For and against

Should steroids be the first line treatment for asthma?

George Strube, Michael Rudolf

Step one of the current British asthma guidelines recommends that inhaled short acting β_2 agonists should be used as required. Some clinicians, including George Strube, a general practitioner from Crawley, believe that this step is unnecessary and that steroids should be introduced earlier. Michael Rudolph, a consultant physician from Ealing Hospital, defends the guidelines.

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FOR Evidence for the inflammatory basis of asthma comes from bronchial biopsies, which show inflammation of the mucosa even in patients with mild intermittent asthma.[1] Mucosal oedema and excess mucus production cause reduction in the lumen and obstruction to airflow. Bronchospasm occurs as the natural "foreign body" response to irritation caused by inflammation, the bronchi become hyperactive and the airflow is further reduced. Persistent inflammation may lead to structural changes in the airways, with reduction in lung function and irreversible airways obstruction.[2]

Steroids and β agonists

Steroids are the most effective anti-inflammatory drugs available. They reduce mucosal oedema and bronchial hyperreactivity thus relieving acute symptoms and preventing structural damage to the lungs. It is therefore best to give them as soon as the diagnosis of asthma has been confirmed.

β Agonists are effective bronchodilators but they have no anti-inflammatory activity and so although they offer temporary clinical improvement the underlying inflammation persists. When their effect wears off there is a return of bronchial hyperreactivity and bronchoconstriction, which may even be increased.[3] If this is countered with further doses of bronchodilator a pattern of dependence can be established with regular use aggravating the asthma it is intended to control. This may even occur in patients already taking steroids, and the dose required for control may need to be increased. Regular use of bronchodilators should therefore be avoided and should be kept in reserve for breakthrough wheezing.

Clinical evidence

Trials comparing the effect of inhaled steroids with β agonists showed that patients taking inhaled corticosteroids had better control of their symptoms and required fewer supplemental drugs. Bronchial hyperreactivity, as measured by tolerance to histamine, was reduced and lung function was preserved.[4–6] Bronchial biopsies showed reduction in inflammatory changes.[7]

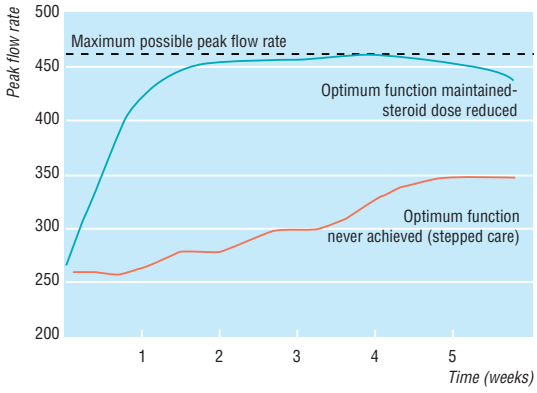
In asthmatic patients regular use of β agonists was less likely to achieve control than regular use of placebo with on demand bronchodilators.[8] Restricting the dose of β agonists in patients taking both β agonists and inhaled steroids improved asthma control, and the dose of inhaled steroids could be reduced.[9] This has also been found in general practice.[10]

This evidence suggests that steroids should be used as early as possible in all asthmatic patients, not only to control symptoms but also to prevent damage to the lungs from the effects of chronic inflammation. The use of β agonist bronchodilators should be kept to a minimum and reserved for emergencies.

The present treatment of asthma

The present treatment of asthma is based on guidelines from the British Thoracic Society,[11] which advise starting patients with "mild" asthma on β agonists alone (step 1), with steroids given only if there is poor control and too much bronchodilator is being used (step 2). β Agonists are therefore widely regarded as the treatment for asthma, with steroids as an optional extra. The evidence shows that the reverse is true but it is difficult to convince patients (and some doctors) of this in the face of the current guidelines, which support the use of β agonists as the drug of first choice. Thus many patients who should be taking inhaled corticosteroids are receiving β agonists only.[12] Even when steroids are given the dose is often insufficient to abolish symptoms due to bronchial hyperreactivity, and most patients are taking more β agonists than is realised.[13]

Confusion over the use of drugs for asthma can lead to poor compliance. The terms "preventer" (inhaled steroids) and "reliever" (bronchodilators) may be misleading so that when symptoms become obtrusive reliance is placed on bronchodilators, and steroids are abandoned causing the vicious circle already described. This is unfortunate as steroids are



Peak flow rate readings show how initial dose of inhaled or oral corticosteroids rapidly achieves optimum lung function in asthmatic patients. Stepped care is less likely to achieve maximum possible peak flow rate

the only true relievers of underlying inflammation, and reluctance to use an adequate dose early enough allows bronchial hyperreactivity to increase and an attack of acute asthma to develop.

A new approach to the treatment of asthma

It should be clearly stated that steroids are the proper treatment for asthma and that bronchodilators must be held in reserve for emergencies. All newly diagnosed asthmatics should be given a high dose of inhaled corticosteroids,[11] continued for 3 months, after which the dose should be gradually reduced to a point where symptoms are controlled and maximum lung function maintained with the minimum dose. Unless there is an emergency β agonists should not be given initially but kept in reserve as rescue drugs.

A satisfactory response over a few days will show the effectiveness of steroids, gain the patient's confidence, and ensure compliance. This also acts as a reversibility test to find the maximum possible peak flow rate (or forced expiratory volume in 1 second and forced vital capacity in elderly patients), which can be used as the target for future control. This procedure allows better lung function to be achieved than when gradual increments in drugs are used, as in stepped care starting with β agonists (figure).

The difficulty in assessing the severity of symptoms, in order to decide on treatment, is avoided as all patients receive inhaled corticosteroids as soon as the diagnosis of asthma is confirmed.—George Strube

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AGAINST Current British asthma guidelines emphasise the importance of gaining control of asthma as soon as possible with a moderately high dose of inhaled corticosteroid and then reducing to the minimal dose needed to maintain control.[1] In a survey designed to assess the awareness of this recommendation, 82% of general practitioners and 74% of practice nurses reported that they did now start with high doses of inhaled corticosteroids.[2]

Shortly after publication of the guidelines it was suggested that inhaled corticosteroids should be used as first line treatment for all newly diagnosed patients irrespective of disease severity and that "as required" inhaled short acting β_2 agonists (step 1) should no longer be recommended as initial therapy for "mild" disease.[3] Although the British guidelines may not distinguish as clearly as they should between "intermittent" and "mild persistent" asthma (terms used in international asthma guidelines[4] and both of which may be interpreted as "mild" disease), inhaled corticosteroids are unquestionably recommended for all adults and schoolchildren who need to use a β agonist more than once daily. Should step 1 now be abolished and all patients with newly diagnosed asthma, however mild or intermittent the disease, be immediately commenced on high dose inhaled corticosteroids?

The case for early intervention with inhaled steroids

An argument for early intervention with inhaled steroids is that airway inflammation is present in patients with mild episodic asthma[5]; a degree of irreversible airflow obstruction, due to structural changes (remodelling) in the airway wall, is correlated with the duration of asthma[6]; steroids are the most effective anti-inflammatory drugs; therefore early control of inflammation with steroids in all patients may prevent the development of these irreversible changes and subsequent progression to more severe disease. Although this argument seems plausible, the evidence quoted in its support does not withstand critical examination. None of the clinical trials[7–9] referred to was actually designed to investigate the hypothesis now being proposed, and although inhaled corticosteroids undoubtedly improve lung function, control symptoms, and reduce airway inflammation, there is conflicting evidence about their ability to reverse or prevent structural changes.[6] Early intervention with inhaled corticosteroids was discussed in a background paper to the British guidelines,[10] with the conclusion that long term controlled trials are needed before this approach can be justified.

The case against

Apart from obvious issues such as the expense and non-compliance with treatment, there are several cogent reasons for not prescribing steroids to all patients newly diagnosed with asthma. Although inhaled corticosteroids have several effects on mucosal inflammation[11] and are currently regarded as the "gold standard" anti-inflammatory drug in asthma the uncomfortable fact remains that they are simply not effective in all patients. In a recent study comparing inhaled beclomethasone with zafirlukast in patients with mild to moderate asthma analysis of individual patient responses showed that 41% of patients on the

steroid failed to show an improvement in peak expiratory flow of at least 5%.[12] It seems illogical to suggest that all patients with mild asthma should be treated with inhaled corticosteroids at a time when newer, alternative treatments are becoming available,[13] especially when the speed of onset of treatment response with leukotriene antagonists is quicker than with inhaled corticosteroids.[14]

The suggestion that all patients with asthma should immediately be started on high doses of steroids needs careful examination. Although it seems entirely logical to start with a high dose (and subsequently tail down) rather than a low dose (and increase progressively if needed), published evidence does not support this approach; starting inhaled corticosteroids at a higher dose is not superior to a lower dose in the treatment of newly detected asthma.[15] Furthermore, there is real concern that when patients are commenced on high dose steroids for any reason the dose is not reduced once control is achieved. This has been shown well in a recent study designed to investigate the effect of montelukast in allowing tapering of steroids in patients with clinically stable asthma.[16] Mean steroid dose was decreased by 37% before randomisation into active treatment and placebo groups and by a further 30% in those subsequently receiving placebo. Thus many patients are receiving much higher doses of steroids than clinically required, and this situation would become much worse if all patients with newly diagnosed mild asthma were routinely started on high dose treatment with inhaled corticosteroids.

The potential disadvantages of aggressive early use of inhaled corticosteroids are even more worrying in children, where there are now real concerns that asthma is overdiagnosed and overtreated.[17 18] There are clearly groups of infants and young children who develop wheezing in association with viral infections yet who subsequently have normal lung function and do not develop asthma.[19] It would seem inappropriate to treat all children who wheeze with long term inhaled corticosteroids especially in view of the continuing debate about the safety of these drugs in children. The study that is always quoted as showing effects of inhaled corticosteroids on prepubertal growth[20] is usually criticised because the children recruited into this trial had only very mild asthma and, under current guidelines, would not be considered appropriate for steroid treatment. Yet this is now precisely the sort of "mild" disease in which early intervention with inhaled corticosteroids is being advocated.

Conclusion

The enormous benefits of treatment with inhaled corticosteroids in asthma are not disputed, and the recommended use of short acting inhaled β_2 agonists only for "as required" symptom relief is acknowledged in British and international guidelines.[1 4] The hypothesis that even earlier intervention with inhaled corticosteroids will prevent airway remodelling and the progressive decline in lung function is at present unproved, and it would be premature to abolish step 1 of the guidelines. If it is indeed true that "beta-agonists are widely regarded as the treatment for asthma with steroids as an optional extra," then it is not the guidelines that need altering but the misunderstanding of them.[21]—Michael Rudolf

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Endpiece

The magic phrase

While working on the material I was reminded of a story George Orwell once told me (I do not recall whether he published it): a friend of his, while living in the Far East, smoked several pipes of opium every night, and every night a single phrase rang in his ear, which contained the whole secret of the universe; but in his euphoria he could not be bothered to write it down and by the morning it was gone. One night he managed to jot down the magic phrase after all, and in the morning he read: "The banana is big, but its skin is even bigger."

From *Return Trip to Nirvana* by Arthur Koestler, *Sunday Telegraph*, 12 March 1961

Submitted by Jeff Aronson, clinical pharmacologist, Oxford