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Asthma Medications and their Potential Adverse Effects in the Elderly

Recommendations for Prescribing

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Contents

Abstract

The incidence of drug-induced adverse effects is likely to increase as a result of advanced age and exposure of elderly patients to polypharmacy. Therefore, pharmacological therapy of asthma and chronic obstructive pulmonary disease (COPD) in the elderly patient can be potentially hazardous.

β_2-agonists, administered as therapy for asthma and COPD, have recognised systemic sequelae, such as hypokalaemia and chronotropic effects, which may be life-threatening in susceptible patients. Adverse effects such as hypokalaemia can be aggravated by concomitant treatment with other drugs promoting potassium loss including diuretics, corticosteorids and theophyllines. In addition, relatively minor adverse events associated with the administration of β_2-agonists, such as tremor and blood pressure changes, may be of significance to the elderly patient leading to impairment in the quality of life. However, long-term treatment with β_2-agonists may reduce the incidence of drug-induced adverse effects as a result of β-receptor subsensitivity.

Oral and inhaled corticosteroids have been used for the treatment of acute asthma and COPD in the elderly patient. Long-term treatment with oral corticosteroids can result in serious systemic adverse effects such as suppressed adrenal

function, bone loss, skin thinning and cataract formation. In contrast to β_2-agonists, oral corticosteroids can upregulate β_2-adrenoceptors and thereby potentiate the systemic sequelae of β_2-agonists. Hence, oral corticosteroids should be administered with caution for as short a duration as possible. Inhaled corticosteroids appear to be relatively well tolerated when administered at doses below approximately 1000μg. However, larger doses of inhaled corticosteroids may affect hypothalamic-pituitary-adrenal function and bone turnover. In the case of inhaled corticosteroids, spacer devices, often used in older patients who cannot operate metered dose inhalers, can potentiate the systemic sequelae of both corticosteroids and β_2-agonists.

The use of theophyllines in the treatment of COPD or chronic asthma is controversial. Theophyllines have a wide adverse effect profile and are prone to drug-drug interactions. The adverse effects may be mild or life threatening and include nausea and vomiting or sinus and supraventricular tachycardias. Therefore, theophyllines should be prescribed with extreme caution to elderly patients with asthma or COPD.

In contrast, inhaled anticholinergic drugs such as ipratropium bromide and oxitropium bromide are generally safe in elderly patients and have useful bronchodilator function. Commonly reported adverse effects are an unpleasant taste and dryness of the mouth. When used as first-line therapy, anticholinergic drugs may optimise the bronchodilator effects of low-dose inhaled β_2-agonists in patients with chronic airflow obstruction, and hence obviate the need for higher doses.

It is a recognised fact that the population of the world is ageing. The US has the third largest population of elderly people (60 years of age and older) in the world, next to China and India, and is second only to China in the size of the population of elderly people who are 80 years of age and older. The projected percentage increase in the population of elderly people ≥ 60 years of age by the year 2020 is 159% in less developed countries, 59% in developed countries and 69% in the United States.[1] In the UK in 1991, 15.7% of the total population of 9.1 million people were 65 years of age or older.[2] It is predicted that this population of elderly people will increase to 22.5% (14.0 million people) by the year 2031. The greatest increase will be among those who will survive into very old age; a group who are believed to place the greatest demand on healthcare services.[3,4] In addition, polypharmacy is common in these age groups and the incidence of polypharmacy is known to increase with age.[5] For example, older North Americans take an average of 4.5 medications at any one time.[6] Furthermore, institutionalised elderly patients are administered a mean of 3 to 8 drugs daily.[7] This is despite improved understanding of inappropriate prescribing and the potential for adverse drug-induced reactions in the elderly population.[8]

It is therefore clear that there is a significant potential for adverse drug reactions (ADRs) among elderly patients and the incidence of such ADRs will increase unless astute, rather than inappropriate, drug prescribing is practiced. The magnitude of the problem is considerable and worrying, with estimates of the incidence of drug-induced illness in older patients in hospital ranging from 6 to 19% with implications of drug related problems in 5 to 17% of hospital admissions among elderly patients.[9-14] The problem of drug-related illness is not solely hospital based and is also recognised among elderly patients in the community.[15,16] Hence, general practitioners as well as hospital physicians should be alert to the situation. However, it is recognised that ADRs may be missed, even though they are often predictable,[17,18] and hence the incidence of drug-induced adverse effects may be underestimated.[19]

ADRs associated with the use of drugs administered for respiratory tract disorders in the elderly patient are not unexpected, when one considers the fact that respiratory symptoms (primarily due to airways obstruction) are prevalent in this age group.[20-22] In addition, major polypharmacy (five or more drugs) has been demonstrated in approximately one in three patients over 65 years of age receiving antiasthmatic drugs and in one in five patients treated with systemic corticosteroids.[23] Hence, the potential is there for all respiratory drugs to cause ADRs in elderly patients, either by direct action or drug-drug interaction.

