

Efficacy and safety of anti-asthma treatment

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There is growing evidence that asthma is a common condition and often under-treated. Up to a quarter of children in the UK will have suffered episodes of wheezing by the time they reach adult life and probably about 5% of the population at any one time is diagnosed as asthma. This high level of cumulative and point prevalence is mirrored by an increasing general practice consultation rate and a rising level of hospital admissions. This may reflect a growth in prevalence but probably also is the result of an increased awareness by the public and medical profession that asthma is inadequately treated and often under-diagnosed being frequently confused with bronchitis. Rising sales of anti-asthma therapy probably reflect more the better diagnosis of asthma than a rise in prevalence but surveys also continue to demonstrate over dependence on bronchodilators and under treatment with anti-inflammatory drugs (9).

The increase in asthma prescriptions has not reduced asthma mortality and this remains a paradox that awaits explanation. Although some asthma treatment may occasionally put life at risk such as theophylline toxicity, surveys of asthma fatalities uniformly reveal under-therapy rather than excessive treatment as the cause of death. It still remains a reasonable proposition that better control of symptoms by reducing morbidity will reduce mortality once sufficient treatment is given to all those that require it and in sufficient doses adequately to suppress symptoms. We are a far away from achieving this ambition and until we do it is impossible to make a final

judgement as the relationship between treatment and asthma mortality.

Pathogenesis

It is unlikely that asthma is a homogenous condition but it is usually treated as such and most accounts of pathogenesis are based upon allergic asthma. In this model a specific allergen triggers the release of mediators from primed inflammatory cells either within the lumen, epithelium or submucosa of the airway and these mediators in turn recruit other inflammatory cells and further mediators may be released to excite inflammation, and increase in bronchial hyperresponsiveness and bronchoconstriction.

Thus bronchoconstriction comes at the end of the process of pathogenesis whereas treatment usually starts with bronchodilators. The exact sequence of events before bronchoconstriction is poorly understood and the mechanisms involved may not be the same for all types of asthma particularly in the absence of a specific allergen causing it (6).

An increase in bronchial hyperresponsiveness to non-specific stimuli frequently accompanies asthma, but its relation to the underlying pathogenetic mechanism remains less than clear. Recent evidence suggests that it parallels the asthma morbidity and is not its cause. It is important to clarify this issue as some therapeutic strategies particularly target hyperresponsiveness for therapeutic control. (4).

In addition to queries about the strategic targets of pathogenesis there is also uncertainty about the anatomical target for effective anti-

asthma medication. Bronchial smooth muscle is usually assumed to be the target but recently the bronchial epithelium has received greater attention and its role in pathogenesis may account for the remarkable effectiveness of inhaled therapy. (1)

Asthma management

These considerations of pathogenesis provide a rational scheme for treatment. In those patients where a specific external cause can be identified allergen avoidance must be considered first. It is clearly better to avoid the cause of asthma than treat it, but unfortunately this is not always possible. For many ubiquitous allergens such as house dust or pollen avoidance remains a difficult task requiring scrupulous attention to detail (3).

Where avoidance of cause is neither possible nor practical, an alternative approach is immunotherapy. Unfortunately, immunotherapy has only a limited role in asthma and its use differs markedly between countries. Attitudes to immunotherapy range from deep scepticism to evangelical enthusiasm which suggests that scientific appraisal is still necessary before reaching a considered view.

Pharmacotherapy

Pharmacotherapy can only palliate symptoms rather than treat the underlying disease and eradicate it. Conventional treatment usually begins with bronchodilators and only employs additional therapy if bronchodilator usage is inadequate and or its effective dosage produces adverse side-effects.

Our increased understanding of pathogenesis now relegates bronchoconstriction as an end effect, leading to an increased use of anti-inflammatory treatment with bronchodilators reserved to treat breakthrough symptoms (5). This reversal of traditional therapy order is keenly debated and hesitation about switching to it largely hinges upon perceptions about the safety of anti-inflammatory treatment and in particular corticosteroids. Thus the cost-benefits and the cost-risks of asthma and its treatment

need to be considered before coming to a judgement about either strategy.

