New Drugs

Respiratory and allergic disease. I.

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Only a few new drugs have been introduced in the treatment of respiratory disease since this subject was last reviewed in this journal.^{1,2} The present review is not comprehensive but will highlight some of the important therapeutic aspects of respiratory medicine that have emerged recently. In addition to newly introduced drugs of potential future value will also be discussed. Part I of this review will cover asthma and allergic rhinitis; part II will review new treatments in chronic obstructive airways disease, antibiotics, and the chemotherapy of tuberculosis.

Asthma

Over the past 10 years there has been an increase in both morbidity and mortality from asthma.^{3,6} Despite the fact that the current trend in deaths from asthma coincides with increasing sales of all classes of drugs for treating asthma⁷ it has been suggested that those who die of asthma have not received optimal treatment.⁸ Too much reliance may have been placed on β adrenoceptor agonists, resulting in the development of tachyphylaxis to such drugs and of possible dangerous arrhythmias,^{9,10} but there is no convincing evidence to support this view.

It is important to realise that inflammatory changes in the airways of asthmatics may underlie the bronchial hyperreactivity and clinical symptoms of asthma.¹¹ Drugs that prevent or suppress inflammation of the airways have been advocated as a prophylaxis against attacks of asthma.¹² In two recent reports the bronchial hyperresponsiveness of mild asthma in children and adults was reduced by regular treatment with inhaled steroids but was worsened, if anything, by regular treatment with inhaled β_2 agonists.^{13,14} These studies raise the important and as yet unresolved issue of whether the strategy for anti-asthma treatment should consist of regular prophylactic treatment, with β_2 agonists being used only for acute relief of wheezing and dyspnoea.

An important development over the past five years has been improved delivery of anti-asthma drugs, such as spacer devices to increase deposition of inhaled aerosols and the development of controlled release theophylline preparations. Nedocromil sodium, a mast cell "stabiliser" and anti-inflammatory agent, has been recently introduced as an asthma prophylactic. A xanthine derivative, enprofylline, that has a wider margin of safety between therapeutic and toxic effects and has potentially fewer side effects than theophylline is currently being clinically evaluated but is not yet on the market.

Drug delivery

SLOW RELEASE BRONCHODILATORS

The introduction of slow release preparations of theophylline has given a new impetus to the use of these methylxanthines in treating asthma. Increased rational use of these preparations has been made possible by the availability of reliable and convenient theophylline assays and subsequently by a greater understanding of their pharmacokinetics. Sustained release preparations have been particularly useful in treating nocturnal asthma, as therapeutic plasma concentrations of theophylline may be maintained overnight by giving a single dose in the evening.¹⁵ The dose of slow release aminophylline needed completely to abolish the nocturnal decrease in peak expiratory flow is about 10 mg/kg body weight, taken once before bedtime.¹⁵

Several slow release theophylline preparations are now available for prescription in the United Kingdom.¹⁶ Though it is possible to tailor the doses of these preparations to achieve therapeutic concentrations throughout the 24 hours, it is most important to prevent bronchoconstriction at night, as asthmatics can resort to inhaled β_2 adrenergic agonists during the day. The temporal variations in plasma theophylline concentrations, with reduced plasma concentrations at night in adults,¹⁷ may be due to posture, as higher theophylline concentrations in the blood are found on standing than when lying down, possibly owing to reduced gastric absorption when lying down.¹⁸

Sustained release theophylline preparations can be given twice daily and provide greater efficacy, fewer side effects, and improved compliance compared with immediate release theophylline preparations.^{19,20} This improvement has been attributed to the reduced fluctuations in plasma concentrations of theophylline seen with the sustained release preparations. More recently an ultrasustained release theophylline, Uniphyllin, suitable for dosing once daily, has become available. A single dose of slow release Uniphyllin (800 mg) in the evening was found to prevent nocturnal wheeze more effectively than theophylline 370 mg twice daily.^{21,22} Dosing with Uniphyllin in the evening rather than in the morning is better at controlling the early morning dip in pulmonary function.²³ When Uniphyllin was given in a dosage of 10 mg/kg to asthmatic patients peak concentrations within the therapeutic range 10-20 mg/kg were achieved within eight hours.²⁴ So that the peak concentrations coincide with the occurrence of early morning wheeze it is probably best to take ultraslow release theophylline at around 8.00 pm.

