New Drugs

New drugs in respiratory disorders: I

D C FLENLEY

Although drugs play a major part in the treatment of respiratory disease, relatively few new ones have been developed in the last few years. Considerable advances, however, have been made in the use of existing agents, particularly bronchodilators and oxygen, and these are discussed in the first of these two articles. As infection is a major cause of respiratory disease the newer antimicrobial drugs will be discussed in the second article and will be compared with established antimicrobials. Finally, cytotoxic chemotherapy for small cell lung cancer and lymphoma, however, are by considered, as the all too high prevalence of this dreadful disease now creates some of the greatest challenges in respiratory medicine in both ethics and practical clinical management.

Bronchodilators

$\beta_2$-agonists

A selective $\beta_2$-agonist (salbutamol, terbutaline, fenoterol, reproterol, rimiterol) will usually be the first choice bronchodilator for both the rapid relief of an asthmatic attack and for the maintenance treatment of chronic asthma or chronic bronchitis and emphysema. These drugs are best given by pressurised aerosol inhaler, one to two puffs up to four times daily in the adult, as side effects (muscle tremor, tachycardia, anxiety) are then minimal. Apart from rimiterol, which has a short duration of action, all these drugs act from five minutes up to three to five hours. The inhalation technique is important: after a fairly full breath out, one puff of the inhaler is taken (either into the open mouth or with the lips closed around the inhaler) just at the start of a slow breath in through the mouth, this being as deep a breath as possible.1 This is then followed by holding the breath at this full inspiration for 2-10 seconds.1 For those who cannot coordinate this manoeuvre alternative methods of administration2 include a dry powder inhaler (Ventolin Rotacaps, salbutamol3), a tube spacer (Bricanyl spacer, terbutaline4), or a short period of continuous nebulisation of a solution of the drug with either an intermittent positive pressure breathing machine or a compressor driven nebuliser. Although all inhalation techniques deliver only about 10% of the dose to the airways, this is enough to be effective. Tolerance to the bronchodilatation produced by any of these $\beta_2$-agonists can develop after using them for two to three weeks, even when given by aerosol, but thereafter the response to a given dose seems to change little.4 Such diminished adrenergic responsiveness, however, may be restored by giving parenteral steroids, and this may be important in treating an acute attack of asthma.3

Ipratropium Bromide

Ipratropium bromide is an atropine derivative that is a powerful anticholinergic inhibitor of vagally mediated bronchomotor tone after aerosol inhalation. The action is local as the drug is slowly be absorbed by the lungs. More than 90% of the effect is only maximal after some 30 minutes, and then lasts for three to five hours. Side effects other than a bitter taste are rare, there being no systemic atropine-like effects and no inhibition of mucociliary clearance.5 In conventional doses (two puffs; about 40 $\mu$g) ipratropium can interact usefully with $\beta_2$-agonists to produce further bronchodilatation in patients with chronic adult asthma6 and even in patients with severe airflow obstruction due to chronic obstructive bronchitis.7 Ipratropium, with or without inhaled $\beta_2$-agonists, is most likely to help asthmatic adults who are over 40, but it is also effective in children aged 6-14.11,12 Ipratropium by inhaler and oral theophylline have a similar interaction if the dose of theophylline yields a therapeutic plasma concentration of 10-20 $\mu$g/ml. In a higher dose (120 $\mu$g; six puffs) ipratropium improved FEV1 (forced expiratory volume in 1 second) for up to six hours in patients with chronic bronchitis and emphysema13 without side effects, but caution should be exercised. A dose of 500 $\mu$g of nebuliser solution (Atrovent nebuliser solution 0.25%) seems as effective as nebulised salbutamol (10 mg respirator solution 0.5%) in treating acute asthma.14 Note that this dose exceeds that recommended in the British National Formulary.

