SUPPLEMENT

Glucocorticosteroids in football: use and misuse

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Br J Sports Med 2006;40(Suppl 1):i48–i54. doi: 10.1136/bjsm.2006.027599

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Background and objectives: Glucocorticosteroids are widely used in medicine and have shown unchallenged therapeutic potential in several chronic inflammatory and other diseases. They are also widely used in sports medicine for the treatment of conditions such as asthma and acute injuries. In fact, as banned substances, most requests for therapeutic use exemption concern glucocorticosteroids. Nevertheless, their beneficial effect in certain conditions in sports, where inflammation is only a secondary reaction, remains to be validated. This paper aimed to provide a comprehensive review of the literature covering the therapeutic use of glucocorticosteroids since 1977 in conditions ranging from chronic rheumatic illness to peritendinous or intra-articular injection in acute injuries.

Methods: Search of the medical literature published between 1977 and 2006 using PubMed. Articles relevant to the question "When and if at all is the use of glucocorticosteroids justified in football?" were selected and analysed.

Results and conclusions: The findings clearly point out that, despite the common use of glucocorticosteroids in acute injuries in sports, there is actually limited evidence of the true benefits of such a practice. Physicians must take the possible adverse effects into consideration. In an athlete with clinically verified asthma, inhalational glucocorticosteroids remain first line therapy. Finally, for the purposes of education and prevention of misuse, it should be stressed that a measurable performance enhancing effect of glucocorticoids could not be proved on the basis of the results of the scientific studies to date.

Glucocorticosteroids are widely used in the management of sports related injuries as well as in the disorders of the musculoskeletal system, such as overuse injuries of muscles and muscle-tendon junctions or insertion tendopathies. According to the World Anti-Doping Code, all orally, rectally, intravenously, and intramuscularly administered glucocorticosteroids are prohibited. Their use requires a standard therapeutic use exemption (TUE). Administration of glucocorticosteroids by all other routes requires an abbreviated TUE, except dermatological preparations, which are not prohibited (Fédération Internationale de Football Association (FIFA) Doping Control Regulations 2006 (www.fifa.com/documents/fifa/regulations/dopingreglement_06_e.pdf); World Anti-Doping Agency Prohibited List, version January 2006 (www.wada-ama.org/rtecontent/document/2006_LIST.pdf)).

This article focuses on the evidence-based, justified indications for glucocorticosteroids and their misuse when medically not justified.

METHODS

Search strategy

We searched the medical literature published between 1977 and 2006 using PubMed and the keywords "glucocorticosteroids" and "cortisol" as first choice. These keywords were matched individually with the following subjects: abuse, adverse effects, application, athletes, complications, doping, effects, football, metabolism, musculoskeletal disorders, pharmacodynamics, pharmacokinetics, risks, screening, sports, and synthetic. The same procedure was performed for synonyms, related topics, and subtitles of each category.

Selection of papers

Relevant articles were selected and analysed keeping in mind the question: When and if at all is the use of glucocorticosteroids justified in football?

RESULTS AND DISCUSSION

Pharmacokinetics

Glucocorticosteroids are physiological hormones produced in the fasciculated zone of the adrenal cortex and released in a circadian rhythm with peak concentrations between 6 am and 8 am and the lowest concentrations between 6 pm and midnight. Their release is regulated by a feedback mechanism between the hypothalamus (corticotropin releasing factor), the anterior lobe of the pituitary gland (adrenocorticotrophic hormone), and the adrenal cortex (cortisol).¹ The circulating hormones are involved in carbohydrate and protein metabolism. The physiological glucocorticosteroids, cortisol and cortisone, are metabolised from cholesterol and have to be distinguished from synthetic derivatives. The chemical structure of cortisol can be seen in fig 1. With the exception of prednisone and prednisolone, synthetic glucocorticosteroids do not have any mineralocorticoid effects.¹

The influence of glucocorticosteroids on the majority of cells involved in inflammatory reactions and stimulation of the synthesis of inflammation mediators explains their anti-inflammatory effects.² They interfere with inflammatory cell-cell adhesion and migration through the vascular endothelium.³ In addition, they inhibit the synthesis of proinflammatory proteins—in particular, cytokines. They also inhibit the expression of cyclo-oxygenase-2, which leads to decreased production of prostanoids, but the production of leukotrienes is not significantly affected. Moreover, glucocorticosteroids inhibit the degranulation of human basophils (histamine release) but have no effect on mast cells. These favourable anti-inflammatory effects have resulted in the development of synthetic compounds with much greater anti-inflammatory capacities than the natural hormones but with reduced mineralocorticoid activity.²

Abbreviations: ACTH, adrenocorticotrophic hormone; EIA, exercise induced asthma; HPA, hypothalamic-pituitary-adrenal; ITBFS, iliotibial band friction syndrome; TUE, therapeutic use exemption

Figure 1 Chemical structure of cortisol.