The side effects of various theophylline preparations do not always seem to be related to the concentration of theophylline in the blood; patients may experience substantial side effects even in the presence of subtherapeutic concentrations.²⁵ The gradual introduction of theophylline has been recommended so that these side effects are minimised.²⁶ Side effects include nervousness, nausea, vomiting, anorexia, abdominal discomfort, and headache. The risk of serious toxic effects such as seizures and cardiac arrhythmias increases when the plasma concentrations exceed 30 mg/l.²⁷ More recently it has been appreciated that theophylline is associated with learning difficulties and sleep disturbance in children.²⁸ This questions the

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value of regular oral theophylline rather than treatment with inhaled bronchodilators in children.

In view of the considerable variation within and between patients in the absorption and clearance of theophylline the dose of slow release preparations should be adjusted according to the clinical response and to blood concentrations of theophylline. The clearance of theophylline may be affected by various factors, including cigarette smoking, age, diet, and drugs such as erythromycin, cimetidine, allopurinol, and propranolol. As different slow release preparations differ in their characteristics of release it is unwise to change from one preparation to another without careful monitoring.

Oral slow release β_2 adrenergic agonists are effective at controlling the morning dip in some patients.²⁹ Both slow release terbutaline and a new controlled release salbutamol preparation may be effective. A recent study showed that infusion of subcutaneous terbutaline (14 $\mu\text{g/kg/day}$) may alleviate the severe morning dip in patients who are not helped by oral treatment.³⁰ This may have been achieved through higher blood concentrations of terbutaline than would have been provided by conventional oral doses.³¹

INHALATION DEVICES

Many patients, particularly elderly patients and young children, cannot properly master the use of the metered dose inhaler, which requires proper coordination between actuation of the inhaler and inspiration, followed by holding the breath. Important advances have been the introduction of the spacer or reservoir devices for use with the metered dose inhaler (for example, Nebuhaler or Volumatic) and of dry powder inhalers (for example, Rotahaler with Rotacaps). These devices circumvent the necessity for coordination between actuation of the metered dose inhaler and inspiration. The spacer devices also increase the amount of aerosol that is actually deposited in the lungs: with the metered dose inhaler attached to a Nebuhaler about 2.5 times more aerosol is deposited in the lungs of patients who have obstructive airways disease than with the metered dose inhaler alone (21% v 9%) during the inhalation of a single puff of aerosol.³³ After four puffs from the metered dose inhaler into a Nebuhaler (R) followed by two inhalations with breath holding 15% deposition was obtained in the lungs.³² Another advantage of using a spacer device is the decreased deposition of aerosol in the oropharynx, with most of the aerosol particles remaining in the spacer reservoir itself.³² This is achieved by slowing down the aerosol in the chamber and by the subsequent evaporation of the fluorocarbon propellant, thus producing a finer and slower moving aerosol cloud to be inhaled into the lungs.

The airway response to a β agonist is greater in normal and asthmatic subjects who use a metered dose inhaler with a Nebuhaler (R) than in those who use a metered dose inhaler alone or even a Mini-neb nebuliser.³³ A nebuhaler is as effective as a nebuliser in chronic stable asthma³⁴ or in acute severe asthma.³⁵ The smaller proportion of oropharyngeal deposition occurring means that less of the inhaled drug is absorbed, resulting in reduced systemic as well as local side effects. High dose inhaled steroid treatment such as budesonide 400-1600 $\mu\text{g/day}$, when used with a nebuhaler is associated with a reduced risk of oropharyngeal candidiasis and with an appreciable increase in anti-asthmatic effect.³⁶ The spacer reservoir can be particularly useful for children receiving inhaled corticosteroids, as a reduction in the systemic absorption of steroids may decrease any potential adverse effects on growth. In addition, the use of a reservoir device makes it possible to administer more potent inhaled corticosteroids and β agonists.

