Curr Geri Rep (2016) 5:124–131
DOI 10.1007/s13670-016-0171-z

The Wrath of Steroids in Elderly Patients with Pulmonary Diseases

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Published online: 29 March 2016

Abstract Pulmonary diseases such as Chronic Obstructive Pulmonary Disease (COPD) and asthma are common in the elderly population. Corticosteroids, systemic and inhaled, are commonly used in their treatment. There are many adverse effects associated with corticosteroid treatment. These include cataracts, osteoporosis, diabetes mellitus, and delirium, which are more common and more dangerous in the elderly population.

Keywords Elderly · Corticosteroids · Inhaled corticosteroids · Adverse effects · Chronic obstructive pulmonary disease · Asthma · Pulmonary disease · Cataract · Cardiovascular disease · Myopathy · Osteoporosis · Fracture · Psychosis · Delirium · Infection · Pneumonia

Introduction

Chronic obstructive pulmonary disease (COPD) is a leading cause of morbidity and mortality throughout the world [1••] and the third most common cause of death in the USA [2]. Prevalence increases with age and is estimated to be over 11 % in those ≥65 [3]. In addition, there is increasing evidence that the prevalence of asthma in advanced age is similar to that in a younger population [4]. In one survey, the prevalence of current asthma in a US elderly population was estimated to be 7 % [5]. Inhaled corticosteroids (ICS) are a mainstay of treatment for both diseases. In asthma, ICS initiation is recommended for all patients with persistent disease, even mild disease [6••]. ICS in combination with long-acting beta-agonist is recommended for severe COPD [1••]. In addition, systemic corticosteroid use is recommended for exacerbations of both asthma [7] and COPD [1••]. In some severe cases, patients can become corticosteroid dependent. It follows that many elderly patients are exposed to ICS or systemic corticosteroids for the treatment of respiratory disease. There are multiple risks associated with ICS [7, 8••] and systemic corticosteroids [9, 10] (Table 1). Aging physiology and increased comorbidity may make the elderly population especially susceptible to these adverse effects. This review will outline the adverse effects of systemic and inhaled corticosteroids and highlight the concerns this use raises in the elderly population who may require more frequent monitoring and additional treatment.

Lipodystrophy/Morphological Changes

Systemic Corticosteroids

Body composition changes with age. Older people have relatively more body fat and less lean mass than in their younger years. Corticosteroid use can accentuate theses changes. Lipodystrophy, the disturbance of body fat, is a frequently cited adverse effect of corticosteroid use [10, 12]. Prevalence varies, but some studies report >60 % [11]. Lipodystrophy may be associated with metabolic syndrome and hypertension which is prevalent in older adults [39]. Weight gain has also been reported. A meta-analysis of glucocorticoid use in rheumatoid arthritis (RA) showed increase body weight of 4–8 % over 2 years [40].

This article is part of the Topical Collection on *Pulmonology and Respiratory Care*

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Table 1 Summary of Adverse Effect by Route of Administration and System

