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Inhaled β_2-adrenoceptor agonists in asthma: help or hindrance?

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Introduction

Inhaled β_2-adrenoceptor agonists have been used extensively over the past three decades and have a well established role as first-line bronchodilator therapy in patients with asthma. Initial concerns regarding the safety of inhaled β_2-adrenoceptor agonists were raised in the 1960s by the transient increase in mortality of young patients with asthma in England and Wales. This appeared to coincide with the increased use of high concentration isoprenaline aerosol sprays (Inman & Adelstein, 1969; Speizer *et al.*, 1968). Various mechanisms were suggested but never proven, and included sensitisation of the myocardium to catecholamines by hydrofluorocarbons and tachyphylaxis to isoprenaline (Paterson *et al.*, 1968; Reisman, 1970). Public awareness of the possible dangers of isoprenaline aerosols together with the introduction of more selective β_2-adrenoceptor agonists such as salbutamol was associated with a parallel return of asthma normality to more 'acceptable' levels.

Subsequently, there was a second increase in asthma mortality in young people reported in New Zealand in the late 1970s (Jackson *et al.*, 1982), which appeared to coincide with the introduction of the β_2-selective agonist fenoterol. Overreliance on high doses of inhaled β_2-adrenoceptor agonist was again implicated together with delays in seeking medical attention (Sears *et al.*, 1987). Recent case-control studies from New Zealand suggested that the use of inhaled fenoterol was associated with an increased risk of death in patients with severe asthma (Crane *et al.*, 1989a; Grainger *et al.*, 1991; Pearce *et al.*, 1990). Studies which have shown that the extrapulmonary effects of fenoterol are greater in comparison with other inhaled β_2-adrenoceptor agonists have resulted in speculation by some authors that the systemic adverse effects of fenoterol might explain the epidemiological mortality data (Crane *et al.*, 1989b; Windom *et al.*, 1990; Wong *et al.*, 1990). There has also been a recent report showing that regular inhaled β_2-adrenoceptor agonist therapy might result in a deterioration of disease control in asthmatics (Sears *et al.*, 1990). This in turn has led to concerns about the safety of the novel long-acting β_2-adrenoceptor agonists such as salmeterol and formoterol.

The current controversy regarding the use of inhaled β_2-adrenoceptor agonists has resulted in a reappraisal of their benefits and risks, and has provided the stimulus for this review. Two main issues will be addressed. Firstly, the systemic effects and selectivity of inhaled β_2-adrenoceptor agonists, and secondly, their possible adverse effects on disease control in patients with asthma.

Molecular structure of β-adrenoceptor agonists

The chemical structure of β-adrenoceptor agonists determines their selectivity for β_2-adrenoceptors. The basic structural nucleus of β-adrenoceptor agonists comprises a benzene ring attached to an ethyl-amine group (Figure 1). β-adrenoceptor agonists can be broadly divided into catecholamines and non-catecholamines, the former including the synthetic compound isoprenaline. The non-catecholamines such as fenoterol, salbutamol and terbutaline differ in their substitutions in the amine group and benzene ring. These structural modifications confer resistance to metabolism by catechol-*o*-methyltransferase and result in a longer half-

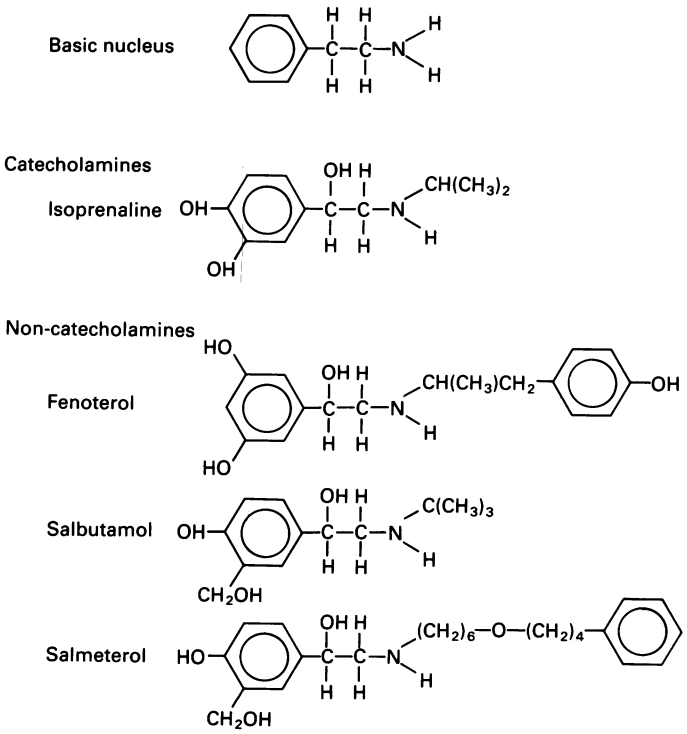

Figure 1 The chemical structure of β-adrenoceptor agonists.

