β-Adrenoceptor Agonists

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Abstract β_2-Adrenoceptor agonist bronchodilators are widely used in the treatment of both asthma and chronic obstructive pulmonary disease (COPD). They provide rapid and effective symptom relief principally by opposing the bronchoconstriction induced by excitatory airway mediators. While asthma is associated with episodic increases in baseline airway tone, it is defined as an inflammatory disease of the airways, and accordingly, therapy generally involves the use of anti-inflammatory as well as bronchodilator therapy. When delivered directly to the lungs by inhalation, β_2-adrenoceptor agonist bronchodilators provide rapid and effective reversal of acute airway obstruction caused by bronchoconstriction, with minimal acute adverse effects on the patient. Importantly, the rapidity of relief provided by inhaled β_2-adrenoceptor agonists is a significant feature of this class of drugs and helps to explain why they are used so widely to reverse the potentially life-threatening effects of bronchoconstriction in asthma. Short-acting β_2-adrenoceptor agonist bronchodilators, such as salbutamol, have durations of action of 4–6 h and provide rapid symptom relief in a large proportion of asthmatics. Long-acting β_2-adrenoceptor agonists, which include salmeterol, have durations of action of up to 12 h and provide effective treatment in asthmatic individuals whose symptoms were not adequately managed with short-acting agents. Given the complementary roles of β_2-adrenoceptor agonists and glucocorticoids in the treatment of asthma, combination therapy using these drugs has been shown to improve disease control and lower exacerbation rates. Accordingly, the consensus is that these β_2-adrenoceptor agonist bronchodilators should not be used as monotherapy in asthma in any but the most mild of cases. Indeed, the powerful bronchodilator actions of short- and long-acting β_2-adrenoceptor agonists may mask the onset and/or deterioration of airway inflammation in asthmatics. COPD is characterized by shortness of breath, cough, sputum production and exercise limitation, with acute exacerbations resulting in worsening of symptoms. While short-acting inhaled β_2-adrenoceptor agonist bronchodilators reduce respiratory symptoms and improve the quality of life in COPD patients, these drugs fail to alter the progression of this disease in the long term. In these individuals however, the recent introduction of long-acting β_2-adrenoceptor agonists has had a positive impact on quality of life. The combined use of bronchodilator/corticosteroid regimes further assists in the management of COPD.

Keywords Asthma · Chronic obstructive pulmonary disease · β_2-Adrenoceptor agonists · Delivery devices · Combination therapy

1 Introduction

β_2-Adrenoceptor agonist bronchodilators are widely used in the treatment of both asthma and chronic obstructive pulmonary disease (COPD) where they can provide rapid and effective symptom relief. The major role of these agents in these diseases is to oppose airway smooth muscle contraction caused by a variety of excitatory airway mediators.

1.1 Asthma

In addition to elevated bronchial tone, a major defining characteristic of asthma is that it is an inflammatory airway disease. The combined effects of these two elements results in a disease involving reversible airway obstruction which may cause persistent systems such as dyspnea, chest tightness, wheezing, cough and sputum production. Variable airflow obstruction and airway hyperresponsiveness to both endogenous and exogenous stimuli are also distinguishing features of asthma. Chronic inflammation of the airways is accompanied by structural changes to the bronchial wall and these phenomena are collectively referred to as airway remodelling. These changes to the normal architecture of airway mucosal and submucosal tissues underlie the development and continued maintenance of this disease. The inflammatory response in the airways is characterized by mucosal and bronchial wall oedema, lymphocyte and eosinophil infiltration, damage to and loss of airway epithelium, and hypersecretion of mucus that may cause plugging and occlusion of the airway lumen. Accordingly, asthma therapy in the modern era has tended to emphasize anti-inflammatory drug approaches since these are predicted to have a positive impact on processes driving airway remodelling.

However, it must be remembered that asthma also involves episodic increases in baseline airway tone resulting from active shortening of airway smooth muscle, causing reduced bronchial airflow and thus impaired lung ventilation. Contraction of airway smooth muscle, like airway wall remodelling, oedema and hypersecretion of mucus, contributes significantly to bronchial obstruction. As a result, the use of bronchodilators remains at the forefront of modern approaches to asthma therapy. This is despite the continuing research and therapeutic emphasis on airway inflammation as a driver of asthma progression and maintenance.

β_2-Adrenoceptor agonist bronchodilators in particular, delivered directly to the airways by inhalation, provide rapid and effective reversal of acute airway obstruction caused by bronchoconstriction, with minimal acute adverse effects on the patient. Importantly, the rapidity of relief provided by inhaled β_2-adrenoceptor agonists is a significant feature of this class of drugs and helps to explain why they are used so widely to reverse the potentially life-threatening effects of bronchoconstriction in asthma.

1.2 COPD

COPD is defined as "a disease state characterized by airflow limitation that is not fully reversible. The airflow limitation is usually both progressive and associated with an abnormal inflammatory response of the lungs to noxious particles or gases" [Global Initiative for Chronic Obstructive Lung Disease (GOLD) Workshop Report 2001]. COPD is characterized by inflammation throughout

the respiratory system, including bronchial and bronchiolar airways, parenchyma and pulmonary vasculature. There are increased numbers of macrophages, T lymphocytes (predominantly $CD8^+$) and neutrophils in the airways (Jeffery 1998; Pesci et al. 1998). These activated inflammatory cells release a variety of mediators, including leukotriene B_4 (LTB_4), interleukin (IL)-8 and tumour necrosis factor (TNF)-α that contribute to widespread degenerative structural changes to the respiratory tract and promote neutrophilic inflammation (Keatings et al. 1996; Mueller et al. 1996; Yamamoto et al. 1997; Pesci et al. 1998; Hill et al. 1999). There is also evidence in COPD for an imbalance in proteases that digest elastin and other structural proteins and antiproteases that protect against this damage (Chapman and Shi 2000). Oxidative stress may also contribute to the pathogenesis of this disease. It is likely that cigarette smoke and other COPD risk factors initiate an inflammatory response in the airways that can lead to this disease. As in asthma, the airflow obstruction seen in COPD patients is often accompanied by airway hyperresponsiveness. The chronic airflow obstruction particularly affects small airways, and lung elasticity is also lost due to enzymatic destruction of the lung parenchyma, resulting in progressively worsening emphysema. Thus, COPD is characterized by shortness of breath, cough, sputum production and exercise limitation, with acute exacerbations resulting in worsening of symptoms. Inhaled bronchodilators, including β_2-adrenoceptor agonists, have been shown to reduce respiratory symptoms and improve the quality of life for COPD patients and are recommended in the management of acute exacerbations of this disease. However, in the long term, β_2-adrenoceptor agonists fail to alter the progression of this disease.