System/condition	Adverse effect	
	Systemic corticosteroid	Inhaled corticosteroid
Morphological changes	Buffalo hump, moon facies, increased abdominal girth in up to 60 % of users [11].	
Skin and soft tissue	Skin thinning, increased bruising, and poor wound healing reported [12, 13]. Increased risk of surgically related pressure ulcers OR 2.808 [14•]. Possible small increase risk of non-melanoma skin cancers [15, 16]	Skin thinning and increased bruising, though to lesser degree than OCS use [17].
Ophthalmologic disorders	Increased risk of posterior subcapsular cataract [18] and any cataract in elderly patients OR 2.6 [19]. Glaucoma risk less well defined.	Modest increase of cataract for each 1000 μg/day increase in the dose of BDP equivalent [20].
Cardiovascular Disease	Increased risk of any cardiovascular event OR 1.25–2.56 [21, 22]. Increased risk for atrial fibrillation OR 3.62 [23]. Hypertension risk poorly defined.	
Renal Effects	Very mild increase hypokalemia 0.2–0.4 mmol/L [24].	
GI Effects	Increases risk in NSAID users [25].	
Myopathy	Wide variety of response, but demonstrated to increase risk of muscle weakness [19].	
Osteoporosis/Fracture	Increased risk for any fracture OR 1.91, hip fracture OR 2.1, vertebral fracture OR 2.86 [26].	Mixed data. Modest increase of 12 % for each 1000 μg/day BDP equivalent [27].
HPA Axis Suppression	Increased risk of clinical adrenal insufficiency OR 1.9, but with very low absolute increased risk [28].	Only rarely clinically significant [29].
Glucose Metabolism	Increased risk for DM in elderly RR 2.31 [30]. High risk of hyperglycemia in hospitalized patients [31].	Mixed data. 34 % increased risk of DM and DM progression [32].
Psychiatric Effects	Prevalence of 27.6 % symptoms and 5.7 % for severe symptoms [33]. HR of 3.26 for severe psychiatric effects [34]. Increased delirium and steroid dementia for elderly patients [34, 35].	
Infection	Increased risk for any infection RR 1.6 [36].	Increased non-fatal pneumonia for fluticasone OR 1.78 and budesonide OR 1.62 [37••]. NNH = 60 [38].

OR odds ratio, *OCS* oral corticosteroids, *BDP* beclomethasone dipropionate, *GI* gastrointestinal, *NSAID* nonsteroidal anti-inflammatory drug, *HPA* hypothalamic-pituitary-adrenal, *DM* diabetes mellitus, *HR* hazard ratio, *RR* relative risk, *NNH* number needed to harm

Skin and Soft Tissue Effects

Systemic Corticosteroids

Skin changes are a hallmark of aging. With aging, the skin thins and looses elasticity. There can be easy bruisability and "senile purpura." Corticosteroids can mimic age-related skin changes in younger patients. Among older patients, corticosteroids can accelerate age-related changes. In one cohort study, skin disorders were noted by 46.2 % of patients taking oral corticosteroids (OCS) for ≥3 months [11]. Most common is skin thinning and increased bruising [12]. Corticosteroids may also inhibit wound healing [13]. Skin thinning and impaired wound healing may be of particular consequence in elderly patients who are at highest risk for pressure ulcers. In a retrospective study of 286 cardiac surgery patients, surgically related pressure ulcers were significantly higher in those receiving perioperative corticosteroids (43.8 %) versus controls (14.8 %) with an adjusted odds ratio (OR) = 2808 (95 % CI 1.062–11.769) [14•].

There may also be a small increase in risk for non-melanoma skin cancers [15, 16]. Though increased risk may be modest, this is of particular importance in the elderly population which has a higher baseline risk.

Inhaled Corticosteroids

In a small cross-sectional study, high-dose ICS users had significantly thinner skin and higher prevalence of bruising compared to controls, though these effects were less than with OCS use [17]. Being older and a woman may increase risk of skin bruising in patients using ICS [41].

Ophthalmological Disorders

Systemic Corticosteroid

The lens of the eye is susceptible to changes with aging. The lens becomes less distensible and yellows. Cataracts are common in late life. The association between posterior subcapsular cataracts (PSC) and OCS was first described in rheumatoid arthritis (RA) patients in 1960 [18]. Dose and duration relationships were subsequently demonstrated [18, 42]. Studies of asthma patients have

had mixed results [43, 44]. In a meta-analysis, rate of PSC in corticosteroid users was 9 % in patients with asthma, 18 % in those with rheumatoid arthritis, and over 40 % in those with either SLE or after renal transplantation [45]. A cross-sectional study of older patients with lung disease reported an increased risk of cataracts in those using continuous or frequent intermittent corticosteroids (18.4 %) compared to controls (8.6 %) [19]. Type of cataract was not specified, but may indicate that age-related cataracts are also increased in corticosteroid users.

