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Referencia : Expediente No. **00 – 034.118**
Asunto : Solicitud de patente para Nuevas **COMPOSICIONES DE MEDICAMENTOS A BASE DE COMPUESTOS ANTICOLINÉRGICAMENTE ACTIVOS Y β -MIMÉTICOS**
Solicitante : **BOEHRINGER INGELHEIM PHARMA GMBH & CO. KG**
Fecha de Solicitud : 11 de Mayo de 2000

1. Yo, Emilio FERRERO, obrando como apoderado del solicitante en el asunto antes identificado, me refiero al oficio número 12615, notificado por fijación en lista el 21 de Abril de 2005.

2. Mediante el oficio número 12615 su Despacho solicitó se adjuntarán los artículos de REES y BARNES, de acuerdo con lo establecido por el Artículo 46 de la Decisión 486 de la Comunidad Andina.

3. Atiendo a las observaciones realizadas mediante el oficio número 12615 presentando junto con este memorial los siguientes artículos:

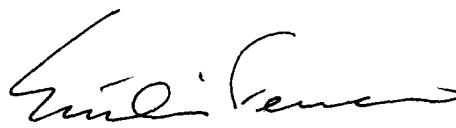
3.1. REES P. J.: "Bronchodilators in the therapy of chronic obstructive pulmonary disease". EUROPEAN RESPIRATORY MONOGRAPH, (1998) 3/7 (135-149)., XP000937584 page 142, paragraph 5 - paragraph 6; figura 8.

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3.2. BARNES P J: "Chronic obstructive pulmonary disease: new opportunities for drug development" TRENDS IN PHARMACOLOGICAL SCIENCES, GB ELSEVIER TRENDS JOURNAL, CAMBRIDGE, vol. 19, no. 10, October 1998 (198-10), pages 415-423, XP004156947. ISSN: 0165-6147 page 416, column 2, paragraph 1.

4. Puesto que se han atendido a cabalidad las observaciones hechas por su Despacho sobre la presente solicitud de patente, atentamente solicito a ustedes que se continúe su tramitación.

Bogotá, 18 JUL. 2005
Señora Jefe,


EMILIO FERRERO
T.P.A. No. 31.929

 COLO 13736-805-024-1
PRP/PRP/ID-000541/WPC13736

Bronchodilators in the therapy of chronic obstructive pulmonary disease

XP-000937584

P.J. Rees

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The use of bronchodilators is an important element in the treatment of chronic obstructive pulmonary disease (COPD), although there is often a limited reversibility of measured airflow obstruction. Bronchodilators currently available have other potential effects in addition to their role in the relaxation of airways smooth muscle. Three types of bronchodilator are in common clinical use: 1) β -adrenoceptor agonists; 2) anticholinergic drugs; and 3) methylxanthines.

Assessment of bronchodilators

The effects of bronchodilators on the airways are most often assessed by measurements of maximal expiratory airflow such as peak expiratory flow and spirometry. These changes in response to bronchodilators cannot be assessed on their own in the distinguishing of COPD from asthma [1], since there is no distinct group of responders; the change produced by bronchodilators seems to be a continuous variable. The changes, seen after bronchodilator administration are often expressed as a percentage increase from the baseline value. These percentage increases are very dependent on the baseline level and in severe COPD changes of 15-20% in forced expiratory volume in one second (FEV₁) are well within the limits of reproducibility of the measurement. Changes are better expressed as absolute change or as a percentage of the predicted FEV₁ [2] (fig. 1). A change which is likely to be clinically significant and outside the variability of the test, is often regarded as an FEV₁ increase of at least 15%, as long as this is at least 200 mL.

Spirometry is a simple measurement and is reproducible if performed carefully. This makes it the most frequently used method of assessment. However, the main aim of treatment in COPD is the relief of symptoms, thus exercise tolerance and quality of life measurements are also important parameters in the evaluation.

It has become evident that the degree of reversibility in response to bronchodilators in patients with COPD is not always a consistent response [3]. This means that it is not necessarily reliable to base longer-term treatment on

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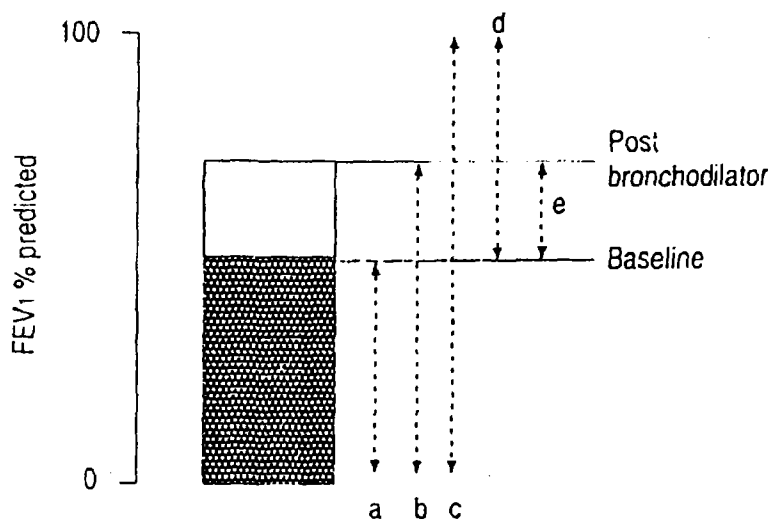


Fig. 1. - Bronchodilator responses in chronic obstructive pulmonary disease: methods of expressing bronchodilator responses. e: absolute change (b-a); $100 \times (e/a)$: percentage changes; $100 \times (e/d)$: percentage of possible change to reach predicted value; $100 \times (e/c)$: change as percentage predicted. FEV₁: forced expiratory volume in one second.

the results of a single test of reversibility [4], although such tests can produce some useful predictive information [5].

In addition to their variability, the changes seen in spirometry do not always correlate with subjective effects or with changes in maximum exercise ability or standard walking tests. A number of studies have found significant increases in walking distances in the absence of any significant changes in spirometric data [6]. Breathlessness may be reduced by prevention of dynamic hyperinflation, which may occur on exercise in patients with COPD [7].

In the assessment of bronchodilator effects a number of elements are important. When a submaximal dose of bronchodilator is used a further effect can be produced by giving a larger dose of the same drug or by adding a second agent. Assessment of the responses can be made after a single dose or as part of a dose-response curve. Even when a maximal initial effect has been obtained, a larger dose of the same drug may increase the duration and usefulness of the response without increasing the peak effect. The variability of the responses and the need for prolonged treatment means that single dose or single day studies need to be supplemented by prolonged studies. These are less frequent in the literature concerning COPD. In addition bronchodilator responses in acute exacerbations of COPD need to be considered separately from responses in stable COPD.

The method of delivery is an important factor in the prescription of bronchodilator drugs in COPD. Theophyllines are given orally and as such, blood levels should be frequently checked as a result of the higher incidence of adverse effects presented by use of the oral route. β -agonists are effective orally but side-effects are reduced by the use of the inhaled route. A variety of inhaler devices are available although these vary between countries and between drugs. The delivery of drug to the lung varies between devices and

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with technique. In general older people are more likely to have problems with inhaler technique [8] although most can be taught to use one of the available devices effectively. The device should be specified as part of the prescription of a bronchodilator and the prescriber must ensure that the patient is taught how to use the device prescribed and that their technique is checked periodically.

β -adrenoceptor agonists

These activate surface β -receptors which are found on airway smooth muscle from trachea to terminal bronchioles. In human airways these receptors are all β_2 -receptors. Stimulation of the receptors increases intracellular cyclic adenosine monophosphate (CAMP), which activates protein kinase A. This produces phosphorylation of several substances and opens potassium activated calcium channels in the cell membrane. They also act as vasodilators, increase mucus secretion and mucociliary clearance. The relevance of any additional effects of β -agonists on inflammatory cells and sensory nerves are uncertain.

In asthma β -agonists are the most effective bronchodilators available. In COPD the picture is less clear. The large intermittent positive pressure breathing (IPPB) trial group study in North America showed that inhaled β -agonists produced a degree of bronchodilatation in most patients at some point in the trial [9].

Oral salbutamol produces a small effect. In one study, 58 patients were given 8 mg controlled release salbutamol *b.i.d.* for 6 weeks. FEV₁ increased slightly, but walking distances did not change significantly. Patients did not detect a benefit and adverse effects such as tremor (in 26% of the group) were common [10]. Such findings suggest that there is little reason to choose oral β -agonists in COPD.

The dose of β -agonist should be adjusted, since there appears to be a dose response to β -agonists [11, 12] and higher doses may extend the length of action [13]. However, tremor is also common at high doses of β -agonists given by inhalation [13].

The Combivent study of β -agonists and anticholinergic drugs in COPD revealed a slight decline in β -agonist-induced bronchodilatation over the 12 weeks of the study [14] (fig. 2). Similar studies in asthma indicate that any decline is small and is easily reversed by a short break in treatment or by corticosteroids. It has been shown that regular use of β -agonists in asthma reduces the protection against bronchoconstriction [15], but this may not be so important in COPD. It has been suggested that the regular use of β -agonists or of anticholinergic drugs may increase the rate of decline of FEV₁ in asthma and COPD [16]. However, the much larger North American Lung Health Study [17] has shown that this is not the case when anticholinergics are used regularly in COPD (fig. 3). This raises considerable doubts about the suggestion of adverse effects from regular β -agonists or from anticholinergics or β -agonists in asthma.

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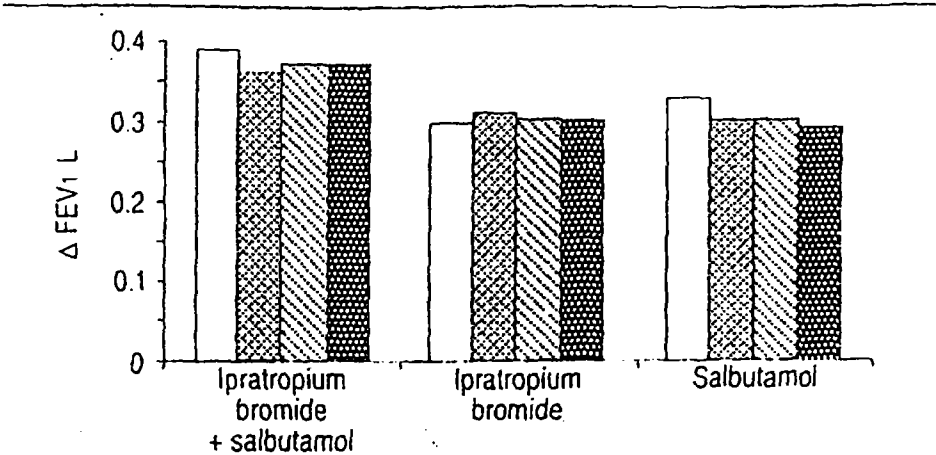


Fig. 2. — Change in maximum forced expiratory volume in one second (ΔFEV_1) produced through 12 weeks of bronchodilator treatment in patients with chronic obstructive pulmonary disease recruited to the combivent study. The greatest responses were seen in those receiving combined therapy at ipratropium bromide and salbutamol. $\square$: at day 1; diagonal lines : at day 29; cross-hatch : at day 57; dots : at day 85. (Adapted from [14]).