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life and also reduce their potency for β_1-receptors making them relatively more β_2-selective.

The novel long-acting β_2-adrenoceptor agonist salmeterol differs in possessing a much longer substitution in the amine head. It is thought that this molecular configuration might result in exo-receptor binding and hence cause prolonged receptor occupancy (Jack, 1991). In this respect, formoterol which is also long-acting, does not possess a long amine side chain, making exo-receptor binding an unlikely mechanism to account for its duration of action. However, both formoterol and salmeterol are highly lipophilic compared with salbutamol which may result in greater bronchial tissue retention and a more prolonged duration of effect (Jeppsson *et al.*, 1989). This same property of lipophilicity might also conceivably result in increased systemic absorption across the lung-vascular bed, and hence lead to greater extrapulmonary adverse effects.

Selectivity of β_2-adrenoceptor agonists *in vitro*

The *in vitro* evaluation of selectivity for β_1- and β_2-receptors has conventionally been based on the relative effects of β-adrenoceptor agonists on guinea-pig isolated atrial and tracheal preparations respectively. Fenoterol has been shown to have a 2.7 fold greater potency for tracheal β_2-receptors compared with salbutamol at equimolar concentrations (O'Donnell & Wanstall, 1978). Calculation of selectivity ratios (β_2:β_1) show fenoterol and salbutamol respectively to be 59 fold and 107 fold more selective for β_2-receptors, in comparison with isoprenaline (O'Donnell, 1972). This infers that salbutamol exhibits a 1.8 fold greater selectivity for β_2-receptors relative to the effects of fenoterol. In another similar study (O'Donnell & Wanstall, 1974), fenoterol and terbutaline respectively showed 102 fold and 182 fold greater selectivity for β_2-receptors compared with isoprenaline. Wagner and co-workers (1973) found that both fenoterol and salbutamol act as full agonists on guinea pig tracheal β_2-adrenoceptors, whereas salbutamol is a partial agonist on atrial β_1-adrenoceptors. Thus, it would appear that the β_2-receptor selectivity of fenoterol is considerably greater than that of isoprenaline, but slightly less compared with terbutaline or salbutamol.

Bronchodilator effects

The goal for bronchodilator therapy should be to produce optimal airway response with minimal systemic adverse effects. Peak bronchodilatation occurs within 30 min of inhaling salbutamol and lasts for between 4–6 h (Lipworth *et al.*, 1989a). Furthermore, inhaled delivery of salbutamol has a much wider therapeutic ratio in comparison with the oral route (Larsson & Svedmyr, 1977; Lipworth *et al.*, 1989a). The novel longer acting inhaled β_2-adrenoceptor agonists salmeterol and formoterol act for up to 12 h, although salmeterol has a much slower onset of action compared with formoterol (Maesen *et al.*, 1990a; Ullman & Svedmyr, 1988).

Inhaled salbutamol in the dose range of 100–4000 μg produces dose-dependent increases in bronchodilator response in asthmatic airways, although there is a wide variation between subjects in terms of the actual magnitude of response (Lipworth *et al.*, 1988). Analyses of individual responses showed that most patients required doses in excess of 500 μg to produce maximal bronchodilatation, and there was no relationship between baseline airway calibre and the dose required to optimise response. It is interesting that in normal airways a plateau in bronchodilatation occurs with much lower doses of inhaled salbutamol (Lipworth & McDevitt, 1989b). This might suggest that β_2-receptors in asthmatic airways are less sensitive to inhaled salbutamol, although inherent differences in airways geometry makes it difficult to compare normal and asthmatic bronchodilator responses. However, *in vitro* studies have not shown any evidence of altered β_2-receptor responsiveness in asthmatic bronchial smooth muscle (Whicker *et al.*, 1988). An alternative explanation might be that there is impaired accessibility to bronchial smooth muscle β_2-receptors because of endobronchial mucosal inflammation in asthmatic airways.

The optimisation of bronchodilator response is more important for those patients who have severe airflow obstruction, although this should be balanced against systemic sequelae and possible adverse effects on disease control. Most patients with asthma may be adequately controlled with an inhaled corticosteroid, using inhaled β_2-adrenoceptor agonists for relief of symptomatic wheeze.