Theophylline

Theophylline has been used for over 50 years, but its precise role in bronchodilator treatment has been much studied recently, particularly in the United States, presumably because inhaled salbutamol (there called albuterol) became available there only in 1981. The toxic/therapeutic ratio of theophylline is low, so that for the most effective safe use concentrations of the drug in plasma should be measured. This may be done by either enzyme multiplied immunoassay or high pressure liquid chromatography.16 These measurements are now becoming available in more and more laboratories in Britain. Aminophylline (ethylene diamine theophylline) contains about 80% of theophylline but seems to have similar absorption and pharmacokinetics to theophylline in man. The plasma half life of theophylline (about 3-10 hours) is reduced in smokers but is prolonged by concurrent treatment with cimetidine (due to inhibition of hepatic metabolism) and possibly erythromycin, and also by antiviral vaccines. The half life is also increased in patients with cirrhosis, congestive heart failure, chronic obstructive lung disease, and cor pulmonale, as well as in acute febrile episodes.16 Thus nausea and vomiting in such a patient during maintenance treatment with oral theophyllines may be due to the temporarily raised drug concentrations and not to the primary illness.

A low dose of 400-500 mg of theophylline by mouth (or 600 mg of aminophylline) over 24 hours will usually yield theo-
Theophylline plasma concentrations of 6–10 μg/ml in the average adult and will give few side effects (nausea, vomiting, headaches, insomnia, and agitation). At this drug concentration, however, maximal bronchodilatation is unlikely to be achieved by the theophylline alone. Higher oral doses, 800 mg aminophylline (or 600 mg theophylline) in the 24 hours, given to a non-smoker or to a patient with cor pulmonale will usually yield plasma concentrations of 10–20 μg/ml, when the therapeutic effects are maximal, but side effects are also more prevalent. Serious arrhythmias and convulsions, which may threaten life, are a real risk if plasma concentrations exceed 40 μg/ml.17 Thus in practice treatment should be started with a low dose and if no serious side effects develop be increased to a higher dose after three to four days. The plasma concentration ideally should be checked some 72 hours after starting the full dose and thereafter once a year during maintenance treatment. This should also be done after the patient changes smoking habits or when drugs that may cause interactions are given.18

SLOW RELEASE PREPARATIONS

Slow release preparations of either aminophylline (Phyllocontin Continus) or theophylline (Slo-Phyllin; Nuelin SA; Theo-Dur; Theo-grad; or Uniphyl Unicon) are preferred as they provide relatively constant plasma concentrations of the drug over at least four to eight hours,18–21 although the oral dose may have to vary up to fourfold between different individuals to achieve optimal plasma concentrations.22 Maintaining a relatively constant drug concentration may be particularly important if the early “morning dip” in peak flow at around 00 am in chronic asthmatics is to be avoided. Thus in asthmatic adults a slow release theophylline, yielding plasma concentrations of 8–15 μg/ml 10 hours after dosing, reduced the need for β2-agonist inhalations during the night and abolished the morning fall in peak expiratory flow in a four week cross over trial,23 but the quality and duration of sleep was not assessed. As the side effects of theophylline at high plasma concentrations include insomnia this may be important.

COMBINING THEOPHYLLINE WITH β2-AGONISTS

In 1962 Butcher and Sutherland proposed that theophylline competitively inhibited cyclic nucleotide phosphodiesterase, thereby raising intracellular cyclic 3′-5′-adenosine monophosphate (cyclic AMP) concentrations and thus relaxing bronchial smooth muscle. This would imply that the combination of a β2-agonist with theophylline would be synergistic in producing bronchodilatation. Phosphodiesterase inhibition, however, requires theophylline concentrations some 10 times higher than those causing bronchodilatation in man in vivo,24 and other drugs that are more potent phosphodiesterase inhibitors are poor bronchodilators in vivo. Furthermore, most studies in man fail to show synergistic bronchodilatation when β2-agonists are combined with theophylline.25 None the less, combining theophylline with a β2-agonist may be of value in clinical practice. Muscle tremor is a major side effect of β2-agonists, particularly when given by mouth, but is only a serious problem with theophylline in doses that yield high plasma concentrations of the drug. Thus combining five puffs of aerosol terbutaline by inhalation (a β2-agonist) with theophylline given either intravenously (theophylline plasma concentration 5–10 μg/ml) or by mouth (plasma concentration 3–10 μg/ml) gave a 30% increase in FEV1, in stable asthmatics when using both drug regimens, but with very little muscle tremor. Although the same rise in FEV1, may also be obtained when five puffs of terbutaline by inhalation are combined with 5 mg terbutaline by mouth, tremor was then pronounced.26 Combining an oral theophylline in a dose to attain maximal therapeutic concentration (15–20 mg/ml) with aerosol salbutamol will also provide further bronchodilatation even in older patients with chronic bronchitis and emphysema, provided that they have some reversibility of airways obstruction to inhaled salbutamol alone.27 In another group of patients with moderately severe chronic bronchitis, however, the average peak flow rate (280 l/min) was only slightly increased, with no improvement in symptoms, when a slow release theophylline was used to produce these plasma theophylline concentrations without an added β2-agonist.28