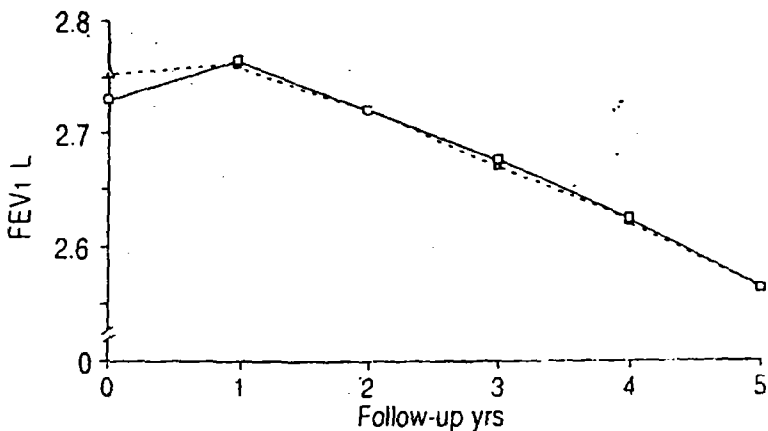


Fig. 3. — Change in forced expiratory volume in one second (FEV_1) with regular ipratropium bromide (—○—) or placebo (---△---) over a period of 5 yrs in the North American Lung Health Study. The rate of decline of FEV_1 was not affected by the use of a regular anticholinergic bronchodilator. (Adapted from [17]).

Some studies have suggested that there is a decrease in response to β -agonists with age [18, 19], but this has not been the finding in all studies [20, 21]. The relationship between age and bronchodilator response in some studies is complicated by the increased prevalence of COPD rather than asthma, in older patients. Anticholinergic responses do not decline with age in these studies.

In acute exacerbations of COPD β -agonists and anticholinergic drugs appear to be equally effective. The vasodilating action of β -agonists means that reversal of hypoxic vasoconstriction and increase in ventilation/perfusion mismatch can lead to a small drop in arterial oxygen tension (P_{aO_2}) in acute

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Table 1. - Effect of salmeterol in chronic obstructive pulmonary disease

	Salmeterol	Placebo
Morning peak flow L·min ⁻¹	238	226
Evening peak flow L·min ⁻¹	242	237
Symptom score	1.9	3.4*
Rescue salbutamol·day ⁻¹	1.7	2.9*

*: $p < 0.05$, compared to salmeterol. (Adapted from [23]).

COPD [22]. This can be prevented by driving the nebulizer with oxygen or by giving oxygen by nasal cannulae during the administration of the β -agonist. The use of oxygen in this way may present difficulties when carbon dioxide retention is a feature of the exacerbation.

The development of long-acting inhaled β -agonists introduces new possibilities in the treatment of COPD. Two available agents, salmeterol and formoterol, have proved useful in asthma. In COPD they have been shown to improve symptoms and morning peak expiratory flow (PEF) [23] (table 1). Their bronchodilating effect lasts for 12 h or more; although one study suggests a slightly shorter action for formoterol than salmeterol at recommended doses [24]. A number of small trials have shown benefits. One study has suggested that addition of an anticholinergic drug to the long-acting β -agonist produced no extra benefit [25]. Where bronchodilators are taken frequently, the long-acting agents may simplify use and reduce symptoms. Further medium- to long-term studies are needed to define more clearly the best role for these long-acting inhaled β -agonists in the management of COPD.

β -agonists can produce transient hypokalaemia. In older patients with ischaemic heart disease the combination of diuretics and β -agonists, even by inhalation, may reduce serum potassium further [26]. However, arrhythmias are not commonly a problem and the reduction of the metabolic effects of β -agonists with regular use [15] may explain the absence of problems with prolonged β -agonist use in COPD.

Anticholinergic agents

Cholinergic nerves are the main pathway for bronchoconstrictor nerves in human airways. The innervation on the smooth muscle is most prominent in the larger airways, being present but to a lesser extent in the smaller airways. Cholinergic nerves are the pathway for reflex bronchoconstriction from stimulation of sensory nerves in the airways or elsewhere. These effects are mediated through muscarinic receptors. Subtypes of muscarinic receptors have been delineated and three of these subtypes have been demonstrated in human airways (table 2, fig. 4).

The available anticholinergic drugs such as ipratropium bromide are not selective, they block M_1 and M_3 receptors. It is possible that drugs which act selectively as M_1 receptor blockers might be more effective in the treatment of COPD.

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Table 2. - Subtypes of muscarinic receptors present in human airways

M ₁ receptors	In autonomic ganglia where they may facilitate the usual nicotinic receptors. They are also present in submucosal glands.
M ₂ receptors	On postganglionic nerves where they inhibit release of acetylcholine. Potentially, blockade of M ₂ receptors alone would result in an increased effect of cholinergic nerve stimulation through removal of the negative feed back.
M ₃ receptors	Present on airway smooth muscle and submucosal glands

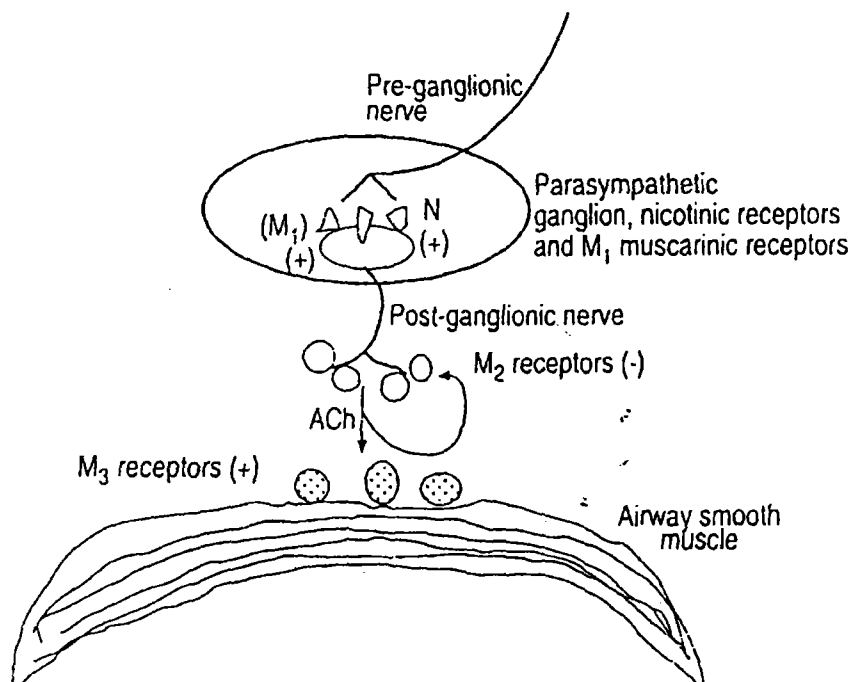


Fig. 4. - Muscarinic receptor subtypes in the human airway. Current anticholinergic drugs are nonspecific. Drugs specific for the M₁ receptors might produce a greater effect leaving the negative feedback (-) of the M₂ receptors on the postganglionic nerve unaffected. ACh: acetylcholine.

Current anticholinergic agents have a slower onset of bronchodilatation than β -agonists [27]. Their peak effect is reached in 30-90 min but the effect lasts longer than conventional short-acting β -agonists, some degree of bronchodilatation being maintained for 6-10 h. Dose-response studies with ipratropium bromide [28] and oxitropium bromide [29] show that the maximal effect is usually produced at doses of 40-80 mcg and 200 mcg, respectively. The conventional dose of ipratropium bromide is 40 mcg although this may be on the low side according to some studies [28].

Oxitropium bromide may act for a slightly longer period of time than ipratropium bromide [29], although newer agents with a substantially longer duration of action are being developed. Tiotropium produces a peak response at 1.5-2 h and the effect persists for 10-15 h [30, 31] (fig. 5). Its protection against the bronchoconstrictor effects of methacholine lasts for 48 h.

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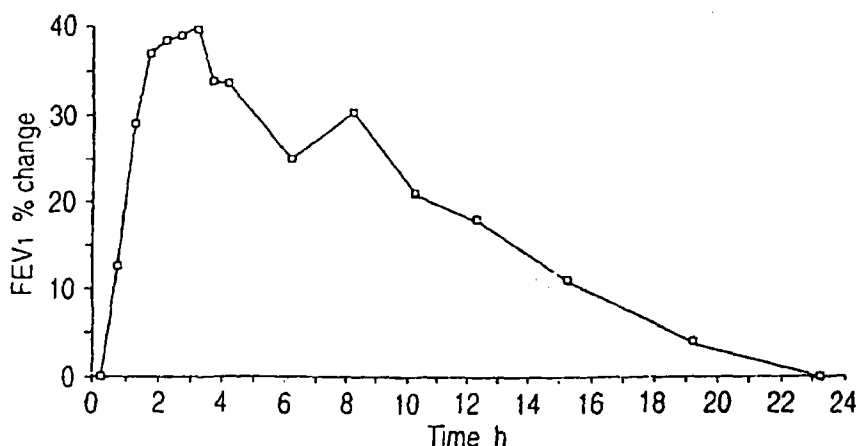


Fig. 5. – The response of tiotropium, a new anticholinergic agent with a prolonged bronchodilator response, in chronic obstructive pulmonary disease. FEV₁: forced expiratory volume in one second. (Adapted from [30]).

One part of the North American Lung Health Study compared the combination of either placebo or ipratropium bromide added to smoking cessation advice [16]. This showed that the bronchodilator effect of ipratropium bromide was maintained over the 5 yrs of the study and that the regular use of ipratropium itself made no difference to the rate of decline of FEV₁ (fig. 3). These results confirm that bronchodilators should be used for their symptomatic effect and cannot be expected to produce any other significant benefit on the natural history of COPD.

On terminating use of regular anticholinergics there is a short-lived rebound decrease in FEV₁ at about 30 h which disappears by 48 h [32]. These effects are small and do not affect the practical use of ipratropium bromide.

In acute exacerbations of COPD anticholinergic agents are effective bronchodilators. The effect is equal to that of β -agonists although of slightly slower onset. Anticholinergics do not produce the vasodilatation shown by β -agonists and, consequently, there is no problem with a reduction in P_{aO_2} [22].

There is an anxiety that anticholinergic drugs might have systemic effects such as urinary retention, constipation, drying of secretions or precipitation of glaucoma. Mucociliary clearance is not impaired by inhaled anticholinergic drugs [33]. The quaternary ammonium compounds such as ipratropium bromide are minimally absorbed and systemic effects are very rarely a practical problem, although intraocular pressure can rise [34] and precipitation of glaucoma has been reported [35]. The presence of glaucoma may be an anxiety with nebulized drugs when local ocular deposition arises as a result of a poor fitting mask.

Methylxanthines

Drugs from this group have a long history of use in COPD. The agent in common use from the methylxanthine group is theophylline. Theophylline

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acts on large and small airways. The mechanism of action of methylxanthines is uncertain. They are inhibitors of phosphodiesterase, increasing intracellular adenosine monophosphate (AMP) concentration and they also inhibit adenosine receptors. In asthma it has been suggested that lower blood levels may be effective through an anti-inflammatory effect.

It has been proposed that methylxanthines have an additional effect on inspiratory muscle strength and may protect against fatigue. The clinical relevance of these findings is disputed [36, 37]. Other studies have suggested a benefit from reduction in trapped gas volume [38], but this may be related to changes in airway obstruction at different levels of the bronchial tree.

There are marked differences in theophylline clearance between individuals and in addition, a reduction in clearance with age [39] and with use of drugs such as erythromycin, cimetidine, ciprofloxacin and allopurinol. The slow release preparations of theophylline have simplified use by allowing a more stable and reliable control of blood levels. Most of the studies in COPD have examined the effects of stable blood levels after 2-12 weeks of therapy. Slow release theophylline has been shown to reduce nocturnal desaturation and night-time symptoms [40] and may provide an alternative to long-acting inhaled agents for such symptoms.

In patients with no significant reversibility to inhaled bronchodilators theophylline as a single agent, can produce a small effect on spirometry and a variable effect on some other assessments. In some of these studies symptoms were reduced [41] but in others patients could not differentiate between theophylline and placebo despite an improvement in spirometry [42]. Blood levels of 15-20 mg·L⁻¹ are required to produce an optimal effect on the airways with little or no benefit identifiable at 10 mg·L⁻¹ [42, 43]. Studies on exercise tolerance show variable results; most show an improvement but comparison with the effects produced by inhaled bronchodilators are uncertain.