Systemic effects

The role of cardiac β_2-receptors

Before comparing the cardiovascular sequelae of different inhaled β_2-adrenoceptor agonists, it is important to have an understanding of the place of cardiac β_2-receptors in mediating these adverse effects. Lands *et al.* (1967) postulated that β-receptors were not homogenous and could be divided into β_1 and β_2 subtypes based on their respective affinity for noradrenaline and adrenaline. Cardiac β-receptors were originally considered to be β_1 and bronchial receptors β_2 type. It is now known that β_2-receptors are more widespread being found in myocardium, as well as in many other sites (Table 1). Radioligand-binding studies have shown that up to 40% of β-receptors in the ventricle and up to 55% in the atrium are of the β_2-subtype (Bristow & Ginsburg, 1986; Brodde *et al.*, 1983; Heitz *et al.*, 1983). *In vitro* studies have shown that cardiac β_1- and β_2-receptors are functionally coupled to adenylate cyclase and responsible for mediating chronotropic and inotropic responses (Ask *et al.*, 1985; Bristow *et al.*, 1986; Brodde *et al.*, 1984; Gillie *et al.*, 1895).

In vivo studies in man have also indicated that myocardial β_2-receptors are functionally active. Firstly, ICI 118,551 (a selective β_2-adrenoceptor antagonist) at doses which had no effect on exercise heart rate and therefore devoid of β_1-adrenoceptor antagonism, attenuated isoprenaline induced tachycardia even after

Table 1 Site and action of human β-adrenoceptors

Tissue	*Receptor*	*Effects*
Heart	B_1, β_2	Inotropic, chronotropic
Airways	β_2	Smooth muscle relaxation Prejunctional inhibition of cholinergic neurotransmission Decreased bronchial hyperreactivity Increased mucociliary clearance Reduction in mucosal oedema Inhibition of mediator release
Lungs	β_1	?
Blood vessels	β_2	Vasodilatation
Skeletal muscle	β_2	Finger tremor, hypokalaemia
Uterus	β_2	Relaxation
Leukocytes, erythrocytes, platelets	β_2	?
Liver, pancreas	β_2	Increased release of: glucose, lactose, pyruvate, insulin, HDL
Kidney	β_2	Increased excretion: Mg, Ca, PO_4
Adipose tissue	β_3	Thermogenesis, lipolysis

atropinisation (Arnold *et al.*, 1985). In the same doses, ICI 118,551 also attenuated isoprenaline induced finger tremor (a known β_2-mediated effect). The inference of these studies is that the heart rate response to isoprenaline is mediated in part by direct stimulation of cardiac β_2-receptors in addition to stimulation of cardiac β_1-receptors and reflex vagal withdrawal. Secondly, whereas neither atenolol nor ICI 118,551 as single agents produces substantial antagonism of isoprenaline tachycardia, in combination their effect is comparable with that of propranolol (Pringle *et al.*, 1988). It is also possible to distinguish between β_1-selective and non-selective β-adrenoceptor blocking drugs by their comparative effects on isoprenaline induced cardiac output and systolic blood pressure responses, suggesting that inotropic effects are at least partially mediated by β_2-receptors (Lipworth *et al.*, 1991a).

In an elegant study, Hall and co-workers (1989) injected salbutamol directly into the right coronary artery (in patients undergoing angiography) with a resultant tachycardia, whereas the same dose injected into the aortic root had no effect, ruling out a systemic effect due to reflex vagal withdrawal. The heart rate response to intracoronary salbutamol was blunted by propranolol but not practolol, showing that the chronotropic effect is due to direct stimulation of cardiac β_2-receptors. These findings are supported by a study which compared the effects of inhaled salbutamol on heart rate, finger tremor and specific airways conductance in the measurement of β_2-adrenoceptor blockade in normal subjects given single oral doses of atenolol (50 mg, 100 mg, 200 mg), propranolol (40 mg) or placebo. The attenuation of airway and tremor responses by atenolol and propranolol were similar in comparison to their effects on heart rate (Lipworth *et al.*, 1989c). It was concluded that in this experimental model, the chronotropic response to inhaled salbutamol may be used in the assessment of β_2-receptor antagonism in man. The cumulative dose of inhaled salbutamol was up to 6200 μg, with the implication that loss of β_2-selectivity was not evident even at these higher concentrations.

The relative effects of selective β-adrenoceptor agonists on cardiac responses also helps to elucidate the relative roles of β_1- and β_2-receptor subtypes. In a study comparing the haemodynamic effects of i.v. prenalterol and salbutamol, the latter caused greater heart rate and diastolic blood pressure responses, whereas prenalterol (selective β_1-adrenoceptor agonist) caused greater inotropic effects on ejection fraction and systolic blood pressure (Corea *et al.*, 1984). Furthermore, Strauss *et al.* (1986), showed that atenolol partially attenuated the systolic blood pressure and inotropic response to infused terbutaline, but had no effect on heart rate. Taken together these data suggest that inotropic responses to β_2-selective agonists are caused partially by stimulation of β_2-receptors, along with dose-related loss of β_2-receptor selectivity; whereas chronotropic effects are predominantly β_2-mediated.