Much of what is known of the basic and clinical pharmacology of β_2-adrenoceptor agonist bronchodilators, such as salbutamol, was established in studies from the 1970s and 1980s. The actions of β_2-adrenoceptor agonists in the lung, particularly in relation to asthma, have previously been extensively reviewed by us (Goldie et al. 1991) and it is appropriate to revisit some of the issues raised at that time. However, significant advances in β_2-adrenoceptor agonist development and therapy in asthma and COPD have been made in recent years and these will also be highlighted in this review.

2
The β-Adrenoceptor and Its Associated Signal Transduction Processes

2.1
β-Adrenoceptor Subtypes

The β-adrenoceptor is a single polypeptide glycoprotein moiety (Gilman 1987), embedded in the plasma membrane of the cell (Stiles et al. 1984). At least three functionally distinct subtypes (β_1, β_2, and β_3) are known to exist and have been cloned. β-Adrenoceptors are found throughout the respiratory tract and, in human bronchial smooth muscle, are entirely of the β_2-subtype (Harms 1976; Goldie et al. 1986b). While β_1-adrenoceptors predominate in human cardiac tis-

Fig. 1 Main pathways promoting airway smooth muscle relaxation associated with the β-adrenoceptor-effector system. The *dashed lines* indicate inhibition of Ca^{2+} entry into the cell via voltage-gated Ca^{2+} channels. The *dotted line* indicates that the exact mechanism is yet to be defined. (Adapted from Thirstrup 2000)

sue, a small functional population of β_2-adrenoceptors is also present. More recently, β_3-adrenoceptors have been found in cardiac muscle, intestinal smooth muscle as well as in white and brown fat. However, β_3-adrenoceptor mRNA has not been detected in human lung (Mak et al. 1996) and β_3-adrenoceptor agonists failed to induce relaxation in human isolated bronchi (Martin et al. 1994).

2.2 Adenylyl Cyclase

Agonist-binding to all β-adrenoceptors subtypes activates the membrane-bound enzyme adenylyl cyclase via a guanine nucleotide regulatory protein (G_s) to convert adenosine 5′-triphosphate (ATP) to cyclic adenosine 3′,5′-monophosphate (cAMP; Benovic et al. 1985) (Fig. 1). Cyclic AMP is produced continuously following β-adrenoceptor activation and is inactivated by hydrolysis to 5′-AMP, through the action of phosphodiesterases. Cyclic AMP acts as an intracellular messenger to regulate many aspects of cellular function including the contraction of smooth muscle. Thus, cAMP activates cAMP-dependent protein kinases to modify cellular function by phosphorylation. For example, relaxation of airway smooth muscle results from phosphorylation, and thus inactivation of myosin light chain kinase, which precludes its interaction with the contractile protein myosin (Thirstrup 2000). In addition, β-adrenoceptor agonists may also decrease airway smooth muscle tone via an interaction with plasma membrane potassium channels (Fig. 1). This results in hyperpolarization of the cell membrane and inhibition of calcium influx via voltage-dependent calcium channels.

Rho, a small monomeric G protein of the Ras superfamily of guanosine triphosphate (GTP)ases, has been shown to control airway smooth muscle tone

following activation of G protein-coupled receptors (Seasholtz et al. 1999; Amano et al. 2000; Schmitz et al. 2000; Somlyo and Somlyo 2000; Pfitzer 2001). Rho activates Rho-kinase (Kimura et al. 1996) which phosphorylates and thus inhibits myosin light chain phosphatase. The latter enzyme acts to de-phosphorylate myosin light chain and promote smooth muscle relaxation. However, the result of Rho-kinase activity is blockade of this process and thus maintenance of smooth muscle tone (Seasholtz et al. 1999; Amano et al. 2000; Somlyo and Somlyo 2000). While Y27632, an inhibitor of Rho-kinase, has been shown to potentiate the relaxant effects of β-adrenoceptor agonists in airway smooth muscle (Iizuka et al. 2000; Nakahara et al. 2000), a linkage between Rho-kinase and the β-adrenoceptor-effector system has yet to be clearly defined.

3 Distribution and Density of β-Adrenoceptors in the Lung

Radioligand binding and autoradiographic studies have been critical to evaluations of the distribution of β-adrenoceptors in both animal and human lung tissue. Over 20 years ago, Rugg and coworkers (1978) using rabbit and rat lung membranes and Szentivanyi (1979) using human lung membrane preparations demonstrated the presence of high densities of β-adrenoceptors (Rugg et al. 1978; Szentivanyi 1979). Subsequent studies in guinea-pig (Barnes et al. 1980; Engel et al. 1981) and hamster lung (Benovic et al. 1983) confirmed that the lung was densely populated with β-adrenoceptors. Furthermore, lung parenchyma contained heterogeneous populations of both β_1- and β_2-adrenoceptors (Dickinson et al. 1981; Engel et al. 1981; Carswell and Nahorski 1983). However, the most important information, i.e. the location of these receptors within the normal structure of the lung, was not revealed in detail until autoradiographic assessments were completed.

Light-microscopic autoradiography (Young and Kuhar 1979) has enabled the detection and localization of β-adrenoceptor subtypes in mammalian airways and lung parenchyma from many animal species including ferret (Barnes et al. 1982), guinea-pig (Goldie et al. 1986a), rabbit (Barnes et al. 1984), rat (Finkel et al. 1984), mouse (Henry et al. 1990) and pig (Goldie et al. 1986a), as well as from the human (Carstairs et al. 1985; Spina et al. 1989).

In human lung, the greatest density of β-adrenoceptors was found in alveolar septae (Carstairs et al. 1984). Approximately 78% of the total human lung tissue volume consists of alveolar tissue, with only 8% being vascular smooth muscle, 3% as airway smooth muscle and the remaining 11% is connective tissue and cartilage (Bertram et al. 1983). Furthermore, β-adrenoceptor numbers were 3 times higher in the alveolar wall than over bronchial smooth muscle and 1.4 times higher than over bronchiolar smooth muscle. Thus, approximately 96% of the β-adrenoceptor population was located in alveolar tissue. However, as might be expected, significant numbers of β-adrenoceptors were found in bronchial and bronchiolar airway smooth muscle, as well as in airway epithelium and in vascular endothelium and smooth muscle.

4 β-Adrenoceptor Agonists

4.1 Adrenaline

The β_2-adrenoceptor agonists used in the therapy of both asthma and COPD are all structurally related to the endogenous catecholamine adrenaline (Fig. 2). It is the powerful β_2 effects of adrenaline that are most important in asthma treatment, although α- and β_1-adrenoceptors are also activated. Adrenaline is not effective when taken orally because it is rapidly metabolized by gastrointestinal and hepatic monoamine oxidase (MAO). Accordingly, in emergency conditions, when the use of adrenaline in asthma is necessary, it is given by parenteral injection.