Combination therapy

In many of the studies available, it is difficult to be sure how the combination therapy investigated would have compared with a higher dose of a single agent. In practice, it may be sensible to consider a combination at a lower dose to minimize the adverse effects of each agent. However, inhaled β-agonists and anticholinergics are relatively free of side-effects.

In acute exacerbations of COPD it appears that high doses of β-agonists and anticholinergic drugs delivered by nebulizer have equivalent effects [44] and that no extra effects and no additional benefit can be achieved by combining the drugs [44, 45] (fig. 6). This is in contrast to the situation in acute asthma where there does appear to be a small benefit over the first 24-48 h from the combination of the two agents. The position of methylxanthines in acute exacerbations of COPD is less clear. In patients who are taking regular oral methylxanthines, the addition of *i.v.* aminophylline may easily produce toxic levels. Ideally, the concentration of bronchodilator in the blood should be ascertained. One study has found no benefit from the addition of aminophylline to nebulized therapy in COPD exacerbations [46].

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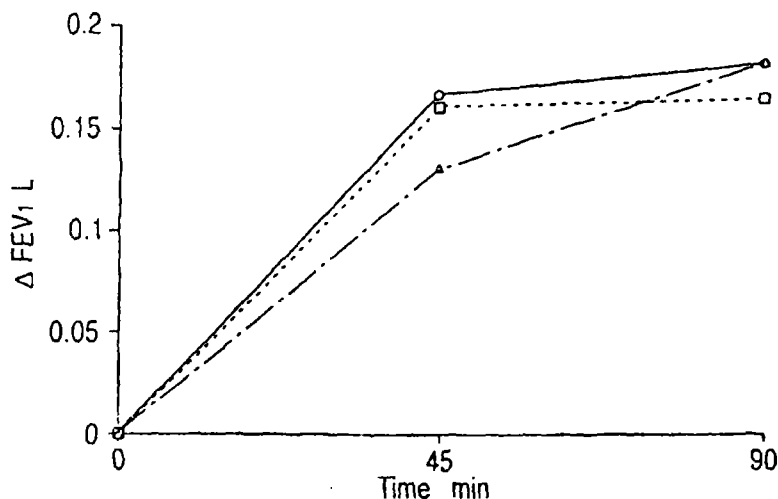


Fig. 6. — Combined bronchodilators in acute exacerbations of chronic obstructive pulmonary disease. Two large doses of β -agonist (fenoterol) and anticholinergic agent (ipratropium bromide) are similar and the combination does not produce a greater response. Δ FEV₁: change in forced expiratory volume in one second. —○— : ipratropium bromide + fenoterol; ---□--- : fenoterol; ---Δ--- : ipratropium. (Adapted from [44]).

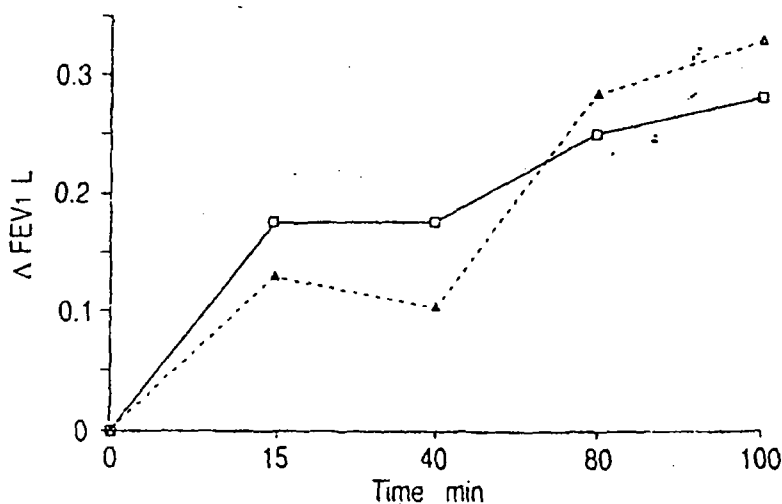


Fig. 7. — Combined bronchodilators in chronic obstructive pulmonary disease. In this study a β -agonist (salbutamol) and methylxanthine (theophylline) are combined with a greater effect produced by the β -agonist. Δ FEV₁: change in forced expiratory volume in one second; —□— : salbutamol followed by theophylline; ---Δ--- : theophylline followed by salbutamol. (Adapted from [47]).

In chronic stable COPD single dose studies show that oral theophylline adds to the effects of 800 mcg inhaled salbutamol [47] (fig. 7). Longer-term studies show that theophylline can produce an additional effect on inhaled treatment at blood levels of 17 mg·L⁻¹, but not at 10 mg·L⁻¹ [43].

Many single-dose studies of lower dose β -agonists and anticholinergics show a benefit from the combination [48, 49]. Whereas in asthma β -agonist

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responses are superior to anticholinergics, studies in COPD indicate a more equivalent position. Comparative studies show that at higher doses the two agents are equal [50]. A number of studies have attempted to achieve a maximal response from β -agonists and then shown that anticholinergics can produce an additional effect on top of this plateau [51-53].

There are, however, individual differences, with some patients responding to one agent and not another [20]. This may be part of the variability of the bronchodilator responsiveness shown in the poor prediction of longer-term responses from individual dose studies.

In a large 12 week study of salbutamol, ipratropium and the combination at usual doses, the combined treatment produced the greatest effect [14] (fig. 2). Most patients were administered treatment *q.i.d.*. Of these patients, 80% were already on theophylline. The combination therapy was maintained throughout the 12 week study with no increase in adverse effects. However, disappointingly, symptom scores were not improved by any of the regimens in this study although the baseline spirometry indicated that they were a severe group (FEV₁ 37% pred). Improvements have been seen in some studies with nebulized drugs [54] although a similar study with nebulized therapy showed a spirometric benefit from combined therapy without differences in symptoms or quality of life [55]. A single dose study of 26 COPD patients has found that, compared with 40 mcg ipratropium bromide alone, doubling the dose had no effect, but the combination of 40 mcg ipratropium and 200 mcg salbutamol produced a greater response [56] (fig. 8). In this study the best response was produced by a higher dose of both agents, 80 mcg ipratropium bromide and 400 mcg salbutamol.

Adherence to therapy

It is well known that adherence to long-term regular therapy is poor in all chronic disease. A partnership between patient and doctor with understanding and agreed goals may help. In the North American Lung Health Study [57], drugs recommended for use *t.i.d.* were prescribed, but only 15% of the subgroup studied achieved average use of more than 2.5 times daily. In contrast 73% claimed to have used the ipratropium bromide *t.i.d.*. Since the rate of FEV₁ decline is not affected by anticholinergics and they are given for symptom relief, the anxieties about compliance with regular use are less of an issue. However, if regular use could improve exercise tolerance then this might maintain skeletal muscle function and allow more effective rehabilitation. In that case there may be long-term benefits to be achieved by the maintenance of optimal bronchodilatation.

Compliance with inhaled therapy is difficult to measure. Some inhaler devices, particularly those with dry powder, have dose counters, but the timing of dose delivery is still uncertain. When patients know that their adherence to therapy is being monitored they may fire a metered dose inhaler repetitively without inhalation, particularly just before a consultation. During theophylline therapy plasma levels provide a method of monitoring adherence with planned therapy.

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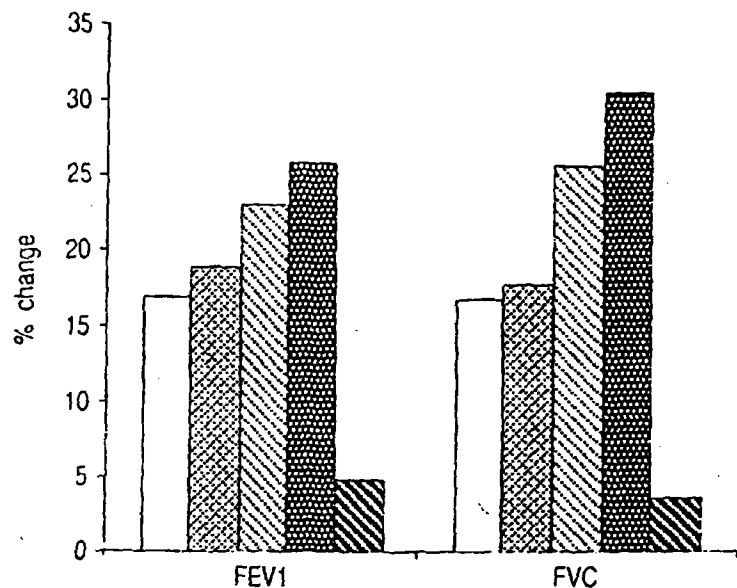


Fig. 8. - Combined therapy in chronic obstructive pulmonary disease. The addition of salbutamol to 40 mcg ipratropium bromide produced a greater effect than doubling the dose of the anticholinergic agent. The best response was produced by 80 mcg ipratropium bromide and 400 mcg salbutamol; both twice the most frequently used doses. FEV₁: forced expiratory volume in one second; FVC: forced vital capacity. □ : 40 mcg ipratropium bromide; ▨ : 80 mcg ipratropium bromide; ▩ : 40 mcg ipratropium bromide + 200 mcg salbutamol; ■ : 80 mcg ipratropium bromide + 400 mcg salbutamol; ▤ : placebo. (Adapted from [56]).

Nebulizers

An important element of inhaled bronchodilator therapy is the delivery of the drug to the patient. A suitable delivery device must be found. This is usually a metered-dose inhaler or dry powder system. Nebulized therapy provides a method of delivering higher doses of β -agonists and anticholinergic drugs to the airways. Both β -agonists and anticholinergics drugs have a shallow dose-response but the higher doses possible with a nebulizer may also extend the length of the response. In most cases the same effects can be produced by other devices such as metered-dose inhalers with chamber devices. Similar problems of compliance exist with nebulizer treatment [58] and there is an additional expense for the compressor, nebulizer and solutions. Many patients are very keen on nebulized treatment and may choose this even in the absence of any subjective or objective benefit [59]. Their use should be assessed over a period of weeks at home [60] although in practice it may be difficult to persuade a patient to give up their nebulizer. A local scheme of continued supervision and machine maintenance is required to back up the provision of nebulized therapy.

Rational use of bronchodilators in COPD

Bronchodilators are prescribed mainly for symptomatic relief. In a chronic condition such as COPD this means finding a drug and delivery system that

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the patient is happy with. Since the obstruction is not completely reversible, administration will often be a regular dose with an additional opportunity for symptom relief.

β -agonists and anticholinergics seem to be more or less equivalent and can be given for either acute or chronic therapy. If the response is inadequate the dose can be increased or a combination prescribed. The introduction of long-acting agents raises the possibility of a more stable background bronchodilation with an additional short-acting agent for relief. If symptoms remain prominent and exercise tolerance limited then addition of theophylline with monitoring of blood levels should be considered.

Throughout the treatment of COPD the physician has an important role in monitoring inhaler technique, explaining the aims of therapy and encouraging a positive attitude.

Summary

Bronchodilators are an important form of treatment to reduce symptoms in chronic obstructive pulmonary disease (COPD). Three categories of bronchodilator are available: β -adrenergic agonists; anticholinergics; and methylxanthines. The first two have the advantage that they can be given by the inhaled route, thus, reducing potential adverse effects. Subjective benefits do not always relate closely to spirometric changes. There is no convincing evidence that bronchodilator drugs alter the natural history of the disease. The effect of anticholinergic drugs is equivalent to or greater than the β -agonist effect in COPD. When the response to a submaximal dose of one agent is inadequate the combination of the two drugs may be helpful. Some studies suggest an additional effect from methylxanthines but the potential for adverse effects is greater. Long-acting inhaled bronchodilators offer a promising addition to bronchodilator therapy in COPD.

In acute exacerbations β -agonists and anticholinergics produce similar effects and there seems to be no benefit from the combination.

Attention must be paid to the ability of the patient to use the delivery device prescribed and to education and explanation to maximize adherence to the therapy. Bronchodilator use should be seen as an important element of an integrated regimen of care in COPD.