Comparative systemic effects of inhaled β_2-adrenoceptor agonists in man

Dose-related airway responses to inhaled salbutamol occur at the expense of systemic adverse effects due to the widespread nature of extrapulmonary β_2-adrenoceptors (Table 1). In addition to inotropic and chronotropic effects, hypokalaemic, electrocardiographic and tremor responses also occur. Systemic effects of inhaled salbutamol are not seen until at least 500 μg has been given, and thereafter occurs in dose-dependent linear fashion (Lipworth *et al.*, 1988, 1989b,d). Such doses of salbutamol in excess of 500 μg are commonly given by nebuliser, or by frequent usage of pressurised aerosols during acute asthmatic attacks.

Hypokalaemic effects are due to intracellular uptake of potassium into skeletal muscle by stimulation of membrane bound Na/K ATP-ase (Brown *et al.*, 1983;

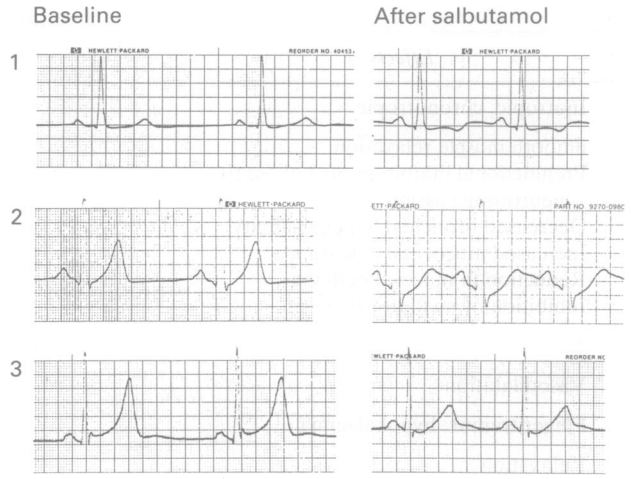

Figure 2 Single lead (II) electrocardiograms from three subjects before and after 2000 μg of inhaled salbutamol. Taken from Lipworth *et al.* (1989d).

Lipworth *et al.*, 1989e). Such falls in serum potassium are accompanied by dose related electrocardiographic effects including T wave flattening, U waves and S-T depression (Figure 2) (Shamroth, 1982; Surawicz, 1967; Weaver & Burchell, 1960). The hypomagnesaemic effects of inhaled β_2-adrenoceptor agonists are too small to account for the prolongation of the Q-Tc interval which also occurs (Lipworth *et al.*, 1989b,d). A direct cardiac sympathomimetic effect is a more likely explanation to account for Q-T effects of inhaled β_2-adrenoceptor agonists, since inhaled isoprenaline causes similar Q-Tc prolongation compared with inhaled salbutamol, whereas isoprenaline only produces minimal hypokalaemia (Lipworth *et al.*, 1991b). Prolongation of the Q-T interval is associated with ventricular arrhythmias and particularly torsades de pointes. In this respect the tachycardia associated with inhaled β_2-adrenoceptor agonists would be likely to protect against torsades de pointes, since the latter is often treated by rapid pacing (Surawicz & Knoebel, 1985).

For the purposes of the present discussion, studies which have evaluated systemic effects of inhaled β_2-adrenoceptor agonists in normal and asthmatic subjects will be considered separately, because of differences in the pattern of response. Previous single-dosing studies in normal subjects comparing equivalent doses (by weight) of inhaled fenoterol and salbutamol have shown the former to produce greater chronotropic and electrocardiographic (T wave and Q-Tc) effects (Crane *et al.*, 1989b; Scheinin *et al.*, 1987). The greater heart rate response with fenoterol has been interpreted by some authors as being indicative that fenoterol is less β_2-selective compared with salbutamol, resulting in dose-related stimulation of cardiac β_1-receptors. In this respect fenoterol also causes greater hypokalaemia in comparison with inhaled salbutamol (Crane *et al.*, 1989b; Deenstra *et al.*, 1988; Scheinin *et al.*, 1987). Thus, inhaled fenoterol would appear to cause greater β_2-mediated systemic effects (heart rate and hypokalaemia). This infers either that systemic absorption of fenoterol is greater in comparison with salbutamol, or that fenoterol exhibits a greater potency at systemic β_2-receptors. Since systemic absorption appears to be due to lung rather than gut absorption (Collier *et al.*, 1980; Kung *et al.*, 1987; Lipworth *et al.*, 1989d), the greater lipophilicity of fenoterol (Deenstra *et al.*, 1988; Jeppsson *et al.*, 1989) could result in a greater propensity for absorption across the lung-vascular bed. There is evidence *in vitro* that fenoterol has a greater potency for β_2-receptors compared with salbutamol, at equimolar concentrations (O'Donnell & Wanstall, 1978).

