ISSN: 2251-0176

International Research Journal of Pharmacy and Pharmacology

July 2013 Vol.3 No. 6

www.interesjournals.org/IRJPP

International Research Journal of Pharmacy and Pharmacology (ISSN 2251-0176) Vol. 3(6) pp. 85-90, July 2013
Available online http://www.interesjournals.org/IRJPP

Review

Current use of corticosteroids in rheumatology

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Abstract

Uncontrolled and irrational use, coupled with easy availability, low cost and the quick onset of drug action which relieves symptoms, have led to the widespread misuse and abuse of corticosteroids (CSs) by some healthcare professionals and many patients. The aim of this review, therefore, is to attempt a summary of the current use of CSs in Rheumatology. A manual literature and internet (Google, Medline, Embase, HINARI, Cochrane Database) search showed that CSs have a wide range of biological actions including anti-inflammatory and immunosuppressive effects. They can improve the symptoms of patients with rheumatic diseases. They may also have a disease-modifying effect in rheumatoid arthritis (RA), but they are not first-line treatment. Adverse effects (AEs) which may be many are related to the dose and duration of treatment. Patients should be aware of this and be prescribed the lowest effective dose and for the shortest time. Recent trials, utilizing novel chronotherapeutic modified-release (MR) Prednisone formulation given at bedtime, have demonstrated a clinically relevant decrease of morning-stiffness of the joints. Dissociated steroids or selective glucocorticoid receptor agonists (SEGRAs), that dissociate transrepression from transactivation, have shown promising results in collagen induced arthritis. The need of the hour is to strike a balance between CS efficacy and adverse effects while individualising treatment. Enlightenment of healthcare professionals and the public is imperative to guide against the inappropriate and injudicious use.

Keywords: Current use, corticosteroids, Rheumatology.

INTRODUCTION

Even at date, the use of CSs has continued to evoke and provoke strong feelings among healthcare professionals. This is due to the complications following unbridled and irrational use, in total disregard of diagnoses or indications. Since the drugs are undeniably effective, the ease of availability, low cost and quick onset of action which gives symptomatic (pain) relief, have led to the widespread misuse and abuse of CSs by many patients and even some healthcare professionals (Madanagopal et al., 2009; McEwen and Kalia, 2010; Sharif et al., 2010; Svenson and Hafstrom, 2011; Handa, 2012; Wu et al., 2013).

The substantial anti-inflammatory activity of CSs was recognised soon after their introduction in 1950. Hailed as a major triumph or “cure” in the fight against RA (based on uncontrolled observations), this discovering culminated in the award of Nobel Prize to Drs Phillip Hench, Edward Kendall and Tadeus Reichstein (Handa, 2012). However, it subsequently became obvious that unacceptable AEs occurred with prolonged use, particularly of high doses. Thus, CSs fell out of favour until recently (from the 1980s) when they were reintroduced for the treatment of several rheumatic conditions (Dorai-Raj and Schrieber, 1998; Handa, 2011). There is now a more rational approach to the use of CSs and a concerted effort to minimise AEs (Aletha et al., 2010; Handa, 2011 and 2012; Avina-Zubieta et al., 2013).

In Nigeria, and in many other developing countries, virtually all non-steroidal anti-inflammatory drugs (NSAIDs) and CSs can be obtained over the counter (OTC) without medical prescription. Some Medicine Vendors and Patent Medicine Dealers recommend 3 or more different NSAIDs sometimes together with a high dose CS such as Prednisolone, to be taken in a single dosage, to their unwary clients. This treatment option, which can be repeated several times in a day, is

popularly known as “selection” and it is adjudged to be very effective in spite of its predisposition to dangerous AEs (Helin-Salmivaara et al., 2007; Risser et al., 2010; Iyalomhe et al., 2012).

The mechanism of action of CSs involves a wide range of biological activities including anti-inflammatory and immunosppressive effects. The anti-inflammatory effects are produced by inhibition of all the classic signs of inflammation including blockade of antigenic response of macrophages and leukocytes; inhibition of vascular permeability by reduction of histamine release and the action of kinins; reducing the prostaglandin, leukotriene and platelet-activating factor synthesis that results from activation of phospholipase A_2; reducing the expression of inducible cyclooxygenase-2 and nitric oxide synthase as well as inhibition of chemokine and cytokine production including interleukin 1 (IL-1), IL-2, IL-3, IL-6, tumour necrosis factor (TNF)-α, and granulocyte-macrophage colony-stimulating factor (GM-CSF). Immunologically, CSs decrease circulating lymphocytes, monocytes, eosinophils and basophils while increasing circulating neutrophils. Long-term therapy results in involution and atrophy of all lymphoid tissues (Chrousos, 2009; Rosenfeld and Loose, 2010).