Keywords: Anticholinergics, β -adrenergic agonists, bronchodilators, methylxanthines.

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Chemical names

ICI164384: *N-n*-butyl-*N*-methyl-11-[3,17 β -dihydroxy-oestra-1,3,5-(10)-trien-7 α -yl]undecanamide

ICI182780: 7 α -[9-(4,4,5,5,5-pentafluoropentylsulphonyl)nonyl]-oestra-1,3,5(10)-triene-3,17 β -diol

Chronic obstructive pulmonary disease: new opportunities for drug development

Peter J. Barnes

Chronic obstructive pulmonary disease (COPD) is common and there is an increasing worldwide prevalence. There are no available treatments to prevent the progression of airflow obstruction, but greater understanding of the molecular and cellular mechanisms involved in COPD has identified many new therapeutic targets, including inflammatory mediators, proteases and adhesion molecules. In this review, **Peter Barnes** considers potential new drugs for this neglected disease.

Chronic obstructive pulmonary disease (COPD), sometimes called chronic obstructive airways disease, is a major health burden and accounts for 10% of all working days lost and over 15 000 deaths each year in the UK (Ref. 1). COPD is characterized by slowly progressive airflow obstruction, resulting in increasing shortness of breath and exercise limitation. It affects 6% of men and 4% of women over 45 years in the UK. It has an increasing worldwide prevalence and now ranks fifth in terms of global burden of disease². Treatment is often unsatisfactory and there are no currently available treatments that influence its progressive course. Many patients with COPD are under-treated, whereas others are treated as though they have asthma, and this is usually inappropriate.

In contrast to the enormous increase in our understanding of the pathophysiology of asthma, COPD has been virtually ignored. The chronic airflow obstruction results from a combination of airway disease, which particularly affects small airways, and loss of lung

elasticity because of enzymatic destruction of the lung parenchyma (Box 1). It is likely that the latter predominates in most patients and, while this might be irreversible, it is likely to be preventable with suitable treatment³. While there have been some recent advances in the treatment of COPD, with improvement in bronchodilator therapy, there is a need for the development of new treatments that prevent the progressive airflow obstruction.

New bronchodilators

Bronchodilators are the mainstay of current management of COPD, but fail to alter the progression of COPD (Ref. 4). The major recent advances have been in the development of long-acting bronchodilators.

New anticholinergics

Anticholinergics are the bronchodilators of choice in the management of COPD and are more effective than short-acting β_2 -adrenoceptor agonists. The existence of several subtypes of muscarinic (M) receptors in airways has suggested that more selective muscarinic antagonists might have advantages over the existing nonselective drugs, such as ipratropium bromide and oxitropium bromide⁵. M_1 receptors are localized to parasympathetic ganglia and their block results in reduced reflex bronchoconstriction. The bronchoconstrictor action of acetylcholine in human airways is mediated entirely via M_1 receptors. By contrast, M_2 receptors located at cholinergic nerve terminals inhibit the release of acetylcholine, thus acting as autoreceptors (Fig. 1). Nonselective anticholinergics block M_1 and M_2 receptors, leading to bronchodilatation. However, blocking prejunctional M_2 receptors leads to an increase in acetylcholine release, and this might work against the postjunctional block of M_1 receptors, making these antagonists less efficient. It has been difficult to develop M_1 -selective antagonists, but darifenacin (UK88525) is reported to be M_1 -selective and is in clinical development⁶. A mixed M_1 / M_2 antagonist revatropate (UK112166) is in clinical development as a bronchodilator for COPD (Ref. 6).

The most interesting drug in development is tiotropium bromide (Ba 679), which has the unique property of kinetic selectivity, with rapid dissociation from

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Box 1. Definition of terms

- *Chronic simple bronchitis* is defined by a productive cough on most days for at least two consecutive years and is a consequence of mucous hyperplasia and is not necessarily related to airway obstruction.
- *Chronic obstructive bronchitis* might be caused by obstruction of peripheral airways as a result of an inflammatory response in peripheral airways (bronchiolitis).
- *Emphysema* is a pathological diagnosis characterized by destruction of alveolar walls, resulting in abnormal enlargement of airspaces and loss of lung elasticity, with consequent obstruction of peripheral airways.
- *Chronic obstructive pulmonary disease (COPD)* is defined physiologically as chronic airflow obstruction and might be the result of a mixture of emphysema and peripheral airway obstruction from chronic bronchitis. Extensive pulmonary damage occurs before the patient is aware of the symptoms (such as exertional dyspnoea) because of the slowly progressive nature of the airflow obstruction and various coping manoeuvres. There might be a small degree of reversibility in airway obstruction (<15%), in contrast to the >15% reversibility and variability in the airflow obstruction in asthma.
- *Chronic hypoxia* occurs late in the illness and might result in *pulmonary hypertension* and right heart failure (*cor pulmonale*).

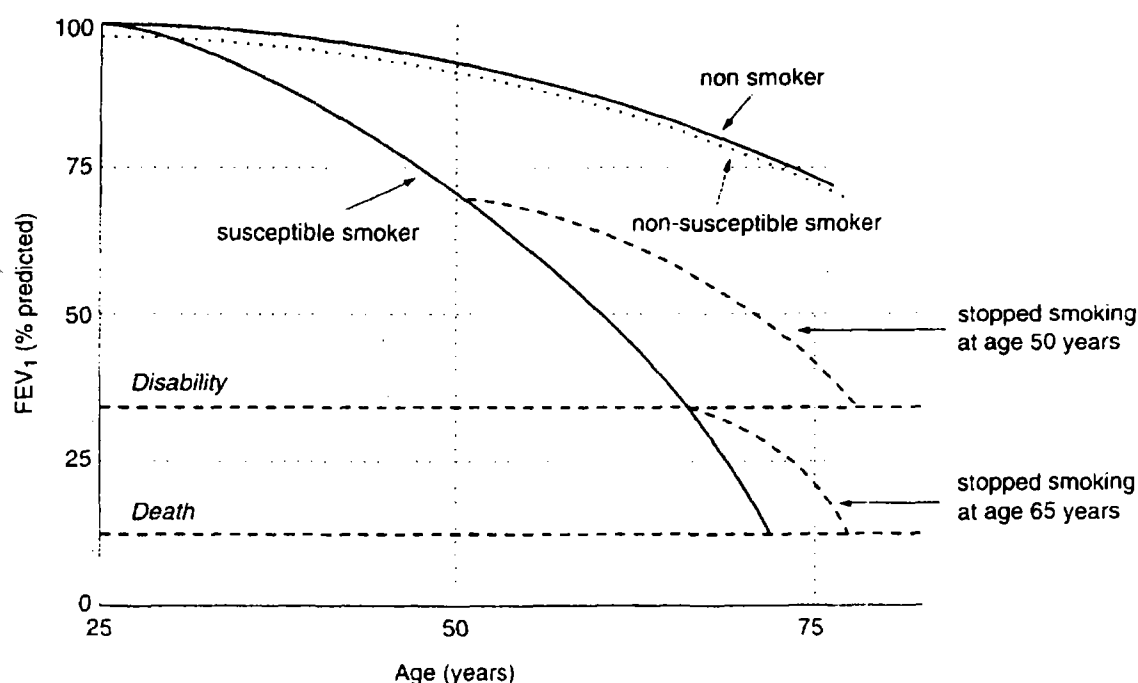


Fig. Annual decline in lung function is accelerated in patients with chronic obstructive pulmonary disease

M₂ receptors and very slow dissociation from M₁ and M₃ receptors⁷. However, whether selective muscarinic antagonists will have advantages over existing nonselective drugs remains to be seen. The most important property of tiotropium bromide is its very long duration of action. It has a high affinity and dissociates very slowly from M₁ and M₃ receptors in human lung, and it produces long-term block of cholinergic neural bronchoconstriction in human airway smooth muscle. However, its effects on acetylcholine release are short-lived, confirming functional selectivity for M₃ compared to M₂ receptors. In studies of patients with COPD, tiotropium bromide gives prolonged bronchodilation, lasting over 24h (Ref. 8). This suggests that tiotropium bromide will be suitable for once daily dosing and it is now in Phase III clinical trials as a once daily dry powder inhalation.

Long-acting β_2 -adrenoceptor agonists

Recent studies have demonstrated that long-acting inhaled β_2 -adrenoceptor agonists salmeterol and formoterol are beneficial in patients with COPD, with improved lung function and symptom control^{9,10}. These treatments might be a useful addition to long-acting anticholinergics, and comparative studies show that they are effective¹¹.

Smoking cessation

Quitting smoking is the only strategy that has so far been shown to reduce the rate of decline in lung function in patients with COPD (Ref. 4). However, less than one third of patients are able to give up smoking, even with support. Nicotine replacement therapy might help some patients and transdermal patches and inhaled nicotine

might be the most effective delivery systems, but continued administration of the addictive principle of cigarettes is a poor approach to smoking cessation and nicotine itself theoretically might have adverse cardiovascular effects. Another approach is to develop nicotine receptor antagonists. The novel antidepressant bupropion (Zyban), which enhances central noradrenergic activity, helps smoking cessation. In a recent study of bupropion given for seven weeks, smoking cessation was 41% compared with only 19% in the placebo group¹².

Anti-inflammatory treatments

COPD is characterized by inflammation of the airways. Bronchoalveolar lavage in patients with COPD demonstrates increased numbers of neutrophils. Bronchial biopsy has demonstrated an infiltration with mononuclear cells – CD4⁺ and particularly CD8⁺ T lymphocytes – rather than neutrophils, suggesting that neutrophils might transit rapidly from the circulation into the airway lumen¹³. Biopsies of ex-smokers show a similar inflammatory process, suggesting that inflammation might persist in the airway once established¹⁴. Induced sputum in COPD patients shows a predominance of neutrophils, even in ex-smokers, in sharp contrast to the elevated eosinophils that are characteristic of asthma¹⁵. The role of neutrophils in the lumen of COPD airways is not yet established, but it is likely that the release of enzymes, such as neutrophil elastase and matrix metalloproteinases (MMPs), might contribute to the pathophysiology of the disease.

The mechanisms of the neutrophilic inflammation in COPD are not yet certain, but it is likely that neutrophil chemotactic factors are released into the airways from activated macrophages and possibly from epithelial cells and CD8⁺ T lymphocytes (Fig. 2). Macrophages might play an important role in driving the inflammatory process in COPD, and might release neutrophil chemotactic factors as well as proteolytic enzymes. Macrophage numbers are increased by five- to tenfold in

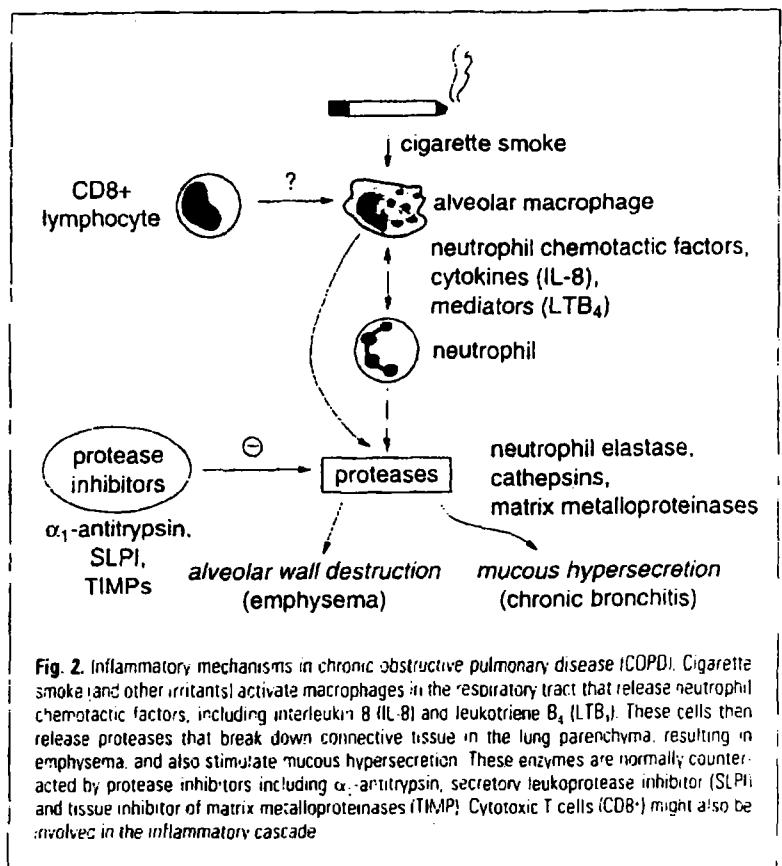


Fig. 2. Inflammatory mechanisms in chronic obstructive pulmonary disease (COPD). Cigarette smoke (and other irritants) activate macrophages in the respiratory tract that release neutrophil chemotactic factors, including interleukin 8 (IL-8) and leukotriene B₄ (LTB₄). These cells then release proteases that break down connective tissue in the lung parenchyma, resulting in emphysema, and also stimulate mucous hypersecretion. These enzymes are normally counteracted by protease inhibitors including α₁-antitrypsin, secretory leukoprotease inhibitor (SLPI) and tissue inhibitor of matrix metalloproteinases (TIMP). Cytotoxic T cells (CD8⁺) might also be involved in the inflammatory cascade.

