Prednisolone

Introduction
Prednisolone is a corticosteroid with anti-inflammatory and immunosuppressive effects and many clinical indications. This includes its established role in the treatment of acute and chronic pulmonary disease. There is evidence for the use of short-term oral prednisolone in acute exacerbations of chronic obstructive pulmonary disease (COPD), with improvements in airflow obstruction and shortened duration of hospital stay, and this is reflected in current guidelines. However, prednisolone has adverse effects on carbohydrate metabolism, causing both new onset hyperglycaemia and worsened glycaemic control in known patients with diabetes.

Pharmacology
Figure 1 outlines the pharmacological action of prednisolone. It is a synthetic glucocorticoid taken orally, usually in a dose of 30–60mg. It is well absorbed with good systemic bioavailability. In order to have its pharmacological effect it needs to get across the cell membrane to bind to specific glucocorticoid receptors in the cytoplasm of target cells to form glucocorticoid receptor (GR) complexes. Thereafter there is translocation to the nucleus and interaction with DNA to modify gene transcription up-regulating the expression of anti-inflammatory proteins (transactivation), and repressing the expression of pro-inflammatory proteins (transrepression). The predominant anti-inflammatory action of prednisolone is mediated by inhibition of prostaglandin (PG) synthesis via two actions on the arachidonic acid (AA) pathway (1 and 2).

Figure 1. The pharmacological action of prednisolone

NOTES. Prednisolone binds to specific glucocorticoid receptors (GRs) in the cytoplasm of target cells to form glucocorticoid receptor (GR) complexes. This complex translocates to the nucleus and interacts with DNA to modify gene transcription up-regulating the expression of anti-inflammatory proteins (transactivation), and represses the expression of pro-inflammatory proteins (transrepression). The predominant anti-inflammatory action of prednisolone is mediated by inhibition of prostaglandin (PG) synthesis via two actions on the arachidonic acid (AA) pathway (1 and 2).
expression and protein synthesis, most effects of steroids are not immediate but become apparent after several hours.

The precise mechanism of action of prednisolone and how it improves airway obstruction in acute exacerbations of COPD is not fully understood, but it is likely that it is mediated through its anti-inflammatory effects given that there is evidence that it reduces airway inflammation and oedema, as well as systemic inflammation.

There are many problems associated with long-term prednisolone use which can be considered in two categories: those resulting from adrenal suppression and those resulting from continued use of doses that are supraphysiological (iatrogenic Cushing’s syndrome). With the short length of courses (five to seven days) normally used in acute exacerbations of COPD neither of these problems would be expected, but should be borne in mind for those patients who require a more protracted course of treatment. However, hyperglycaemia is a specific and major adverse effect associated with short-term prednisolone therapy. There are several mechanisms that contribute to the development of steroid induced hyperglycaemia, including decreased peripheral insulin sensitivity, increased hepatic glucose production and inhibition of pancreatic insulin production and secretion.

Trials of safety and efficacy

In a randomised controlled trial, 56 patients with severe COPD admitted with non-acidotic exacerbations were assigned oral prednisolone 30mg once daily or placebo for 14 days. Post bronchodilator FEV1 values were significantly increased in the corticosteroid group (predicted FEV1 rose from 25.7% to 32.2% in the placebo group, compared with 28.2% to 41.5% in the corticosteroid group). The spirometric changes were matched by improvements in symptoms during admission. Additionally, the median length of hospital stay was reduced by two days in the corticosteroid group. Although this benefit in acute exacerbations is significant, the benefits were not maintained between the groups after six weeks of follow up. Transient glycosuria was the major adverse effect reported in the corticosteroid group.

In a further outpatient-based, randomised controlled trial, a cohort of patients (n=147) with severe exacerbations of COPD were randomised to receive a 10-day course of prednisolone (a pro-drug of prednisolone) 40mg once daily or placebo, following discharge from the emergency department. The primary endpoint was relapse, defined as readmission to the emergency department or unscheduled visit to the physician’s office, within 30 days following randomisation. The overall relapse rate was significantly lower in the patients treated with prednisone, compared with placebo (27% vs 43%). After 10 days of treatment, the prednisone group had significant improvement in symptoms of dyspnoea, but also post bronchodilator FEV1 compared with the placebo group. There was no significant difference in hospitalisation rates or mortality. There was a higher rate of adverse effects reported for the prednisone group; however, serum glucose levels were not measured as part of this study.

Specific evidence for use in diabetes

There are no studies reported for the use of prednisolone in acute exacerbations of COPD in patients with diabetes. In 2009, a Cochrane Review investigating systemic corticosteroids (both orally and parenterally) in acute exacerbations of COPD showed there was a significantly increased risk of hyperglycaemia in patients treated with corticosteroid. Overall, one extra participant developed hyperglycaemia for every 13 patients treated with systemic corticosteroids.

Hyperglycaemia is associated with increased mortality rates in patients admitted with acute exacerbations of COPD, independent of age, sex and prior diagnosis of diabetes. There are several features of acute exacerbations of COPD predisposing to hyperglycaemia, including systemic inflammation, respiratory acidosis, and corticosteroid treatment. One retrospective study found a random blood glucose >7mmol/L in patients admitted with acute exacerbation of COPD was associated with an increased risk of death or prolonged hospital stay. The relative contribution of prednisolone in hyperglycaemia in acute exacerbations of COPD is not known.

Discussion

Current NICE guidelines (2010) advocate a short-term course of oral prednisolone for treatment of acute exacerbations of COPD. There is robust evidence showing that oral corticosteroids are associated with improvements in symptoms and FEV1, and reductions in treatment failure and duration of hospital stay in exacerbations of COPD. However, systemic corticosteroids are associated with hyperglycaemia, which is a poor prognostic factor in patients admitted with acute exacerbations of COPD. There are no published guidelines on the management of hyperglycaemia in acute exacerbations of COPD. Patients admitted with acute exacerbations of COPD often initially have poor nutritional intake; therefore, early dietetic input to optimise energy and protein intake, and limit intake of high glycaemic index carbohydrates, may improve glycaemic control. In terms of glycaemic targets it would seem reasonable to adopt a pragmatic approach, similar to that used in critically ill patients in intensive care units, using insulin where required to maintain blood glucose levels between 8–10mmol/L.

Declaration of interests

There are no conflicts of interest declared.

References

References are available online at www.practicaldiabetes.com.
References