Windom and co-workers (1990) compared equivalent doses by weight (400–1600 μg) of inhaled fenoterol, salbutamol, and isoprenaline in 12 asthmatic patients, all of whom were receiving regular inhaled β_2-adrenoceptor agonist therapy. There were no significant differences between fenoterol and salbutamol for their effects on heart rate and Q-Tc, although hypokalaemia was slightly greater with fenoterol (mean difference of 0.3 mmol l^{-1}). The relative systemic potencies of β_2-adrenoceptor agonists in asthmatics can only be properly evaluated by comparing doses which produce equivalent bronchodilator effects, as assessed from individual dose-response curves. In this respect, interpretation of the Windom paper is limited, since fenoterol caused a greater increase in FEV_1 at all doses. It was also of particular interest that the highest doses of both drugs did not produce any increases in systolic blood pressure, inferring that inhaled fenoterol did not lose its β_2-selectivity at higher doses in asthmatic patients. The same authors had previously shown substantially greater systemic effects with similar doses of inhaled fenoterol in normal subjects (Crane *et al.*, 1989b). The blunting of extrapulmonary responses in the asthmatics reported by Windom *et al.* (1990) may be attributed to β_2-receptor down-regulation from their previous β_2-adrenoceptor agonist exposure (Brodde *et al.*, 1985, 1988). This is known to result in tachyphylaxis of *in vivo* systemic β_2-responses (Figure 3a,b) (Lipworth *et al.*, 1989f, 1990a,b).

In another study, Wong and colleagues (1990) studied 10 patients with mild asthma on inhaled β_2-adrenoceptor agonist therapy alone. Cumultive puffs of inhaled fenoterol (200 μg per puff), salbutamol (100 μg per puff) and terbutaline (250 μg per puff) were given up to a total of 26 puffs. This design was used to mirror the dose of drug delivered by each puff, as occurs in clinical practice. Conventional low doses (2 puffs) of all three drugs produced equal bronchodilatation and did not cause any systemic effects. It was only at much higher doses that any separation of systemic effects between fenoterol and the other β_2-adrenoceptor agonists emerged. The lowest doses of all three drugs produced FEV_1 responses near the top of the dose-response curve, whereas systemic effects did not occur until after 8 puffs. Thus it was not possible to compare systemic effects at equivalent bronchodilator doses. Furthermore, the gradients from the steep part of the chronotropic dose-response curve were similar for fenoterol and salbutamol, inferring that loss of β_2-selectivity did not occur with higher doses of fenoterol. Unfortunately, no measurement of systolic blood pressure was made to support this interpretation. In an earlier study, Gray and co-workers (1982) compared inhaled fenoterol (100 μg per puff) and terbutaline (250 μg per puff) in 12 asthmatics given a cumulative dose of 15 puffs. All patients were taking regular inhaled β_2-adrenoceptor agonists.