bronchoalveolar lavage of patients with COPD, and are concentrated in the centriacinar zones, where emphysema is most marked. Furthermore, the numbers of macrophages and T lymphocytes, but not the numbers of neutrophils, in the alveolar wall correlate with the amount of parenchymal destruction¹⁶. Macrophages might be responsible for the continued proteolytic activity in the lungs of patients with emphysema. Interleukin 8 (IL-8) is selectively chemoattractant to neutrophils and is present in high concentrations in induced sputum of patients with COPD (Ref. 15). IL-8 might be secreted by macrophages, neutrophils and by airway epithelial cells¹⁷. Tumour necrosis factor α (TNF-α), also present in high concentration in the sputum of COPD patients, might activate the transcription factor nuclear factor-κB (NF-κB), which switches on the transcription of the IL-8 gene¹⁸. Leukotriene B₄ (LTB₄) is also a potent chemotactic agent for neutrophils in the airways and is increased in the sputum of patients with COPD (Ref. 19). Alveolar macrophages from patients with α₁-antitrypsin deficiency secrete greater amounts of LTB₄ (Ref. 20). There are several approaches that could be adopted to inhibit neutrophilic inflammation (Box 2).

Corticosteroids

Because there is chronic inflammation in COPD airways it was argued that inhaled corticosteroids might prevent the progression of the disease. However, there is little evidence that inhaled corticosteroids are beneficial

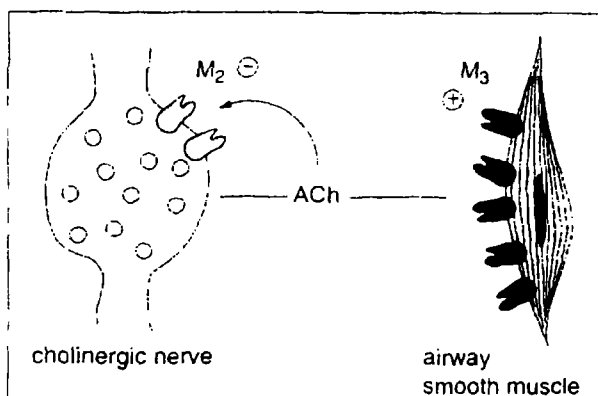


Fig. 1. Muscarinic (M) autoreceptors in airway cholinergic nerves. Acetylcholine (ACh) released from cholinergic nerves causes bronchoconstriction via activation of M₃ receptors and inhibits ACh release via presynaptic M₂ receptors. Therefore, nonselective muscarinic antagonists increase ACh release and make postsynaptic block less efficient.

in COPD, although there might be a minority of patients (~10%) who have some response to steroids, and these patients should probably be regarded as having concomitant asthma²¹. There is a small reduction in the severity of exacerbations with high-dose inhaled corticosteroids²². A large study (EUROSCOP) in patients with mild COPD showed no overall effect of an inhaled corticosteroid (budesonide, 800 µg daily) on the accelerated decline in lung function, although some subgroups appear to benefit²³. Neither inhaled nor oral steroids have any significant effect on neutrophil counts, granule proteins or inflammatory cytokines in induced sputum²⁴, although a trivial inhibitory effect on neutrophil chemotaxis and neutrophil elastase activity has been reported²⁵. This is consistent with a lack of effect of corticosteroids on disease progression but in marked contrast to the efficacy of corticosteroids in asthma and their ability to reduce eosinophil counts in induced sputum²⁴. However, corticosteroids are effective in treating acute exacerbations in COPD, presumably via some as yet undefined anti-inflammatory effect²⁶.

Chemokine inhibitors

Several chemokines are involved in neutrophil chemotaxis²⁷. These belong to the CXC family of chemokines, and the most prominent member is IL-8, which is markedly elevated in the sputum of patients with COPD (Ref. 15). Blocking antibodies to IL-8 and related chemokines inhibit certain types of neutrophilic inflammation in experimental animals, but have not yet been used in clinical studies. It is unlikely that a humanized monoclonal antibody would be suitable for long-term therapy in COPD. IL-8 works through a common G protein-coupled receptor on neutrophils shared by other members of the CXC family (CXCR2) and an additional

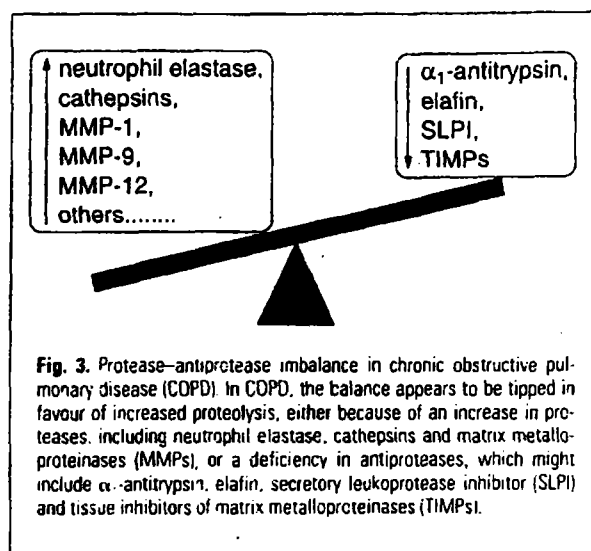


Fig. 3. Protease-antiprotease imbalance in chronic obstructive pulmonary disease (COPD). In COPD, the balance appears to be tipped in favour of increased proteolysis, either because of an increase in proteases, including neutrophil elastase, cathepsins and matrix metalloproteinases (MMPs), or a deficiency in antiproteases, which might include α₁-antitrypsin, elafin, secretory leukoprotease inhibitor (SLPI) and tissue inhibitors of matrix metalloproteinases (TIMPs).

unique receptor (CXCR1). It might be possible to discover a nonpeptidic inhibitor of these receptors by high throughput drug screening, but whether such drugs would be safe in long-term dosing would require careful assessment. High concentrations of corticosteroids inhibit IL-8 gene transcription in airway epithelial cells¹⁷, yet neither inhaled nor oral steroids reduce sputum IL-8 levels in COPD patients, suggesting that it is relatively resistant to steroid inhibition *in vivo*.

Chemokines such as IL-8 are induced by NF-κB, and there are several approaches to developing inhibitors for NF-κB (Ref. 18). TNF-α levels are raised in the sputum of COPD patients and induce IL-8 in airway cells¹⁷. Humanized anti-TNF antibodies have now been developed for clinical use and are effective in other chronic inflammatory disease, such as rheumatoid arthritis and Crohn's disease. Soluble TNF receptors, which sequester released TNF, have also been developed and have entered clinical trials.

Box 2. Inhibitors of neutrophilic inflammation

Leukotriene B₄ antagonists (LY293111, SC53228, CP105696, SB201146)
Interleukin 8 inhibitors (IL-8 synthesis inhibitors, CXC receptor antagonists)
NF-κB inhibitors (IκB kinase inhibitors, IκB-α gene transfer)
Tumour necrosis factor (TNF) inhibitors (monoclonal antibodies, soluble receptors, TNF convertase inhibitors)
Adhesion molecule inhibitors (anti-CD11/CD18, anti-ICAM-1, E-selectin inhibitors)
Phosphodiesterase 4 inhibitors (SB207499, CP80633, CDP-840)
Prostaglandin E analogues (misoprostil, butaprost)
Interleukin 10
Colchicine
Macrolide antibiotics (erythromycin, clarithromycin, roxithromycin)
Antioxidants (N-acetyl cysteine, glutathione analogues, vitamins C and E, nitrones)

LTB₄ inhibitors

LTB₄ is a potent chemoattractant of neutrophils and is increased in the sputum of patients with COPD (Ref. 19). It is probably derived from alveolar macrophages²⁸ and might act synergistically with IL-8. Selective LTB₄ receptor antagonists have now been developed. A potent LTB₄ antagonist (LY293111) is ineffective against allergen challenge in asthmatic patients, although interestingly it inhibits the neutrophil recruitment into the airways during the late response, indicating the capacity to inhibit neutrophil chemotaxis in the airways²⁸. Several other potent LTB₄ antagonists are now in development (including SC53228, CP105696, SB201146). LTB₄ is synthesized by 5'-lipoxygenase (5-LO), of which there are now several potent inhibitors. 5-LO inhibitors, such as zileuton, are now available in some countries for the treatment of asthma, because they also inhibit the synthesis of cysteinyl-leukotrienes, but it is not certain whether they are effective in COPD.

Adhesion molecule blockers

Neutrophil recruitment into the lungs and respiratory tract is dependent on adhesion molecules expressed on neutrophils and endothelial cells in the pulmonary and bronchial circulations. Neutrophil adhesion in response to chemotactic factors is characterized by expression of the β_2 integrins CD11a/CD18 (LFA-1) and CD11b/CD18 (Mac-1) on the surface of the neutrophil and their interaction with their counter-receptors, including intercellular adhesion molecule 1 (ICAM-1), on endothelial cells. E-selectin on endothelial cells also interacts with sialyl-Lewis^x on neutrophils. Bronchial biopsies of patients with COPD have demonstrated increased expression of E-selectin on vessels and ICAM-1 on epithelial cells²⁹. Therefore, drugs that interfere with these adhesion molecules should inhibit neutrophil inflammation in COPD. Monoclonal antibodies to CD18, ICAM-1 and E-selectin inhibit neutrophil accumulation in animal models of lung inflammation. However, there are concerns about this therapeutic approach for a chronic disease, as an impaired neutrophilic response might increase the susceptibility to infections. Indeed, a congenital deficiency of β_2 integrins results in leukocyte adhesion deficiency syndrome characterized by recurrent septicaemia.

Phosphodiesterase inhibitors

Inhibition of phosphodiesterases (PDEs) increases the cAMP content of neutrophils, resulting in reduced chemotaxis, activation, degranulation and adherence³⁰. The predominant isoenzyme is PDE4 and several PDE4 inhibitors are now in clinical development for asthma. It is not yet certain whether these drugs will be useful, and many of the first generation PDE4 inhibitors have been limited by side-effects, particularly nausea. In second generation PDE4 inhibitors, such as SB207499, this might be less of a problem. Theophylline is a weak and non-selective PDE inhibitor and has inhibitory effects on neutrophil function *in vitro*³¹. Unlike corticosteroids, treatment of COPD patients with theophylline reduces neutrophil counts in induced sputum³². PDE4 inhibitors might also be effective because they not only have

direct effects on neutrophil functions, but they also inhibit the release of chemotactic factors from alveolar macrophages in which PDE4 is the predominant PDE subtype.