With regard to athletes, the most interesting systemic effect of the glucocorticosteroids is energy production by stimulation of gluconeogenesis and mobilisation of amino acids and fatty acids.⁴ A possible increase in cardiovascular performance is a matter of debate as there is no evidence for such effects. As a consequence, systemic glucocorticosteroids have been misused for decades to enhance performance, and they once belonged to the group of most commonly used doping substances in sports. Athletes also took them to alleviate pain and reduce tiredness, ignoring the possible adverse effects such as diabetes, myopathy, and growth retardation.⁵ At the Olympic Winter Games in Lillehammer in 1994, Patrick Schamach, at that time Chairman of the Medical Commission of the International Olympic Committee, observed an extremely high number of athletes "suffering from asthma" and therefore needing to take specific medications such as glucocorticosteroids. Even though it has been the general point of view in sports that adrenocorticotrophic hormone (ACTH) and corticosteroids improve maximal performance, this review of literature could not corroborate this hypothesis. In a study with counterbalanced, double blind design, Soetens *et al* injected 16 professional cyclists with 1 mg ACTH or placebo before cycling for an hour. An increase of maximal performance with ACTH was not observed.⁶

In the blood glucocorticosteroids are bound to the cortisol binding protein and to albumin. Stress such as exercise, infection, or surgery may increase cortisol production by up to four times.^{1,7} Athletes show a lower anabolic/catabolic balance than untrained individuals indicated by the testosterone/cortisol ratio. The concentrations of testosterone and cortisol are negatively related as they are competitive agonists at the receptor level of muscular cells: the plasma cortisol concentration is higher, whereas the testosterone concentration is lower.^{8,9}

Glucocorticosteroids can be administered systemically (intravenously, orally) or locally (subcutaneously, intramuscularly, rectally, or by inhalation or intra-articular injection). The different properties/effects and the ratio of topical to systemic activity are dependent on variables such as: dose; frequency of administration; pharmacologic properties, such as drug delivery device, absorption of the drug, drug distribution, drug metabolism, drug clearance; and pharmacodynamic properties, such as the relative glucocorticosteroid potency or the concentration producing the half-maximal effect.^{10–12} The most commonly prescribed systemic glucocorticosteroids are hydrocortisone, prednisolone, methylprednisolone, and dexamethasone. These glucocorticosteroids are known to have good oral bioavailability. They are primarily eliminated by hepatic metabolism and the metabolites excreted by the kidney.¹⁰

Glucocorticosteroids were first purified and manufactured in the 1930s and 1940s following the discovery of their potent anti-inflammatory actions.¹³ The first use of cortisone in rheumatoid arthritis therapy was reported in 1949.¹⁴ The efficacy of glucocorticosteroids and their indications have been debated for decades. A detailed knowledge of their

metabolic effects is required, as the use of glucocorticosteroids is widespread in clinical practice.¹⁵ Specifically, glucocorticosteroids influence carbohydrate, protein, and lipid metabolism. The hepatic capacity for gluconeogenesis is increased and catabolic actions on muscle, skin, lymphoid, adipose, and connective tissues are enhanced. Clinicians must think carefully about the benefits versus the inevitable, undesirable risks of extended treatment on an individual basis. Thus, it follows that it is essential to keep in mind that the enhanced anti-inflammatory activity of the various synthetic derivatives of cortisol cannot totally be dissociated from the catabolic actions of glucocorticosteroid hormones.¹⁵

The use of glucocorticosteroid injections in the treatment of orthopaedic injuries is a matter of debate. Some studies have reported that intra-articular injection of low dose glucocorticosteroids causes markedly reduced incidence and severity of cartilage erosions and osteophyte arrangement.³ Conversely, animal studies have demonstrated destruction of articular cartilage after hydrocortisone injections as well as a dose dependent decrease in cartilage matrix production.¹⁶ There have been many cases reports of tendon or fascial ruptures induced by glucocorticosteroid injections—for example, between 1992 and 1995 Acevedo and Beskin reported 765 patients with a clinical diagnosis of plantar fasciitis.¹⁷ Of these patients, 51 had plantar fascia rupture, and 44 of these ruptures were related to glucocorticosteroid injection. Twenty six patients still had foot problems one year later.¹⁷ Besides, the injection of glucocorticosteroids in and around tendons and ligaments is controversial.