In addition to this action as a bronchodilator, theophylline can also potentiate diuretics and increase cardiac output, even in patients with chronic hypoxic cor pulmonale.29 Intravenous terbutaline also raises cardiac output and reduces the pulmonary vascular resistance without producing any further fall in the arterial Po2 in similar patients.30 We have recently seen the same effects in patients with hypoxic cor pulmonale after giving the new β2-agonist pirbuterol by mouth, the effect being preserved after six weeks of chronic oral pirbuterol.31 Nevertheless, the possibility of a valuable interaction between theophylline and such a β2-agonist (presumably both given by mouth) in producing such pulmonary vasodilatation and increase in cardiac output in cor pulmonale has not yet been studied.

Another new action of theophylline has recently been described, as the drug may improve the mechanical performance of the diaphragm at therapeutic plasma concentrations, at least in acute studies of normal subjects who voluntarily fatigued their respiratory muscles.32 These potential actions on the heart, pulmonary circulation, and respiratory muscles may also contribute to the therapeutic benefit obtained from theophyllines and β2-agonists in practice in patients with asthma or hypoxic cor pulmonale.

Prevention of asthmatic attacks

Variability in airway calibre is the hallmark of asthma, whereas in chronic bronchitis and emphysema airflow limitation is relatively persistent. Prevention of the asthmatic attack depends on avoiding of trigger factors (pollen grains, housemice faecal particles, cold air, sulphur dioxide, etc) and also drug treatment to mitigate these effects. The underlying abnormality of the hyperreactive airways in the asthmatic patient may itself be reduced by preventing acute attacks, thus breaking a vicious cycle, so that regular bronchodilator treatment may itself serve to prevent further attacks.

inhaled steroids

inhaled steroids, as beclomethasone diproprionate (Becotide) or betamethasone valerate (Bestasol), both given by metered dose inhaler (or powder inhaler—Becotide Rotacaps) as two puffs up to four times daily in the adult, provide effective prevention that allows many asthmatics to be managed without oral steroids, or with a lower dose of oral steroids if these are necessary at all.33 Side effects are few, but rarely oral thrush occurs in high doses (up to eight puffs or more daily) and suppression of the pituitary adrenal axis may occur with very high doses (16 puffs a day). As with all preventive treatment for asthma, regular administration is essential even if the patient is not wheezy.

SODIUM CROMOGLYCATE

Sodium cromoglycate (Intal), by powder inhalation (Spincaps: 20 mg, 4-8 Spincaps daily) or pressurised aerosol inhaler (1 mg per puff, as two puffs 4-8 times daily) or as a nebuliser solution (20 mg in 2 ml, four times daily over two to five minutes by powered nebuliser) remains an effective method of preventing asthmatic attacks in many patients when used regularly.34 Cromoglycate is one of the safest drugs in medicine, but inhaling...
the dry powder occasionally induces mild bronchospasm. Like \( \beta_2 \)-agonists by inhaler, cromoglycate is valuable in preventing exercise induced asthma if taken beforehand. Although some patients find the powder (SpinCaps) preferable,\(^3\) others\(^4\) find equal benefit in prophylaxis with aerosol cromoglycate, despite the dose being 10 times less. Training in the coordination of nebuliser activation with the start of inhalation is essential, as with other aerosol inhalers, whereas the Spinhaler needs a hard suck to activate the device. SpinCaps do not work when high humidity, as in the tropics, causes the powder to clump.\(^5\)