The aim of this review is to illustrate these drug effects and offer recommendations for safe prescribing. The leukotriene receptor antagonists will not be considered here as most study populations related to these antagonists involve children[24] or have a mean population age of 30 to 35 years.[25-27] Furthermore, the exact position of leukotriene receptor antagonists in the treatment of asthma is not yet established because of a variety of factors including lack of active comparator studies.[28]

1. β_2-Agonists

For many years, β-agonists have been used as inhaled and oral bronchodilators in patients with asthma and chronic obstructive pulmonary disease (COPD). A wide variety of inhaled short-acting [e.g. salbutamol (albuterol),terbutaline] and long-acting (e.g. salmeterol, eformoterol) β-agonists are available. Oral salbutamol (albuterol), terbutaline and, more recently, bambuterol, a once-daily prodrug of terbutaline, have been licensed for prescription. Their modes of action and adverse effects are similar and well documented.

For simplicity, the adverse drug effects of inhaled and oral β_2-agonists will be discussed together, although it is recognised that oral therapy may have a slower onset of action compared with inhaled therapy.

It is important to note that the majority of published data are in younger patient populations. However, to date, there is little evidence to suggest that, compared with the younger patients, elderly patients respond differently to inhaled β_2-agonists systemically.[29]In addition, dose-dependent increases in forced expiratory volume in 1 sec and forced vital capacity have been observed in older patients after the administration of terbutaline,[30] although it has been suggested that β_2-receptor function in the airways declines with age.[31,32]

1.1 Systemic Adverse Effects

The administration of inhaled (and oral) β_2-agonists can be accompanied by dose-dependent systemic adverse effects which include hypokalaemia, electrocardiographic sequelae, finger tremor and chronotropic and inotropic responses (fig. 1).[33-35] The inhaled drug is primarily absorbed across the lung-vascular bed[35-37] with over 80% of the dose administered being deposited in the oropharynx and subsequently swallowed.[38,39] Spacer devices can reduce oropharyngeal deposition and increase lung deposition by reducing particle size and velocity.[40] However, the use of spacer devices will subsequently increase drug absorption across the lung-vascular bed and exaggerate extra pulmonary adverse effects.[35,41] The latter factor is of considerable importance in elderly patients who frequently struggle to operate conventional metered-dose inhalers because of cognitive and physical problems and are supplied with spacer devices to overcome these difficulties and aid drug delivery.[42-44]

Oral medication is absorbed *via* the stomach and small intestine. The pharmacologically active component of the drug is subsequently subjected to inactivation by first-pass metabolism in the liver. However, because of the high oral bioavailability of the drug, systemic adverse effects occur commonly. Recent data have suggested that oral bambuterol has a better effect/adverse effect ratio compared with standard terbutaline and is relatively well tolerated in elderly patients.[45] Systemic adverse effects may be tempered by tachyphylaxis as a result of β_2-receptor down-regulation. The latter effect has been demonstrated in patients who have been exposed previously to inhaled short-acting (fig. 2)[30,46,47] and long-acting β_2-agonists (fig. 3).[48,49] Conversely, oral prednisolone has

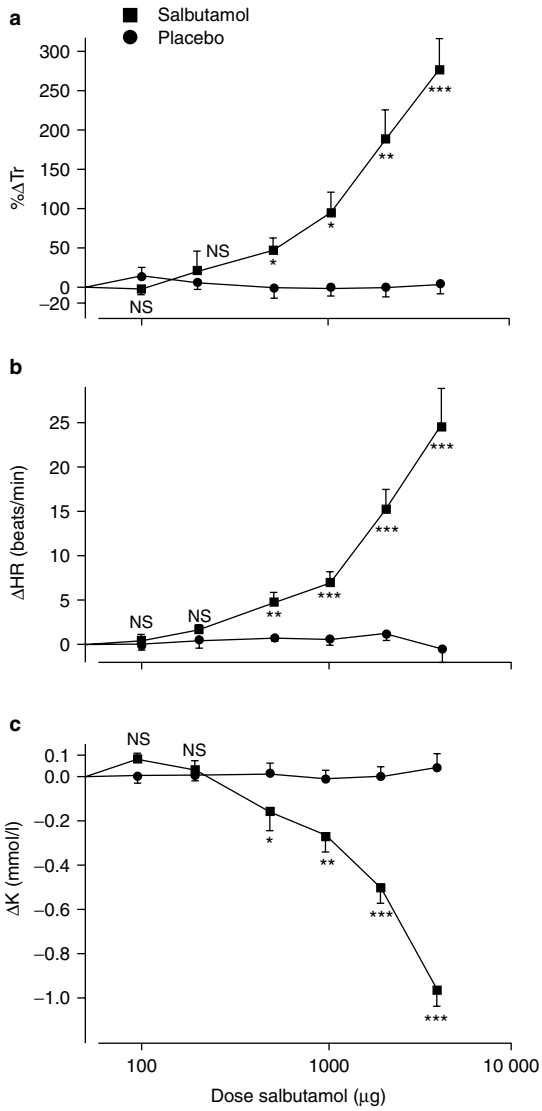

Fig. 1. Effects of cumulative doses of inhaled salbutamol (albuterol) 100μg to 4000μg on finger tremor (Tr), heart rate (HR) and plasma potassium (K), as change from baseline (delta, Δ), in healthy individuals (reproduced from Lipworth et al.,[34] with permission). * $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$.