Fig. 2 β-Adrenoceptor agonists

4.2 Isoprenaline

Isoprenaline is an *N*-isopropyl derivative of adrenaline that has no significant agonist effect at α-adrenoceptors, and was the first β-adrenoceptor-selective agonist introduced into asthma therapy. Isoprenaline, like adrenaline, is a catecholamine and so is not useful orally since it is metabolized rapidly by catechol-*O*-methyltransferase (COMT). However, significant cardiac stimulation induced via activation of β_1-adrenoceptors, even after inhalational administration, reduces its acceptability as a bronchodilator.

4.3 Selective β_2-Adrenoceptor Agonists

A major advance occurred with the development and introduction of β_2-adrenoceptor-selective agonists that could be given orally or by inhalation and had extended durations of action compared with adrenaline or isoprenaline. Orciprenaline was the first of this new generation of bronchodilator amines and is a resorcinol derivative rather than a catecholamine and thus is not inactivated by extraneuronal COMT. Furthermore, this tertiary amine is not metabolized by MAO. Although orciprenaline is metabolized by sulpho-conjugation, enough free drug is absorbed to make it an effective oral bronchodilator. However, selectivity for the β_2-adrenoceptor is only slightly improved over that of isoprenaline (Mcevoy et al. 1973).

Salbutamol (Brittain et al. 1968) and terbutaline (Bergman et al. 1969) possess much greater selectivity for β_2-adrenoceptors than orciprenaline. Both compounds are active orally, as well as by inhalation and intravenous injection. All of the newer orally active β_2-adrenoceptor agonists are used in various inhalation formulations. The great virtue of being able to administer these new β_2-adrenoceptor agonists by inhalation is that small but highly effective doses can be delivered to the lung, giving the desired therapeutic effect rapidly (onset 5–10 min) and with an extended duration of action (up to 6 h). Negligible plasma concentrations of the active drug result from these inhaled doses.

4.4 Long-Acting β_2-Adrenoceptor Agonists

Members of the first generation of β_2-adrenoceptor-selective agonist bronchodilators, such as salbutamol, are considered to be short-acting since they have a duration of action of 4–6 h. These agents are effective in a large proportion of asthmatics where they provide rapid symptom relief. Short-acting β_2-adrenoceptor agonists are also used to prevent asthma exacerbations that may, for example, be triggered by exposure to cold air or exercise. However, in some asthmatic patients, these short-acting drugs need to be administered several times a day for adequate symptom relief. In addition, treatment of nocturnal

symptoms in susceptible patients may be problematic given the relatively short duration of action of these drugs. In order to provide effective treatment in asthmatic individuals whose symptoms were not adequately managed with short-acting agents, β_2-adrenoceptor agonist bronchodilators were developed that had durations of action of up to 12 h. Their use in asthma has recently been reviewed (Kips and Pauwels 2001). Long-acting β_2-adrenoceptor agonists have been shown to be more effective than salbutamol in reducing asthma symptoms and improving lung function in mild-to-moderate asthmatics (Pearlman et al. 1992; Leblanc et al. 1996; Taylor et al. 1998). Since long-acting β_2-adrenoceptor agonists are relatively new drugs, their safety and efficacy has been compared to both theophylline and the cysteinyl leukotriene receptor antagonist zafirlukast. Here, salmeterol has been found to provide significantly greater improvement in the management of asthma symptoms than either theophylline or zafirlukast (Davies et al. 1998; Busse et al. 1999).

Salmeterol (Ullman and Svedmyr 1988) (Fig. 2) was specifically designed to prolong the duration of action of the short-acting β_2-adrenoceptor agonist salbutamol. While formoterol (Fig. 2) was not deliberately designed to have this property, it was found to have a 12-h duration of action when administered by inhalation (Hekking et al. 1990). The agonist activity profiles of formoterol and salmeterol are distinct, suggesting that the extended duration of action of these agents is achieved via different mechanisms. Furthermore, salmeterol is a partial β_2-adrenoceptor agonist, whereas formoterol has higher intrinsic activity and is a full agonist (Linden et al. 1993; Naline et al. 1994). Unlike salbutamol, which is hydrophilic, both salmeterol and formoterol possess lipophilic properties which allow them to remain in airway tissues in close proximity to the β_2-adrenoceptor. This partly explains why the duration of action of these long-acting β_2-adrenoceptor agonist bronchodilators is at least 12 h. In addition to being lipophilic, formoterol is also water soluble, ensuring rapid access to the β_2-adrenoceptor and thus rapid bronchodilator activity. In contrast, salmeterol, being highly lipophilic, probably diffuses more slowly to the β_2-adrenoceptor laterally through the cell membrane and has a slower onset of action (Lotvall 2001; Kottakis et al. 2002). Salmeterol contains the saligenin head of salbutamol that binds to the active site of the β_2-adrenoceptor. This saligenin head is coupled to a long aliphatic side chain that significantly increases the lipophilicity of salmeterol. The side chain then binds to a discrete "exosite" that anchors it to the receptor and enables repetitive receptor activation (Green et al. 1996). The exact mechanism by which formoterol exerts its prolonged effects is unclear but may result from its lipophilicity, allowing formoterol to enter the plasma membrane where it is held for a prolonged period. From this site, formoterol diffuses over time to activate the β_2-adrenoceptor. Inhaled formoterol has also been shown to have a longer duration of action than orally administered formoterol, probably as a result of high concentrations building in the bronchial periciliary fluid (Anderson et al. 1994).

4.5
Delivery of β_2-Adrenoceptor Agonists

The metered dose inhaler (MDI) is the most commonly prescribed patient-operated device for the delivery of asthma therapies, including β_2-adrenoceptor agonists, with approximately 340 million units used every year world-wide (Partridge 1994; Woodcock 1995). The popularity of the MDI is by virtue of its effectiveness and ability to deliver a wide range of drugs (Woodcock 1995). Indeed, salbutamol, when administered via MDI and spacer is as effective and more cost-effective when compared with delivery via a nebulizer (Newman et al. 2002). MDIs were formulated with a combination of the chlorofluorocarbon (CFC) propellants 11 and 12. However, because of the ozone-depleting potential of CFCs, the ozone-friendly propellant hydrofluoroalkane (HFA) 134a has now replaced CFCs. Studies have demonstrated that the effectiveness and safety of salbutamol/HFA 134a is comparable to that of salbutamol/CFC (Hawksworth et al. 2002; Langley et al. 2002).

5
Major Sites of Therapeutic Action

5.1
Airway Smooth Muscle

Both contraction studies in vitro (Goldie et al. 1982) and autoradiographic studies have confirmed that only β_2-adrenoceptors are expressed and mediate relaxation to β-adrenoceptor agonists in human airway smooth muscle (Spina et al. 1989). This explains why β_1-adrenoceptor-selective agents such as prenalterol given intravenously, elevate heart rate without inducing bronchodilatation (Lofdahl and Svedmyr 1982). Agonist stimulation of β_2-adrenoceptors reverses airway obstruction in asthmatics primarily by causing relaxation of central and peripheral airway smooth muscle. However, given that β_2-adrenoceptors are widely distributed throughout the lung, the beneficial actions of β_2-adrenoceptor agonists may in part be the result of actions at other sites. For example, reversal or blunting of the actions of inflammatory mediators causing airway wall oedema would be expected to relieve that component of bronchial obstruction.