Despite polemics, the report of Caplan et al. (2007) showed that one-third of RA patients use CSs while as many as two-thirds were exposed to these agents over the period of observation (life-time). The present review examines in brief the current use of CSs in Rheumatology, discussing old practices in the light of new understanding.

CORTICOSTEROID USE

Nomenclature

The European League Against Rheumatism (EULAR) Standing Committee on International Clinical Studies Including Therapeutic Trials has recommended a standardised nomenclature for CS dosages (Table 1).

Formulations used

Oral preparations are most commonly used, often as adjunctive therapy. Intravenous preparations have a more restricted role. Intra-articular/intralesional preparations are also commonly used. CSs are divided into short to medium-acting, intermediate-acting and long-acting based on their biological half lives (t1/2s) and also have different anti-inflammatory and salt-retaining properties (Table 2). Short to medium-acting preparations are more commonly used in practice as they cause less inhibition of hypothalamo-pituitary-adrenal (HPA) axis (Chrousos, 2009).

Corticosteroids in early RA

In the context of steroid therapy, it is critically important to differentiate established RA (a disease duration in excess of 1-3 years) and early RA (a disease duration of less than 1-3 years) because the treatment modalities are different (Aletha et al., 2010; Handa, 2012). NSAIDs provide rapid symptomatic relief in very early RA. However, the evidence available as of date suggests that low dose Prednisolone of 7.5 mg/day or less should be added to disease modifying anti-rheumatic drugs (DMARDS) like Methotrexate in patients with early RA of < 2 years when the disease is severe and unresponsive to other measures or when the disease is life or sight threatening (Da Silva et al., 2006; Kirwan et al., 2007; Handa, 2012).

Even for patients of disease duration of > 2 years, the above regimen is also adjudged to be beneficial although firm evidence is necessary to extrapolate into longer disease durations. Nonetheless, a reappraisal of steroid therapy that began in the 1980s has clearly established that long-term low-dose CSs in doses of 5 – 7.5 mg/day or less, had minimal toxicities and considerable efficacy for many patients. Thus, the side effect profile of low dose CSs has been shown to be very different from high dose CSs (Pincus et al., 2002; Da Silva et al., 2006; Handa, 2012; Avina-Zubieta et al., 2013). However, it cannot be overemphasised that CSs should never be used as the sole disease modifying agents in RA.

Corticosteroids in established RA

CSs are used in established RA in the following settings (Brunton and Parker, 2008; Handa, 2012):

- In established RA, a DMARD is usually introduced to prevent the development of bony erosions and to induce disease remission. However, most DMARDs such as Methotrexate or Sulfasalazine, take several weeks and in some cases up to 6 months to take effect. Patients may require oral CSs for symptomatic relief if NSAIDs produce an inadequate response. Thus, CSs are used as “bridge therapy” for 10-12 weeks and the dose tapered off before DMARDs take effect.
- In patients who cannot tolerate NSAIDs or in whom the use of DMARDs has proven to be problematic e.g. excessive AEs, monitoring difficulties or poor compliance, the use of a low dose CS such as Prednisolone 5 – 7.5 mg/day may provide good control of symptoms and improve function (Doherty et al., 2006).
- In pregnancy and lactation, low dose Prednisolone is safe. It does not cross the placenta or blood brain barrier (DMARDs that are safe during pregnancy and lactation include Hydroxychloroquine and Sulfasalazine) (Schimmer and Parker, 2006).
- In disease flares when CSs may be used for a few weeks to suppress disease activity.

Table 1. Nomenclature of corticosteroid dosing

Nomenclature	Dosage
Low dose	≤ 7.5 mg Prednisone equivalent a day
Medium dose	> 7.5 mg but < 30 mg Prednisone equivalent a day
High dose	> 30 mg but < 100 mg Prednisone equivalent a day
Very high dose	> 100 mg Prednisone equivalent a day
Pulse therapy	> 250 mg Prednisone equivalent a day for one or a few days

Adapted from Buttgereit et al. (2002).

Table 2. Corticosteroid preparations: potency, equivalent doses, sodium retaining and half-life

Agent	Anti-inflammatory Potency	Equivalent dose (mg)	Sodium retaining	Biological half-life (hours)
Short to medium-acting				
Hydrocortisone (Cortisol)	1	20	1	8-12
Cortisone	0.8	25	0.8	8-12
Prednisone	4	5	0.3	8-12
Prednisolone	5	5	0.3	8-12
Methylprednisolone	5	4	0.25	8-12
Intermediate-acting				
Triamcinolone	5	4	0	18-36
Long-acting				
Bethamethazone	25-40	0.6	0	36-54
Dexamethazone	30	0.75	0	36-54

Adapted from Chrousos, 2009.