**KETOTIFEN (ZADITEN)**

Ketotifen (Zaditen), a new oral agent for preventing asthma, has impressive antihistaminic and antianaphylactic actions in animals. Reports on the effectiveness of ketotifen as an asthma prophylactic have been variable, possibly as earlier studies may have used inadequate doses, and the drug is now known to produce its effects only after several weeks of treatment. In a double blind trial in 60 atopic children aged 3 to 10 years, 1 mg ketotifen twice daily improved symptoms (particularly nocturnal wheeze and cough) but only after eight to 12 weeks of treatment,\(^6\) whereas in a double blind trial in 50 atopic asthmatic adults 2 mg of ketotifen twice daily only slightly reduced the use of a salbutamol inhaler, or of symptoms, and then only in patients who were not maintained on inhaled steroids.\(^7\) Furthermore, a double blind comparison of 1 mg of ketotifen twice daily showed no advantage over inhaled cromoglycate in 32 asthmatic adults.\(^8\)

Drowsiness is a main side effect of ketotifen, commonly at the start of treatment, when it may occur in 14% of patients within the first month, but this declines to about 2% of patients after 12 months.\(^9\) One milligram of ketotifen, however, given once only slightly improved the quality and duration of nocturnal sleep in 10 adults whose asthma was stable, in a double blind comparison with placebo, and did not aggravate the mild nocturnal hypoxaemia that occurs when the depth of breathing falls during the rapid eye movement phase of sleep in such patients.\(^10\)\(^11\)

**ORAL STEROIDS**

Oral steroids (prednisolone) are still the mainstay of preventive treatment for the patient with severe asthma if other regimens, including inhaled steroids, fail to control symptoms adequately. A maintenance dose not exceeding 10 mg prednisolone a day in the adult should be the aim, as higher doses for prolonged periods carry the proven risk of severe side effects such as mooning of the face, obesity, purple skin striae, hypertension, osteoporosis, diabetes mellitus, hypokalaemic alkalosis, susceptibility to infections, and suppression of the pituitary adrenal axis. Higher doses for short periods of one week or under to control a severe attack are relatively free of such side effects, but the doses should be rapidly reduced to not more than 10 mg a day, and these higher doses should not be repeated too often if side effects are to be avoided.

The asthmatic patient must know to seek medical help urgently if regular medication (bronchodilators or preventive treatment) fails to provide the usual relief of his wheeze, for this may herald a life threatening attack of acute severe asthma.

**Acute severe asthma**

Acute severe asthma, a term now replacing the older status asthmaticus, is a medical emergency clinically recognised by severe wheeze (rarely, and gravely, the silent chest); inability to speak sentences without pausing for breath; a pulse rate over 100/min in the adult (rates over 130/min being very serious); possibly pulsus paradoxus; and central cyanosis, which may be difficult to recognise. Occasionally the attack may come on very rapidly\(^12\) and although proof is lacking,\(^13\) it seems probable that an emergency admission register (which allows self referral to hospital for the known “at risk” asthmatic) can save lives.\(^14\)

While in the home and arranging admission the general practitioner should give 200 mg of hydrocortisone intravenously slowly, followed by either 0-5 mg of salbutamol or terbutaline intramuscularly\(^15\) and oxygen, and also ensure that oxygen is given in the ambulance. These and subsequent doses apply to the average adult. In hospital 200 mg of hydrocortisone intravenously is repeated every six hours until the patient can take oral prednisolone 20 mg every six hours. Either nebulised salbutamol\(^16\) or terbutaline,\(^17\) both as 2-5 mg up to even 10 mg using a nebuliser driven by oxygen, with or without intermittent positive pressure breathing,\(^18\) are immediately given over three to six minutes, to be repeated every two to four hours.\(^19\) The role of an intravenous aminophylline infusion is less certain, but a recent study in moderately severe asthmatic adults (mean FEV\(_1\), 1-3 l, with values below 1-0 l in half the patients) showed that intravenous aminophylline (6 mg/kg over 20 minutes as a loading dose, followed by 0-6 mg/kg each hour, as recommended by the US Food and Drug Administration, 1980) gave no advantage in terms of improving forced expiratory volume in one hour that over all obtained by isoprenaline given every 20 minutes by a hand held nebuliser.\(^20\) Modern \( \beta_2 \)-agonists were not used in this North American study. Furthermore, elixir of aminophylline by mouth also raised plasma concentrations of the drug as rapidly as did the intravenous infusion in these patients. If aminophylline is infused both the loading and continuation doses should be halved if the patient is known to have been taking aminophylline, but in this case the only safe way of giving aminophylline is to monitor the plasma concentrations.\(^21\)

Oxygen should also be given continuously as 2-4 l/min by nasal prongs, for in these patients hypoxaemia is almost invariably when the FEV\(_1\) is below 1-0 l,\(^22\) so that severe asthmatics may be very hypoxic when breathing air during an acute attack. This is usually associated with a low PC\(_{\text{O}_2}\) and respiratory alkalosis, however, but a high PC\(_{\text{O}_2}\) particularly if it is rising, is an indication for mechanical ventilation in the asthmatic attack. Thus in addition to a plain chest x ray examination to exclude a potentially lethal pneumothorax the emergency assessment should include measurement of arterial blood gas tensions and electrocardiograph monitoring during the first 24 hours. Mechanical ventilation is rarely needed,\(^23\) but indications include severe drowsiness, confusion, exhaustion, or a PC\(_{\text{O}_2}\) rising above normal levels.\(^24\)

**Oxygen treatment**

Oxygen treatment aims at restoring adequate delivery of oxygen to body cells. Arterial hypoxaemia, the main reason for oxygen treatment in lung disease, is clinically recognised by central cyanosis that is detectable when 1-5 g/dl of reduced haemoglobin is present in arterial blood.\(^25\) This occurs when the arterial PC\(_{\text{O}_2}\) is 50-60 mm Hg (6-7-9 kPa). The widely quoted textbook figure of 5 g/dl of reduced haemoglobin as necessary for detection of cyanosis implies that the arterial PC\(_{\text{O}_2}\) is 30-40 mm Hg (4-0-5-3 kPa), which experience suggests is much too low. Oxygen at concentrations of 25-35% is best given by nasal prongs which are tolerated far better than any mask.\(^26\) At a normal respiratory rate, 21 l/min of oxygen by nasal prongs gives an inspired oxygen of 25-30%.\(^27\) Nasal prongs are particularly useful for such controlled oxygen treatment during an exacerbation of chronic bronchitis and emphysema, when CO\(_2\) retention complicates arterial hypoxaemia (type 11 respiratory failure). Controlled oxygen treatment should then be used to raise the arterial PC\(_{\text{O}_2}\) to over 50 mm Hg (6-6 kPa) without the arterial pH falling below 7-25, or hydrogen ion above 55 mmol/l, this being a much better guide to treatment than the level of PC\(_{\text{O}_2}\) in these patients.\(^28\)
PULMONARY OXYGEN TOXICITY

Pulmonary oxygen toxicity starts as damage to the pulmonary vascular endothelium but may lead to severe lung injury. This is a real risk in patients who are continuously exposed to oxygen concentrations over 50% for more than 48 hours. It is thus a problem in treating the adult respiratory distress syndrome where arterial hypoxaemia arises from shunting of blood through unventilated alveoli, so making the hypoxaemia relatively refractory to increases in the inspired oxygen concentration. This poses an agonising dilemma as giving further oxygen will increase lung damage, yet it is essential to maintain a mixed venous Po2 of 30 mm Hg (4 kPa) and thus keep the patient alive. Pulmonary oxygen toxicity arises from short lived activated chemical species of oxygen, potentiated by chemotactic attraction of polymorphs into the damaged lungs, the polymorphs themselves releasing further activated oxygen in their microbial killing by the phagosomal myeloperoxidase halide system.

Possible solutions to this oxygenation dilemma in the adult respiratory distress syndrome include giving just enough oxygen to keep the mixed venous Po2 above 30 mm Hg; mechanical ventilation with positive end expiratory pressure; or prolonged extracorporeal membrane oxygenation—possibly the most expensive treatment in medicine. A controlled trial of extracorporeal membrane oxygenation showed no advantage over mechanical ventilation with positive end expiratory pressure, at least in desperately ill patients with this syndrome, although combining CO2 removal by partial extracorporeal membrane oxygenation with provision of oxygen by ventilation at two breaths a minute may be successful in some patients. Mechanical ventilation at very high frequencies may yet solve this dilemma, but although current experimental work is exciting, the technique has yet to be tested by controlled trial in the adult respiratory distress syndrome.

LONG TERM CONTINUOUS OXYGEN TREATMENT

Long term continuous oxygen treatment has recently been the subject of two controlled trials in patients with cor pulmonale and hypoxaemia from chronic bronchitis and emphysema. Combining the results indicates that for these patients treatment without oxygen carries a very bad prognosis (66%, mortality at three years) but that oxygen given for part of the day can improve survival, whereas oxygen given for most of the day is best of all. Putting these notions into practice means that oxygen should be provided for patients with cor pulmonale due to chronic bronchitis and emphysema who have a Po2 of 50 mm Hg (6-6 kPa) or below measured when they are awake breathing air if other considerations, including age, social circumstances, absence of other life threatening disease, no cigarette smoking (see below) all indicate that such expensive long term treatment is reasonable. Oxygen should be given for 20 or more hours in 24 hours, at a flow rate sufficient to bring the arterial Po2 to over 70 mm Hg (9-3 kPa). This usually means 1-3 l/min of oxygen by nasal prongs. This is most economically provided at home by the oxygen concentrator and most expensively by oxygen in cylinders, as 20 F-size cylinders (1340 litres, 48 cu ft) are required each week. Unfortunately, cylinders are currently the only method available on the National Health Service drug tariff but concentrators are more and more in use, and it is hoped that they will shortly become available for the NHS, thus uniquely both improving the quality of the service and also saving money. Long term oxygen treatment can prevent progression of pulmonary hypertension in these patients and correct polycythemia but only in the patient stopping smoking. The treatment is therefore only recommended for such hypoxic patients if their blood carboxyhaemoglobin concentration is below 5%, on repeated testing, as this then indicates that they are not chronic cigarette smokers. Smoking also carries a life threatening hazard from burns if they smoke while receiving oxygen. It has been suggested that oxygen at night causes dangerous CO2 retention in patients with concomitant sleep apnoea. Although recurrent transient hypoxaemia during sleep when breathing air is common, however, and may be profound in these "blue and bloated" patients, this is rarely due to sleep apnoea but is much more likely the result of hypoventilation during rapid eye movement sleep. Furthermore, both of the controlled trials suggest that CO2 retention is more a theoretical than a practical problem for these patients when given controlled low concentrations of oxygen (1-3 l/min).

References

(R—Review article)

1. Allen CJ, Campbell P, Davies SP, Pavia D, Clarke SW. How should a pressurised β-


When and why did the disease “disseminated sclerosis” change its name to “multiple sclerosis”? 

Charcot first named the disease “sclérose en plaques disséminées” when he recognised it as an entity and detailed the main clinical and pathological features. Within a few years it was also known as “insular sclerosis” and “multiple sclerosis” in German pathology publications. The alternative terms “disseminated” and “multiple” have been used throughout this century with most references in British publications using the former until the 1940s and 1950s. The Quarterly Cumulative Index Medicus changed from disseminated to multiple as the principal term of reference in 1946. McAlpine and others followed the shift of preference in 1955 and explained that calling the disease disseminated unjustifiably implied that a causative agent is disseminated by blood or cerebrospinal fluid channels.——ALAN TURNER, registrar in neurology, London.

Should the early death of his brother from bronchial pneumonia, status epilepticus, and cerebral lipodosis worry the father of a 6 month old boy? Does this suggest a familial condition, and is whooping cough vaccination contraindicated?

Most cerebral lipodoses are inherited as autosomal recessive conditions. Presuming this to be the inheritance in this case (X-linkage is not a question as the father cannot transmit the gene to his son), the father whose sibling died at the age of 6 years has a two-thirds chance of carrying the same gene. He would, however, need to marry another carrier to have an affected child. This would be highly unlikely provided that he did not marry a relative. Tay Sachs disease and Neiman Pick disease are common lipodases in Ashkenazi, but death at the age of 6 years makes Tay Sachs disease unlikely. If this is an Ashkenazi family, however, I would recommend carrier testing for the man and his wife for these two conditions. If this is not the case the risks are to the 6 month old boy, and indeed to further children on this couple, are very low. Amniocentesis would not be indicated. Whooping cough vaccination is not contraindicated.—MICHAEL BARAITSER, consultant clinical geneticist, London.