5.2
Tracheobronchial Microvessels

It has long been established that airway wall oedema is an obligatory accompaniment to airway inflammation. This phenomenon involves the exudation of plasma from tracheobronchial microvessels into the extravascular space in these airways and thereby contributes significantly to airway narrowing in asthma and possibly to epithelial shedding and bronchial hyperresponsiveness (Persson et al. 1986). The infiltration of inflammatory cells from the vascular space into

the submucosa and thence into the mucosa itself, is a natural consequence of this increased microvascular permeability in response to neuropeptides, histamine, endothelin-1 and other mediators of asthma. The tracheobronchial circulation consists of a subepithelial capillary network, with postcapillary venules as the main site of plasma extravasation. While the mechanisms that provoke plasma protein extravasation are incompletely understood, a variety of stimuli such as antigen, histamine, platelet-activating factor (PAF) and substance P induce direct plasma extravasation from bronchial microvessels. The targets of such mediators and thus the major sites of microvascular plasma leakage leading to a generalized airway wall oedema, are postcapillary venular endothelial cells which contract, leaving intercellular gaps which act as pores facilitating plasma leakage (Persson 1987). Airway oedema contributes to airway narrowing as well as to bronchial hyperresponsiveness. Thus, inhibition of microvascular permeability could improve airway calibre and also reduce airway inflammation, thereby providing both therapeutic and prophylactic benefit.

β_2-Adrenoceptor agonists have the potential to inhibit mediator-induced microvascular plasma extravasation by relaxing post-capillary endothelial cells and thus opposing the spasmogenic actions of various mediators that induce intercellular gap formation (Persson 1986). Indeed, such activity has been demonstrated for β_2-adrenoceptor agonists in vitro (Langeler and Van Hinsbergh 1991) and in vivo (Rippe and Grega 1978; Baluk and Mcdonald 1994). With respect to its effects on endothelial barrier function, cAMP stabilizes endothelial tight junctions, inhibits myosin light chain kinase, reduces actin-non-muscle interaction and the formation of stress fibres and prevents agonist-induced endothelial gap formation (Moy et al. 1993; Siflinger-Birnboim et al. 1993; Adamson et al. 1998).

The long acting β_2-adrenoceptor agonist formoterol reduced histamine-induced microvascular leakage in guinea-pig airways (Erjefalt and Persson 1991; Advenier et al. 1992) and salmeterol reduced both early- and late-phase microvascular plasma leakage in rat. Furthermore, inhaled procaterol inhibited histamine-induced microvascular leakage in not only non-sensitized control guinea-pigs but also in animals sensitized and challenged with ovalbumin (Mirza et al. 1998). This suggests that β_2-adrenoceptor agonists may be effective in reversing oedema in the airway wall associated with allergic inflammation. Furthermore, β_2-adrenoceptor agonists can potentiate the inhibitory effects of both non-selective and selective phosphodiesterase IV inhibitors against antigen-induced microvascular leakage (Planquois et al. 1998). The long acting β_2-adrenoceptor agonist salmeterol may also reduce angiogenesis and vascular remodelling in the airways (Orsida et al. 2001). Another controversial action of β_2-adrenoceptor agonists is their potential to inhibit the release of inflammatory mediators from sensory nerves (Advenier et al. 1992; Verleden et al. 1993). This raises the possibility that β_2-adrenoceptor agonists have an anti-inflammatory impact and might attenuate oedema via this indirect mechanism.

These positive findings are to some extent countered by the observations that formoterol was less effective in the presence of ozone-induced airway inflamma-

tion (Inoue et al. 1997). Indeed, it has previously been shown in cases of established airway microvascular leakage that pretreatment with a β_2-adrenoceptor agonist does not always reduce the leakage of molecules induced by a further inflammatory stimulus (Erjefalt et al. 1985; Persson 1987). Furthermore, established oedema in the tracheobronchial model associated with airway inflammation does not resolve rapidly in the presence of a conventional (short-acting) β_2-adrenoceptor agonist. Hence, the therapeutic importance of the relaxant effect of β_2-adrenoceptor agonists on post-capillary endothelial cells is controversial. Despite this misgiving, formoterol has been shown to reduce plasma exudation in induced sputum in normal subjects (Greiff et al. 1998).

6
Other Potential Therapeutic Tissue Targets

6.1
Inflammatory Cells

It has long been known that β_2-adrenoceptors are expressed on inflammatory cells including mast cells (Butchers et al. 1980; Hughes et al. 1983), peripheral blood lymphocytes (Williams et al. 1976; Koeter et al. 1982; Sano et al. 1983), polymorphonuclear leukocytes (PMNL) (Galant et al. 1980; Davis et al. 1986; Nielson 1987), peritoneal macrophages (Schenkelaars and Bonta 1984), alveolar macrophages; (Fuller et al. 1988), platelets (Cook et al. 1987) and eosinophils (Koeter et al. 1982; Kraan et al. 1985). The established effects of β_2-adrenoceptor stimulation in some of these cells may be relevant to the therapeutic benefits of these agents in asthma. For example, it is well established that the response of both normal volunteers and of asthmatics to intramuscular β-adrenoceptor agonists such as adrenaline is for blood eosinophil numbers to fall dramatically (Koch-Weser 1968; Reed et al. 1970), an apparent anti-inflammatory reaction. However, in the case of the inhaled β_2-selective bronchodilator terbutaline, no such decrease in circulating eosinophils was observed.

Arguably, the most important potential anti-inflammatory action of the relatively short-acting β_2-adrenoceptor agonist bronchodilators such as salbutamol and terbutaline, is their capacity to suppress pro-inflammatory mediator release from inflammatory cells. For example, in the case of lymphocytes, inhibition of lymphokine secretion (and of proliferation) is well established (Bourne et al. 1974; Reed 1985). In PMNL, inhibition of superoxide radical generation and leukotriene release has been reported (Busse and Sosman 1984; Mack et al. 1986). In the case of human lung mast cells, salbutamol is a potent inhibitor of antigen-induced release of histamine and leukotrienes (Peters et al. 1982; Church and Young 1983). Indeed, salbutamol is 10–100 times more potent that disodium cromoglycate in this regard (Church and Hiroi 1987).