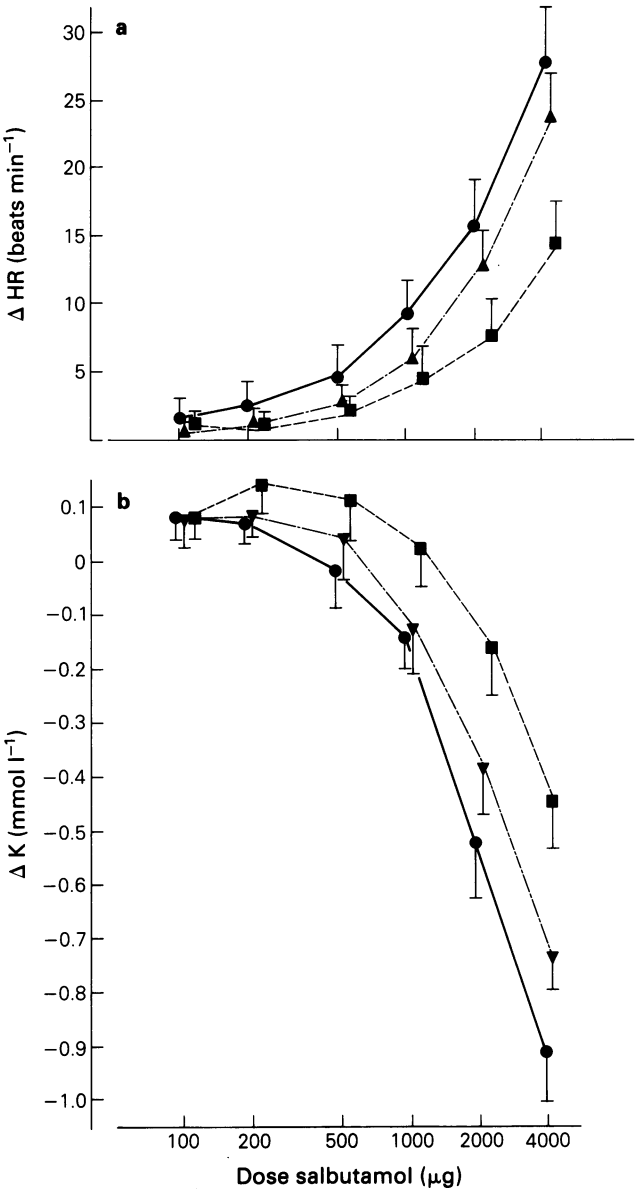

Figure 3 Changes in a) heart rate (HR) and b) plasma potassium (K) in response to cumulative doubling doses of inhaled salbutamol in 12 asthmatic patients after pretreatment for 2 weeks with either placebo (circles), low dose inhaled salbutamol (triangles), or high dose inhaled salbutamol (squares). Taken from Lipworth *et al.* (1989f).

Measurements of FEV_1 and sGaw showed equivalence of bronchodilator effects on a 'puff per puff' basis. Dose-response curves for heart rate showed a greater response with fenoterol, although the mean difference between the highest doses of fenoterol (1500 μg) and terbutaline (3750 μg) was only 10 beats min^{-1}. In summary, at higher than conventional dosage (2 puffs), inhaled fenoterol (100 μg per puff) causes greater β_2-mediated systemic effects compared with salbutamol (100 μg per puff), although there is no evidence in man to suggest that fenoterol is any less β_2-selective.

There are few published papers on the dose-response relationships for the systemic effects of the novel inhaled long-acting β_2-adrenoceptor agonists. Ullman & Svedmyr (1988) showed only minimal differences between peak and duration of bronchodilator response between 50 μg, 100 μg and 200 μg doses of inhaled salmeterol, in 8 asthmatic patients. Increases in heart rate occurred with only the 200 μg dose with a mean increase of 6 beats min^{-1}. Mean dose ratios (compared with placebo) for objective finger tremor were 1.4 for salbutamol 200 μg and salmeterol 50 μg and 2.2 for salmeterol 200 μg. The 200 μg dose of salmeterol caused a mean fall in diastolic blood pressure of 11 mm Hg, but did not increase systolic blood pressure, suggesting that β_2-selectivity is retained at the higher dose. Comparison of dose-response curves in nine asthmatic patients showed that inhaled formoterol in a cumulative dose of 123 μg produced equivalent peak bronchodilator effects to salbutamol in a cumulative dose of 1300 μg (Lofdahl & Svedmyr, 1989). The same doses of formoterol and salbutamol caused mean increases in heart rate of 5 beats min^{-1}, and dose-ratios for finger tremor of 3 and 1.7 respectively. The small magnitude of systemic effects in the above two studies is probably a reflection of tachyphylaxis from previous β_2-adrenoceptor agonist exposure rather than specific properties of salmeterol or formoterol. The duration of systemic like bronchodilator effects is also greater with the long-acting inhaled β_2-adrenoceptor agonists.

What is the clinical relevance of the systemic adverse effects? There are factors which might conceivably alter extrapulmonary β_2-responses in patients with asthma. Excessive use of inhaled β_2-adrenoceptor agonists during an exacerbation of asthma might cause further down-regulation of β_2-receptors resulting in further blunting of systemic effects (Lipworth *et al.*, 1989f). Administration of corticosteroids during an acute attack might reverse the subsensitivity of *in vivo* responses, by up-regulating β_2-receptors (Brodde *et al.*, 1985, 1988). The effects of hypoxaemia on cardiac responses in man are unknown, although in hypoxic dogs infused with isoprenaline, death occurred from bradycardia and pump failure, rather than from ventricular arrhythmias (McDevitt *et al.*, 1974). It is known that the extracellular potassium ion concentration is the single most important determinant of myocardial membrane potential (Dangman *et al.*, 1982; Roden & Iansmith, 1987; Surawicz *et al.*, 1959), and the arrhythmogenicity of hypokalaemia in patients with ischaemic heart disease is well documented (Nordrehaug *et al.*, 1985; Stewart *et al.*, 1985). There are reports in the literature of an association between the use of high dose inhaled β_2-adrenoceptor agonists and arrhythmias (Higgins *et al.*, 1987; Tandon, 1980). However, the link between β_2-adrenoceptor agonists, hypokalaemia and sudden death in acute severe asthma has never actually been proven (Sears *et al.*, 1987). Clinicians should also be aware that other potassium losing drugs such as diuretics, theophyllines or corticosteroids may potentiate β-adrenoceptor agonist induced hypokalaemia (Lipworth *et al.*, 1989g; Whyte *et al.*, 1988).