Interleukin 10

IL-10 is a cytokine with a wide spectrum of anti-inflammatory actions. It inhibits the secretion of TNF- α and IL-8 from macrophages, but tips the balance in favour of antiproteases, by decreasing the expression of MMPs, while increasing the expression of tissue inhibitors of MMPs (TIMPs)³³. IL-10 is currently in clinical trials for other chronic inflammatory diseases and might have therapeutic potential in COPD, especially if a selective activator of IL-10 receptors or signal transduction pathways can be developed.

Other neutrophil inhibitors

Prostaglandin E₂ (PGE₂) is a potent inhibitor of the oxidative burst in neutrophils and its effects are mediated via EP₂ receptor receptors³⁴. Therefore, selective EP₂ receptor agonists, such as misoprostil and butaprost, might be effective in suppressing neutrophil activation, but have not been studied in COPD.

Colchicine potently inhibits neutrophil activation, enzyme release and chemotaxis by disrupting cytoskeletal microtubule structure. A controlled trial of colchicine in COPD showed some reduction in neutrophil elastase activity³⁵.

Enzyme inhibitors

There is compelling evidence in COPD for an imbalance between proteases that digest elastin (and other structural proteins) and antiproteases that protect against this³⁶ (Fig. 3). This suggests that either inhibiting these proteolytic enzymes or increasing antiproteases might be beneficial and theoretically should prevent the progression of airflow obstruction in COPD (Box 3). Considerable progress has been made in identifying the enzymes involved in elastolytic activity in emphysema and in characterizing the endogenous antiproteases that counteract this activity.

Box 3. Enzyme inhibitors for chronic obstructive pulmonary disease (COPD) therapy

Neutrophil elastase inhibitors (ICI200355, ONO5046)
Cathepsin inhibitors (suramin)
Matrix metalloproteinase (MMP) inhibitors (batimastat, marimastat, selective MMP-inhibitors)
 α_1 -Antitrypsin (purified, human recombinant, gene transfer)
Elafin
Secretory leukoprotease inhibitor (human recombinant)

Neutrophil elastase inhibitors

Neutrophil elastase, a neutral serine protease, is a major constituent of lung elastolytic activity and also potently stimulates mucous secretion. In addition, neutrophil elastase induces IL-8 release from epithelial cells and, therefore, might perpetuate the inflammatory state. This has led to a search for neutrophil elastase inhibitors. Peptide inhibitors of neutrophil elastase, such as ICI200355, and non-peptide inhibitors, such as ONO5046, have been developed which have high potency^{37,38}. These drugs inhibit neutrophil elastase-induced lung injury in experimental animals, whether given by inhalation or systemically³⁷ and inhibit neutrophil elastase-induced mucous secretion *in vitro*³⁹. There are few clinical studies with neutrophil elastase in

COPD. A clinical study with oral MR889 administered for four weeks showed no overall effect on plasma elastin-derived peptides or urinary desmosine (markers of elastolytic activity), but these might not be sensitive markers⁴⁰. Although neutrophil elastase is likely to be the major mechanism mediating elastolysis in patients with α_1 -antitrypsin (α_1 -AT) deficiency, it may well not be the major elastolytic enzyme in smoking-related COPD, and it is important to consider other enzymes as targets for inhibition.

Cathepsin inhibitors

Neutrophil elastase is not the only proteolytic enzyme secreted by neutrophils. Cathepsin G and proteinase 3 have elastolytic activity and might need to be inhibited together with neutrophil elastase. Cathepsins (cathepsins B, L and S) are also released from macrophages. Suramin, a hexasulphonated naphthylurea that has been used as an antitumour drug, is a potent inhibitor of cathepsin G, proteinase 3 and neutrophil elastase⁴¹.

MMP inhibitors

The MMPs are a group of over 20 closely related endopeptidases that are capable of degrading all of the components of the extracellular matrix of lung parenchyma including elastin, collagen, proteoglycans, laminin and fibronectin. They are produced by neutrophils, alveolar macrophages and airway epithelial cells⁴². Increased levels of collagenase (MMP-1) and gelatinase B (MMP-9) have been detected in bronchoalveolar lavage fluid of patients with emphysema⁴³. Lavaged macrophages from patients with emphysema express more MMP-9 and MMP-1 than cells from control subjects, suggesting that these cells, rather than neutrophils, might be the major cellular source⁴⁴. Alveolar macrophages also express a unique MMP, macrophage metalloelastase (MMP-12)⁴⁵. MMP-12 knockout mice do not develop emphysema and do not show the expected increases in lung macrophages after long-term exposure to cigarette smoke⁴⁶. TIMPs are endogenous inhibitors of these potent enzymes and several TIMPs have now been characterized.

There are several approaches to inhibiting MMPs (Ref. 47). One approach is to enhance the secretion of TIMPs and another is to inhibit the induction of MMPs in COPD. MMPs might show increased expression with cigarette smoking through induction in response to inflammatory cytokines, oxidants and other enzymes, such as neutrophil elastase. It might be possible to prevent this induction with specific transcription inhibitors. Another approach is to develop specific inhibitors. Tetracyclines and hydroxamates, such as batimastat (BB-94) and the orally active marimastat (BB-2516), are nonselective MMP inhibitors⁴⁸. However, side effects of such drugs might be a problem in long-term use. More selective inhibitors of individual MMPs, such as MMP-9 and MMP-12, are now in development and are likely to be better tolerated in chronic therapy. However, it is still not

clear whether there is one predominant MMP in COPD or whether a broad-spectrum inhibitor will be necessary.

α_1 -Antitrypsin

The association of α_1 -AT deficiency with early onset emphysema suggested that this endogenous inhibitor of neutrophil elastase might be of therapeutic benefit in COPD. Cigarette smoking might inactivate α_1 -AT, resulting in unopposed activity of neutrophil elastase and cathepsins. Extraction of α_1 -AT from human plasma is very expensive and extracted α_1 -AT is only available in a few countries. This treatment has to be given intravenously and has a half-life of only five days. This has led to the development of inhaled formulations, although these are inefficient and expensive⁴⁹. Recombinant α_1 -AT with amino acid substitutions to increase stability might result in a more stable product. Gene therapy is another possibility using an adenovirus vector or liposomes, but there have been major problems in developing efficient delivery systems. There is a particular problem with gene transfer in α_1 -AT deficiency because large amounts of protein (1–2 g) need to be synthesized each day. Human α_1 -AT has now been available for over ten years, but even in patients with severe α_1 -AT deficiency and emphysema, there is only a marginal effect on the rate of decline in lung function (Ref. 50). There is no evidence that α_1 -AT treatment would halt the progression of COPD and emphysema in patients who have normal plasma concentrations.

Serpins

Other serum protease inhibitors (serpins), such as elafin, might also be important in counteracting elastolytic activity in the lung. Elafin, an elastase-specific inhibitor, is found in bronchoalveolar lavage and is synthesized by epithelial cells in response to inflammatory stimuli⁵¹. Serpins might not be able to inhibit neutrophil elastase at the sites of elastin destruction, because of tight adherence of the inflammatory cell to connective tissue. Furthermore, these proteins might be inactivated by the inflammatory process and the action of oxidants, so that they might not be able to counteract elastolytic activity in the lung unless used in conjunction with other treatments.

Secretory leukoprotease inhibitor

Secretory leukoprotease inhibitor (SLPI) is a 12 kDa serpin that appears to be a major inhibitor of elastase activity in the airways. It is secreted by epithelial cells⁵¹ and its secretion is increased by corticosteroids⁵². *In vitro* recombinant human SLPI is more effective at inhibiting neutrophil-mediated proteolysis than α_1 -AT (Ref. 53). Recombinant human SLPI given by aerosolization increases antineutrophil elastase activity in epithelial lining fluid for over 12 h, indicating potential therapeutic use, particularly if the structure is modified to resist oxidative damage⁵⁴.

Mediator antagonists

Antioxidants

There is considerable evidence that oxidative stress is increased in patients with COPD and that reactive oxygen species contribute to its pathophysiology⁵⁵. Oxidants are present in cigarette smoke and are produced endogenously by activated inflammatory cells, including neutrophils and alveolar macrophages. Increased production of endogenous oxidants is demonstrated by the increased levels of hydrogen peroxide (H_2O_2) in expired condensates from patients with COPD, particularly during exacerbations⁵⁶. Oxidants might contribute to the pathophysiology of COPD in several ways, including damage of serpins, potentiation of elastase activity and increased mucous secretion. In addition, oxidants activate NF- κ B, which orchestrates the transcription of many inflammatory genes, including IL-8, inducible nitric oxide synthase and inducible cyclooxygenase (COX-2)¹⁵.

This suggests that antioxidants might be of use in the therapy of COPD. *N*-acetyl cysteine provides cysteine for enhanced production of glutathione (GSH) and has antioxidant effects *in vitro* and *in vivo*. In clinical studies, *N*-acetyl cysteine reduces the number of exacerbations of COPD and in an uncontrolled study appeared to reduce the rate of decline in FEV₁ over a two-year period⁵⁷. Although epidemiological studies have linked COPD to poor intake of dietary antioxidants, such as vitamins C and E, there have been no controlled trials of these vitamins in COPD. It is likely that more effective antioxidants will be developed for clinical use in the future. Spin-trap antioxidants, such as α -phenyl-*N*-tert-butyl nitron are much more potent and inhibit intracellular reactive oxygen species formation by forming stable compounds⁵⁸. These compounds are effective in animal models of oxidative stress and are now entering clinical trials.

Prostanoid inhibitors

Oxidative stress might result in the non-enzymatic formation of prostanoid mediators, isoprostanes, directly from arachidonic acid without the involvement of cyclooxygenase⁵⁹. There is increased formation of isoprostanes in COPD (Ref. 60). The most abundant isoprostane, 8-epi-prostaglandin F_{2 α} , is a potent constrictor of human airways *in vitro*, acting via stimulation of thromboxane (TP) receptors⁶¹. This suggests that TP receptor antagonists, such as seratrodast and Bayu3405, might be beneficial in COPD.

The role of prostaglandins in COPD is unknown. In patients with bronchiectasis, indomethacin has an inhibitory effect on chemotaxis of peripheral neutrophils, but no effect on neutrophils in sputum⁶². It is likely that such an effect is mediated via induction of COX-2, and selective COX-2 inhibitors, such as L745337 and celecoxib (SC58635), which might have a reduced tendency to cause gastrointestinal problems, have now been developed.

Mucoregulators

Increased secretion of mucous is found in all patients who smoke heavily, irrespective of airflow obstruction. However, recent epidemiological data suggest that mucous hypersecretion is associated significantly with a more rapid decline in FEV₁ and increased hospitalization of patients with COPD (Ref. 63). This suggests that it might be important to develop drugs that inhibit the hypersecretion of mucous, although it is important to find drugs that do not suppress the normal mucous secretion or impair mucociliary clearance. There are several types of mucoregulatory drug in development.

Tachykinin receptor antagonists

Tachykinins are potent stimulants of mucous secretion from submucosal glands and goblet cells in human and animal airways and act via tachykinin NK₁ receptors. In animal studies, cigarette smoke induces airway mucous secretion via release of tachykinins from sensory nerves though a local axon reflex mechanism⁶⁴. NK₁ receptor antagonists, which markedly inhibit neurogenic mucous secretion⁶⁵, might therefore have potential as mucoregulators in cigarette smoke-induced chronic bronchitis. Several potent nonpeptide NK₁ receptor antagonists, such as CP99994 and SR140333, are now in clinical development, and while it is unlikely that they will be useful in asthma, they might have a role as regulators of mucous hypersecretion in COPD.

