Endocrine (2015) 48:410–416
DOI 10.1007/s12020-014-0409-5

MINI REVIEW

Intra-articular glucocorticoid injections and their effect on hypothalamic–pituitary–adrenal (HPA)-axis function

Philip C. Johnston · M. Cecilia Lansang · Soumya Chatterjee · Laurence Kennedy

Received: 9 July 2014 / Accepted: 26 August 2014 / Published online: 3 September 2014

Abstract The use of intra-articular (IA) glucocorticoids for reducing pain and inflammation in patients with osteoarthritis, rheumatoid arthritis, and other inflammatory arthropathies is widespread among primary care physicians, specialists, and non-specialists in the United States. Injectable glucocorticoids have anti-inflammatory and analgesic properties which can be effective in improving clinical parameters such as pain, range of motion, and quality of life. After injection into the IA space, glucocorticoids may be systemically absorbed; the degree of absorption can depend on the size of the joint injected, the injectable glucocorticoid preparation used, the dosage, and the frequency of the injection. The adverse effects of intra-articular glucocorticoid injections (IAGC) can often be overlooked by both the patient and physicians who administer them, in particular the potential deleterious effect on the hypothalamic–pituitary−adrenal (HPA)-axis which can result in adrenal suppression and/or iatrogenic Cushing syndrome. In this paper we provide an overview on the often under-recognized effects of IAGC on HPA-axis function.

Keywords Intra-articular glucocorticoid injection · Hypothalamic−pituitary–adrenal (HPA) axis · Adrenal suppression · Cushing syndrome · Cortisol · Triamcinolone (Kenalog) · Methylprednisolone (Depo-medrol)

P. C. Johnston (✉) · M. C. Lansang · L. Kennedy
Department of Endocrinology, Diabetes and Metabolism, Cleveland Clinic Foundation, 9500 Euclid Avenue Desk F20, Cleveland, OH 44195, USA
e-mail: pcjohnston@doctors.org.uk

S. Chatterjee
Department of Rheumatic and Immunologic Diseases, Cleveland Clinic Foundation, 9500 Euclid Avenue, Cleveland, OH 44195, USA

Introduction

Intra-articular glucocorticoid injections (IAGC) were first administered in the 1950s and are routinely used for the localized treatment of joint pain [1, 2]. The most commonly injected joints are the knee and shoulder [3]. Intra-articular glucocorticoids are typically indicated for the treatment of rheumatoid arthritis, osteoarthritis, crystalline arthropathies, and other inflammatory arthropathies when conventional therapy has not controlled pain [4, 5]. A survey by Hochberg of American rheumatologists indicated that the overwhelming majority administer IAGC in their practice [6]. Although the injected glucocorticoid suspension is normally confined to the intra-articular cavity, systemic absorption has been widely recognized as evidenced by the beneficial effects on other joints that have not been injected [7, 8]. A common misperception is that the glucocorticoid injection only acts locally and has a limited systemic absorption profile. Triamcinolone acetonide (TA), otherwise known by its proprietary name 'Kenalog' and triamcinolone hexacetonide (TH), 'Aristospan' as well as methylprednisolone acetate (MPA), and 'Depo-medrol' typically at doses of 40–80 mg are the most commonly used preparations. Other FDA approved preparations are betamethasone acetate, betamethasone sodium phosphate ('Celestone soluspan'), as well as dexamethasone [9]. A recommendation of up to three glucocorticoid injections per year with a minimum of thirty days between injections has been advocated due to the concern regarding hypothalamic–pituitary–adrenal (HPA)-axis suppression; however, guidelines on the frequency and interval between

injections are currently lacking [10–14]. The majority of studies examining the effects of glucocorticoid joint injections on HPA-axis function have been in adult patients with osteoarthritis and rheumatoid arthritis, in addition these studies have particularly focused on the knee joint which has a large synovial resorption area, therefore, the influence of IAGC and their subsequent effects on HPA-axis are not always seen with other joint/s injected [15–17].

