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 chronic asthma at 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.4-5 In the study by Dockhorn et al the improvement in forced expiratory volume in one second (FEV1) was apparent even in those patients treated with inhaled corticosteroids.6 Studies of corticosteroid inhibition of stimulated leucocytes in vitro have shown variable effects on leukotriene production.7-8 In vivo, however, steroid treatment of asthmatics suggests that corticosteroids, both oral and inhaled, have little effect on the basal and stimulated generation of leukotrienes.9 Pre-treatment of asthmatic patients with inhaled fluticasone was also unable to inhibit generation of leukotrienes in response to allergen challenge. This suggests that antagonism of the effects of the leukotrienes might provide additional benefit by suppressing that part of the asthmatic response not sensitive to inhaled and/or oral corticosteroids.

While treatment with inhaled and oral corticosteroids results in improvement in lung function, studies with montelukast and zafirlukast have shown that, even in the presence of moderate and high dose inhaled steroids, further improvements in lung function are possible.10-12 In one study with zafirlukast 80 mg twice daily, patients already on high dose inhaled steroids continued to show an improvement in lung function for more than six weeks.7 This gradual improvement may be secondary to an anti-inflammatory activity additional to that of inhaled steroids since the LTRAs also reduce peripheral blood, sputum, and airway eosinophilia.11-12 In a four way comparison between placebo, montelukast alone, 400 µg beclomethasone alone, or montelukast plus beclomethasone, the greatest improvement was seen with combination treatment.10 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.13

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.14 Gaddy et al reported similar findings with MK-571 given intravenously.15 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 mechanism is 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.16-18 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.19-20 Several studies in adults and children have reported increased levels of leukotrienes in acute asthma that fall as the attack resolves.16 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 bronchodilation 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 heterogeneous 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 specialities. 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 cause.
factor, and most of the deaths caused by smoking are in fact due to respiratory diseases.\textsuperscript{2} Smoking cessation in patients with COPD reduces the accelerated rate of decline of forced expiratory volume in one second (FEV\textsubscript{1}) and is one of only two interventions which improve the long term prognosis, the other being long term oxygen therapy.\textsuperscript{13,14} Active support and treatment of nicotine addiction in these patients should therefore be considered to be an essential component for medical management of this disease.

If nicotine addiction is accepted to be a fundamental issue in preventing smokers from successfully stopping smoking, it is clear that simple advice alone is not always adequate to address the problem. Active help and support such as psychological counselling and pharmacological treatments need to be made available to increase the chances of success. Other addictions such as those to heroin and alcohol are already treated and funded by the NHS, and although funding is now being made available to establish smoking cessation services in selected areas of Britain, it is time to make the treatment of nicotine addiction available and affordable for all smokers through the NHS. Smoking cessation interventions give good value for money and the cost implications of providing smoking cessation services in the UK are well established.\textsuperscript{15} The report by the Royal College of Physicians adds further urgency to the need for the implementation of smoking cessation services.

It is also important for all health professionals to take an active role in advising and helping smokers to stop.\textsuperscript{16} For this to be achieved, there must be better education and training for health professionals in both the knowledge of the adverse effects of active and passive smoking and in smoking cessation methods. Unfortunately, marked deficiencies in knowledge of tobacco control and prevention have been shown amongst medical students from all over the world.\textsuperscript{17} Few medical schools include education on tobacco issues in their undergraduate curriculum and the prevalence of smoking amongst medical students increased during their medical school careers. Even for specialist registrars training in respiratory medicine, the current curriculum does not include a recommendation for training in smoking cessation as an essential part of the syllabus.\textsuperscript{18}

What messages can respiratory physicians take from the latest Royal College of Physicians report? Many of our patients need help and support to stop smoking and, because so many of our patients have smoking related diseases, it would be appropriate for respiratory specialists to take ownership of the problem and become lead physicians for tobacco control within their NHS trusts or districts. This would involve a more active role in the education and training of medical students, junior doctors, general practitioners, and other health care professionals in smoking issues especially, and for respiratory physicians to become expert in smoking cessation interventions. Respiratory physicians should actively campaign for and request the appointment of smoking cessation counsellors in all NHS hospitals to provide advice and psychological support for patients and staff. They could work closely with such individuals who could have their base within respiratory medicine departments. The pharmacological aspects of smoking cessation could also become part of the expertise of the respiratory specialist.

