Thorax

Editorials

Long acting β_2 agonists and the risk of life threatening asthma

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Salmeterol was introduced on the market in the UK in 1990 and subsequently elsewhere amid controversy surrounding the safety of short acting β_2 agents. This controversy led to caution on the part of physicians, except maybe in the USA, and a wide adoption of long acting β_2 agonists was, at the least, delayed; impressions left by the controversy probably still limit the sale of this agent. US physicians became wary following the report of deaths among patients who misused salmeterol for acute relief after the drug was marketed as first line therapy for asthma.[1]

Concern regarding long acting β_2 agonists relates to a possible increase in the risk of life threatening attacks and, potentially related to such an increase, the possibility that β_2 agonists in general may cause an increase in the severity of asthma over time when used regularly. A post-marketing or phase IV clinical trial of salmeterol compared with salbutamol four times daily did little to allay concerns regarding an increase in the risk of life threatening asthma by providing a best estimate of a threefold increase in the risk of death in the salmeterol group[2]; while not statistically significant, this effect is, if accurate, clinically important. Thankfully, near fatal and fatal attacks of asthma remain rare events and are therefore not amenable to study in randomised clinical trials nor with all but the largest cohort studies. The most efficient design for the study of such rare events is the case-control study. Williams and colleagues in the current issue of *Thorax*[3] report on a case-control study of the relationship between asthma therapy, principally salmeterol, and near fatal asthma. They found that subjects admitted to an intensive care unit (ICU) during an acute attack of asthma were more than twice as likely (odds ratio 2.32) to have been prescribed salmeterol than patients admitted to hospital, but not to the ICU. Use of medications prior to the acute attack was determined by close examination of clinical information available at presentation of the patients (both cases and controls) to one of 14 district hospitals. After restricting the comparison to the more severe group of patients who had been admitted to hospital in the previous 12 months, the association was lessened (odds ratio 1.42) and was no longer statistically significant. The authors conclude that a true causal link between salmeterol use and life threatening asthma is unlikely and that any apparent association is probably due to confounding by indication – that is, patients with severe asthma are more likely both to have a near fatal attack and to be prescribed salmeterol by their physician.

In support of this interpretation of their findings, the authors provide evidence to suggest that, in the population they studied, salmeterol was preferentially prescribed to patients with more severe disease. Such targeted use has been proposed by the BTS and other guidelines[4 5] and has been confirmed to occur in a general practice setting in the UK.[6] Such channelling of prescriptions has also been clearly shown to have occurred for the short acting β_2 agent fenoterol and remains the most likely explanation for the link between this medication and life threatening asthma described in New Zealand and in Saskatchewan.[7 8] Similarly, the relationship between excessive and increasing use of short acting β_2 agents as a class and the occurrence of life threatening asthma is best explained by the increasing need for immediate relief among patients experiencing progressive loss of control of their disease.[9 10] The attempt by Williams and colleagues to dissociate such confounding by severity as an explanation for the link between salmeterol and life threatening asthma from that suggested as the probable explanation for the link between fenoterol and life threatening asthma is not convincing.

A second concern is that regular or sustained use of β_2 agonists may cause worsening of asthma severity over time as first suggested by Sears *et al.*[11] Certainly there is now ample evidence that sustained use of β_2 agents is associated with loss of bronchoprotection to non-specific broncho-constrictors such as methacholine and adenosine and, of potentially greater clinical importance, may result in a greater inflammatory response of the airways to allergens.[12] Such tolerance is not avoided by the concomitant use of inhaled corticosteroids.[13] By contrast, there is good evidence that use of long acting β_2 agonists for periods of at least six months results in excellent and continued control of asthma symptoms and that the beneficial effect on lung function is maintained.[14] Furthermore, several studies have now shown that, among patients whose asthma is under-treated, both formoterol and salmeterol provide long term control of symptoms and lung function (FEV_1 or PEF) across a wide range of doses of inhaled corticosteroids and the benefit obtained is approximately equivalent to doubling the dose of inhaled corticosteroids.[15–17] Salmeterol also allows a reduction in the daily dose of inhaled cortico-steroids in patients with stable asthma.[18] Preliminary evidence suggests, however, that this may be at the cost of an increase in inflammation of the airways.[12 19] The potential long term implications of such inflammation and the airway remodelling which may result is unknown.

Of potential concern when prescribing a long acting β_2 agonist is a decrease in response to short acting agents if asthma worsens acutely. While decreased sensitivity to salbutamol with the use of salmeterol can be demonstrated,[20] at least in stable patients, no lessening in the combined degree of brochodilatation nor a decrease in the response to a short acting agent is seen after stopping salmeterol.[18 21] There are no studies available among patients with acute severe attacks, however, and such

studies would probably be difficult to interpret if carried out. Patients receiving a long acting β_2 agonist require a clear plan of action as to steps to undertake when control of their asthma deteriorates.

What is the role of long acting β_2 agonists in the treatment of asthma? They should not be first-line agents; this is also the case for formoterol which, in contrast to salmeterol, has a rapid onset of action. Short acting β_2 agents are very effective and inexpensive in the role of rapid reliever of bronchospasm. Long acting β_2 agonists have no significant anti-inflammatory effect and are therefore not indicated without concomitant inhaled corticosteroids. They will therefore be prescribed as an additional medication to rescue β_2 agonists and inhaled corticosteroids.[5] This limits their use to patients with asthma of at least moderate severity. This is a group among whom inhaled cortico-steroids continue to be underprescribed[22] with resultant excess morbidity that is likely to be far more important than even a worse case scenario for the purported adverse effects of long acting β_2 agonists. The dose of inhaled corticosteroids at which additional treatment with long acting β_2 agonists is prescribed is likely to be of limited importance given the protective effect of inhaled cortico-steroids against major adverse outcomes, especially since this protection is conferred even at low doses.[23 24] The cost of adding a third medication, the possible effect on adherence to therapy, and the supplemental educational intervention likely to be required will all have to be taken into account when deciding upon the addition of a long acting β_2 agonist to a patient's treatment regimen. The study by Williams in this issue of *Thorax*, as well as the report of the British cohort by Meir and Jick,[4] suggests that long acting β_2 agonists are at least as safe as theo-phylline when used as an additional agent and should be used preferentially to theophylline given the latter agent's weaker bronchodilator potency and its association with substantial morbidity.[25] The two currently available long acting β_2 agonists, salmeterol and formoterol, appear com-parable in safety and efficacy[26]; the choice between the two agents will be based principally on patient and physician preference for a specific delivery device.

In summary, increasing experience with long acting β_2 agonists has confirmed their impressive capacity to control asthma symptoms and improve lung function. Their ad-verse effect profile appears to be acceptable in patients adhering to regular treatment with inhaled corticosteroids and is better than alternative agents such as theophylline. Long acting β_2 agonists are currently the best available additional therapy for patients who remain symptomatic on "optimal" doses of inhaled corticosteroids or in whom the patient or physician wishes to maintain control of asthma on a lower dose of inhaled corticosteroid.

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