However, while the early asthmatic response is inhibited by β_2-adrenoceptor agonists, their impact on the late response to allergen is much less impressive (Cockcroft and Murdock 1987). Thus, the anti-inflammatory effects of

monotherapy with inhaled, short-acting β_2-adrenoceptor agonist bronchodilators is minimal (Juniper et al. 1990; Haahtela et al. 1991; Van Essen-Zandvliet et al. 1992). Accordingly, it is generally accepted that the airway smooth muscle relaxant activity of β_2-adrenoceptor agonists is the action of primary importance in asthma. Paradoxically, it is this very powerful bronchodilator action that can harbour dangers for the asthmatic, since the sense of relative well-being and control over symptoms that accompanies the use of β_2-adrenoceptor agonists can mask the underlying progression and deterioration of this disease. This potential problem has been recognized and is a driver of recommendations for the combined use of such bronchodilators with an anti-inflammatory glucocorticoid (Kips and Pauwels 2001).

The advent of long-acting β_2-adrenoceptor agonist bronchodilators such as formoterol and salmeterol has re-ignited the question of whether or not a real therapeutic benefit is obtained in terms of the suppression of mediator release from inflammatory cells, even though these agents are also delivered by inhalation. It could be argued that the longer duration of action of these agents increases the likelihood of such an effect. Predictably, long-acting β_2-adrenoceptor agonists have been shown in animal studies both in vivo and in vitro, to effectively suppress pro-inflammatory mediator release and cytokine production and/or release from inflammatory cells. These actions have been demonstrated in human and/or animal T lymphocytes (Sekut et al. 1995; Holen and Elsayed 1998), macrophages (Linden 1992; Baker et al. 1994; Oddera et al. 1998), mast cells (Butchers et al. 1991; Gentilini et al. 1994; Lau et al. 1994; Nials et al. 1994; Bissonnette and Befus 1997; Chong et al. 1998; Drury et al. 1998), eosinophils (Eda et al. 1993; Rabe et al. 1993; Munoz et al. 1995) and neutrophils (Anderson et al. 1996). Furthermore, these agonists are also known to inhibit chemotaxis and recruitment of eosinophils (Whelan and Johnson 1992; Eda et al. 1993; Whelan et al. 1993; Teixeira et al. 1995; Teixeira and Hellewell 1997) and to delay apoptosis in these cells (Kankaanranta et al. 2000). However, it is now clear that monotherapy with long-acting agents such as salmeterol does not provide significant anti-inflammatory effect in asthma (Simons 1997; Verberne et al. 1997).

6.2 Secretory Cells

The deleterious impact of mucous hypersecretion and impaired mucociliary clearance on the effective bronchial lumen diameter and thus on bronchial airflow, can be life-threatening in the poorly controlled, severe asthmatic. Submucosal glands in human airways contain β_2-adrenoceptors (Carstairs et al. 1985), the stimulation of which increases mucus output. Importantly, β_2-adrenoceptor agonists also stimulate increases in ciliary beat frequency (Verdugo et al. 1980; Lopez-Vidriero et al. 1985) and in the movement of water towards the mucosal surface where it can hydrate mucus (Phipps et al. 1980). The net effect of these actions appears to be to improve mucociliary transport in asthmatics (Mossberg et al. 1976). However, in patients with significantly damaged bronchial epitheli-

um, it seems likely that cilia function will be impaired, raising the possibility that in some patients, β_2-adrenoceptor agonist-stimulated mucous secretion could be detrimental.

7 Adverse Reactions to β_2-Adrenoceptor Agonists

7.1 Primary Adverse Reactions

The most widely reported adverse effects of therapeutic doses of β_2-adrenoceptor agonists mediated via β_2-adrenoceptors are skeletal muscle tremor (Larsson and Svedmyr 1977), cardiac effects (Paterson et al. 1979), metabolic changes including hyperglycaemia, hypokalaemia and decreased partial pressure of arterial oxygen (PaO_2) (Tai and Read 1967; Smith and Kendall 1984). These effects are seen in both healthy volunteers and in asthmatics. However, tolerance usually develops to the tremorogenic effects of β_2-adrenoceptor agonists in patients receiving long-term treatment (Svedmyr et al. 1976; Paterson et al. 1979). Furthermore, while there is little evidence that recommended aerosolized doses exacerbate pre-existing cardiac arrhythmias, caution should be taken in such cases.

7.2 Other Significant Direct Adverse Reactions

β_2-Adrenoceptor agonist bronchodilators can induce the mobilization of triglycerides resulting in elevated blood levels of fatty acids and glycerol (Smith and Kendall 1984), although it is the β_1-adrenoceptor that is responsible for mediating this effect. Salbutamol, terbutaline and fenoterol can induce mild appetite suppression, headache, nausea and sleep disturbances (Miller and Rice 1980; Pratt 1982). This is consistent with their ability to cross the blood–brain barrier, leading to CNS levels approximately 5% of those seen in plasma (Caccia and Fong 1984).

7.3 Stereoisomers of Salbutamol

Salbutamol, the most widely used β_2-adrenoceptor agonist bronchodilator, is a racemic mixture of equal parts of *R*-salbutamol and *S*-salbutamol. β_2-Adrenoceptor-mediated bronchodilatation is stereoselective, with *R*-salbutamol being wholly responsible for β_2 adrenoceptor-mediated bronchodilation and *S*-salbutamol being inactive in humans (Prior et al. 1998; Zhang et al. 1998). Since *S*-salbutamol has previously been shown to cause a small increase in airway reactivity in vitro (Mazzoni et al. 1994; Yamaguchi and Mccullough 1996), it was suggested that the *S*-enantiomer of racemic β_2-adrenoceptor agonists may cause airway hyperreactivity and even contribute to increased mortality

(Perrin-Fayolle et al. 1996; Handley et al. 1998). This potential safety concern, coupled with the finding that repeated administration of *R*, *S*-salbutamol resulted in *S*-salbutamol accumulation (Gumbhir-Shah et al. 1998; Dhand et al. 1999; Schmekel et al. 1999), resulted in the development of the optically pure *R*-salbutamol, levalbuterol, recently introduced into the U.S. market. Importantly, studies have now demonstrated that *S*-salbutamol has no deleterious effect on airway responsiveness to methacholine in asthmatic patients (Cockcroft and Swystun 1997; Cockcroft et al. 1999). Thus, *R*-salbutamol cannot claim to be safer than *R*,*S*-salbutamol based on the argument that *S*-salbutamol increases airway reactivity. Indeed, *R*,*S*-salbutamol has been found to be as safe as *R*-salbutamol in patients with asthma (Gumbhir-Shah et al. 1998; Nelson et al. 1998; Gawchik et al. 1999). Furthermore, evidence in both adults and children with stable asthma indicates that *R*-salbutamol is as effective a bronchodilator as equimolar doses of *R*,*S*-salbutamol (*R*-salbutamol 1.25 mg=*R*,*S*-salbutamol 2.5 mg) (Nelson et al. 1998; Gawchik et al. 1999). As an added disadvantage, *R*-salbutamol is likely to be more expensive than a comparable generic racemic salbutamol preparation. Taken together, the evidence indicates that *R*-salbutamol offers no genuine advantage with respect to safety or clinical efficacy over racemic salbutamol (Ahrens and Weinberger 2001; Boulton and Fawcett 2001).