been shown to increase lymphocyte β_2-receptor density in patients with asthma as reflected by an increase in bronchodilator responsiveness.[50] It was thought previously that β_2-adrenoceptor up-regulation did not occur with inhaled corticosteroids.[51] However, more recent data has demonstrated that inhaled corticosteroids can re-sensitise cardiac β_2-adrenoceptors in the presence of β_2-agonists.[52] Hence, the use of oral or inhaled corticosteroids in elderly patients may increase the risk of potential adverse effects to inhaled β_2-agonists.

1.2 Hypokalaemic and Electrocardiographic Effects

β_2-agonists induce hypokalaemia by way of an intracellular shift of potassium into skeletal muscle, as a result of stimulation of Na+/K+-ATPase on cell membranes.[53,54] It is a well recognised fact that the extracellular potassium ion level is vitally important in determining myocardial membrane stability.[55-57]

Furthermore, in patients with ischaemic heart disease, a common occurrence among elderly patients, the arrhythmogenic potential of hypokalaemia has been documented in the literature.[58,59] Higgins et al.[60] and Tandon [61] have also described an association between high-dose inhaled β_2-agonists and cardiac arrhythmias. Clearly, there is a significant potential risk of cardiac dysrhythmias in elderly patients prescribed inhaled or oral β_2-agonist therapy and this risk is increased by polypharmacy, whose prevalence, as mentioned earlier, increases with age.[5] Other drugs promoting potassium loss, such as diuretics, corticosteroids and the theophyllines, if prescribed in conjunction with β_2-agonists, can potentiate the hypokalaemia.[62-64] The hypokalaemic effect of β_2-agonists is not prevented by the use of a potassium-sparing diuretic such as triamterene administered in conventional doses.[62] However, other studies have noted a degree of protection from hypokalaemia induced by β_2-agonists, following the administration of high dose (200mg) triamterene and conventional doses of spironolactone.[65] However, in view of the other biochemical sequelae associated with diuretic therapy in elderly patients, there appears to be more risk than benefit for the patient receiving these drugs, and their use solely to protect against β_2-

agonist induced hypokalaemia cannot be advocated.

Hypokalaemia may also cause cardiac sequelae in elderly patients by way of electrocardiographic changes including T wave inversion, ST segment depression and U waves.[66-68] Prolongation of the QTc interval also occurs with β_2-agonist therapy, but this is thought to be due to direct cardiac sympathomimetic stimulation rather than hypokalaemia.[29] It is recognised that the prolongation of the QTc interval may predispose patients to developing torsade de pointes.[69]

The predominant dysrhythmia of torsade de pointes is bradycardia, which is treated conventionally by rapid pacing. Therefore, the tachycardia induced by β_2-agonists (see section 1.3) may confer a degree of protection against this arrhythmia. At this point, it is important to reiterate the effect of regularly used β_2-agonists (i.e. reduced sensitivity – tachyphylaxis) and corticosteroids (i.e. increased sensitivity – upregulation) on β_2-adrenoceptors, as this will have a significant bearing on the risk of serious systemic adverse effects in elderly patients.

1.3 Chronotropic and Inotropic Effects

The effect of β_2-agonists on heart rate is complex and may be due to peripheral vasodilation[70] or direct β_2-adrenoceptor stimulation.[71,72] There has been some debate as to whether cardiac β_1-adrenoceptor stimulation contributes to the tachycardia induced by fenoterol, as a result of loss of β_2-receptor selectivity at higher than conventional doses.[73,74] This fact is of relevance to the elderly patient as fenoterol is a component in combination inhalers (e.g. fenoterol and ipratropium bromide) often used in older patients. It is conceivable that elderly patients may be exposed to high doses of fenoterol during an exacerbation of their airways disease, as a result of multiple inhalations of the β_2-agonist. Previous literature has associated high doses of fenoterol with an increased risk of death in patients with acute severe asthma.[75] However, more recent data have suggested that there is no difference in the respective chronotropic or inotro-