Surveys have confirmed that asthma has a high morbidity based on its prevalence and incidence within the community and patients are also at significant risk of sudden death. By contrast, mortality from asthma treatment is probably very rare. There are occasional deaths from theophylline toxicity. Other asthma medication has not been implicated in asthma mortality other than by statistical inference. Over use of bronchodilator aerosols coincided with asthma fatalities in the 1960's and fears about their use persist but have never been substantiated by detailed surveys into asthma fatalities which usually incriminate under treatment. Over-use of bronchodilator treatment, however, may delay access to care in patients teetering on the brink of fatality; thus bronchodilator treatment may not cause death through toxicological mechanisms but by giving patients a false sense of security. The potential harm of over-reliance on bronchodilators has also been recognised by the increasing use of anti-inflammatory treatment. Recent studies have also suggested that regular beta agonist therapy may increase bronchial responsiveness after treatment stops which may lead to vulnerability (10).

Symptom suppression versus symptomatic relief

The present debate about asthma treatment therefore largely centres on how best to ensure effective inhaled therapy and whether to use anti-inflammatory treatment first or as second-line therapy.

The better use of inhaled therapy involves consideration of delivery systems with increasing use of powder aerosols and expansion chambers both to improve patient compliance and reduce risks of adverse local oropharyngeal side effects.

Symptom relief: Inhaled beta agonists are mainly used to palliate symptoms produced by bronchoconstriction. Modern selective beta agonists by inhalation combine efficacy with safety but their length of action is often insufficient to control overnight symptoms. Under these circum-

stances, conventional strategy would indicate oral medication with slow release formulations of bronchodilator, such as slow release theophylline or aminophylline whose risks of toxicity is much reduced by limiting the dose to night time and by careful monitoring of blood levels. Slow or continuous release preparations of beta agonists may also provide comparable efficacy and further reduce risks of toxicity. The frequency of sleep disturbance has renewed interest in long acting bronchodilator preparations (5).

Symptom Suppression: For patients not responding to bronchodilators suppressive therapy is used. This is sometimes known as anti-allergic or prophylactic therapy but the term suppression has a more general meaning without prejudice to its mode of action and is to be preferred.

Many treatments may suppress asthma and these include bronchodilators such as beta agonists which can modulate mediator release from inflammatory cells but the fact that anti-inflammatory treatment is required to treat symptoms in many patients already taking bronchodilators suggests that their suppressive role is limited.

The most effective anti-inflammatory agents are corticosteroids but fears concerning absorption of inhaled steroids continue despite many years experience with this treatment which has not revealed significant systemic morbidity. The main side effects appear to be confirmed to the oropharynx with dysphonia being the most troublesome. Some systemic absorption may occur even at conventional doses but most clinicians think that this is of minor or trivial clinical importance. Only in children where growth might be affected by systemic absorption does there remain significant concern (8) but even under these circumstances many studies have shown little or no affect on growth (2).

Cromoglycate and nedocromil as well as ketotifen are also commonly used as suppressive agents but for milder asthma. Calcium channel blockers have not proved to be successful in suppressing asthma despite theoretical reasons for their use, and many antagonists are being sought for multitudes of mediators but these are still under investigation and none have yet

clearly shown to provide better prospects than current available therapy. The antagonism of a single mediator, however important it may be, may be insufficient to control the cascade of inflammatory interactions that follow the triggering of an attack of asthma and therefore the role of a more comprehensive anti-inflammatory agent such as a corticosteroid may remain more effective (6, 7). A better understanding of how corticosteroids achieve their effect may enable a better targeting for a non-corticosteroid successor.

In the occasional patient with severe steroid dependent asthma drugs sometimes described as disease modifying agents such as gold or methotrexate have been used but a final verdict is awaited as to their usefulness. No medication appears successfully to modify chronic asthma which usually relapses when treatment stops.

CONCLUSIONS

This brief review of asthma therapy has concentrated on the relationship of pathogenesis and treatment as well as the balance between risks of asthma and its treatment.

By delivering small doses and minimising systemic side effects inhaled therapy should provide the standard route of administration for all asthma therapy and in patients with relatively mild and infrequent attacks symptom relief with inhaled bronchodilators is likely to continue to be the preferred therapeutic option.

In patients whose symptoms are more intrusive or frequent or require more than conventional doses of inhaled bronchodilator suppressive therapy is being introduced more early and more effectively than before. Inhaled steroids appear the most potent but other anti-inflammatory agents are available and further studies are required to compare their relative effectiveness with inhaled steroids both with respect to efficacy and safety especially in the treatment of mild asthma and control of bronchial hyperresponsiveness (4, 7).

Thus earlier use of effective inhaled anti-inflammatory treatment to control the inflammatory process and bronchial hyperresponsiveness is becoming the preferred strategy for asth-

ma treatment and this should be appraised with respect to the safety and effectiveness of more traditional treatment regimens. Whichever turns out to be best should not obscure the fact that many patients with asthma continue to be underdetected and undertreated.

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