- Patients with refractory disease may require low dose CSs to maintain an acceptable standard of life.
- Pulse therapy using intravenous Methylprednisolone usually in high doses can be used in RA with extra-articular major organ manifestation such as interstitial lung disease, vasculitis, mononeuritis multiplex (Harvey and Champe, 2009).
- Eye conditions such as scleritis may require topical CSs while the odd, recalcitrant joint, that is active in the face of globally quiescent disease, can be injected with intra-articular steroids rather than increasing systemic doses.

Corticosteroids in other arthritides/soft tissue rheumatism

Unlike RA, the response to systemic CSs is not as good in spondarthritides (SpA). Prolonged oral CS therapy is best avoided. Intra-articular CSs are recommended for the persistent synovitis of the knee or ankle in peripheral SpA. Painful enthesopathy or refractory plantar fascitis may also benefit from local CS injection. Direct injection into tendons should be avoided in order to prevent tendor rupture (Dorai-Raj and Schrieber, 1998; Handa, 2012).

Both polymyalgia rheumatica and giant cell arteritis are treated with oral CSs. Lower doses (15 – 20 mg) are used initially in polymyalgia, whereas higher doses e.g. 40 – 50 mg/day are used in giant cell arteritis. The drugs are continued for a few weeks and then, depending on the symptoms and laboratory indices e.g. erythrocyte sedimentation rate or C-reactive protein, the dose can be reduced to the lowest maintenance dose possible e.g. 5 – 10 mg/day. Both conditions require treatment with steroids for a period of about two years. The need for ongoing therapy after two years of treatment should prompt the consideration of an alternative diagnosis, and referral for specialist evaluation (Dorai-Raj and Schrieber, 1998; Hutchings et al., 2007; Dasgupta et al., 2009).

CSs may be used in patients with acute gout if they have contra-indications to the use of NSAIDs. While NSAIDs remain the treatment of choice for acute attacks of gout, some patients have co-morbidities like renal failure or congestive cardiac failure that preclude the use of NSAIDs. Oral Prednisolone 20-40 mg daily tapered over 2 weeks or intramuscular Methylprednisolone 40-120 mg may be used in such patients. There is no consensus on agent, dose or route of administration. Intra-articular CSs are extremely effective in acute gout (Robinson et al., 2013; Stamp and Chapman, 2013).

Table 3: Adverse effects of corticosteroids

Metabolic	Obesity, electrolyte imbalance, glucose/protein/lipid metabolism
Predisposition to infections	
Musculoskeletal	Osteoporosis, myopathy, osteonecrosis
Gastrointestinal	Peptic ulcer disease, pancreatitis
Opthalmic	Cataract, glaucoma
Central nervous system	Psychosis, depression, benign intracranial hypertension
Dermatological	Acne, striae, alopecia, bruising, skin atrophy, hirsutism
Growth retardation	In children
Hypothalamo-pituitary-adrenal axis suppression	Iatrogenic Addison's disease
Corticosteroid withdrawal syndrome	Myalgia, fatigue, anorexia, nausea, weight loss

Adapted from Dorai-Raj and Schrieber, 1998; Handa, 2012.

Intra-articular CSs are effective adjuncts in managing knee osteoarthritis with effusion provided infection is ruled out and strict aseptic technique is maintained (Falase and Akinkugbe, 2007). Local intra-articular or intralesional CS injection into the site of inflammation can avoid most of the problems caused by large oral doses. This is beneficial in soft tissue conditions like tenosynovitis (tennis elbow), bursitis, plantar fasciitis, adhesive capsulitis of shoulder, nerve entrapment as in carpal tunnel syndrome etc (Harvey and Champe, 2009). However, situations where a local CS injection is contraindicated include periarticular sepsis, bacteraemia, unstable joints, intra-articular fractures, septic joints and bleeding disorders (relative contraindication) (Falase and Akinkugbe, 2007; Handa, 2012).

Corticosteroids in connective tissue (CT) diseases

CT diseases such as systemic lupus erythematosus (SLE), vasculitis and polymyositis require systemic CS therapy for effective control. Since these diseases vary greatly in the extent and severity of organ involvement, there is a need to individualise treatment. In severe flares, high dose oral or intravenous CSs are usually required (Doherty et al., 2006). It is important to emphasise that management of these conditions should be under the guidance of a Consultant Physician e.g. a Rheumatologist experienced in treating these complex disorders.