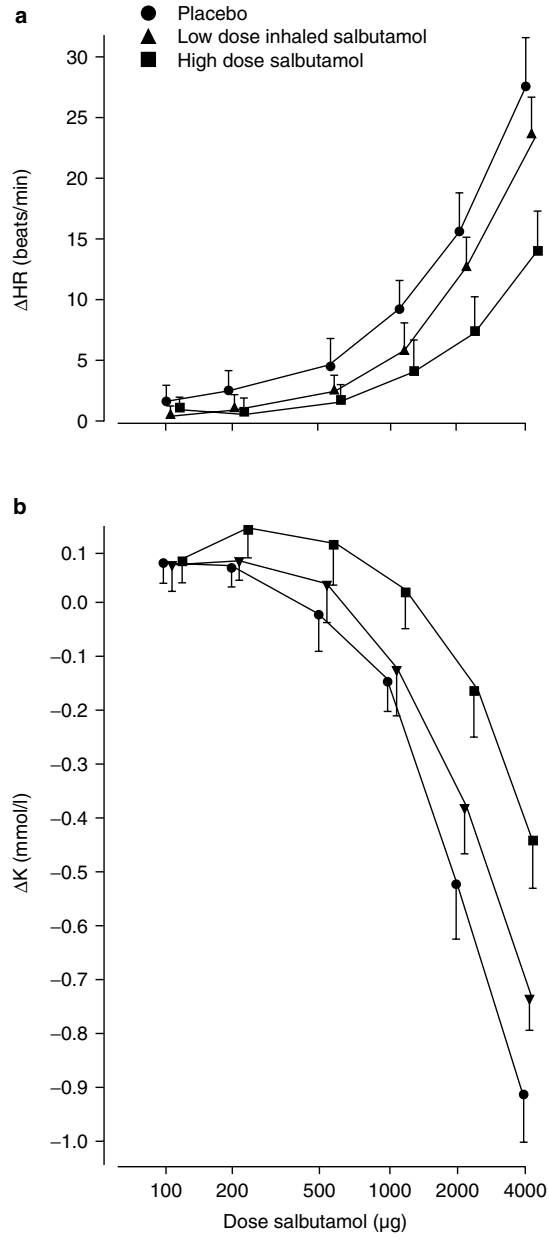

Fig. 2. Changes in heart rate (HR) and plasma potassium (K) in response to cumulative doubling doses of inhaled salbutamol (albuterol) [100μg to 4000μg on log scale] in patients with asthma after pretreatment with placebo, low dose inhaled salbutamol and high dose salbutamol, demonstrating right-shift of the dose-response curve (reproduced from Lipworth et al.,[46] with permission).

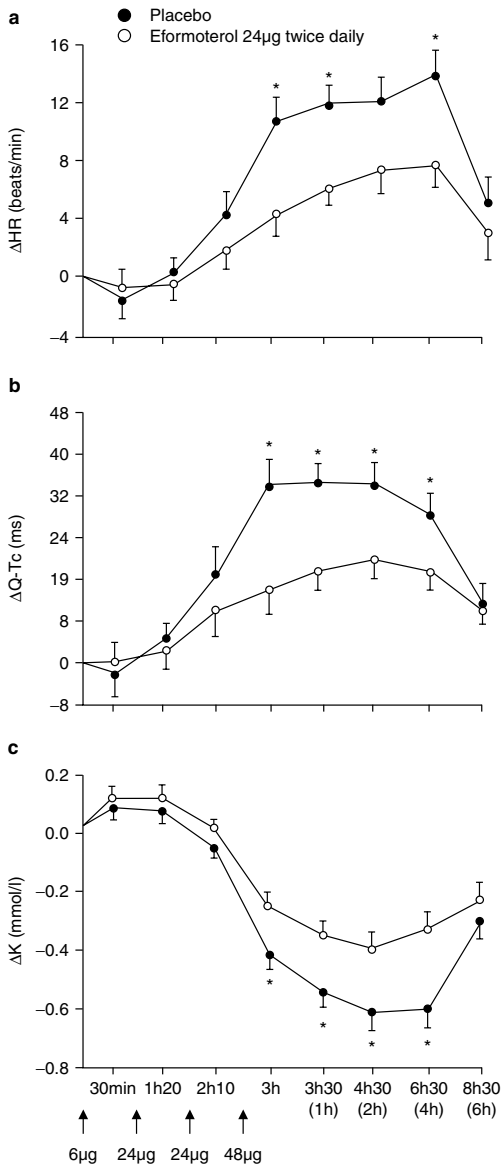

Fig. 3. Response time profiles for heart rate (HR), potassium (K) and QTc interval, as change from baseline (delta, Δ) after treatment for 4 weeks with either placebo or eformoterol 24μg twice daily. Times are given following inhalation of the first dose of eformoterol (6μg) and in brackets for time after inhalation of the last dose (48μg). Asterisks denote a significant difference ($p < 0.05$) between the value after treatment with placebo compared with eformoterol and demonstrate right-shift of the dose-response curve (reproduced from Newnham et al.,[49] with permission).

pic effects of fenoterol and salbutamol (albuterol) on cardiac β_1- or β_2-adrenoceptors at high doses.[76] Hence, sudden death in asthma may be due to hypoxaemia rather than loss of β_2 selectivity.

Tachycardia, per se, may not constitute a serious adverse effect in younger patients treated with inhaled β_2-agonists, although the feeling of palpitation may be unpleasant. However, in older patients, who may have concomitant ischaemic heart disease with symptomatic angina or atrial fibrillation, significant tachycardia can cause troublesome symptoms. For example, in elderly patients with naive β_2-adrenoceptors, an increase in the heart rate of 39 beats/min over baseline was observed after the inhalation of salbutamol (albuterol) 4000μg.[29] Such increases in heart rate, coupled with the hypoxaemia of an acute exacerbation, may clearly constitute a serious health risk in susceptible elderly patients.