HOME NEBULISERS

Nebulisers driven by compressed air for use at home have increased in popularity recently and are used to administer bronchodilator aerosols. Many patients, particularly those who have moderately severe obstruction, find greater subjective relief from bronchodilators delivered from such nebulisers than from those delivered from their metered dose inhaler. There is little

evidence, however, that these nebulisers used at home provide more bronchodilatation or that they are more clinically effective than the metered dose inhaler, particularly when the metered dose inhaler is used with a spacer device.^{33 37 38} Though home nebulisers are of undoubted benefit in treating small children and patients who have acute asthma, allowing larger doses of bronchodilators to be administered,³⁹ they should be prescribed with caution for adult asthmatics, as increasing dependence solely on β agonists for relief of symptoms may mask the need for corticosteroid treatment.⁴⁰

Nedocromil sodium

Nedocromil sodium is a pyranoquinoline dicarboxylic acid that has recently been developed and marketed for prophylactic use in adults who have asthma. Though nedocromil sodium is chemically remote from sodium cromoglycate, it retains the same anti-allergic properties but has increased anti-inflammatory effects. In the classical models of immediate hypersensitivity in the rat nedocromil sodium is as effective as sodium cromoglycate.⁴¹ Nedocromil sodium, however, but not sodium cromoglycate, considerably inhibits the release of inflammatory mediators from mast cells that have been obtained by bronchoalveolar lavage from sensitised monkeys and humans and challenged with antigen or anti-IgE.^{42 43} Nedocromil sodium also inhibits bronchoconstriction induced by antigens *in vivo* in monkeys⁴⁴ and humans.⁴⁵ The activation of human eosinophils and neutrophils,⁴⁶ human macrophages,⁴⁷ and rat platelets⁴⁸ is also inhibited.

Studies of asthmatic patients have shown that nedocromil sodium has a similar range of activity, with usually greater potency, against several triggers of bronchoconstriction. Thus nedocromil sodium in single therapeutic doses can inhibit both the early and late phase responses after antigen challenge,⁴⁹ asthma induced by exercise,^{50 51} and bronchoconstriction induced by inhaling cold air,⁵² sulphur dioxide,^{53 54} and fog.⁵⁵ Small but appreciable improvements in bronchial hyperreactivity have been seen in asthmatics sensitive to pollen during the pollen season.⁵⁶

In several clinical trials nedocromil sodium, taken over four or twelve weeks, was better than placebo at controlling symptoms of asthma in both atopic and non-atopic asthmatics receiving only bronchodilator treatment.⁵⁷ In patients previously regularly treated with inhaled steroids nedocromil sodium was not able totally to replace the steroids, particularly when their use was tailed off rapidly.⁵⁷ There may, however, be further improvement when nedocromil sodium is added to the treatment of patients already regularly receiving inhaled steroids.⁵⁷ Whether nedocromil sodium can compensate for the gradual withdrawal of oral corticosteroids from patients who are receiving both oral and inhaled steroids is not yet known.

Nedocromil sodium (Tilade R) is formulated as a pressurised aerosol, and the recommended dose is two puffs (2 mg a puff) twice daily; the dose may be increased to four times daily. It has been well tolerated by asthmatics who have taken it for up to one year.⁵⁸ No great side effects have been reported, but some patients complain of an unpleasant taste and occasional nausea. When inhaled by normal subjects nedocromil sodium is rapidly absorbed and is excreted totally unchanged in the bile and urine. There is no accumulation of the drug on multiple dosing.

Though nedocromil sodium has been shown to be effective in treating asthma, its exact place in managing asthma remains to be determined. The initial studies suggest that nedocromil sodium is more active in a wider range of asthmatics, including adult and non-atopic patients, than sodium cromoglycate. Long term comparisons with inhaled steroids are needed.