RECENT ADVANCES

CSs are usually recommended as a single morning dose to reduce AEs but this does not eliminate the morning stiffness in all patients. A clinically relevant reduction of morning stiffness of the joints was recently demonstrated by the Circadian Administration of Prednisone in Rheumatoid Arthritis trial (CAPRA-I), an active-controlled clinical trial in which a novel chronotropic MR Prednisone formulation given at bed time releases the steroid at about 2:00 AM, to coincide with the rising phase of the circadian cycle prior to the rise of early morning pro-inflammatory cytokines. According to recent reports, such use overcomes inadequate cortisol in RA, presumably leading to better clinical effects because of less disturbance of HPA axis (Buttgereit et al., 2008; Handa, 2012).

Dissociated steroids or SEGRAs, dissociate transrepression from transactivation i.e. they demonstrate a selective antagonistic effect on pro-inflammatory transcription factors but are devoid of agonistic effects on glucocorticoid response elements (GREs) driven genes that contribute to the endocrine effects of glucocorticoids. The initial results in collagen-induced arthritis are promising (Elewaut, 2009).

ADVERSE EFFECTS OF CORTICOSTEROIDS

CS therapy, irrespective of dose, is associated with many possible AEs (Table 3). For example, Mazzantini et al. (2010) reported that low dose steroid users treated for RA showed a higher prevalence of fractures, arterial hypertension, myocardial infarction and serious infections especially after 5 years of treatment, than patients never treated with steroids. Thus, strategies to minimise complications like bone protective agents etc should be instituted concurrently with the steroid if treatment is likely to be continued for ≥ 6 months. The lowest dose for the shortest time should be employed. More common AEs with long-term use include weight gain and Cushinghoid features like moon face and buffalo hump, hirsutism, skin atrophy, bruising, posterior subscapular cataract, mood changes and osteoporosis. Some of the more serious AEs that may require monitoring include elevation of

blood glucose level, especially if the patient is a diabetic; hypertension, increased susceptibility to infections and avascular necrosis of bone (Wolf and Taylor-butler, 2000; Roy and O'Neil, 2005).

Practical Prescribing Tips

- Decision to use steroids in a given patient should be individualised, taking cognizance of any contraindications or precautions e.g. diabetes mellitus, hypertension, osteoporosis.
- Steroids should always be used in combination with other DMARDs like methotrexate and never as the sole disease modifying drugs in RA.
- Steroids lower disease activity in established RA and can be used to treat disease flares. The lowest dose for the shortest possible time should be used because AEs are time and dose related. Early morning dose causes less HPA axis suppression but in severe and active disease, a split larger early morning dose and smaller evening dose may be necessary.
- Chronotherapeutic manipulation like the use of MR Prednisone may offer better relief from early morning stiffness.
- Intra-articular steroids are helpful in knee osteoarthritis with effusion provided adequate precautions are taken.
- Despite the favourable risk/benefit ratio of low dose steroids, no dose is absolutely safe. Patients should be made to know this fact and should be warned against stopping CSs suddenly and advised to wear medic-alert badges while on long-term treatment.
- Patients treated with long-term moderate or low doses of CSs should have their CS dose reduced and withdrawn slowly. The reasons for this are to:
  - Allow time for the HPA axis to recover as it can be suppressed by only 3 weeks of systemic treatment.
  - Reduce the likelihood of relapse of the underlying condition being treated, particularly symptomatic inflammatory disease e.g. RA
  - Avoid the CS withdrawal syndrome (myalgia, fatigue, anorexia, nausea, weight loss).
- For children on long-term CSs, alternate day administration of the same total CS dose is now preferred because it may reduce inhibition of linear growth and delay epiphyseal closure. This regimen is also possible in adults when their disease is stable. The AEs associated with this form of therapy are less compared to daily administration. However, RA patients who experience a flare in their symptoms on the day off treatment may be unable to tolerate this regimen.
- All patients on steroids should be monitored for adverse effects and appropriate steps taken to minimize their occurrence e.g. bone protection strategies etc.

CONCLUSION

CSs have an important role in the management of rheumatic disease. Their toxicity requires that they are used only when necessary; at the lowest dose possible and for the shortest time. Consideration should be paid to the measures that can be taken to limit toxicity. SEGRAs represent an important new class of steroids whereas chronobiology permits the use of MR Prednisone to combat early morning stiffness. The real need of the hour is to strike a balance between efficacy and AEs while individualising treatment. Enlightenment of healthcare professionals and the public, to intensify appropriate and judicious use of CSs, is imperative in this regard.

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