Changes in blood pressure also occur with the administration of β_2-agonists although, on paper at least, these are relatively small. Blood pressure changes are thought to be mediated predominantly by β_2-adrenoceptor stimulation.[77] Changes of the order of 8 or 9mm Hg have been demonstrated in systolic (increase) and diastolic (decrease) pressures following inhalation of salbutamol (albuterol) 4000μg or isoprenaline (isoproterenol).[29] Although small, these variations in blood pressure have to be considered in the context of elderly patients who have blunting of the baroreflex,[78] which occurs primarily up until the age of forty, with little decline thereafter.[79] In addition, concomitant use of other drugs such as diuretics or antiparkinsonian drugs may further increase the risk of significant changes in blood pressure.

1.4 Finger Tremor

An increase in β_2-adrenoceptor mediated finger tremor is well recognised with β_2-agonist therapy.[33,34,41] As with heart rate, an increase in tremor may not be a significant problem in most individuals. However, in the elderly population, who may have concomitant Parkinson's disease or essential tremor, significant impairment in activities

of daily living may result. This may occur in a wide variety of activities ranging from those requiring fine movements (fastening buttons) to everyday tasks (making or holding a cup of tea). In the elderly patient, because quality of life and activities of daily living may already be affected by their chronic airways disease,[80] the addition of finger tremor would produce a cumulative adverse effect, which may impair their ability to live at home.

2. Corticosteroids

Corticosteroids have been used in the treatment of acute asthma for many years.[81-83] These drugs have also been used to treat severe chronic asthma and severe acute exacerbations of asthma.[84,85] However, it is recognised that the therapeutic effect of corticosteroids may be delayed both in acute asthma[86] and when the disease is stable,[87] unlike β_2-agonists which produce a prompt therapeutic effect.[88] The development of aerosol formulations has significantly improved the safety of corticosteroid therapy, allowing it to be used in patients with moderate asthma.[89] Indeed, guidelines now recommend the use of inhaled corticosteroids as first-line therapy for all except mild grades of asthma.[90]

Elderly patients are more likely to have COPD rather than asthma. Inhaled and oral corticosteroids are used widely in the treatment of COPD. However, the efficacy of corticosteroids in the treatment of COPD may vary and depend on underlying factors, such as atopy and reversibility.[91-93] Furthermore, a more recent review on inhaled corticosteroids has suggested variable beneficial effects in short-term and long-term studies with fluticasone propionate, where clinical benefits were limited to symptom relief rather than improved lung function.[94]

Oral corticosteroid therapy can give rise to significant and serious systemic adverse effects, such as suppressed adrenal function, bone loss, skin thinning and increased cataract formation, especially in those patients receiving long-term therapy.[85,89] By contrast, inhaled corticosteroid therapy is thought to be relatively well tolerated, although there are concerns that adverse effects similar to oral corticosteroids may be seen in those patients who require treatment with high doses of inhaled corticosteroids over a long treatment period.[84,89] Potential adverse effects are summarised in table I.

2.1 Local Adverse Effects

Oral candidiasis and dysphonia can be problematic in elderly patients, as a result of deposition of corticosteroid particles in the oropharynx and larynx. The incidence of these adverse events is low, in general, but their frequency can increase if the corticosteroid is administered more than twice daily.[96] In older patients, significant oral candidiasis can cause poor oral intake and even body weight loss due to the mucosal irritation. The incidence of these adverse effects can be lowered by mouth rinsing and by using spacer devices to decrease oropharyngeal deposition.[97]

The hydrofluoroalkane (HFA) beclomethasone dipropionate inhaler also appears to reduce drug deposition in the throat, presumably because of the predominance of small particles. This inhaler has produced a comparable incidence of dysphonia

Table I. Potential adverse effects associated with inhaled corticosteroids (reproduced from Pavord et al.,[95] with permission)

Adverse effect	Risk
Hypothalamic-pituitary-adrenal axis suppression	No significant risk until dosages of budesonide or beclomethasone are increased to 800-1000μg daily
Bone resorption	Can occur at dosages of budesonide > 1600μg daily or beclomethasone > 400μg daily but generally < 800μg daily is acceptable
Cataracts	Anecdotal reports, risk generally unproven
Skin thinning	Dosage-related effects may occur with beclomethasone up to 2000μg daily
Carbohydrate and lipid metabolism	Only minor changes occur
Purpura	Dosage-related effects may occur with beclomethasone up to 2000μg daily
Dysphonia	Usually of little consequence
Candidiasis	Incidence <5%, reduced by use of a spacer device

(3%) to chlorofluorocarbon (CFC) beclomethasone.[98] A local myopathic effect associated with inhaled corticosteroid may have some bearing on dysphonia, and can occur without the presence of oral candidiasis.[89,99]

2.2 Effects on Hypothalamic–Pituitary-Adrenal Function

This is especially significant in elderly patients as suppression of hypothalamic-pituitary-adrenal (HPA) function may present atypically and the diagnosis can be missed resulting in chronic illness or decline.