Effects of inhaled β_2-adrenoceptor agonists on disease control

The introduction of the novel longer-acting inhaled β_2-adrenoceptor agonists salmeterol and formoterol represents a significant advance in inhaled bronchodilator therapy (Maesen *et al.*, 1990a,b; McAlpine *et al.*, 1990;

Newnham *et al.*, 1991; Ullman & Svedmyr, 1988), and particularly in comparison with slow-release oral salbutamol or theophylline in terms of systemic effects. Inhaled salmeterol also appears to prevent the early and late phase airway response to inhaled allergen in patients with asthma (Twentyman *et al.*, 1990). The late response to allergen is thought to be due to airway inflammation, mainly via influx and activation of eosinophils; whereas the early response is caused by bronchospastic mediators released from mast cells. In this respect, inhaled salbutamol is a potent inhibitor of mast cell degranulation and abolishes the early but not late allergen response (Cockroft *et al.*, 1987; Howarth *et al.*, 1985). However, the late phase protection exhibited by salmeterol may simply represent a prolonged inhibitory effect on bronchial smooth muscle contraction, rather than a true anti-inflammatory effect as such (Britton *et al.*, 1991; Rogers *et al.*, 1991). There is *in vitro* evidence to show that salmeterol is a potent inhibitor of inflammatory mediator release from mast cells and alveolar macrophages (Baker & Fuller, 1990; Butchers *et al.*, 1987). It has been shown that after 4 h there is no difference between salmeterol and salbutamol in terms of supression of *in vivo* inflammatory mediator release, despite more prolonged protection against allergen challenge with salmeterol (O'Shaughnessy *et al.*, 1991). This also tends to support a direct bronchorelaxant effect as the probable mechanism for the prolonged inhibitory effect of salmeterol on allergen response. It is therefore too early to assess whether salmeterol possesses any useful anti-inflammatory activity. Such claims for anti-inflammatory properties should not result in prescribing salmeterol as first line anti-inflammatory therapy in place of inhaled steroid.

In a recent cross-over study from New Zealand (Sears *et al.*, 1990), regular compared with occasional usage of inhaled fenoterol for 6 months resulted in a deterioration in various parameters of asthma control, which appeared to be independent of concomitant inhaled steroid therapy. Single doses of inhaled β_2-adrenoceptor agonist exhibit a protective effect against histamine induced bronchial hyperreactivity (Britton *et al.*, 1988), although this protection is attenuated during chronic dosing with a rebound effect on stopping inhaled β_2-adrenoceptor agonists (Vathenen *et al.*, 1988). Other studies in which inhaled β_2-adrenoceptor agonists were given for up to 12 months have all shown small increases in bronchial hyperreactivity in asthmatic airways (Kerrebijn *et al.*, 1987; Kraan *et al.*, 1985; van Schayck *et al.*, 1990). However, increased airway reactivity to methacholine occurred in only 34% of cases taking regular compared with occasional inhaled β_2-adrenoceptor agonists in the study of Sears *et al.* (1990), inferring that this is not the sole cause of deteriorating asthma control. It is also possible that greater airways accessibility to inhaled antigen from regular β_2-adrenoceptor agonist therapy might have caused increased airway inflammation and reactivity (Lai *et al.*, 1989), and hence worsening asthma control. If this is the case, then β_2-adrenoceptor agonists with a longer duration of action might perhaps be expected to be more harmful in this respect. It would be interesting to compare the effects of regular β_2-adrenoceptor agonist and anticholinergic therapy on disease control and bronchial hyperreactivity, in order to assess whether this effect is specific to a particular class of bronchodilator drug. However, it is known that change in airway calibre as such is not a major determinant of the effects of inhaled β_2-adrenoceptor agonists on airway reactivity (Britton *et al.*, 1988). Page (1991) has hypothesised that inhaled β_2-adrenoceptor agonists might have adverse effects on asthma control by their inhibition of the body's own natural anti-inflammatory mechanisms which may result in persistent endobronchial mucosal injury. A further concern regarding regular use of β_2-adrenoceptor agonists and paticularly the longer-acting agents, is that supression of symptoms by bronchodilator therapy in the absence of inhaled steroids might mask the persistent airway inflammation.

An important issue which remains unclear is whether bronchodilator tachyphylaxis occurs during prolonged therapy with the novel long-acting β_2-adrenoceptor agonists. Bronchodilator tolerance does not occur with higher than conventional doses of inhaled salbutamol or terbutaline in patients with airflow obstruction (Figure 4) (Lipworth *et al.*, 1989f, 1990a). This is also consistent with studies showing that human bronchi but not peripheral mononuclear leukocyte β_2-receptors are spared from down-regulation on exposure to β_2-adrenoceptor agonists (Hauck *et al.*, 1990). However, prolonged receptor occupancy with the long-acting β_2-adrenoceptor agonists might conceivably result in down-regulation or G-protein uncoupling of airway β_2-receptors. Ullman *et al.* (1990) showed no subsensitivity of the bronchodilator responsiveness to inhaled salbutamol after treatment for 2 weeks with either inhaled salmeterol (50 μg twice daily) or salbutamol (200 μg four times daily), in a crossover study in 12 stable asthmatics. Interpretation of this study is however, limited by the absence of a washout period without β_2-adrenoceptor agonists before each treatment period.