Enprofylline

Slow release preparations of theophylline are used to manage nocturnal and early morning wheeze and chronic asthma not adequately controlled by β agonist and steroid aerosols. Though there is now a better understanding of the pharmacokinetics of

theophylline, and plasma concentrations of theophylline can be monitored, the wide variation in the rate of hepatic metabolism may make it difficult to achieve adequate therapeutic concentrations in individual patients. The toxicity and side effects of theophylline also remain a great problem.

Of great interest is the recently developed xanthine derivative enprofylline, which is five times more potent than theophylline in causing bronchodilatation but lacks the stimulating effects on the central nervous system such as anxiety, tremor, seizures, and respiratory stimulation.⁵⁹ In contrast with theophylline enprofylline does not increase gastric secretion; nor does it cause diuresis or the release of free fatty acids into the circulation. Both drugs, however, cause a similar degree of nausea (which is the most troublesome side effect of theophylline), relaxation of the lower oesophageal sphincter, and headache, which is presumably due to vasodilatation of cerebral arteries.⁵⁹

The mechanism of action of enprofylline as a bronchodilator is uncertain.⁶⁰ In contrast with theophylline enprofylline is not an adenosine antagonist, which probably explains the lack of side effects on the central nervous and cardiac systems. Theophylline antagonises the effect of infused adenosine in man, but enprofylline has no such effect,⁶¹ indicating that theophylline probably exerts its anti-asthma effect through another mechanism. Methylxanthines may have effects other than relaxation of the smooth muscle in airways, such as inhibition of microvascular leakage and thus inhibition of oedema in airways. Enprofylline and theophylline both inhibit the late phase response to antigen challenge,⁶² an effect that may be related to the inflammation of airways.

Enprofylline is well absorbed throughout the gastrointestinal tract, is metabolised to only a minimal extent, and is eliminated unchanged by the kidneys.⁶³ Thus in contrast with theophylline enprofylline is not dependent on a variable hepatic rate of metabolism. The renal clearance of enprofylline is linearly related to renal function in patients who have varying types of renal dysfunction.⁶⁴ A sustained release preparation given twice daily will maintain therapeutic plasma concentrations over 24 hours.

Oral enprofylline in a single dose (4 mg/kg) caused a similar degree of bronchodilatation to a standard oral dose of terbutaline (5 mg) in stable asthmatics.⁶⁵ When given intravenously at doses of 0.5, 1.0, and 1.5 mg/kg enprofylline induced dose related bronchodilatation in acute asthma.⁶⁶ Asthmatics treated with enprofylline for two weeks had a lower score for asthmatic symptoms than when they were receiving theophylline, but there was a greater prevalence of headaches.⁶⁷ Long term studies with enprofylline are being performed, and whether it will prove to be a useful replacement for theophylline remains to be seen.

Acute asthma

The treatment of acute asthma has for a long time remained empirical, and only recently has objective data been obtained about the effectiveness and possible toxic effects of various bronchodilator treatments. No new drugs (apart from enprofylline), for the treatment of acute asthma have been developed, and recent studies have evaluated β agonists, aminophylline, and anticholinergic drugs.

Corticosteroids are undoubtedly beneficial in the treatment of acute asthma.⁶⁸⁻⁷¹ A recent study has shown that the use of intravenous hydrocortisone does not confer additional advantages when used together with oral prednisolone and bronchodilators to treat acute severe asthma without ventilatory failure.⁷² Nebulised β_2 agonists, rather than intravenous aminophylline or parenteral β_2 agonists, remain the bronchodilator treatment of choice in acute asthma, as they produce prompt relief of wheezing and dyspnoea with few side effects.⁷³⁻⁷⁴ The combination of aminophylline and β agonists does not seem to offer any advantage and could lead to increased side effects.⁷⁵ In addition, theophylline toxicity may be a problem in patients who are already taking slow release methylxanthines.