Sensory neuropeptide release inhibitors

Another approach to blocking tachykinin-mediated effects is to inhibit the release of tachykinins from sensory nerve endings, via activation of prejunctional receptors⁶⁶. Of these receptors, μ -opioid receptors are most effective and the μ -opioid agonist morphine potently inhibits cigarette smoke-induced mucous secretion in animal airways⁶⁷. In human airways *in vitro* morphine inhibits mucous secretion activated via stimulation of sensory nerves⁶⁸. While morphine itself might not be useful as a therapeutic agent because of addiction, peripherally acting opioid agonists that do not cross the blood-brain barrier, such as BW443, might be of use.

Many prejunctional receptors appear to operate via the opening of a common K⁺ channel, suggesting that K⁺ channel openers might be useful in blocking mucous secretion. Openers of ATP-dependent K⁺ channels, such as levcromakalim, have an inhibitory effect on cigarette smoke-induced mucous secretion in animals⁶⁹.

Mediator and enzyme inhibitors

Many mediators stimulate mucous secretion from submucosal glands and/or goblet cells and, therefore, might contribute to increased mucous secretion in COPD. It is unlikely, however, that any mediator antagonists (such as antileukotrienes) would have a major effect on mucous secretion. Neutrophil elastase, and other proteases, are potent stimulants of submucosal gland and goblet cell secretion, suggesting that protease

inhibitors might have inhibitory effects on mucous secretion, as well as inhibiting lung destruction. Inhalation of the cyclooxygenase inhibitor indomethacin is reported to reduce mucous hypersecretion in patients with COPD (Ref. 70), but long-term trials of COX inhibitors have not yet been undertaken.

MUC gene suppressors

Nine MUC genes that code for mucin synthesis have already been cloned and many are expressed in human airways⁷¹. MUC5AC (particularly in goblet cells), MUC5B (particularly in submucosal glands), MUC4 and MUC8 appear to be important in airway mucous. MUC5AC might be upregulated by inflammatory cytokines and inhibited by glucocorticoids⁷². It is possible that drugs could be developed that inhibit the abnormally increased expression of MUC genes in COPD, while preserving baseline secretion of MUC2. Such drugs, other than corticosteroids, have not yet been developed.

Mucolytic agents

Several drugs were developed to reduce the viscosity of mucous, thus aiding clearance from the respiratory tract. These drugs include cysteine derivatives, such as N-acetyl cysteine, methyl cysteine and carbocysteine, which are effective in reducing mucous viscosity *in vitro*, but there is little convincing evidence that they increase mucous clearance in patients with COPD. DNase also reduces sputum viscosity, particularly when sputum is infected, as DNA is a major determinant of sputum viscosity. Although nebulized recombinant human DNase (dornase alfa) appears to improve the rheological properties of mucous in patients with cystic fibrosis, this has not been reported in COPD. It is possible that more effective mucolytic agents will be developed in the future.

Macrolide antibiotics

Erythromycin inhibits mucin secretion from human airways *in vitro* and appears to interact with corticosteroids⁷³. This property does not appear to be related to its antibiotic activity and is consistent with other studies demonstrating an inhibitory action of erythromycin on cell secretion. There is a clinical case report of the efficacy of erythromycin in treating mucous hypersecretion⁷⁴. The molecular mechanisms involved in these effects need to be defined and controlled studies in COPD might be indicated.

Drugs affecting remodelling

A major mechanism of airway obstruction in COPD is loss of elastic recoil (as a result of proteolytic destruction of lung parenchyma), and it seems unlikely that this could be reversed by drug therapy, although it might be possible to reduce the rate of progression by preventing the inflammatory and enzymatic disease processes. Retinoic acid increases the number of alveoli in rats and

remarkably, reverses the histological and physiological changes induced by elastase treatment⁷⁵. However, it is not certain whether such alveolar proliferation is possible in adult human lungs. Retinoic acid activates intracellular retinoic acid receptors, which act as transcription factors to regulate the expression of many genes. The molecular mechanisms involved, and whether this can be extrapolated to humans, is not yet known. Several retinoic acid receptor subtype agonists have now been developed that might have a greater selectivity for this effect.

Future directions

New drugs for the treatment of COPD are needed. While preventing and quitting smoking is the obvious preferred approach, this has proved to be very difficult in the majority of patients. In addition, it is likely that the inflammatory process initiated by cigarette smoking might continue even when smoking has ceased. Furthermore, ~10% of patients with COPD are non-smokers. COPD might be caused by other environmental factors (pollutants, passive smoking and other inhaled toxins) or development changes in the lungs.

It is important to identify the factors that determine why only 15% of smokers develop COPD. So far, this is little understood, although it is likely that genetic factors are important⁷⁶. A clearly established genetic risk factor for COPD is the ZZ allele of the α_1 -AT gene, although heterozygotes might be at slightly increased risk. There is also an association with a polymorphism of the TNF- α gene (TNF2) that is associated with greater inducibility of TNF- α (Ref. 77). There are also weak associations with α_1 -antichymotrypsin, α_2 -macroglobulin and vitamin D-binding protein. Recently a polymorphism in the gene for an enzyme, microsomal epoxide hydrolase, that is responsible for metabolism of reactive epoxide intermediates (which might be generated in tobacco smoke), has been associated with a four- to fivefold increased risk of COPD and emphysema⁷⁸. It is likely that many other genetic polymorphisms will be discovered that confer a risk for the development of COPD and emphysema on smokers, so that it will eventually be possible to identify at risk patients and focus more effective therapies on these patients before lung function becomes too impaired.

Several drugs that are now in development might be useful in COPD. These include LTB₄ antagonists and 5-lipoxygenase inhibitors, PDE4 inhibitors, new antioxidants and inhibitors of neutrophil elastase and MMP. It will be difficult to demonstrate the efficacy of such treatments, as determination of the effect of any drug on the rate of decline in lung function will require large studies over at least two years. There is an urgent need to develop surrogate markers, such as analysis of sputum parameters (cells, mediators and enzymes) that might predict the clinical usefulness of such drugs. More research on the basic cellular and molecular mechanism of COPD and emphysema are needed urgently to aid the

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logical development of new therapies for this common and important disease for which no effective preventative treatments currently exist.

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Chemical names

- CP80633: (2'S)-5-[3-(2'-exobicyclo[2.2.1]-heptyloxy)-4-methoxyphenyl]tetrahydro-2(1H) pyrimidinone
- CP99994: (+)-(2S,3S)-3-(2-methoxybenzylamino)-2-phenylpiperidine
- CP105696: (+)-1-(3S,4R)-[3-(4-phenylbenzyl)-4-hydroxy-chroman-7-yl]cyclopropane carboxylic acid
- ICI200355: [4-(4-bromophenyl)sulfonylcarbamoyl]benzoyl-L-valyl-L-proline 1 (8S)-(1-trifluoroacetyl-2-methyl-propyl)amide]
- LY293111: 2-[2-propyl-3-[3-(2-ethyl-4-(4-fluorophenyl)-5-hydroxyphenoxy]propoxy]phenoxy]benzoic acid
- ONO5046: N-[2-[4-(2,2-dimethylpropionyloxy)phenyl-sulphonylamino]benzoyl]aminoacetic acid
- SB201146: (E)-3-[6][(2,6-dichlorophenyl)thio]methyl]-3-(2-phenylethoxy)-2-pyridinyl]-2-propenoic acid
- SB207499: cis-4-cyano-4-[3-(cyclopentylloxy)-4-methoxy-phenyl]cyclohexane-1-carboxylic acid
- SC53228: (+)-(S)-7-[3-(2-cyclopropyl-methyl)-3-methoxy-4-[(methylamino) carbonyl]phenoxy]propoxy]-3,4-dihydro-8-propyl-2H-1-benzopyran-2-propanoic acid
- SR140333: (S)-1-(2-[3-(3,4-dichlorophenyl)-1-(3-iso-propoxyphenyl)acetyl]piperidin-3-yl)ethyl-4-phenyl-1-azobicyclo[2.2.2]octane chloride

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SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
DIVISIÓN DE NUEVAS CREACIONES

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2005-09-01

2020/
Bogotá, D.C.,

Doctor
Emilio Ferrero
Apoderado

Oficio N° 7733

REFERENCIA	Radicación	00 35809
	Trámite	002
	Evento	001
	Actuación	430
	Folios	008

Como resultado del examen de patentabilidad de la solicitud de patente de invención N° 00 34118, realizado según el artículo 45 de la decisión 486 de la comisión de la Comunidad Andina, se notifica:

Documentos estudiados:

- . Descripción: folios 2-14
- . Ejemplos: folios 15-24
- . Capítulo reivindicatorio estudiado: folios 25-32
- . Se reivindica prioridad presentada en Alemania el 12.05.99 bajo el número 19921693.2

Objeto de la invención

Según las reivindicaciones 1 a 15 de la presente solicitud, se refiere a una composición farmacéutica caracterizada porque contiene un anticolinérgico de larga acción y un beta adrenergico de larga acción.

Clasificación internacional de patentes A 61 K 31/165

Condiciones a la patentabilidad

El artículo 14 de la decisión 486 de la comisión de la comunidad andina establece que: *"los miembros otorgarán patentes para las invenciones, sean de producto o de proceso, en todos los campos de la tecnología, siempre que sean nuevas, tengan actividad y sean susceptibles de aplicación industrial"*

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Teniendo en cuenta lo anterior, el contenido de las reivindicaciones 14 y 15, que trata de “Empleo de una composición...”, no es patentable ya que la legislación vigente no contempla los uso como objeto de patente.

Determinación del estado de la técnica:

Consultadas las fuentes de información con que cuenta este despacho, se encontraron los siguientes documentos, anteriores a la fecha de prioridad de la presente solicitud - 12.05.99-, relacionados con la materia de la presente solicitud:

Nº	Documento	Título	Fecha de publicación
1		“Broncodilatadores en la terapia de la enfermedad pulmonar obstructiva crónica”	1998
2		“Enfermedad pulmonar obstructiva crónica: nuevas oportunidades para el desarrollo de medicamentos”	31.10.98
3	WO 9734871	“Compuestos nitrosados y nitrosilados, composiciones y su uso para el tratamiento de desórdenes respiratorios”	25.09.97

Evaluación de los requisitos de patentabilidad:

El artículo 14 de la decisión 486 de la comisión de la comunidad andina establece que: *“Los países miembros otorgarán patentes para las invenciones, sean de producto o de procedimiento, en todos los campos de la tecnología, siempre que sean nuevas, tengan nivel inventivo y sean susceptibles de aplicación industrial”*

En cumplimiento del artículo 14 de la decisión 486 de la comisión de la comunidad andina, se procedió a evaluar los requisitos de novedad, nivel inventivo y aplicación industrial con el fin de establecer la patentabilidad de la invención reivindicada en la solicitud en estudio.

Evaluación de la NOVEDAD

El art. 16 de la decisión 486 establece que *“Una invención se considerará nueva cuando no está comprendida en el estado de la técnica”*

La publicación WO 9734871 se relaciona con composiciones que comprenden una cantidad efectiva de un beta-mimético y un anticolinérgico, junto con auxiliares farmacéuticos.

El artículo “Broncodilatadores en la terapia de la enfermedad pulmonar obstructiva crónica” se describe la combinación de beta-agonistas con anticolinérgicos en el tratamiento del asma y la enfermedad pulmonar crónica obstructiva, especialmente la combinación salbutamol-ipratropio.

El artículo “Enfermedad pulmonar obstructiva crónica: nuevas oportunidades para el desarrollo de medicamentos” se describen combinaciones de de un beta agonista, como salmeterol y formoterol junto con anticolinérgicos de larga duración.

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Comparando elemento por elemento, las composiciones de las reivindicaciones 1-9 son iguales a las descritas en las anterioridades citadas y pueden afectar la novedad de la presente composición.

Evaluación del NIVEL INVENTIVO

El artículo 18 de la decisión 486 establece que *“Se considerará que una invención tiene nivel inventivo, si para una persona del oficio normalmente versada en la materia técnica correspondiente, esa invención no hubiese resultado obvia ni se hubiese derivado de manera evidente del estado de la técnica”*

La publicación WO 9734871 se relaciona con composiciones que comprenden una cantidad efectiva de un beta-mimético y un anticolinérgico, junto con auxiliares farmacéuticos.