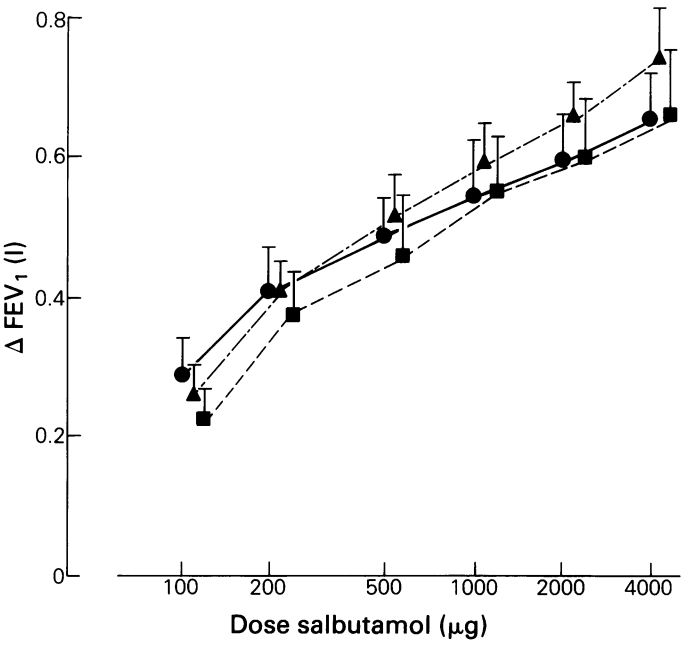

Figure 4 Changes in FEV_1 in response to cumulative doubling doses of inhaled salbutamol in 12 asthmatic patients after pretreatment for 2 weeks with either placebo (circles), low dose inhaled salbutamol (triangles), or high dose inhaled salbutamol (squares). Taken from Lipworth *et al.* (1989f).

Thus, it is possible that previous β_2-adrenoceptor agonist exposure may have caused down-regulation of β_2-receptors prior to the study. This would be consistent with the absence of tachyphylaxis to tremor responses when comparing dose-response curves before and after treatment with salbutamol or salmeterol.

Arvidsson *et al.* (1989) compared dose-response curves to inhaled salbutamol in 20 asthmatics before and after treatment for 2 weeks with inhaled salbutamol (200 μg twice daily) or formoterol (12 μg twice daily), and also found no evidence of bronchodilator tolerance. The 1 week duration of washout between the two treatments was probably too short to prevent any carry-over effect of β_2-receptor down-regulation. Regular inhaled β_2-adrenoceptor agonist therapy without a run-in period may also have induced down-regulation of β_2-receptors prior to the first treatment phase. In another comparison of formoterol (24 μg twice daily) and salbutamol (400 μg twice daily) given for 4 weeks to 16 asthmatics, the bronchodilator response to salbutamol was unimpaired, although only the response to a single 400 μg dose was assessed (Wallin *et al.*, 1990). Once again, inhaled β_2-adrenoceptor agonists were not withdrawn during a so called 'run-in' period. More prolonged studies (published only in abstract form) for up to 3 months with salmeterol (Britton, 1990; Dahl, 1989; Viskum, 1990) and for 12 months with formoterol (Clauzel *et al.*, 1990; Rosenhall *et al.*, 1990) have shown that disease control and bronchodilator efficacy are maintained, although full dose-response curves were not evaluated.

Summary

Conventional low doses of inhaled β_2-adrenoceptor agonists produce effective bronchodilation without systemic effects. Higher doses of inhaled β_2-adrenoceptor agonists may produce substantial improvements in bronchodilator response, which may be helpful to patients with more severe airway obstruction. At higher than recommended doses, in asthmatic patients, fenoterol appears to cause greater dose-related systemic β_2-responses compared with salbutamol or terbutaline, although there is no evidence to suggest that fenoterol is any less β_2-selective *in vivo*. Furthermore, tolerance develops to systemic but not to bronchodilator effects during chronic treatment with inhaled β_2-adrenoceptor agonists. The link between asthma mortality and systemic adverse effects of inhaled β_2-adrenoceptor agonists at present remains unproven. A critical reappraisal of the regular use of inhaled β_2-adrenoceptor agonists including long-acting drugs is now indicated in the light of their possible adverse effects on disease control. Patients requiring regular use of inhaled β_2-adrenoceptor agonists should be given additional anti-inflammatory therapy with inhaled corticosteroids.

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