8
Combination Therapy

8.1
Long-Acting β_2-Adrenoceptor Agonists and Glucocorticoids

The scientific rationale for the use of long-acting β_2-adrenoceptor agonists in combination with a corticosteroid has recently been summarized (Barnes 2002). The use of long-acting β_2-adrenoceptor agonists has been examined in asthmatic patients whose symptoms persisted despite treatment with low-dose glucocorticoids. In a randomized, double-blind, parallel-group trial, 429 adult asthmatics receiving 200 μg twice daily of inhaled beclomethasone dipropionate were selected. These mild-to-moderate asthmatics were symptomatic despite treatment with inhaled glucocorticoids. Subjects were assigned to receive either 50 μg salmeterol plus 200 μg beclomethasone or 500 μg beclomethasone alone twice daily for 6 months (Greening et al. 1994). There were significant advantages in favour of salmeterol plus beclomethasone compared with the higher dose of beclomethasone alone with respect to lung function and symptom control. Woolcock et al. (1996) recruited 738 moderate-to-severe asthmatics, whose symptoms were not controlled by twice daily 500 μg beclomethasone dipropionate. In this study, the administration of either 50 μg or 100 μg salmeterol twice daily with 500 μg beclomethasone had a more rapid and pronounced beneficial effect on control of asthma symptoms and lung function than doubling the dose of beclomethasone (twice daily 1000 μg) (Woolcock et al. 1996). Importantly, the addition of salmeterol was found to not increase bronchial hyperre-

sponsiveness or asthma exacerbation rates (Greening et al. 1994; Woolcock et al. 1996). Furthermore, meta analysis of nine parallel group trials revealed that addition of salmeterol to low to moderate doses of inhaled glucocorticoid in symptomatic patients was superior to doubling the dose of inhaled glucocorticoid (Shrewsbury et al. 2000).

These studies demonstrate that interactions between β_2-adrenoceptor agonists and glucocorticoids are predominantly positive, with combinations of the two drugs improving asthma control and exacerbation rates. While this is particularly true for long-acting β_2-adrenoceptor agonists, the exact mechanism remains unclear. For example, the effects of long-acting β_2-adrenoceptor agonists and glucocorticoids may be merely additive; with the former causing prolonged bronchodilation and the latter reducing or reversing airway inflammation. Alternately, there may be true synergy between these agents with long-acting β_2-adrenoceptor agonists enhancing the effects of glucocorticoids (Kips and Pauwels 2001; Barnes 2002). It has been suggested that long-acting β_2-adrenoceptor agonists may have "steroid-enhancing" or "steroid-sparing" effects. However, it is important to note that monotherapy with long-acting β_2-adrenoceptor agonists is less effective than inhaled glucocorticoids alone, suggesting that these terms need to be used cautiously (Lazarus et al. 2001).

Based on the complementary roles of β_2-adrenoceptor agonists and glucocorticoids, the long-acting β_2-adrenoceptor agonist salmeterol and the glucocorticoid fluticasone have been combined in a single inhaler with the potential to treat both the airway smooth muscle dysfunction and inflammatory components of asthma. Such combination products have the potential to limit overuse of β_2-adrenoceptor agonist bronchodilators in the absence of anti-inflammatory therapy, thus ensuring that β_2-adrenoceptor agonists are not used as monotherapy. However, the use of "fixed" combination inhalers may be associated with the overuse of both drugs in the management of asthma, as control over individual drug dosages is lost.

In spite of these shortcomings, combination inhalers are effective in the treatment of many asthmatics and this format for combination therapy may become the method of choice in the near future in patients with persistent asthma (Barnes 2002). Studies in adults and adolescents have demonstrated improvements in forced expiratory volume in 1 s (FEV_1), peak expiratory flow (PEF), and asthma symptoms with a combination product containing salmeterol (50 μg) and fluticasone propionate (100, 250 or 500 μg) delivered via the dry powder Diskus inhaler (Seretide) (Aubier et al. 1999; Chapman et al. 1999; Bateman et al. 2001). Additionally, children aged 4–11 years who were symptomatic while receiving inhaled glucocorticoids, had similar improvements in FEV_1, PEF and asthma symptoms with salmeterol/fluticasone propionate (50/100 μg) (Van den Berg et al. 2000). The combination of fluticasone propionate and salmeterol via the Diskus device has also been found to improve lung function and reduce the severity of dyspnea in patients with COPD (Mahler et al. 2002). More recently, a salmeterol/fluticasone propionate MDI has been developed to provide an alternative choice of delivery system. Three strengths of the salmeterol/fluticas-

one propionate MDI are available each containing a constant dose of salmeterol (25 μg) combined with fluticasone (50, 125 or 250 μg) per actuation. Since each dose is given as two actuations, these preparations are equivalent to the three strengths of the salmeterol/fluticasone propionate Diskus indicated above. The efficacy and safety of salmeterol/fluticasone propionate (50/100 μg) was found to be comparable whether administered via MDI or dry powder Diskus inhaler, allowing a choice of delivery systems (Bateman et al. 2001).

8.2 D_2-Receptor Agonists

A different approach to combination therapy is to incorporate multiple pharmacological actions within the one drug molecule. Airway hyperreactivity, a feature of both asthma and COPD, is associated with neural reflex pathways that include sensory afferent nerves. While the receptors that modulate the activity of these airway nerves have yet to be characterized, reflex nerve activity may be controlled by modulating the activity of afferent nerves. For example, dopamine, via stimulation of D_2-receptors, may play a role in the control of lung function by reducing the ability of sensory nerves to produce harmful reflex activity. Indeed, D_2-receptor mRNA has been detected in rat vagal afferent neurones (Lawrence et al. 1995) and dorsal root ganglia (Xie et al. 1998), nerves associated with reflex pathways. Thus, D_2-receptor agonists should reduce reflex bronchoconstriction, dyspnea, cough and mucus production, without any direct bronchodilator activity. A dual dopamine D_2-receptor and β_2-adrenoceptor agonist would combine the modulating effects of a dopamine D_2-receptor agonist on sensory afferent nerves with the bronchodilator action of a β_2-adrenoceptor agonist in the one molecule. An example of such a compound is AR-C68397AA (Viozan) (Bonnert et al. 1998). Combination therapy of this sort may provide effective symptomatic treatment for both asthma and COPD with the added advantage of reducing neurogenic inflammation in the airways. Interestingly, the benzothiazole structure of the synthetic compound AR-C68397AA has since been found to occur in the natural β_2-adrenoceptor agonist S1319 (4-hydroxy-7-[1-(1-hydroxy-2-methylamino)ethyl]-1,3-benzothiazole-2(3H)-one) found in a marine sponge *Dysidea sp*. (Suzuki et al. 1999).