El artículo “Broncodilatadores en la terapia de la enfermedad pulmonar obstructiva crónica” se describe la combinación de beta-agonistas con anticolinérgicos en el tratamiento del asma y la enfermedad pulmonar crónica obstructiva, especialmente la combinación salbutamol-ipratropio.

El artículo “Enfermedad pulmonar obstructiva crónica: nuevas oportunidades para el desarrollo de medicamentos” se describen combinaciones de de un beta agonista, como salmeterol y formoterol junto con anticolinérgicos de larga duración.

Teniendo en cuenta el objeto de la solicitud, el cual es proveer composiciones de beta miméticos y anticolinérgicos, es una derivación evidente del estado de la técnica ya que los documentos citados presentan composiciones similares que tienen el mismo efecto.

Un técnico con sus conocimientos y las enseñanzas de los documentos citados llegaría a sintetizar los compuestos que se pretenden proteger.

Finalmente no se demuestran ventajas sorprendentes o efectos inesperados de las composiciones de la presente solicitud en relación a las que se encuentran reveladas en el estado de la técnica.

En conclusión los requisitos de patentabilidad de la presente solicitud se encuentran afectados así:

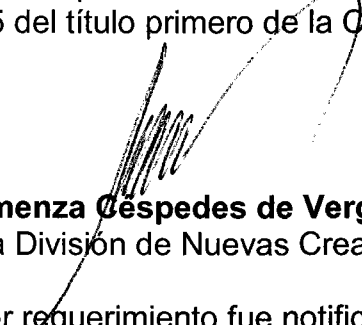
Nº	Documento	Reivindicaciones afectadas	Requisito que afecta
1	WO 9734871	1-9, 12-13	Novedad
		10-11	Nivel Inventivo
2	“Broncodilatadores en la terapia de la enfermedad pulmonar obstructiva crónica”	1-9, 12-13	Novedad
		10-11	Nivel Inventivo
3	“Enfermedad pulmonar obstructiva crónica: nuevas oportunidades para el desarrollo de medicamentos”	1-9, 12-13	Novedad
		10-11	Nivel Inventivo

En cumplimiento del artículo 45 de la Decisión 486 de la Comisión de la Comunidad Andina, se le indica que debe dar respuesta dentro del término de sesenta días contados

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a partir de la fecha de la notificación de la presente comunicación. En caso de no dar respuesta al presente requerimiento, o si a pesar de la respuesta subsistieran los impedimentos para la concesión, se denegará la patente.

Notifíquese el presente oficio conforme a lo dispuesto en el numeral 5.2, literal e), del capítulo 5 del título primero de la Circular Única N° 10 de 2001


Álix Carmenza Céspedes de Vergel
Jefe de la División de Nuevas Creaciones

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El anterior requerimiento fue notificado por fijación en lista, de fecha _____

CONCEPTO TÉCNICO Número 1218	EXAMINADOR TÉCNICO Código 202024
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PCT

WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau



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INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification ⁶: C07D 211/18, 211/32, 211/68, 213/40, 223/10, 243/00, 279/12, 311/74, 401/06, C07J 7/00	A1	(11) International Publication Number: WO 97/34871 (43) International Publication Date: 25 September 1997 (25.09.97)
(21) International Application Number: PCT/US97/04319 (22) International Filing Date: 19 March 1997 (19.03.97) (30) Priority Data: 08/620,882 22 March 1996 (22.03.96) US (60) Parent Application or Grant (63) Related by Continuation US 08/620,882 (CIP) Filed on 22 March 1996 (22.03.96) (71) Applicant (for all designated States except US): NITROMED, INC. [US/US]; 801 Albany Street, Boston, MA 02118 (US). (72) Inventors; and (75) Inventors/Applicants (for US only): GARVEY, David, S. [US/US]; 10 Grand Hill Drive, Dover, MA 02030 (US). LETTIS, L., Gordon [AU/US]; 12 Abbott Road, Dover, MA 02030 (US). RENFROE, H., Burt [US/US]; 90 Bristol Road, Wellesley, MA 02181 (US). RICHARDSON, Stewart, K. [GB/US]; 194 Southworth Drive, Ashford, CT 06278 (US).	(74) Agents: HERRON, Charles, J. et al.; Carella, Byrne, Bain, Gilfillan, Cecchi, Stewart & Olstein, 6 Becker Farm Road, Roseland, NJ 07068 (US). (81) Designated States: AU, CA, JP, US, European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE). Published <i>With international search report. Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.</i>	
(54) Title: NITROSATED AND NITROSYLATED COMPOUNDS AND COMPOSITIONS AND THEIR USE FOR TREATING RESPIRATORY DISORDERS		
(57) Abstract Disclosed are (i) compounds of a steroid, a β-agonist, an anticholinergic, a mast cell stabilizer and a phosphodiesterase (PDE) inhibitor directly or indirectly linked to a NO or NO₂ group or a group which stimulates endogenous production of NO or EDRF <i>in vivo</i>; (ii) compositions of steroids, β-agonists, anticholinergics, mast cell stabilizers and PDE inhibitors, which can optionally be substituted with at least one NO or NO₂ moiety or a group which stimulates endogenous production of NO or EDRF <i>in vivo</i>, and a compound that donates, transfers or releases nitric oxide as a charged species, i.e., nitrosonium (NO⁺) or nitroxyl (NO⁻), or as the neutral species, nitric oxide (NO) or that stimulates endogenous production of NO or EDRF <i>in vivo</i>; and (iii) uses for them in preventing and/or treating respiratory disorders.		

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Another group of such adducts are 2-hydroxy-2-nitrosohydrazines which donate, transfer or release nitric oxide and have a $R_{61}R_{62}-N(O-M^+)-NO$ group wherein R_{61} and R_{62} include polypeptides, amino acids, sugars, modified and unmodified oligonucleotides, hydrocarbons where the hydrocarbon can be a branched or unbranched, and saturated or unsaturated aliphatic hydrocarbon or an aromatic hydrocarbon, hydrocarbons having one or more substituent groups and heterocyclic compounds. M^+ is a metal cation, such as, for example, a Group I metal cation.

Another group of such adducts are thionitrates which donate, transfer or release nitric oxide and have the structure $R_{61}-S-NO_2$ wherein R_{61} is as described above.

Compounds that stimulate endogenous synthesis of NO or EDRF *in vivo* include L-arginine, the substrate for nitric oxide synthase, cytokines, adenosine, bradykinin, calreticulin, bisacodyl, phenolphthalein, and endothelin.

The compounds and compositions of the invention are useful in the treatment of a large number of disorders, particularly those related to or characterized by pulmonary dysfunction. Examples of such indications include preventing (if given prior to the onset of symptoms) or reversing the following: acute pulmonary vasoconstriction, such as may result from pneumonia, traumatic injury, aspiration of inhalation injury, fat embolism in the lung, acidosis, inflammation of the lung, adult respiratory distress syndrome, acute pulmonary edema, acute mountain sickness, asthma, post cardiac surgery acute pulmonary hypertension, persistent pulmonary hypertension of the newborn, perinatal aspiration syndrome, hyaline membrane disease, acute pulmonary thromboembolism, heparin-protamine reactions, sepsis, asthma, status asthmaticus, or hypoxia (including that which may occur during one-lung anesthesia), as well as those cases of chronic pulmonary vasoconstriction which have a reversible component, such as may result from chronic pulmonary hypertension, bronchopulmonary dysplasia, chronic pulmonary thromboembolism, idiopathic or primary pulmonary hypertension, or chronic hypoxia.

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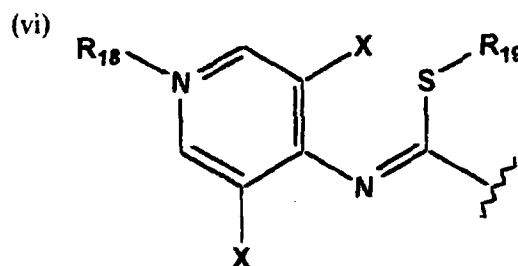
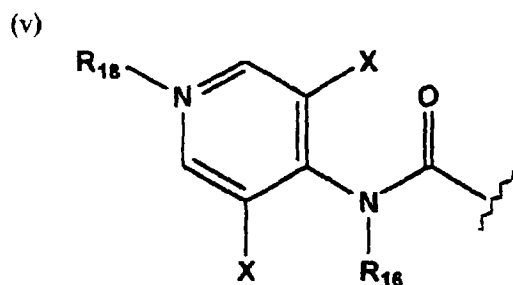
When administered *in vivo*, the nitric oxide adduct may be administered in combination with pharmaceutical carriers and in dosages described herein.

The instant disclosure, particularly in combination with the significant body of literature, commercially available pharmaceutically acceptable liquid, solid and gaseous carriers and vehicles, volume expanders, tableting and encapsulation materials, enteric and other coatings, and inhalant and intranasal delivery devices and the ordinary skill of those practicing in the field, amply teaches the reader how to use the compounds and compositions of the invention in the methods of the invention and particularly for oral and nasal inhalation and intranasal therapy. The following is supplementary to and exemplary thereof.

The pharmaceutical compositions utilized in this invention can be administered preferably by inhalation(oral and/or nasal), and also by intranasal mucosal administration, oral, enteral, topical, vaginal, sublingual, rectal, intramuscular, intravenous, or subcutaneous means.

The compounds of this invention can be employed in combination with conventional excipients; *i.e.*, pharmaceutically acceptable organic or inorganic carrier substances suitable for parenteral, enteral or intranasal application which do not deleteriously react with the active compounds. Suitable pharmaceutically acceptable carriers include, but are not limited to, water, salt solutions, alcohol, vegetable oils, polyethylene glycols, gelatin, lactose, amylose, magnesium stearate, talc, silicic acid, viscous paraffin, perfume oil, fatty acid monoglycerides and diglycerides, petroethral fatty acid esters, hydroxymethylcellulose, polyvinylpyrrolidone, *etc.* The pharmaceutical preparations can be sterilized and if desired, mixed with auxiliary agents, *e.g.*, lubricants, preservatives, stabilizers, wetting agents, emulsifiers, salts for influencing osmotic pressure, buffers, colorings, flavoring and/or aromatic substances and the like which do not deleteriously react with the active compounds.

Many therapeutically active ingredients have been administered or applied to the body by means of inhalation, such as in aerosol dosage form. One of the main reasons for the rapid and widespread acceptance of the inhalation dosage forms for the administration of therapeutically active agents is that it affords many and

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wherein X is halogen and R_{26} is selected from D or M and wherein R_{16} , R_{18} , and R_{19} are defined as above.

3. A composition comprising (i) a therapeutically effective amount of a steroid, a β -agonist, an anticholinergic, a mast cell stabilizer or a PDE inhibitor and (ii) a compound that donates, transfers or releases nitric oxide or stimulates endogenous production of NO or EDRF *in vivo*.

4. The composition of claim 3 wherein

(i) the steroid is selected from the group consisting of beclomethasone, fluticasone, flunisolide, triamcinolone, butixocort, dexamethasone, fluocortin, budesonide, tixocortol, tipredane and mometasone;

(ii) the β -agonist is selected from the group consisting of salmeterol, albuterol, metaproterenol, terbutaline, pirbuterol, rimiterol, clenbuterol, bitolterol and reproterol;

(iii) the anticholinergic is selected from the group consisting of ipratropium, flutropium, tiotropium and rispenzepine;

(iv) the mast cell stabilizer is selected from the group consisting of cromolyn and nedocromil; and

(v) the PDE inhibitor is selected from the group consisting of tolafentrine, piclamilast, rolipram, flaminast, denbufylline, and zardaverine.

5. The composition of claim 3 wherein the compound that donates, transfers or releases nitric oxide is a S-nitrosothiol.

6. The composition of claim 5 wherein the S-nitrosothiol is selected from the group consisting of those having the structures:

