Leukotriene receptor antagonists: useful in acute asthma?

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The leukotriene receptor antagonists (LTRAs) constitute the first completely new class of drugs for use in asthma for 25 years. Their development was based on the recognition that cysteinyl leukotrienes exhibit biological activities that mimic some of the clinical features of asthma and are detectable in increased amounts in asthmatic patients, particularly during exacerbations of asthma. Potent and specific LTRAs have been developed and marketed for use in the treatment of asthma in the UK. Their use by clinicians in the UK is usually as “add-on” therapy in the treatment of asthma in steps 3, 4, or 5 of the BTS asthma guidelines.

In this issue of Thorax Dockhorn et al compare the effect of intravenous and oral administration of the LTRA montelukast on airway function.1 Their results confirm those of previous studies that have shown improved pulmonary function after administration of an LTRA in asthmatic patients, and they also found that intravenous montelukast had a rapid onset of action and a duration of action of about 24 hours in 51 patients with mild to moderate asthma.

Early studies with the LTRAs showed that administration of a single dose (orally or intravenously) was predictably associated with an improvement in lung function.2,3 This suggested that, in patients with asthma, leukotrienes were contributing to the increase in airway smooth muscle tone. This is in contrast to that of normal subjects in whom the LTRAs do not lead to any alteration in lung function.4

The results of clinical trials with LTRAs have been interpreted variably, with claims ranging from an improvement in lung function to no change at all. However, the results of the studies by Dockhorn et al are consistent with those of other recent investigations.5 Montelukast plus beclomethasone, the greatest improvement was seen with combination treatment.6 A steroid tapering study has also shown that it is possible to maintain asthma control while reducing inhaled steroids by adding montelukast to the treatment regimen.7

An unexpected finding of some of the early studies of the LTRAs was the additive improvement in lung function seen with the β2 agonists and the LTRAs. The study by Hui et al showed that, while ICI 204,219 (zafirlukast) caused bronchodilatation, the addition of inhaled salbutamol caused a further improvement in lung function.8 Gaddy et al reported similar findings with MK-571 given intravenously.9 Again there was bronchodilatation with a further improvement with inhaled salbutamol and then nebulised salbutamol. While both β2 agonists and LTRAs improve lung function, they appear to do it by separate yet complementary mechanisms; however, the exact mechanisms are not yet clear. It is possible that β2 agonists and the LTRAs act at anatomically distinct sites, with some of the actions of the LTRAs being due to their effects on airway oedema. Clinical studies suggest that the two treatments are complementary and therefore can be used together to improve function.

Increased levels of leukotrienes are detectable in peripheral blood, bronchoalveolar lavage (BAL) fluid, sputum, and urine of patients with asthma, even when stable.10-12 In BAL fluid and urine there is, however, a considerable overlap between asthmatic patients and normal subjects. Leukotriene levels rise further following allergen challenge, and following aspirin challenge in aspirin sensitive asthmatic subjects.13-16 Several studies in adults and children have reported increased levels of leukotrienes in acute asthma that fall as the attack resolves.17 While existing studies have focused on the use of the LTRAs in chronic asthma, the findings in the paper by Dockhorn et al raise the possibility that leukotriene inhibition may also be beneficial in acute asthma. Dockhorn et al demonstrated a rapid onset of bronchodilatation, particularly with the intravenous formulation, but even the oral formulation achieved a peak effect within two hours. With these results it is tempting to speculate, as the authors do, that montelukast should be considered for the treatment of acute asthma. It is worth noting that the patients studied by Dockhorn and colleagues had mild to moderate asthma, in whom conventional treatment usually works. It may be that in these patients treatment with an additional drug will not provide a significant benefit over and above the usual treatment, but in those with more severe asthma, where aerosolised drug distribution to the airways in the presence of severe airways obstruction may be poor, the availability of an intravenous (or oral) drug with significant bronchodilator effect would be advantageous. It would be interest-
ing to see if these results are also applicable to acutely unwell severe asthmatic subjects. There are anecdotal reports of the use of LTRAs in patients who are ventilated with acute severe asthma.

Finally, the effect of montelukast on airway function relates to the dosages used. The authors used 7 mg intravenously, based on previous pharmacokinetic and pharmacodynamic data which suggested that the maximum benefit obtained was with 10 mg orally. Preliminary dose response studies with montelukast showed that there was little further bronchodilation above 10 mg daily, even when doses as high as 50 mg were used. The results of Dockhorn and colleagues show, however, that superior bronchodilatation is achieved with intravenous montelukast in a dose of 7 mg compared with an oral dose of 10 mg which suggests that the oral dose of 10 mg may not, in fact, be the dose associated with a maximal clinical response. At present it is only licensed for use in the UK as a 10 mg tablet in adults and a 5 mg chewable tablet in children over the age of six years.

It is hoped that the study by Dockhorn and colleagues will pave the way for more studies of the use of the LTRAs in the treatment of acute asthma and, in particular, to examine whether they prevent hospital admissions, reduce the length of hospital stay, and prevent intubation and ventilation for acute severe asthma. Any such studies should evaluate doses of 10 mg and higher.

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Stopping smoking: the importance of nicotine addiction

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The Royal College of Physicians has produced several reports on the adverse effects of smoking on health in the past 40 years. Its latest report entitled “Nicotine Addiction in Britain” emphasises the importance and role of nicotine addiction as a major factor in making many smokers unable to stop. Recognition of the addictive nature of nicotine has important implications for the way that nicotine products should be regulated in society, and one important conclusion of the report is that tobacco based nicotine products should be subject to the same regulatory control as any other drug delivery device. However, the report also argues that nicotine addiction should become recognised and accepted as a medical problem, much as any other manifestation of drug addiction, and this argument has special relevance to respiratory physicians.

Most people who attempt to stop smoking relapse within a very short time and, in the USA, less than 10% of smokers who stop for one day remain non-smokers at 12 months. Nicotine replacement therapy has been shown to improve cessation rates in many controlled randomised studies, but these success rates apply mainly to smokers recruited from the general population and general practice. However, smokers are a heterogenous population and those with established smoking related diseases often have even greater difficulty in quitting smoking. Furthermore, amongst patients admitted to hospital, the relative effectiveness of nicotine replacement therapy and of counselling and psychological support may be different, since these three multicentre studies of smoking cessation in hospital inpatients and outpatients carried out in the 1980s by the British Thoracic Society showed that simple advice from chest physicians with follow up letters of support and encouragement improved quit rates at one year, and that in this context nicotine replacement therapy did not improve the success rate. The importance of psychological support and counselling in achieving a quit rate of over 20% at one year, with or without nicotine replacement treatment, has been confirmed by a recent study from Cardiff in hospital patients.

Patients with smoking related diseases present to a wide range of hospital specialties. However, respiratory physicians in particular see large numbers of patients with lung cancer and chronic obstructive pulmonary disease (COPD), diseases where smoking is the major aetiological
Orthostatic increase of respiratory gas exchange in hyperventilation syndrome

William Gardner

The paper by Malmberg et al in the current issue of Thorax deals with the difficult subject of the hyperventilation syndrome and finds that these patients have a disproportionately high ventilatory response to change of body position from supine to standing. The authors suggest that this can be used as a diagnostic criterion for hyperventilation syndrome. Hyperventilation is a confused and poorly documented subject and the publication of this paper provides an opportunity to review some of the particularly controversial aspects of this subject.

The first issue concerns the basis for the labelling of these patients as “hyperventilation syndrome”. Some of the controversies about the use of this term have recently been reviewed by Folgering and by Gardner. The physiological definition of hyperventilation is alveolar ventilation that is inappropriately high for the metabolic production of carbon dioxide, leading to reduction of arterial PCO₂ (PaCO₂) below the normal range ( hypocapnia ) and respiratory alkalosis. The combination can lead both to vasoconstriction in selected vascular beds and to neuronal...
hypeexcitability producing symptoms involving most systems of the body. Many psychosomatic syndromes have been described in the past in which hyperventilation has a variable and uncertain role but the term “hyperventilation syndrome” was first used in 1938 to describe patients with the somatic symptoms of both hypcapnia and anxiety. This theme was extended by subsequent authors and the definition arrived at by Lewis and Howell in 1986 on the basis of a questionnaire of delegates at a psychophysiology meeting was “a syndrome induced by physiologically inappropriate hyperventilation and usually reproduced in whole or in part by voluntary hyperventilation”. However, the term “hyperventilation syndrome” is now used in so many different contexts that it could be argued that it has ceased to have any universal meaning. Some physicians diagnose it in the presence of the somatic symptoms of hypcapnia either at rest or induced by voluntary overbreathing without assumptions about aetiology, or regard it primarily as an abnormality of respiratory control or as a variant of disproportionate breathlessness. Folgering accepts that anxiety may be absent and has recently suggested a new definition as “a dysregulation of ventilation causing hypcapnia in the absence of organic causes for hyperventilation, with symptoms and complaints not exclusively associated with hypcapnia”. Many refuse to recognise it as a separate entity or regard it as secondary to organic disease and especially to asthma. Many would not use the term in the presence of any organic cause of hypcapnia or in the presence of hyperventilation by organic and psychiatric factors are usually difficult to separate. Lum regards hyperventilation as a form of conditioned response and avoids use of the term “hyperventilation syndrome”. Gardner believes that it is not useful in the clinical context to label a patient with hypcapnia as “hyperventilation syndrome” and that the term should be abandoned. He believes that hyperventilation is often due to a complex interaction between a range of organic, psychogonic, and physiological factors and that, in all cases, the initiating and sustaining cause or causes of the increased respiratory drive causing the hyperventilation should be sought and documented. Use of a label such as “hyperventilation syndrome” tends to preclude further search for underlying aetiological factors and can be dangerous in the context of the emergency room. It is difficult to assess which of the current definitions applies to the patients in the study by Malmberg et al. There was no clear evidence of anxiety or organic causes of hyperventilation and the end tidal PCO_2 was recorded as being no different from the control value at rest. However, the history suggested hypcapnia at other times although the presence of a low PCO_2 at that time was not documented. About the only certain statement that can be made is that these patients do not have chronic hyperventilation.