9 Pharmacogenetics of β_2-Adrenoceptor Agonists in Asthma

Pharmacogenetics is the study of the role of genetic determinants in the variable response to therapy. Within the human population, the β_2-adrenoceptor is polymorphic, with some of these polymorphic receptors having different pharmacological properties. Recent studies have suggested that genetic factors may underlie some of the variability in treatment responses to β-adrenoceptor agonists seen in asthmatics. Both single-nucleotide polymorphisms (SNPs) and variable nucleotide tandem repeats (VNTRs) are genetic polymorphisms that have been

shown to have pharmacogenetic effects in asthma. A total of 13 polymorphisms in the β_2-adrenoceptor gene and its transcriptional regulator β-upstream peptide have been identified (Liggett 2000a,b).

Within the β_2-adrenoceptor gene, coding variants at positions 16 and 27, in the extracellular N-terminal domain, have been shown to be functionally important in vitro (Green et al. 1994; Mcgraw et al. 1999). While the Gly-16 receptor exhibits enhanced downregulation in vitro following exposure to an agonist (Green et al. 1994), Arg-16 receptors are more resistant to desensitization. However, N-terminal polymorphisms at position 16 failed to alter either the rates of new receptor synthesis following irreversible alkylation or the rate of agonist-promoted internalization of the receptor to the intracellular pool (Green et al. 1994). Due to linkage disequilibrium, individuals who are Arg/Arg-16 are much more likely to be Glu/Glu-27 and individuals who are Gly/Gly-16 are much more likely to be Gln/Gln-27. Furthermore, the position 27 genotypes influence but do not abolish the effect of position 16 polymorphisms with respect to downregulation of phenotypes in vitro (Green et al. 1994; Mcgraw et al. 1999). The potentially protective Glu-27 polymorphism has been reported to be associated with decreased airway reactivity in asthma (Hall et al. 1995) but it did not seem to influence nocturnal asthma (Turki et al. 1995) or bronchodilator responsiveness (Martinez et al. 1997). In contrast, the Gln-27 polymorphism has been associated with elevated IgE levels and an increase in self-reported asthma in children (Dewar et al. 1997). Israel and co-workers (2001) noted a decrease in morning peak expiratory flow in patients who were Arg/Arg-16 and who regularly used salbutamol (Israel et al. 2001).

In an attempt to explain the apparent disparity between in vitro and patient data, Liggett has proposed that Gly/Gly-16 individuals are already downregulated as a result of exposure to endogenous catecholamines (Liggett 2000b). As such, desensitization caused by recurrent exogenous β-adrenoceptor agonist exposure would be more apparent in Arg/Arg patients with functional β-adrenoceptors. In this scenario, the initial response to salbutamol in β-adrenoceptor agonist-naïve patients would be depressed in Gly/Gly individuals, since their receptors would have been downregulated to a greater extent due to endogenous catecholamines. The bronchodilator response obtained after administration of a single dose of salbutamol has also been examined (Martinez et al. 1997). Here, β-adrenoceptor agonist-naïve asthmatic and non-asthmatic children in the Arg/Arg-16 group showed a greater bronchodilator response, with Arg/Arg-16 children being 5.3-fold more likely to exhibit a positive bronchodilator response to salbutamol compared with Gly/Gly-16 children.

It is important to note that pharmacogenetic studies of treatment response are often negative (Hancox et al. 1998) or involve small subject numbers (Tan et al. 1997; Lipworth et al. 1999). Larger scale pharmacogenetic studies will need to be conducted in order to detect large effects associated with a SNP. The data obtained so far suggest that β_2-adrenoceptor polymorphisms may alter the response to β-adrenoceptor agonists. However, it is still unclear whether β_2-adre-

noceptor polymorphisms will have any great clinical relevance for most patients.

10 Clinical Application

10.1 Asthma

In general, asthma medication can be divided into two groups; reliever and preventer medications. The major group of asthma reliever medications are β_2-adrenoceptor agonist bronchodilators which act quickly and effectively to relieve bronchoconstriction and the associated asthma symptoms of chest tightness, wheezing and cough. The main asthma preventer medications are the glucocorticoids which are used prophylactically and as maintenance therapy to reduce, reverse and prevent airway inflammation. It is vital that all asthmatic patients learn to manage their own asthma and that they have a good understanding of the role of reliever and preventer medications in treating their disease. The goal of asthma management is to achieve and maintain best lung function and an ideal starting point is the institution of an asthma management plan (National Asthma Campaign—Asthma Management Handbook 2002). Typically, the first step in such a plan is the assessment of the patient's asthma severity. The patient may then be treated intensively, with reliever and/or preventer medication, until best lung function is achieved. The types and quantity of drug used can then be back-titrated to the least number of medications and lowest dose required for good control of asthma symptoms and maintenance of best lung function. Since prevention is the key to successful asthma management, an important component of any asthma management plan is the identification and avoidance or control of asthma triggers such as allergen, exercise and cold air. In addition, an individualized action plan needs to be developed to manage any ongoing asthma symptoms and exacerbations. An effective asthma management plan necessitates regular review and ongoing patient education.

The severity of asthma may be classified based on an assessment of asthma symptoms and lung function in combination with the types and quantity of drug required to reduce or avoid symptoms. In this way, patients with asthma may be classified as having mild intermittent, mild persistent, moderate or severe disease (NIH: NHLBI 1997; 1998; NHLBI/WHO Workshop report 1995). The clinical classification of asthma severity forms the basis of the stepwise approach to asthma pharmacotherapy, with the number and frequency of medications increasing (step up) as the severity of asthma increases and decreasing (step down) when asthma is under control (Table 1). However, classifying asthma severity is not intended to restrict the type of drug therapy received by an individual patient, but is intended as a guide to the level of therapy that may be required to achieve symptom control. Furthermore, patients diagnosed with any

Table 1 Classification of asthma severity and the therapeutic use of β_2-adrenoceptor agonists

	Mild intermittent	Mild persistent	Moderate persistent	Severe
Clinical Features:				
Symptom frequency	<1 a week	>1 a week but <1 a day	Daily	Continuous
Nocturnal symptoms	$\leq$2 a month	>2 a month	>1 a week	Frequent
Exacerbations	Brief, asymptomatic and normal lung function between exacerbations	Exacerbations may affect activity and sleep	>2 a week, exacerbations affect activity and sleep	Frequent
Lung function	PEF or FEV_1 $\geq$80% predicted, variability <20%	PEF or FEV_1 $\geq$80% predicted, variability 20%–30%	PEF or FEV_1 60%–79% predicted, variability >30%	PEF or FEV_1 < 60% predicted, variability >30%
Drug treatment:				
Reliever: β_2-adrenoceptor agonist	Short-acting inhaled β_2-adrenoceptor agonist should be taken as needed for symptom relief	Regular short-acting inhaled β_2-adrenoceptor agonist	Regular long-acting inhaled β_2-adrenoceptor agonist and short-acting β_2-adrenoceptor agonist as needed	Regular long-acting inhaled β_2-adrenoceptor agonist
Preventer: Glucocorticoid		Low-dose inhaled glucocorticoid	Low-dose inhaled glucocorticoid	High-dose inhaled and oral glucocorticoid

level of asthma may have mild, moderate or severe exacerbations and these exacerbations also require appropriate management.