Glaucomatous changes have been described as a result of topical corticosteroids [46]. It is less clear if there are similar responses from systemic glucocorticoids. There have been no large studies that focus on those with lung disease or the elderly, who might be at especially high risk for developing glaucoma.

Inhaled Corticosteroids

Initial studies, often of small-sized samples and young ages, did not find any relationship between ICS and cataracts [47–49]. Subsequent studies on elderly patients have had positive results. A case-control study in Canada of patients ≥70 demonstrated an increased risk of cataract extraction in those using ICS for >3 years with OR = 3.06 (95 % CI 1.53–6.13) [50]. Other population-based studies showed similar, though more modest results, with dose and duration relationships described [51]. A meta-analysis approximated a 25 % elevation in the risk of cataract for each 1000 μg/day increase in the dose of beclomethasone dipropionate (BDP) [20].

A case control study of >40,000 patients did not show current users ICS to be at increased risk for ocular hypertension or open angle glaucoma [52].

Cardiovascular Diseases

Systemic Corticosteroids

Cardiovascular disease is the leading cause of death in the USA [2], and age is a major risk factor [21]. Two large observational studies (>50,000 cases) have demonstrated a link between systemic corticosteroid use and any cardiovascular event. A Scottish study reported an OR of 2.56 (95 % CI 2.18–2.99) [22], and a study from the United Kingdom (UK) reported OR of 1.25 (95 % CI 1.21–1.29) [53]. Highest risk was for heart failure which increased approximately 3-fold. Risk was higher in those with COPD, those receiving continuous prescriptions [22], current users compared to prior users, and those receiving highest doses [53]. Risk for acute myocardial infarction may be most pronounced in the first 30 days [54].

A population-based study from Denmark of 20,221 patients demonstrated that current glucocorticoid users were almost twice as likely to develop atrial fibrillation or atrial flutter. Risk was highest among new users with OR of 3.62 (95 % CI 3.11–4.22) [23].

Risk of hypertension has been long recognized though not well described. A retrospective meta-analysis reported a significant relationship for hypertension incidence with OR 2.2 (95 % CI 1.4–3.8) [55] among corticosteroid users. Risk may be dose dependent [10], and appears to develop early after initiation of corticosteroids [56].

Renal Effects

Systemic Corticosteroids

While natural corticosteroids induce fluid and sodium retention and potassium depletion, synthetic corticosteroids have far less mineralocorticoid action [12]. Clinical fluid retention, ankle swelling, has been reported in 10 % of corticosteroid users [10]. Though there have been case reports of hypokalemia [57], effect is minimal. A literature review concluded that long-term corticosteroid reduces potassium 0.2–0.4 mmol/L [24]. Potassium may be more affected in short-term high-dose therapy, especially in the ill and those with difficulty maintaining homeostasis.

GI Effects

Systemic Corticosteroids

GI adverse effects are a matter of debate. A meta-analysis from 1983 reported a relative risk of 2.3 (95 % CI 14–3.7) [58] for peptic ulcer disease. However, when separate analyses were done for only double blind studies, only use of only oral corticosteroids, or excluding those with a history of ulcer, results did not always reach statistical significance. Moreover, a subsequent more rigorous meta-analysis showed no significantly increased risk [55]. It is more likely that risk is mediated in association with nonsteroidal anti-inflammatory drugs (NSAIDs) [25, 59].

Myopathy

Systemic Corticosteroids

With aging, there is a loss lean body mass. Myopathy is a concern for frail elders. In a cross-sectional study, muscle weakness was more common in those with lung disease using corticosteroids with OR 6.7 (95 % CI 4.8–9.3) [19]. Though, there is a wide variation in response, dose effect has been demonstrated [19, 60]. Inactivity may also increase risk [61]. There is evidence that physical training can prevent and

improve corticosteroid-induced myopathy [62]. This should be recommended to corticosteroid users.