Therapeutic use of glucocorticosteroids in exercise, training, and competitions

Glucocorticosteroids have been used by athletes to improve their performance since the 1960s, but their use is restricted in professional sports.¹⁴ Chronic misuse can be documented by the analysis of hair and urine, which can be used for doping control if required.^{18–20}

On the basis of their potent anti-inflammatory pharmacological effects, and possibly due to down regulating of genetic expression of several proinflammatory proteins, glucocorticosteroids have been used extensively in the management of rheumatological diseases and athletic musculoskeletal disorders.²¹ Intra-articular, intrabursal, and peritendinous injections of glucocorticosteroids are used to in the treatment of different kinds of musculoskeletal disorder. Acute tendon injuries, tendon disorders, and tendon pain often occur in athletes.²² According to Alfredson, the etiology and the pathological mechanisms are unknown.²³ One approach deals with a degenerative process occurring in the tendon mainly due to overuse. The spontaneous tendon rupture can be seen as the clinical endstage manifestation of the affected tendon and paratendon tissue. Subsequently, the tenocytes lose their reparative ability, which further weakens collagen cross-linking, the non-collagenous matrix, and the vascular elements of the tendon. Extensive performance compromises the micro and macrovasculature of the tendon, which leads to insufficient blood circulation in the affected area. Hypoxia, inadequate nutrition, and energy metabolism are some of the consequences.²² The use of intra-articular and periarticular glucocorticosteroids is thought to temporarily reduce pain and inflammation in the affected musculoskeletal structures. Besides this, motion and function are facilitated.²¹ However, no study has found any evidence of reparative mechanisms. Instead, recent animal studies have shown that dexamethasone causes a dose dependent decrease of tenocyte proliferation and reduction in collagen production by tenocytes cultured in vitro. Moreover, the recruitment of tendon progenitor cells has been shown to be modulated.²⁴

Systemic administration of glucocorticosteroids in athletes has reduced due to serious adverse effects such as glucose intolerance,²⁵ Cushing's syndrome,^{25, 26} and osteoporosis.^{27–30} However, the benefits and risks of locally injected or systemically administered glucocorticosteroids in the treatment of athletic injuries are still unclear.¹⁴ Nichols undertook a critical review of research published between 1966 and 2003 concerning glucocorticosteroids and athletics related injuries using three databases, Medline, CINAHL, and the Cochrane Clinical Trial Register. The rate of complications among 1078 athletes who had received a glucocorticosteroid infiltration was about 22.6%. The first part of the review primarily dealt with the usage of glucocorticosteroid injection therapies. A total of 983 subjects with different kinds of athletic injury received different kinds of glucocorticosteroid injection for conditions such as lateral/medial epicondylitis, osteitis pubis, olecranon bursitis, rotator cuff lesions, subacromial impingement syndrome, rotator cuff tendonitis, plantar fasciitis, patellar fasciitis, Achilles' paratendonitis, and hamstring strains. Only 15.2% reported side effects, and 9.7% had post-injection pain. The second part of the review focused on complications occurring after glucocorticosteroids injection. Rupture of the plantar fascia was reported to be the predominant problem (53.7%). Nichols did not find any studies dealing with either the use of or the complications of systemically administered glucocorticosteroids in the treatment of athletic injuries—although tibial stress fracture and multifocal osteonecrosis were observed in patients being treated for non-athletic trauma. There is no conclusive evidence for the efficacy of glucocorticosteroids injections in the treatment of the human musculoskeletal structures. Nichols pointed out that the medical literature leading up to 2003 does not present the incidence of complication rates associated with therapeutic use of injected or systemic glucocorticosteroids in the treatment of athletic injuries.¹⁴ However, complications exist, and these cannot be ignored and athletes have to be informed.