The α agonist activity of adrenaline could have an anti-oedema effect that may be useful in treating acute asthma. When compared

with an inhaled β agonist, however, nebulised adrenaline was no better at relieving airways obstruction in acute asthma.⁷⁶ Similarly, subcutaneous adrenaline was no more effective than subcutaneous terbutaline in treating acute asthma.⁷⁷

The anticholinergic drug atropine sulphate is less effective as a bronchodilator drug than as a β agonist in acute severe asthma.⁷⁸ The use of nebulised salbutamol followed by another anticholinergic agent, ipratropium bromide, however, produces considerably more bronchodilatation in acute severe asthma than sequential treatments with salbutamol alone.⁷⁹ A mixture of a β_2 agonist and an anticholinergic may be more effective than a β_2 agonist alone.

Future directions in treatment of asthma

There are few new drugs under development that are likely to have a great impact. Improving the topical potency of inhaled steroids may be useful, as this will allow greater control of inflammation and may be helpful to asthmatic patients who still need oral corticosteroid treatment despite maximal doses of the inhaled steroids currently available. Perhaps steroids that have topical potency but that are metabolised locally with reduced systemic absorption would be useful. An increase in the understanding of the mechanism of action of corticosteroids may make it possible to develop drugs that retain the beneficial anti-inflammatory effects (such as the anti-eosinophil action) without the harmful effects.

Glucocorticosteroids may act by inducing the synthesis of a new protein, lipocortin, which inhibits phospholipase A2 and thus the generation by inflammatory cells of prostaglandins, leukotrienes, and platelet activating factor.⁸⁰ Lipocortin may represent the forerunner of a new generation of anti-inflammatory drugs for several diseases, including asthma. Drugs such as oxatomide and lodoxamide, which stabilise mast cells, have not proved to be of clinical benefit in asthma. Antagonists of putative mediators involved in asthma are now available. Potent antihistamines such as terfenadine (see below) have considerable effects in antagonising bronchoconstriction induced by histamine⁸¹ but are unlikely to be useful in asthma.⁸² Antagonists of leukotrienes are currently being tested for their effectiveness in asthma, but the initial compounds have shown weak inhibitory effects in the airways and appreciable side effects.⁸³ There has also been increasing interest in platelet activating factor as a mediator of asthma, as it is able to induce sustained bronchial hyperresponsiveness in humans.⁸⁴ Platelet activating factor antagonists are now being tested clinically,⁸⁵ but whether they will be useful in asthma is not yet certain. Because symptoms of asthma may result from an interaction among these mediators a combination of these antagonists would presumably be necessary.

The development of novel bronchodilators is probably unnecessary, as inhaled β_2 agonists are effective and do not have appreciable side effects. Other bronchodilators, such as prostaglandin E, vasoactive intestinal peptide, and forskolin (which directly activates adenylate cyclase), have not proved to be clinically useful.⁸⁶ Similarly, calcium antagonists such as nifedipine and verapamil have been disappointing, with no bronchodilator response and only a weak protective effect against induced bronchoconstriction.⁸⁷ The only important potential advance is the development of an inhaled β_2 agonist with a more prolonged bronchodilator effect. Such β_2 agonists (for example, formoterol and salmeterol) are now undergoing clinical trials and may be effective in controlling nocturnal asthma.

Allergic rhinitis

The introduction of non-sedating H1 antihistamines has improved the treatment of several allergic conditions, including allergic rhinitis, urticaria, and allergic conjunctivitis. The use of previously available antihistamines such as chlorpheniramine was severely limited by their sedative side effects.

Two new antihistamines, terfenadine and astemizole, are now

available and do not possess the central sedative and anticholinergic side effects of other preparations.^{88,89} These drugs differ appreciably in their pharmacokinetics. Astemizole has a slow onset of action, with a long half life of up to 19 days. It is released slowly from hepatic lysozymes, binds almost irreversibly to H1 receptors, and also has some affinity for serotonin receptors.⁹⁰ Astemizole is therefore better used for maintenance treatment, and its once daily dosage may help long term compliance. On the other hand, terfenadine has a rapid onset and offset of action, making it ideal for intermittent use.⁹¹ Nevertheless, a prophylactic effect may be obtained by taking 60 mg twice daily. Terfenadine may also help in an acute attack of urticaria.