Osteoporosis

Systemic Corticosteroids

Patients with COPD are at high risk for osteoporosis [63] and advancing age is also a major risk factor [64]. Role of corticosteroids in bone loss has been well described. It is the most common form of secondary osteoporosis. A meta-analysis found increased fracture risk in those on corticosteroids for any fracture OR = 1.91 (95 % CI 1.68–21.5), hip fracture OR 2.1 (1.74–2.29), and vertebral fracture OR 2.86 (2.56–3.16) [26]. Increase risk was apparent within first 3 months of treatment [65]. Intermittent dosing of OCS has also been linked with osteoporosis, especially with increasing number of prescriptions [66]. The American College of Rheumatology has published recommendations for the treatment and prevention of glucocorticoid-induced osteoporosis [67]. Adequate calcium and vitamin D intake must be insured. Bisphosphonate therapy should be considered depending on risk category as determined by FRAX® score and dose and duration of corticosteroid use.

Inhaled Corticosteroids

Data is mixed for ICS and fracture risk. In an elderly population, there was increased risk of hip fracture, adjusted OR 1.19 (95 % CI 1.10–1.28) [68]. Alternatively, another large case-control study showed no increased risk of fracture in elderly patients followed for at least 4 years [27]. A meta-analysis of five case-control studies of non-vertebral fractures reported a modest increased risk of 12 % for each 1000 μg/day BDP equivalent. Similarly, a meta-analysis of 16 RCTs and 7 observational studies concluded that a 500 μg/day BDP equivalent is associated with 9 % increase in risk of fractures [69]. Risk increase is modest and significance depends on baseline risk.

Hypothalamic-Pituitary-Adrenal (HPA) Axis Suppression

Systemic Corticosteroids

Exogenous steroids would be expected to result in negative feedback on the HPA [70]. The clinical significance of this effect was first noted in a corticosteroid user who developed post-surgical shock [71]. Larger studies revealed a wide range of individual variability with no reliable predictors for HPA suppression [72]. Though patients demonstrated decreased response to adrenal stimulation tests [72, 73], clinical significance is rare [12]. A case-control study demonstrated increased risk of clinical adrenal insufficiency in OCS users with an adjusted OR of 1.9 (95 % CI 1.5–2.4) per course of treatment per year [28]. Given low prevalence, absolute risk was low. Even in situations, possibly requiring stress response, stress dose steroids are not routinely indicated [74].

Inhaled Corticosteroids

ICS have been demonstrated to suppress endogenous cortisol levels [75] and affect dynamic adrenal stimulation tests [76, 77]. This effect may be more pronounced with fluticasone compared to other ICS [78]. Whether these tests have clinical significance is less clear. Cases of clinically significant adrenal insufficiency, mostly in children, have been described [29]; however, observational data has not shown ICS exposure to infer increased adrenal insufficiency risk [28].

Hyperglycemia and Diabetes Mellitus

Systemic Corticosteroids

With physiologic aging, insulin resistance has been demonstrated. Diabetes mellitus (DM) prevalence is increased substantially in elderly patients [79] including the nursing home population [80], and patients with COPD have a higher prevalence and incidence of DM [81]. Several studies have shown correlation between corticosteroids and DM; however, risk of developing corticosteroid-induced DM is poorly characterized and increase in glucose is variable [82]. Observational studies have reported increased risk of 1.26–2.31 for diabetes among glucocorticoid users [30, 83, 84]. Risk is dose dependent and higher if glucocorticoid use was recent [85]. Risk may be higher in elderly subjects [84, 85].

Corticosteroids are the main cause of drug-induced hyperglycemia [86]. In one study of hospitalized patients, hyperglycemia was documented in 64 % of patients receiving high doses of corticosteroids [31]. In most cases, hyperglycemia occurs within 1–2 days of corticosteroid initiation [87•].

Inhaled Corticosteroids

Increased or worsened DM was not a noted adverse effect in large randomized clinical trials for ICS [88, 89]. Increased risk was also not found in the elderly subjects [90]. Criticisms of these studies included short follow-up and use of lower dose ICS. In a large population-based study of Quebec registry, current use of ICS was associated with 34 % increase in risk of DM and 34 % increased risk of DM progression [32]. Risk was greatest when using high-dose ICS. On the contrary, a more recent study of 4305 subjects found no significant relationship between ICS and new onset DM or worsening DM [91••].

Psychiatric Effects

Systemic Corticosteroids

Psychiatric and cognitive effects are of particular concern in elderly patients. These effects are common though often mild [92]. Hypomania and euphoria are most common. Steroid psychosis is much less likely and dose dependent [93, 94]. Prevalence varies with one meta-analysis reporting averages of 27.6 % for psychiatric symptoms and 5.7 % for severe symptoms [33]. A large observational study found an increased risk of serious psychiatric adverse effects with a hazard ratio (HR) of 3.26 (3.14–3.37) [34]. Age may be a risk factor, especially for delirium, confusion, and disorientation [34]. Older adults may develop steroid dementia [35]. Psychiatric symptoms often present early in the course [95, 96]. Older adults should be monitored for neuropsychiatric symptoms which typically resolve with dose reduction or discontinuation of corticosteroid [97]. Baseline formal assessment of cognitive status and mood would seem prudent, if possible, prior to initiating steroids.

Infection

Systemic Corticosteroids

Multiple factors increase infection risk in older adults [98]. Corticosteroids also affect the immune system. There are multiple smaller studies that demonstrate increased risk for infections including varicella [99], herpes zoster [100], tuberculosis [101], invasive fungal disease [102], and parasites (e.g., Strongyloides [103]). However, it is difficult to extrapolate this data to the general population, especially for those taking corticosteroids for respiratory disease. A meta-analysis that reviewed 71 clinical trials found rate of infection to be 12.7 % in corticosteroid users and 8.0 % in controls [36]. Functional status and older age may increase risk of infection with corticosteroid users [104].

Inhaled Corticosteroids

Local infection with Candida (thrush) is known to occur with ICS [7]. Large clinical trials of ICS have demonstrated increased risk of pneumonia [105]. This is of particular concern in elderly patients since pneumonia portends higher morbidity and mortality [106]. A Cochrane Review concluded that fluticasone increased non-fatal serious pneumonia events with OR of 1.78 (95 % CI 1.50–2.12) [37••], and budesonide increased risk with OR 1.62 (95 % CI 1–2.62). A meta-analysis reported a number needed to harm of 60 [38]. The risk was especially high in more severe disease and among elderly patients. Some studies have indicated that risk may be lower with use of budesonide versus fluticasone [107].

A meta-analysis of 25 randomized trials found an increased risk of tuberculosis in ICS users with OR 2.29 (1.04–5.03) [108].

Conclusion

Corticosteroids, inhaled and systemic, are routinely used in the treatment of respiratory disease in elderly patients. The Global Initiative for Asthma (GINA) notes the challenges of treating older adults with comorbidities including poor eyesight, arthritis, and cognitive impairment [7], and the Global Initiative for Chronic Obstructive Lung Disease (GOLD) addresses relationship between COPD and comorbid illnesses including cognitive impairment. In addition to the challenges of administering these treatment regimens, the adverse effect profile of corticosteroids, systemic and inhaled, are also of concern in elderly patients. Diseases increased by corticosteroid use are often already highly prevalent in older patients. These include, among others, cataracts, osteoporosis, cardiovascular disease, and diabetes mellitus. In addition, adverse effects such as fracture, pneumonia, and delirium portend significant morbidity and mortality in older adults. The use of the lowest effective dose of corticosteroids is important in the elderly population. Older adults should be monitored for adverse effects and treated appropriately.

Acknowledgments The authors would like to acknowledge that assistance of H Raff PhD in guiding the creation of this manuscript.

Compliance with Ethical Standards

Conflict of Interest Angela Beckert declares that she has no conflict of interest.

Edmund Duthie reports grants from Reynolds Foundation, Health Services Resources Administration, Elsevier, and the American Board of Internal Medicine.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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