Considerable data have been published regarding the effect of inhaled corticosteroids on HPA function. However, the different sensitivities of the methods used to evaluate HPA function and the different inhaler devices studied, make interpretation of the results rather difficult.[100] However, in general, dose-related HPA-axis suppression occurs with inhaled beclomethasone or budesonide at doses in excess of 1000µg daily.[101] Beclomethasone has lower hepatic first pass extraction than either budesonide or fluticasone propionate[102] and therefore gut bioavailability is important when considering HPA suppression.[101] Hence, the use of a spacer device has been shown to decrease adrenal suppression caused by beclomethasone.[103]

Both fluticasone propionate and budesonide undergo more extensive first pass hepatic metabolism than beclomethasone, and lung bioavailability determines systemic activity. This may give rise to the expectation that greater lung deposition (and hence more drug absorption from the lung) may increase the risk of HPA suppression. When given by standard metered dose inhaler, budesonide and fluticasone propionate at high doses (>1500 µg/day) have less effect on HPA function than CFC-beclomethasone.[104,105] However, the use of a spacer has been shown to increase the effect of budesonide on serum cortisol, suggesting that improved delivery of inhaled budesonide to the lung may increase its systemic effect.[106] HFA beclomethasone 800µg appears to have less effect on morning plasma cortisol levels compared with CFC beclomethasone 1500µg, with significantly fewer patients treated with HFA beclomethasone compared with CFC beclomethasone (4.4 *vs* 14.6%, $p = 0.024$) having below normal cortisol values.[107]

It should be pointed out that the patients recruited in the above studies may have been exposed to intermittent courses of oral prednisolone administered for acute exacerbations. This factor has the potential to affect results and make data interpretation difficult because it is known that oral prednisolone may affect HPA function for several weeks after cessation of treatment.[99]

2.3 Effects on Bone Turnover

It is well recognised that elderly patients, especially women, are at significant risk of osteoporosis and subsequent fracture because of post menopausal hormonal effects on bones and ingestion of diets devoid of vitamin D and calcium. Any drug which exacerbates osteoporosis should be prescribed with extreme caution in the elderly. In this regard, oral prednisolone should be given careful consideration. However, the effects of inhaled corticosteroids on osteoporosis are less clear.

Studies to date have been rather conflicting in their conclusions as to whether significant changes in bone resorption occur with inhaled corticosteroids. Bone density in premenopausal women receiving inhaled corticosteroids was slightly lower than age-matched controls in one study,[108] although comparisons with patients with asthma not receiving inhaled corticosteroids were not carried out. In another study, the effect of inhaled corticosteroids on bone density was confounded by the fact that patients also received intermittent courses of oral corticosteroid.[109] Inhaled corticosteroids in doses up to 2000µg have no effect on urinary calcium excretion. However, reversible dose-related suppression of plasma osteocalcin (a marker of bone formation) has been reported with CFC beclomethasone and budesonide at these doses administered by metered dose inhalers.[110,111] In contrast, no effect on plasma osteocalcin was seen in patients administered up to 2000µg of CFC beclomethasone or budesonide by spacer device.[103]

However, high dose CFC beclomethasone has been shown to increase urinary hydroxyproline levels.[112] Comparative studies on fluticasone propionate and budesonide have demonstrated similar effects of the two drugs on markers of bone metabolism.[113,114]

Although the effects of high dose inhaled corticosteroids on bone metabolism are unclear, in general, it is accepted that inhaled dosages up to 800μg daily are relatively free of significant effects on bone turnover.[101]

2.4 Effects on Connective Tissue

Elderly patients are prone to skin changes and senile purpura as a result of the ageing process affecting the connective tissue. Oral corticosteroids are well known to worsen dermal thinning and increase purpura especially with long-term therapy. There have been reports of increased purpura and skin bruising in patients receiving inhaled budesonide,[115,116] although clearly this is a cosmetic nuisance rather than a serious systemic adverse effect.

2.5 Cataracts

Eyesight is vital in order to carry out the activities of daily living. Loss of sight in the elderly may increase the risk of falls and subsequent fractures with their associated morbidity and mortality. Oral corticosteroids are known to increase the incidence of posterior subcapsular cataracts. There are also infrequent reports of inhaled corticosteroids predisposing to cataract formation.[99] The development of cataracts may correlate more closely with the dose and duration of drug administration in the case of orally administered corticosteroids compared with corticosteroids administered by inhalation.[117]

2.6 Metabolic effects

Despite the well recognised effects of oral corticosteroid therapy on body glucose and potassium, there is little or no evidence that inhaled corticosteroids produce important metabolic effects even at high doses. In adult patients, fasting plasma glucose and insulin levels remain essentially unchanged after treatment with inhaled corticosteroids at dosages up to 2000μg daily.[118]