In one study astemizole was more effective than placebo or terfenadine after eight weeks of treatment at controlling itchy eyes, sneezing, and runny but not blocked nose, but there was a high failure rate for both drugs.⁹² In a double blind study, terfenadine was found to be as effective as chlorpheniramine at improving all symptoms of allergic rhinitis and conjunctivitis.⁹³ Both astemizole and terfenadine were found to be more effective than placebo at controlling symptoms of hay fever.⁹⁴ Patients taking terfenadine noticed alleviation of their symptoms within hours, whereas those taking astemizole noticed it within days. Astemizole reached a similar degree of efficacy to terfenadine before the fourth day of treatment. The efficacy of H1 antihistamines in chronic perennial rhinitis remains less clear. Terfenadine provides only a modest benefit in the treatment of perennial rhinitis, and its effect is no different from chlorpheniramine (8 mg twice daily) or placebo.⁹⁵

The treatment of allergic rhinitis has also improved considerably with the introduction of topically acting corticosteroids such as beclomethasone, flunisolide, and budesonide.⁹⁶ These corticosteroids are extremely effective at controlling allergic rhinitis, particularly when used in combination with histamine H1 antagonists. Topical steroids have no systemic side effects, and local adverse reactions, such as dryness and bleeding, occur only occasionally.

We thank Madeleine Wray for her utmost care during the preparation of this manuscript.

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Everyday Aids and Appliances

OLIVER J CORRADO

HEARING AIDS

Nearly one in 10 adults in England and Wales are disabled. The use of technical aids can enable these disabled people to do more for themselves and therefore feel better; they can also make caring easier. But despite the many disabled people who can benefit from aids and the high cost of provision, far less attention is given to rehabilitation aids than to equipment used for diagnosis and treatment.

In this series we aim to help clinicians become more aware of the range of items available and of their appropriateness and safety. Disability is most prevalent in the elderly: two thirds of the seriously handicapped are over 75; 80% of visually disabled people are over retirement age; only 64% of the elderly are fully independent in bathing; and over half the women over 85 living at home need aids or help to get to and from the toilet. Thus we will concentrate particularly on the relatively simple aids required for the elderly disabled but will also consider some of the more complex aids required by younger handicapped people. We consider aids that are attached to the body (hearing aids, stomas, collars and corsets, pads and pants, catheters, special footwear, stockings, artificial legs); those held by but not necessarily fixed to the body (mobility aids, low visual aids, certain communication aids); and equipment in the home which allows independence in everyday activities (bath and toilet aids, wheelchairs, hoists). We will also describe the functions of disabled

living centres and ask how we can improve the provision of aids and appliances.—GRAHAM MULLEY, consultant geriatrician, Leeds, and editor of the series.

Deafness is a common problem which increases in prevalence with age, 60% of people over 70 having some degree of hearing loss. There are two types of hearing loss: conductive, caused by lesions which interfere with the transmission of sound anywhere from the exterior to the end of the ossicular chain; and sensorineural, caused by lesions of the cochlea or auditory nerve. Hearing aids should be considered for patients with impaired hearing when definitive treatment is complete or when it is impossible. They act by amplifying incoming sound so that it is heard at a more effective level.¹

Obtaining an aid

Twenty per cent of hearing aids are not used within six months of being supplied, so before referring adult patients it is worth ensuring that hearing loss is affecting their lifestyle and that they are prepared to wear an aid once it is supplied. An aid should be considered for any child whose deafness is impeding natural speech development.² To obtain a National Health Service hearing aid a patient must be referred to an ear, nose, and throat consultant, who will assess the patient and arrange a pure tone audiogram. If the patient is a suitable candidate for a hearing aid an ear mould impression will be taken and an aid supplied later. Aids with temporary earpieces may be supplied in the interim. The whole