There has been substantial discussion regarding when and if all oral glucocorticosteroids are indicated for musculoskeletal injury³¹ too. Oral glucocorticosteroids are frequently prescribed by sports medicine physicians, although there is no documentation of this practice in the literature. Harmon and Hawley's study³¹ aimed, on the one hand, to report patterns corticosteroid prescribing among primary care sports medicine physicians and, on the other hand, to look for evidence based indications. Of the 195 physicians who took part in the study, 58.6% reported using oral glucocorticosteroids for musculoskeletal disorders with an average of 6.6 prescriptions per month. Prednisone was administered most often (82%) and the average length of prescription was seven days; 51.7% of the physicians tapered the dose with a starting dose of about 60 mg.³¹

In conclusion, glucocorticosteroids are frequently prescribed in sports medicine although there is little evidence to support their use.³¹

Selected indications of glucocorticosteroids relevant to football and complications

Glucocorticosteroids possess pleiotropic effects.¹⁰ Therefore, they are widely used in football for different kinds of problem concerning the musculoskeletal system to hasten the return of the player to the game.¹⁶

Hamstring injuries

Hamstring injuries can lead to a significant loss of playing time for athletes. Levine *et al* analysed the safety of intramuscular corticosteroid injection in selected, severe hamstring injuries in professional American football players.¹⁶ They reviewed the computer database (between

January 1985 and January 1998) of one National American Football League team for all hamstring injuries requiring treatment. Among 431 players with such an injury, 58 (13%) sustained severe, discrete injuries—that is, type IIB (discrete lesion, localised with fingertip, palpable defect). They were treated with an intramuscular injection of either 4 mg dexamethasone or 3 ml of 1% lidocaine hydrochloride. Although the main problem with glucocorticosteroid injections around muscle–tendon units is incomplete healing or rupture of the tendon, there were no complications in relation to the injection of glucocorticosteroids. The average time to return to full practice was 7.6 days. Lack of a control group limits conclusions about the efficacy of the injection. Levine *et al* concluded that intramuscular glucocorticosteroid injection hastens players' return to full play and lessens the game and practice time they miss. This hypothesis needs to be evaluated further as the presented observational study is of limited value.

Achilles' tendonitis

There is insufficient published data concerning Achilles' tendonitis to evaluate the pros and cons of glucocorticosteroid injection. According to Shrier *et al* glucocorticosteroid infiltration in Achilles' tendonitis did not have an advantage over placebo. Animal studies emphasise the reduced tendon strength after intratendinous injections.³² In sports medicine, intratendinous infiltration has to be considered a medical error. Csizy and Hintermann reported on three cases of Achilles' tendon rupture after local steroid injection for Achilles' tendonitis.³³ An unusual rupture mechanism was demonstrated in all cases. Moreover, necrotic tendon changes were seen during the subsequent operation. It is assumed that 75% of all Achilles tendon ruptures occur in sports, and most ruptures (34%) occur in football.³⁴ Other tendon ruptures, such as the patellar or quadriceps tendon rupture, or rupture of the plantar fascia after glucocorticosteroid injection have also been described by different authors.^{14, 35, 36}

In a randomised, double blind, placebo controlled study in athletes with chronic Achilles' and patella tendonitis, ultrasonography increased diagnostic accuracy and optimised the delivery of the peritendinous injection of a long acting glucocorticosteroid. Moreover, this method can objectively monitor the effect of treatment. With this technique of infiltration, there was stabilisation of the ultrasonographic picture of pathological defects in the Achilles' and patellar tendons. However, when combined with an early rehabilitation programme consisting of running after a few days, many athletes experienced relapse of symptoms within six months.³⁷

Non-articular soft tissue disease

In one study, 300 athletes with minor non-articular soft tissue injuries received a single treatment with a repository steroid (methylprednisolone acetate). The response to treatment was determined five days later. Fitness to take part in sport was used as a guide. Excellent results were observed in 133 patients (44%) and good results in 103 (34%), whereas 64 (21%) had poor results.³⁸

Lateral epicondylitis

Smidt *et al* compared the efficacy of glucocorticosteroid injection, physiotherapy, and wait-and-see policy with respect to time.³⁹ After six weeks, glucocorticosteroid injections achieved significantly higher rates of success than both the other treatment options for all outcome measures. However, long term differences between injection and physiotherapy were significantly in favour of physiotherapy. Besides, the rate of recurrence in the injection group was the highest. Newcomer *et al* confirmed these observations to a

certain extent. They showed that patients with lateral epicondylitis of a short duration (less than four weeks) did not benefit substantially from a glucocorticosteroid injection. They emphasised that a rehabilitation programme should be the first line treatment.⁴⁰

Non-specific pain syndrome

With respect to the efficacy of glucocorticosteroids, pain need to be differentiated into acute and chronic pain. To find out whether a local injection of 40 mg methylprednisolone acetate was efficient in reducing pain during running in runners with recent onset iliotibial band friction syndrome (ITBFS; that is, less than two weeks), 18 runners with at least grade 2 ITBFS underwent baseline measurements and received either infiltrated glucocorticosteroids or placebo. During the course of a treadmill running test a visual analogue scale was used to record the degree of pain after every minute.⁴¹ The results of the study showed that the local glucocorticosteroid infiltration, in contrast with placebo infiltration, effectively decreased pain during running in the first two weeks of treatment in patients with recent onset ITBFS.

Radicular pain

Ng *et al* aimed to determine the treatment effect of periradicular infiltration of glucocorticosteroids for chronic radicular pain.⁴² Eligible patients had radicular pain, unilateral symptoms, and were failing conservative management. The patients were randomised to a single injection with bupivacaine and methylprednisolone or bupivacaine only. Clinical improvement occurred in both groups of patients. The results clearly indicated that there was no statistically significant difference in the outcome measures between the groups at three months. Thus there were no additional benefits of the glucocorticosteroid treatment.⁴²

Neurotrauma

There is evidence of benefit from corticosteroids in acute spinal cord injury. The second US National Acute Spinal Cord Injury Study (NASCIS 2) compared 24 hour corticosteroid (methylprednisolone) treatment with placebo in 333 patients with acute spinal cord injury. At six months, patients who had received corticosteroids within eight hours of injury had greater improvement in motor function and sensation to pinprick and touch.⁴³ Similar results were reported in a Japanese trial of 151 patients who received the same regimen.⁴³ More recent trials of methylprednisolone in acute spinal cord injury indicated slightly more neurological recovery with 48 hours than with 24 hours of treatment.⁴³ On the basis of these results high dose (30 mg/kg body weight) methylprednisolone is now widely used in the treatment of acute spinal cord injury.

Corticosteroids have also been used to treat severe head injury for over 30 years, although their value was questioned more recently because of the failure to demonstrate effectiveness in randomised trials.⁴⁴ In 2004, the results of the multicentre international collaborative CRASH trial were published.⁴⁵ This study demonstrated that in 10 008 adults with head injury and a Glasgow Coma Scale score of 14 or less within eight hours of injury, who were randomly allocated to methylprednisolone or placebo, the risk of death from all causes was higher in the group given corticosteroids ($p = 0.0001$). Similarly, there is no published evidence to support the use of corticosteroids in mild traumatic brain injury or concussion. As a result, corticosteroids are not recommended for the routine treatment of brain injury.

Chronic osteoarthritis

Intra-articular glucocorticosteroids have been used in the therapy of osteoarthritis, the commonest form of arthritis. As already mentioned before, there is no convincing evidence that glucocorticosteroid infiltration alters the progression of osteoarthritis.³ As glucocorticosteroids can be associated with a high risk of tendon rupture and infection, intra-articular injections of hyaluronic acid have become more popular. Decrease in pain and improved functional outcomes following the treatment of osteoarthritis of the knee with these injections has been shown.⁴⁶ Uthman *et al* distinguish between a knee with effusion and a symptomatic “dry knee”. According to their studies a knee with effusion may be treated with an intra-articular injection of a glucocorticosteroid, whereas hyaluronic acid should be used for a “dry knee”.³

Adhesive capsulitis

Adhesive capsulitis is characterised by pain and tenderness in the shoulder joint. One study found that a local steroid injection (group A: 40 mg methylprednisolone acetate injection with local anaesthetic) was as effective as physical therapy plus non-steroidal anti-inflammatory drugs (group B) for the treatment of adhesive capsulitis.⁴⁷ Another study pointed to the efficacy of the combination of intra-articular injection of glucocorticosteroids with a simple home exercise programme in improving shoulder pain and reducing disability in patients with adhesive capsulitis. The improvement in shoulder range and motion is accentuated by the addition of supervised physiotherapy to glucocorticosteroid infiltration.⁴⁸