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Orthostatic increase of respiratory gas exchange in hyperventilation syndrome

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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\textsuperscript{7} and by Gardner.\textsuperscript{8} The physiological definition of hyperventilation is alveolar ventilation that is inappropriately high for the metabolic production of carbon dioxide, leading to reduction of arterial PaCO\textsubscript{2} below the normal range (hypocapnia) and respiratory alkalosis. The combination can lead both to vasoconstriction in selected vascular beds and to neuronal...
hyperventilation 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 hypocapnia 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 hypocapnia 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 hypocapnia in the absence of organic causes for hyperventilation, with symptoms and complaints not exclusively associated with hypocapnia". 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 hyperventilation. Organic and psychiatric factors are usually difficult to separate. Lam 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 hypocapnia 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, psychogenic, 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 hypocapnia 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 hypocapnia, 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 spot sampling. 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.

Hypocapnia 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 hypocapnia 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 hypocapnia, 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 PACO$_2$ 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
anxiety, or anxiety may be induced by hyperventilation. Anxiety can be associated with both mild hyperventilation and abnormalities of breathing pattern. Endogenous non-retarded depression can be associated with hyperventilation and phobic patients have a high prevalence of breathing difficulties. The predisposition to overbreath in response to stress may be dependent on biological vulnerability, personality, and cognitive variables as well as individual interpretation of the hyperventilation induced somatic symptoms, and may become a conditioned response. Because of the complexities of this subject, it could be argued that any paper about hyperventilation requires a collaborative input from a psychiatrist or psychologist. At a clinical level such an input is often required for no reason other than to counter the assumptions of the referring clinician that a patient with hyperventilation must automatically have an anxiety state. Often there is a complex interaction between organic and psychiatric factors such as depression and phobic states which require a combined input from a physician and a psychiatrist.

The authors describe their patients as having a history of recurrent or episodic dyspnoea. Howell regards disproportionate dyspnoea as being synonymous with hyperventilation syndrome, and he has described the characteristics of these patients. Gardner has argued that the two are not synonymous and that, if a patient is breathless for reasons that are not clear, it is the breathlessness that is the primary condition for which a cause should be sought and that, if hyperventilation is also present, it is usually secondary to the breathlessness and of little clinical importance. Patients are often referred with a label of psychogenic dyspnoea when the degree of distress seems disproportionate to the clinical findings and lung function or blood gas data, but there is almost no literature on this subject. Dyspnoea is what the patient reports and it is therefore difficult to dispute. Studies of breathlessness are impeded by uncertainty about the basic mechanisms and there are probably many different forms. Air hunger, or a sensation of inability to take a satisfying breath or to fill the lungs, was reported by patients in the Malmberg study and may indicate a psychogenic component to breathlessness. It was a universal feature of the patients with chronic hyperventilation studied by Gardner and Bass and more recently Gardner has reported patients in whom the primary presentation is air hunger which leads to variable degrees of panic and hyperventilation.

Asthma is a common underlying basis for hyperventilation and Gardner has argued that many patients with a primary presentation of hyperventilation have very mild and often previously undiagnosed asthma. Malmberg et al describe the exclusion of “physician diagnosed” asthma but give no details about how this was achieved, although patients had “histamine provocation tests and pulmonary diffusion capacity if clinically indicated”. Asthma is a surprisingly difficult and controversial diagnosis and many physicians would argue that these indications should be clarified. In summary, it would seem that the patients in the study by Malmberg and colleagues might fit more accurately into a classification of dyspnoea and air hunger with secondary intermittent hyperventilation rather than receiving an automatic label of “hyperventilation syndrome”. Such a reclassification may lead to a different interpretation of these clearly interesting results and may suggest lines of enquiry for possible mechanisms of air hunger. The physiological basis for these responses requires investigation 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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