In patients with mild intermittent asthma, short-acting inhaled β_2-adrenoceptor agonists, including salbutamol and terbutaline, are the treatment of choice and should be used as required to relieve symptoms and prevent those induced by exercise or exposure to allergen. If this regimen fails to control asthma symptoms, an increase in β_2-adrenoceptor agonist use needs to be considered. Usually, the infrequent nature of symptoms in this group of patients does not warrant continuous β_2-adrenoceptor agonist therapy.

Patients with mild persistent asthma should be treated with low-dose inhaled glucocorticoids to treat airway inflammation. In addition, the regular use of short-acting inhaled β_2-adrenoceptor agonists is required for the relief of acute asthma symptoms. If best lung function is not maintained under this treatment regimen, the dose of inhaled glucocorticoid can be increased and/or a long-acting β_2-adrenoceptor agonist used, particularly when breakthrough and/or night-time symptoms persist.

The treatment of moderate persistent asthma involves inhaled glucocorticoids and the regular use of long-acting β_2-adrenoceptor agonists, such as salmeterol and formoterol. The latter are particularly useful for the control of night-time symptoms. The addition of a long-acting β-adrenoceptor agonist to the treatment regimen may also have a steroid-sparing effect in these patients. Short-acting β_2-adrenoceptor agonists may be used in these patients for the rapid treatment of acute symptoms.

In most cases, patients with severe asthma should receive high doses of inhaled glucocorticoids and the regular use of long-acting β_2-adrenoceptor agonists. Short-acting β-adrenoceptor agonist medications should be used for acute symptom relief. Asthma exacerbations in this group of patients may also require a course of oral glucocorticoid therapy.

10.2 COPD

The severity of COPD may be classified into four stages (GOLD 2001; Table 2). However, the management of COPD is driven largely by symptomology and there is often no direct relationship between the degree of airflow limitation and the presence of symptoms. Thus, disease classification provides only a very general indication of the approach to be given to management of COPD.

The goals of effective COPD management are to prevent disease progression, relieve symptoms, improve exercise tolerance, improve health status, prevent and treat complications, prevent and treat exacerbations and reduce mortality. Pharmacotherapy is used to prevent and control symptoms, reduce the frequency and severity of exacerbations, improve health status and improve exercise tolerance. Importantly, existing medications used for the treatment of COPD have not been shown to modify the long-term decline in lung function associated with this disease. Bronchodilator medications including β_2-adrenoceptor ag-

Table 2 Classification of COPD by severity (GOLD 2001)

Stage	Characteristics
0: At Risk	Normal spirometry Chronic symptoms (cough, sputum production)
I: Mild COPD	$FEV_1/FVC<70\%$ $FEV_1 \geq 80\%$ predicted With or without chronic symptoms (cough, sputum production)
II: Moderate COPD	$FEV_1/FVC<70\%$ $30\% \geq FEV_1 < 80\%$ predicted With or without chronic symptoms (cough, sputum production)
III: Severe COPD	$FEV_1/FVC<70\%$ $FEV_1<30\%$ predicted or $FEV_1<50\%$ predicted plus respiratory failure or clinical signs of right heart failure

FEV_1 values refer to post-bronchodilator values; FVC, forced vital capacity.

onists, anticholinergics and theophylline, given alone or in combination, have a role to play in relieving symptoms as well as preventing and treating exacerbations (Chrystyn et al. 1988; Vathenen et al. 1988; Gross et al. 1989; Higgins et al. 1991; Anthonisen et al. 1994). These bronchodilators may be used either on an as needed basis for the relief of persistent or worsening symptoms, or on a regular basis to prevent or reduce symptoms. The choice between β_2-adrenoceptor agonist, anticholinergic, theophylline (or related compound) or some combination of these drug therapies depends on the response obtained by the individual in terms of symptom relief and side effects. A combination of bronchodilators may produce additional improvements in lung function and health status while decreasing the risk of side effects compared with increasing the dose of a single bronchodilator (Taylor et al. 1985; Guyatt et al. 1987; Gross et al. 1998; Van Noord et al. 2000).

A key diagnostic feature of COPD is poor reversibility of airflow limitation following inhalation of a short-acting β_2-adrenoceptor agonist. Importantly, β_2-adrenoceptor agonist bronchodilators have been shown to improve hyperinflation, exercise capacity and quality of life in COPD patients, without necessarily producing significant changes in FEV_1 (Guyatt et al. 1987; Jenkins et al. 1987; Cazzola et al. 1995; Boyd et al. 1997). Recent studies have shown that long-acting inhaled β_2-adrenoceptor agonists significantly improve symptoms and increase health-related quality of life in COPD patients (Ulrik 1995; Jones and Bosh 1997; Mahler et al. 1999).

11 Concluding Remarks

The airway smooth muscle relaxant effect of β_2-adrenoceptor agonists is their primary beneficial action in asthma and COPD, although positive therapeutic influences on mucus production and clearance and bronchial oedema may also

occur. β_2-Adrenoceptor agonists appear to be largely ineffective in suppressing or controlling airway inflammation in asthmatics and are likely to be equally ineffective in COPD patients. Accordingly, in asthma, despite their relative lack of significant, direct detrimental side effects, there is consensus that β_2-adrenoceptor agonist bronchodilators, whether or not they are long acting, should not be used as monotherapy in any but the most mild of cases. Indeed, the powerful bronchodilator (reliever) actions of both long- and short-acting β_2-adrenoceptor agonists may mask the onset and/or deterioration of on-going airway inflammation in asthmatics. The increased emphasis on anti-inflammatory therapies in recent years is now complemented by the use of β_2-adrenoceptor agonists in therapeutic regimes centred on the combined use of corticosteroids and β_2-adrenoceptor agonist bronchodilators. Indeed, the introduction of single administration formulations of inhaled steroid with a bronchodilator is finding increasing acceptance in the treatment of persistent asthma. Unfortunately, in COPD, bronchodilator therapies do not alter the long-term decline in lung function. However, β_2-adrenoceptor agonist bronchodilators and anticholinergics and theophylline, given alone or in combination, can relieve symptoms and help to reverse exacerbations. The introduction of long-acting β_2-adrenoceptor agonists has produced significant improvements in symptoms in COPD patients and thus has had a positive impact on quality of life in these patients. The use of combination bronchodilator/corticosteroid regimes further assists in the management of this disease.

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