Asthma and allergic rhinitis

Asthma and allergic rhinitis are regarded to be synonyms of the same allergic syndrome.¹² Inhaled glucocorticosteroids are used for treatment of bronchial asthma, for which they provide highly effective first line treatment.^{49–51} To minimise the degree of systemic exposure and eliminate associated systemic and local adverse effects, one study used the “soft drug approach” to deliver potent anti-inflammatory agents close to their site of reaction.⁴⁹ However, the prescription of high dose inhalational glucocorticosteroids, particularly fluticasone, should be critically analysed, as life threatening adrenal failure has been reported in asthmatic children inhaling glucocorticosteroids. Appropriate management for asthma—that is, early use of steroid sparing alternatives, such as a long acting β agonist or leukotriene receptor antagonist—is emphasised. These drugs might reduce the morbidity caused by inhaled glucocorticosteroids, although the systemic effects of the latter cannot be avoided in some children who have an increased sensitivity to inhaled glucocorticosteroid treatment.⁵² Athletes with exercise induced asthma (EIA) have to have their asthma controlled in order to safely participate in training and competition without respiratory disadvantages. Any additional performance enhancing advantages from medication to control asthma and EIA have not been proved: β_2 agonists, sodium cromoglycate and glucocorticosteroids are not considered to be ergogenic. However, some athletes may unnecessarily use oral and perhaps parenteral glucocorticosteroids to achieve certain side effects.⁵³

Allergic rhinitis may be seasonal, intranasal, or persistent. In patients with seasonal allergic rhinitis, intranasal glucocorticosteroids have been proved to be more effective than an antileukotriene drug or combined antileukotriene–antihistamine treatment in reducing pollen induced nasal eosinophilic inflammation and for controlling nasal symptoms.⁵⁴

What is already known about this topic

Glucocorticosteroids are widely used in sports medicine for the treatment of medical conditions such as asthma, injuries, and musculoskeletal disorders. There is abundant literature on their use, specially in the latter indications. However, to date there has been no review summarising their beneficial potential on the one hand and their adverse effects on the other hand with respect to the various sporting indications.

Non-specific cough

One study dealt with the efficiency of beclometasone dipropionate (400 µg per day) in the treatment of non-specific chronic cough in children. The researchers came to the conclusion that there was no difference between the drug and placebo in reducing the frequency of cough measured objectively or scored subjectively. A small improvement with very high dose inhaled corticosteroid is debatable.⁵⁵

Selected general side effects

An understanding of the hypothalamic–pituitary–adrenal (HPA) axis and the reasons for use of glucocorticosteroids is essential. All athletes in whom treatment with glucocorticosteroids is intended, should be examined and informed about conditions which would make glucocorticosteroids inadvisable and about other medications that might cause drug interactions. The physical examination should cover all systems predisposed to adverse effects caused by glucocorticosteroids—for example frequent evaluations of weight and blood pressure. Moreover, blood chemistry should be evaluated on a regular basis along with glucose, electrolytes, and serum lipids.³⁰

Infiltration therapy

The role of glucocorticosteroid injection therapy in spontaneous tendon rupture has been discussed above. Wong *et al* studied in vitro the effects of dexamethasone and triamcinolone on proteoglycan production by cultured human tenocytes explanted from healthy human patellar tendon. Suppression of proteoglycan production in cultured human tenocytes was observed after the application of dexamethasone. The simultaneous addition of platelet derived growth factor reversed the suppression of proteoglycan production. To conclude, suppression of proteoglycan production influences the viscoelastic properties of the tendon and increases the risk of spontaneous rupture.⁵⁶ These results are similar to those of Scutt *et al*.²⁴ Another animal investigation demonstrated the significantly inferior biomechanical properties of tendons after bilateral injections in comparison with unilateral injections of glucocorticosteroids for retrocalcaneal bursitis.⁵⁷ However, whether the results of the animal models can be extrapolated to humans is not known. Nevertheless, musculoskeletal structures of athletes are more stressed than those of non-athletes. Consequently, glucocorticosteroid infiltration predisposes to tendon rupture, ligament weakening, and articular cartilage damage.¹⁴

Septic arthritis due to an intra-articular steroid injection of the knee can probably be regarded as a rare complication. However, there are no studies dealing with the incidence of post-steroid injection arthritis.⁵⁸

Inhalation therapy

The risks of inhalational glucocorticosteroids might be compared with the complications occurring after their systemic administration. Suppression of the HPA axis can be regarded as the most important potential complication of inhaled glucocorticosteroids.⁵⁰

What this study adds

This review of the literature from 1977 to date reveals that there is insufficient scientific evidence for substantial benefits of glucocorticosteroids in the treatment of sport related injuries and musculoskeletal disorders. It describes the relevant side effects that have to be weighed against the therapeutic gain. The review concludes that adequate rehabilitation and physiotherapy should be considered as the treatment of choice in these indications. The diagnosis of asthma has to be clinically verified. A true performance enhancing effect of glucocorticosteroids could not be substantiated.

Oral therapy

Long term glucocorticosteroid treatment is considered to induce osteopenia and osteoporosis.^{15 27 30} Hirayama *et al*, in an experimental study, examined the influence of the synthetic glucocorticosteroid dexamethasone on human osteoclast formation and bone resorbing activity. They found that dexamethasone directly influences osteoclast formation and activity. The addition of dexamethasone enhances the proliferation and differentiation of human osteoclast precursor cells.⁵⁹

Persisting psychiatric reactions have to be mentioned as another adverse effect of glucocorticosteroids. Declarative, hippocampus dependent memory seems to be particularly affected—impaired functioning of concentration, attention, learning, and memory as well as melancholic depression and anxiety have been reported.^{60–62} Moreover, steroid resistance or steroid induced suppression of the HPA axis with inhibition of pituitary gonadotropin, growth hormone, or thyrotropin has been described by several authors.^{15 50 63} As glucocorticosteroids induce an increase of blood glucose, decrease of the glucose tolerance level is another common problem of glucocorticosteroid therapy and an essential characteristic of Cushing's disease: glucocorticosteroids induce insulin resistance, which leads to an increase in hepatic gluconeogenesis.²⁵ Latent diabetes mellitus might be unmasked.¹⁵ Sodium retention and/or elevation of mean arterial blood pressure has also been described, probably because of the above mentioned mineralocorticoid properties.¹⁵ Proximal muscle weakness and muscle atrophy due to the catabolic action are important consideration, especially for athletes contemplating the use of glucocorticosteroids. Due to immunosuppressive properties, such as reduction in the number of lymphocytes and diminishing lymphocyte function, the rate of infection increases. Moreover, latent infections, such as tuberculosis or Epstein–Barr virus infection, might be reactivated.⁶⁴

CONCLUSION AND RECOMMENDATIONS

Glucocorticosteroids possess potent anti-inflammatory pharmacological properties and so they are indicated in chronic diseases such as rheumatoid arthritis or clinically diagnosed asthma. For the same reason they are essential in the treatment of medical emergencies, such as necrotising vasculitis, asthmatic state, and anaphylactic shock.^{1 14 15} These conditions are all characterised by either inflammation or a high number of lymphocytes as the primary pathology. Conversely, the inflammatory reaction in the course of athletic injuries is a secondary reaction to the musculoskeletal trauma and part of the healing process. As a consequence, the use of glucocorticosteroids, particularly intra-articular or intramuscular injections, has to be carefully assessed and these drugs used only if there is a rational, evidence based indication. Nichols' critical review in 2005

revealed that the existing medical literature does not provide precise estimates of the rates of complications following the therapeutic use of injected or systemic glucocorticosteroids in the treatment of athletic injuries.¹⁴ Tendon and fascial ruptures are reported complications of injected glucocorticosteroids, whereas tibial stress fractures and multifocal osteonecrosis were described with systemic glucocorticosteroids.¹⁴ In this respect, the potential benefit, which in selected cases may be evidence based, should always be considered in relation to the potential side effects and complications of glucocorticosteroid use. In the case of sport related injuries, appropriate rehabilitation and physiotherapeutic approaches should be considered as the treatment of choice—before use of intra-articular and/or intramuscular glucocorticosteroid injections.

As a result, any TUE for glucocorticosteroids has to be carefully evaluated by the respective granting body in order to reduce or even avoid the misuse of glucocorticosteroids. With regard to prevention of misuse and for education purposes it has to be stressed that a measurable performance enhancing effect of glucocorticosteroids cannot be proved by the results of scientific studies conducted to date.

ACKNOWLEDGEMENTS

The authors would like to thank Drs L Avois, P Bärtsch, M D'Hooghe, T Edwards, D Kirkendall, B Mandelbaum, M Saugy, and Y Zerguini and C McCammon for their critical review of the manuscript.

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Competing interests: none declared

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