What Are the Clinical Implications of β 2-adrenoreceptor Polymorphisms for the Treatment of Asthma?

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Adrenoreceptor agonists have long been the agents of choice for relieving acute symptoms of asthma since the first report of epinephrine use for acute asthma in 1900. Considerable pharmacologic research has subsequently gone into the development of variations of these receptor agonists. The extraction of ephedrine from the ancient Chinese herb Ma Huang provided an oral alternative to epinephrine.¹ The progressive alteration of the molecule to isoproterenol (isoprenaline), isoetharine, albuterol (salbutamol), metaproterenol (orciprenaline), terbutaline, bitolterol, and pirbuterol eventually permitted more specific targeting of the β 2-adrenoreceptor and also longer duration of action than epinephrine. More recently, even longer acting β 2-adrenoreceptor agonists, salmeterol and formoterol, have been introduced, not for acute intervention but as maintenance therapy for chronic asthma.

The manuscript by Binaei and colleagues² in the issue of the Journal elegantly describes the current growing literature that relates polymorphisms in the β 2-adrenoreceptor to both asthma severity and variability in the response to these pharmacological agents that have played such a major role in treating asthma over the years. Are we entering a brave new world where pharmacologic agents are chosen following pharmacogenetic analysis of the individual patient? Per-

haps someday, but certainly not yet. Rather, we must consider the implications of this new knowledge for clinical care on a more empirical basis.

Population studies identify increased risk from continuous scheduled use of β 2-receptor agonists but don't identify those individuals most at risk.^{3,4} The studies of β 2-adrenoreceptor polymorphisms reviewed by Binaei et. al.² suggest that it is a sub-population who may be most at risk because of down-regulation of the β 2-adrenoreceptor when there is repeated use of β 2-adrenoreceptor agonists. Despite the common practice of prescribing regularly scheduled use of shorter-acting β 2-adrenoreceptor agonists such as albuterol, there is no therapeutic rationale for such continuous use. These agents are primarily indicated for as-needed use to relieve acute symptoms. The current standard of care further mandates that frequent use of a bronchodilator for relief of acute symptoms indicates the need for anti-inflammatory therapy. A short course of an oral corticosteroid is the agent of choice for an acute exacerbation associated with subresponsiveness to a β 2-agonist, and an inhaled corticosteroid is the agent of choice for persistent symptoms of asthma.⁵ While the inhaled corticosteroids alone are often sufficient to control the daily symptoms of chronic asthma, not all patients are adequately controlled on conventional low doses, and higher doses are associated with progressive risk of small but measurable systemic effects that can include growth suppression in addition to suppression of the hypothalamic-pituitary axis in children.⁶

Data have demonstrated that the addition of

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Table. Exercise-induced bronchospasm with 2 or 4 inhalations of pirbuterol from a Maxair Autohaler

Maintenance Medication	Pre-exercise Medication*	Pre-exercise FEV1 (predicted 3.45 L)	% Decrease in FEV1
Salmeterol† 50 μ g b.i.d.‡	2 inhalations	3.26	55%
	4 inhalations	3.45	42%
SR theophylline§ 225 mg b.i.d.‡	4 inhalations	3.6	1%
SR theophylline§ 300 mg b.i.d.‡	4 inhalations	3.56	1%

* Pirbuterol (Maxair Autohaler)

† Serevent MDI

‡ plus 200 μ g Budesonide (Pulmicort Turbuhaler)

§ Theodur

a long-acting β 2-agonist to an inhaled steroid permits greater effectiveness than even substantially increased doses of the inhaled steroid.^{7,8} A similar degree of additive effect has been demonstrated for theophylline,⁹ which has the disadvantage of requiring therapeutic drug monitoring. Some additive effect has also been described for montelukast, a leukotriene antagonist,¹⁰ but the magnitude of benefit appears to be less than for the long-acting β 2-agonists and theophylline. Although the clinical trials of adding a long-acting β 2-agonist demonstrated no adverse effects, the question raised by the studies of β 2-adrenoreceptor polymorphisms suggest that some individuals with asthma may not benefit from the addition of a long-acting β 2-agonist to an inhaled corticosteroid, and some may even have detrimental effects from such an addition.

We have seen at least an occasional patient where such a detrimental effect appears to occur. One was particularly dramatic in the loss of bronchoprotective effect from pirbuterol (a therapeutic equivalent of albuterol) while receiving salmeterol, 50 μ g twice daily, in addition to budesonide 200 μ g twice daily in the controlled environment of an in-patient extended care facility. Four treadmill exercise studies were performed on this 15-year-old boy with severe chronic asthma who had not been manageable on an outpatient basis. The first 2 studies, performed two days apart, showed profound exercise-induced bronchospasm that was not blocked with either 2 or 4 inhalations of pirbuterol from a Maxair Autohaler (Table). Whereas a β 2-adrenoreceptor agonist such as pirbuterol would normally completely block exercise-induced bronchospasm for someone starting with normal pulmonary function, there was

no effective blocking in this patient while he was receiving salmeterol despite otherwise good control of his asthma. After stopping the salmeterol and substituting theophylline while continuing the same dose of inhaled steroid, complete blocking of exercise-induced bronchospasm was now attained with pirbuterol on 2 subsequent exercise studies. The dramatic improvement in the ability of pirbuterol to block exercise induced bronchospasm in this patient is consistent with reports that salmeterol can decrease the bronchoprotective effect of the usual β 2-agonist effect,^{11,12} including blocking exercise-induced bronchospasm.¹³ While we did not have a genetic analysis of this patient's β 2-adrenoreceptors, this clinical vignette illustrates what may happen in an occasional patient treated with a long-acting β 2-agonist as maintenance medication for chronic asthma, even when an inhaled corticosteroid is also being used.¹⁴

A potential for added concern regarding long-acting β 2-adrenergic agents has been recently raised by release of information regarding a Phase 4 study conducted by GlaxoSmithKline involving 26,000 subjects in a 28-week trial who received the standard dose of salmeterol or placebo. A small statistically non-significant increase in serious events including fatalities was observed in the population as a whole with those reaching statistical significance in the African-American population.^{15,16} This is consistent with a previous report from the U.K.¹⁷ In both of these studies, the drug was not consistently used with an inhaled corticosteroid, which is considered the standard of care, and the serious events may have simply been inadequately treated, worsening asthma perhaps compounded by misuse of the salmeterol MDI and using it

repeatedly for acute bronchodilatation in a manner previously associated with fatalities with other β 2-adrenoreceptor agonists.¹⁸ While the general conclusion has been that it was the worsening asthma that resulted in deaths, it is interesting to speculate that perhaps it is those with specific polymorphisms of the β 2-adrenoreceptor that are at the greatest risk from such inappropriate use.

Further work regarding identification of those at special risk or for whom long-acting β 2-adrenergic agents present either risk or decreased benefit may eventually provide clinical guidance. Meanwhile, clinicians need to be alert to the potential for some patients to respond differently and perhaps adversely to agents that generally appear useful based on controlled clinical trials. Despite this caveat, I agree with the statement in the recent FDA talk paper, "Based on available data, the benefits of Serevent (salmeterol) for the asthma population continue to outweigh the risks FDA further emphasizes that all asthma drugs, including Serevent, should be given as a part of a comprehensive treatment plan that takes into account the patient's asthma severity and fully educates the patient in the disease and its proper treatment."

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