3. Theophyllines

The use of theophyllines in the treatment of COPD or chronic asthma is controversial with published data demonstrating differing views on clinical benefit.[119-121] Theophyllines act primarily by way of smooth muscle relaxation in the airways,[122] but these drugs have other effects such as improved skeletal muscle contractiblity including the diaphragm,[123] and a diuretic action.[124]

The potential adverse effects of theophyllines are well recognised, and elderly patients may be more prone to these adverse effects as a result of clinical circumstance and drug-drug interactions. The adverse effects vary from mild to life threatening (table II) resulting from acute poisoning or chronic over medication with theophyllines. In one study of theophylline toxicity which reviewed 116 consecutive cases of acute poisoning or chronic over medication,[125] the majority of patients experienced gastrointestinal disturbances with nausea and vomiting. Approximately 75% of patients developed cardiovascular adverse effects, the most common being sinus tachycardia. However, 18% of patients experienced supraventricular tachycardias and 20% of patients experienced ventricular premature beats with one case of sustained ventricular tachycardia. Such life threatening adverse events have been documented in other studies.[126] These significant cardiovascular effects are of great importance in susceptible elderly patients. This is also true for adverse effects related to the CNS. Sessler[125] noted CNS adverse effects in nearly 50% of patients treated with theophyllines. The most commonly observed adverse events were tremor, nervousness and confusional states, with the latter being observed particularly in the elderly patients. 6% of patients developed seizures which may have been related to the type of theophylline toxicity, with acute poisoning perhaps more prone to cause this adverse effect. One epidemiological study has suggested that serious adverse effects related to theophylline may be less common than ex-

Table II. Summary table of manifestations of theophylline toxicity (reproduced from Sessler,[125] with permission)

Grade 1[a]
Vomiting
Tremor
Tachycardia (>120 beats/min)
Abdominal pain
Mild hypokalaemia (>2.5 and <3.5m Eq/L)
Diarrhoea
Nervousness
Grade 2[a]
Haematemesis
Frequent ventricular premature beats
Severe hypokalaemia (<2.5 mEq/L)
Lethargy and disorientation
Rhabdomyolysis
Supraventricular tachyarrhythmia[b]
Hypotension (mean blood pressure < 60mm Hg, improves with standard therapy)
Grade 3[a]
Seizure (non repetitive)
Sustained ventricular tachycardia
Shock (mean blood pressure < 60mm Hg, refractory to standard therapy)
Grade 4[a]
Status epilepticus
Ventricular fibrillation
Cardiac arrest

a Grades of toxicity are defined as: Grade 1, self-limited toxicity that typically has no major impact; Grade 2, toxicity that typically requires close observation, Electrocardiographic monitoring or specific medical intervention. Grade 3, toxicity that requires immediate intervention and/or often progresses to Grade 4 toxicity; and Grade 4, toxicity that is often fatal.

b Includes atrial fibrillation or flutter, multifocal atrial tachycardia and paroxysmal supraventricular tachycardia.

pected, with a prevalence of less than one case per 1000 patient years.[127] However, it is important to note that in the latter study, the risk of theophylline-induced adverse effects was 5 times greater in the elderly patients compared with the younger patient population.

Two specific problems associated with theophylline should be mentioned here. First, the drug has a narrow therapeutic range and adverse effects may occur at drug concentrations only slightly outside this range. Secondly, the pharmacokinetics of theophylline are profoundly affected by a wide variety of diseases and drugs, resulting in increased plasma theophylline concentrations. Hence, it is easy to see why the elderly population may be at greater risk from theophylline toxicity. Liver disease, cardiac decompensation and cor pulmonale can increase serum theophylline concentrations,[128] while cigarette smoking can increase elimination of the drug.[129] Salbutamol (albuterol) administered orally to children has been shown to decrease serum theophylline concentrations,[130] but there is little evidence that inhaled salbutamol(albuterol) affects theophylline pharmacokinetics. Oral or parenteral corticosteroids appear to have a variable effect on theophylline pharmacokinetics with some data demonstrating an increase in theophylline levels[131] and other data demonstrating no effect at all.[132]

There is no doubt that macrolide antibacterials, such as erythromycin, increase theophylline concenrations by reducing elimination,[133] and this may lead to life-threatening illness as reported in a recent case report.[134] Other antibacterials are thought to be safer for administration to elderly patients with regard to theophylline pharmacokinetics.

It is worth mentioning that many other drugs, commonly used in elderly patients, also interact with theophylline including calcium channel antagonists, anticonvulsants and histamine H_2 receptor antagonists (histamine antagonists). Hence, the risk of drug-drug interactions with theophylline is extremely high.

4. Anticholinergic Drugs

The inhaled anticholinergic drugs, ipratropium bromide and oxitropium bromide are useful bronchodilators in all age groups because of their relative lack of significant adverse effects. Some physicians however, feel that they lack bronchodilator efficacy. The lipid solubility of ipratropium bromide prevents significant absorption either from the airway or the gut. Hence, the pharmacological actions of these drugs seem to be confined primarily to the mouth and airways.

