) who took inhaled fenoterol on-demand for symptoms rather than on a regular-interval basis (four times daily)[28]. The disadvantage of regular fenoterol treatment was evident even in patients who were taking inhaled corticosteroids as well. A large prospective study in patients with asthma and chronic bronchitis receiving bronchodilator monotherapy (inhaled sabutamol or ipratropium bromide) over two years compared continuous regular (four times daily) treatment with on-demand treatment[29]. The decline in FEV_1 in the 113 patients who were on regular continuous treatment was three to four times that of the 110 patients who received on-demand treatment (–0.072 versus –0.02 L/year respectively).

These adverse effects of the inhaled β_2-adrenergic agonists are not unexpected on the basis of the chronic inflammatory nature of asthma. Inhaled β_2-adrenergic agonists relieve symptoms effectively, and so may mask the underlying airway inflammation. This scenario is particularly relevant to patients with symptomatically mild asthma. Endobronchial biopsies in these patients have shown persistent airway inflammation[30,31]. Yet it is this group of patients who mainly rely on inhaled β_2-adrenergic agonists as monotherapy, and therefore leave the inflamed airways untreated.

CONCLUSION

After decades of use, guidelines on the optimal use of β_2-adrenergic agonists are now emerging. The rationale for these guidelines is based on results derived from carefully controlled studies. With the exception of the mildest cases of asthma, inhaled β_2-adrenergic agonists should not be used as monotherapy. In addition inhaled corticosteroids should be used to suppress airway inflammation and prevent decline in lung functions. Long term inhaled β_2-adrenergic agonists should be used on a on-demand basis rather than as regular-interval daily therapy. Both physicians and patients should be aware that even while using β_2-adrenergic agonists regularly, severe breakthrough bronchoconstrictions can develop rapidly. Furthermore, the cumulative risk of cardiovascular side effects during such an asthmatic attack is under-estimated. The newly introduced long-acting β_2-adrenergic agonists have extended the spectrum of clinical applications of this group of drug. It is important that the enthusiasm to embrace the use of these long-acting β_2-adrenergic agonists should not obscure potential unwanted side effects, particularly in view of the lessons learnt from the short acting β_2-adrenergic agonists. However, the β_2-adrenergic agonists remain the most potent and effective bronchodilators known at present despite the drawbacks outlined above. No doubt, the optimum use of inhaled β_2-adrenergic agonists continues to evolve with new knowledge.

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