Hyperventilation occurs in many different specialties including neurology, cardiology, chest medicine, and psychiatry. The patient population to which the term is applied will vary greatly between specialties. Without a clear understanding of the patient population being studied it is difficult to understand the significance of any findings concerning this subject, and the source of the patients and the clinical context from which they were recruited into the study requires particular emphasis in any study about hyperventilation. There is considerable ignorance among physicians about psychiatry and the precise criteria that are used for psychiatric diagnoses. Many physicians in medical specialties assume that the demonstration of a low arterial PCO_2 automatically diagnoses hyperventilation syndrome with an assumption that the patient has some unspecified psychiatric condition. Such patients are then considered to be no longer of interest to the physician. This is often unfair to the patient, and ignores the wide range of organic, behavioural and physiological causes of hyperventilation, many of which can and usually do coexist. These uncertainties reflect the complexity of this subject which falls between psychiatry, clinical medicine, and physiology.

It is difficult to determine the significance of the suggestion in the paper by Malmberg et al that their findings should be used as the basis for a diagnostic test for hyperventilation syndrome. At a physiological level this finding requires a more detailed physiological study to evaluate mechanisms before its significance can be ascertained. At a clinical level ventilation is difficult to measure and most routine lung function laboratories do not have tilt tables or the facilities for measurement of respiratory control variables, especially while the patient is moving from one position to another. The methodology for diagnosing hyperventilation is even more controversial than the issues surrounding the definition, and it could be argued that diagnostic criteria cannot adequately be defined unless the issue of definition has been clarified. Strict adherence to the physiological definition would require documentation of hypcapnia, but hyperventilation may be sporadic and there are few current techniques for measuring PCO_2 over prolonged periods of time outside the laboratory. As in the present study, hyperventilation is often diagnosed with, not only no evidence of a low arterial, end tidal or transcutaneous PCO_2, but even with evidence of a normal PCO_2 on an otherwise apparently normal examination. While it is possible to provide convincing evidence of hyperventilation on behavioural grounds, using the term hyperventilation in the presence of a normal PCO_2 puts an onus on the authors to be more meticulous than usual in documenting the criteria by which hyperventilation was diagnosed. Many such descriptions are sadly unconvincing.

Hypcapnia induces a range of symptoms, and symptom checklists such as the Nijmegen questionnaire have often been used for diagnosing the hyperventilation syndrome. However, many would argue that most of these symptoms are non-specific and do not provide an adequate basis for diagnosis when used alone. It could be argued that the only symptoms specific to hypcapnia are paraesthesiae and tetany, possibly combined with symptoms due to cerebral vasoconstriction and hypoxia. In clinical practice the clinical finding of a low arterial or end tidal PCO_2 is of little relevance in itself if there are no associated symptoms of hypcapnia, or if the symptoms are of minor importance compared with the symptoms of the disorder causing the hyperventilation. In other situations the symptoms of hyperventilation are pivotal to the clinical presentation of the patients. The reporting of familiar symptoms during voluntary hyperventilation is often used as a basis for diagnosis, but this has been criticised by Hornsveld et al in that similar symptoms are also reported when the PCO_2 is artificially maintained at normal levels during voluntary overbreathing.

The role of anxiety disorders in the paper by Malmberg and colleagues is unclear. No psychiatric disorders were reported but their patients nevertheless had symptoms of “episodic dyspnoea or air hunger” and “palpitations, sweating, trembling, dryness of the mouth or other symptoms of overactivity of the autonomic nervous system . . . suggestive of panic disorder”. This definition of panic is imprecise and no formal psychiatric assessment was apparently performed. Contrary to the statement in the introduction to the paper, the association between anxiety and panic is still controversial. Although anxiety was a core component in the original description of hyperventilation syndrome, the relation of hyperventilation to anxiety is not simple and hyperventilation can occur without
Hyperventilation syndrome

Asthma is a common underlying basis for hyperventilation and may provide useful insights into mechanisms by which postural changes can influence control of breathing and respiratory sensations. It is probably unhelpful to suggest this as the basis for yet another indirect diagnostic test for hyperventilation syndrome.

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Orthostatic increase of respiratory gas exchange in hyperventilation syndrome

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