Clinical trials in patients with COPD have demonstrated that ipratropium bromide produces a more pronounced bronchodilator response than inhaled β_2-agonists.[135,136] In addition, the initial use of ipratropium bromide may allow optimal achievable bronchodilatation to occur with a low inhaled dose of β_2-agonist.[137] However, in asthmatic patients, overall clinical responses seem better with inhaled β_2-agonists rather than ipratropium bromide,[32] although a significant bronchodilator effect is still seen with the administration of ipratropium bromide.[138]

This combination of limited adverse effects and good bronchodilatation makes ipratropium bromide and oxitropium bromide useful therapeutic agents in elderly patients although one must bear in mind that not all patients may respond satisfactorily to anticholingeric therapy. The most common adverse effect is an unpleasant taste or dry mouth. However, even this adverse effect is not that frequently reported. In one study, only six of 32 patients reported a dry mouth when ipratropium bromide was administered [139] and no adverse effects related to ipratropium bromide therapy were reported in a multicentre study involving 274 patients.[140] There has been concern that the anticholinergic drugs may cause drying of the respiratory secretions, resulting in reduced mucociliary clearance but this has not been confirmed.[141] Similarly, fears of idiosyncratic hypersensitivity in some patients[142] have not been documented further. In view of its atropine-like action, there is the potential for ipratropium bromide, in theory, to produce urinary hesitancy, constipation and exacerbations of glaucoma, all of which would be significant in elderly patients. In truth, however, when inhaled even in large doses, anticholinergics have little or no effect on heart rate, blood pressure, bladder function, intraocular pressure or papillary diameter.[143,144] However, in patients with glaucoma, requiring nebulised anticholinergic therapy, it may be prudent to use a mouthpiece rather than a facemask, in order to minimise the likelihood of solution droplets entering the eye.

5. Recommendations for Prescribing

It is a fact that as patients get older, the risk of polypharmacy, drug-drug interactions and potentially serious drug adverse effects increases. Although not all patients will experience adverse effects from the drugs summarised in this review, the potential for harmful effects is there and is accentuated by the age of the elderly patient population. Therefore, on the basis of good clinical practice there is justification in making recommendations for prescribing, in order to improve symptoms and minimise harm to the patient. Hence, the following recommendations, if followed, may go some way towards minimising the risk of systemic drug effects in the treatment of asthma and COPD.

- Caution should be exercised when prescribing drugs for elderly patients, in view of the risk of adverse effects and drug-drug interactions.
- The use of concomitant medications such as corticosteroids and diuretics may augment the metabolic and systemic adverse effects of inhaled β_2-agonists. Careful prescribing is required under these circumstances. If diuretics are required in addition to β_2-agonists, spironolactone may afford some protection against β_2-agonist mediated hypokalaemia.
- In elderly patients unable to use metered-dose inhalers, spacer devices can increase drug deposition in the lung and exaggerate extrapulmonary effects of β_2-agonists. Seemingly innocuous adverse effects, such as finger tremor and blood pressure changes may then significantly impair quality of life. However, with prolonged treatment, receptor subsensitivity may reduce the severity of systemic adverse effects. Hence cautious use of spacer devices is recommended. Patient education with reference to potential adverse effects is important.
- Oral, and perhaps inhaled, corticosteroids can upregulate β_2-adrenoceptors and potentiate the systemic adverse effects of β_2-agonists. Oral prednisolone can produce widespread and serious systemic adverse effects and their use in elderly patients should be kept to a minimum.

- Inhaled corticosteroids are generally well tolerated, but doses greater than 1000μg can affect HPA function and doses greater than 800μg can affect bone turnover. The effect of budesonide on plasma cortisol levels may be increased when using a spacer device for drug delivery. HFA beclomethasone has less effect on HPA function compared with CFC beclomethasone. Safe prescribing of less than 1000 μg/day of inhaled corticosteroids is recommended and HFA beclomethasone may be the drug of choice. If higher doses are needed, regular health checks and prophylaxis against osteoporosis must be considered.
- Oral theophyllines have an extensive adverse effect profile and are prone to significant drug-drug interactions. Therefore, they are not recommended for treatment of asthma in elderly patients. If theophyllines are prescribed, regular review and cautious prescribing of other drugs are advocated.
- Inhaled anticholinergic drugs are relatively well tolerated and are a useful addition to the treatment options available, for some elderly patients. Anticholinergic drug-induced adverse effects are usually mild and they produce satisfactory bronchodilatation in patients with COPD. When prescribed in combination with β_2-agonists, anticholinergic drugs can obviate the need for high doses of β_2-agonists, provided the anticholinergic drug is administered first. However, in those patients where little or no symptomatic relief occurs, the anticholinergic drug should be discontinued.

It is clear that drug prescribing in the elderly is complex and, at times, difficult. However, with astute prescribing and therapeutic awareness, it is possible to treat asthma and COPD in the elderly patient with minimal drug-induced adverse effects.

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