Mechanism of action

The purpose of IAGC is to provide a high synovial fluid concentration and thus act locally at the joint to reduce pain and inflammation through anti-inflammatory and immunosuppressive effects, while at the same time limiting systemic absorption [18]. Synthetic glucocorticoids are lipophilic and possess higher glucocorticoid receptor binding affinity compared to the endogenous form and are thus more potent. They modulate the immune and inflammatory cascade, in particular suppression of pro-inflammatory cytokines including interleukin 1β and IFNα, in addition to mediation of inflammatory enzymes including arachidonic acid and its metabolites [19, 20]. They also have effects on cell function by acting directly on nuclear steroid receptors affecting synthesis of mRNA and proteins [21], in addition to alterations in B-and T-cell function [22]. IAGC are absorbed at a slower rate when injected into a joint in contrast to a comparable oral dose, and are typically retained in the IA cavity for 2–3 weeks after a single injection [23]. However, screening urine as far along as nine months after the most recent steroid injection, has detected the presence of synthetic glucocorticoids in some instances, and demonstrates the potential for a long systemic duration of action even after a single depot injection [24]. As the administration of steroid is localized, it is generally assumed that intra-articular injections tend to avoid the side effects more commonly observed with prolonged oral preparations including adrenal suppression, as well as the effects of hypercortisolism such as bruising, thin skin, hypertension, hyperglycemia, osteoporosis, and increased risk of infection [7, 25].

Pharmacology

After injection into the joint space the glucocorticoid depot acts by modulating pain and inflammatory indices, invariably absorption occurs via the systemic circulation, metabolism occurs in the liver and excretion by the kidney. Glucocorticoid injections are classified into short, intermediate, or long acting preparations. The absorption and duration of action of the injected steroid is inversely related to its solubility; typically injected glucocorticoids are detected in synovial fluid for two days after injection. TH has the least solubility profile and thus longer duration of action, it has no affinity for the mineralocorticoid receptor. TA has the second least soluble profile followed by prednisolone tebutate, MPA, and then hydrocortisone acetate [26].

The effect of systemic absorption of the injected steroid is also dependent on a number of other factors including vascularity of the synovium, chronic renal and liver disease, hypo- or hyperthyroidism as well as obesity, and the use of enzyme inducers, medications that can affect cytochrome p450 (CYP) enzyme inhibition have also been implicated [27–29]. A group at risk appears to be patients with human immuno-deficiency virus (HIV) who take protease inhibitor therapies particularly ritonavir [30]. The absorption profile of intra-articular steroids is different in the juvenile population as they tend to have inflammatory and not degenerative arthropathies; glucocorticoids are absorbed at a greater extent in inflammed joints and in more highly vascularized areas such as the growth plates. In adults, TA and TH typically achieve peak levels eight hours following intra-articular injections of 20 mg and are completely absorbed from the injection site within 2–3 weeks, with no difference observed between resting and mobile patients [31]. The typical dose of MPA at 40 or 80 mg demonstrates peak levels of between 2 and 12 h and complete clearance after five days [32].

Intra-articular glucocorticoid injections and HPA-axis function

Endogenous glucocorticoids are produced in the adrenal cortex and regulated by the HPA-axis as demonstrated in Fig. 1. Corticotropin-releasing hormone (CRH) produced by the hypothalamus stimulates the pituitary gland to produce adrenocorticotropic hormone (ACTH) which signals production of cortisol from the adrenal cortex, cortisol exerts negative feedback on the hypothalamus and pituitary. Exogenous glucocorticoids can suppress the release of ACTH from the pituitary leading to adrenal suppression and cessation of endogenous cortisol production. The extent to which adrenal suppression occurs can depend on the site of the joint injected, frequency, and dose of injection. When the suppressing medication/steroid is reduced or discontinued adrenal insufficiency or steroid withdrawal symptoms can occur. Signs and symptoms of adrenal insufficiency can include fatigue, nausea, and vomiting as well as hypotension. Cushing syndrome can also result from IAGC, although this is not as commonly reported as adrenal suppression in this context. Chronic inflammatory conditions such as rheumatoid arthritis can in

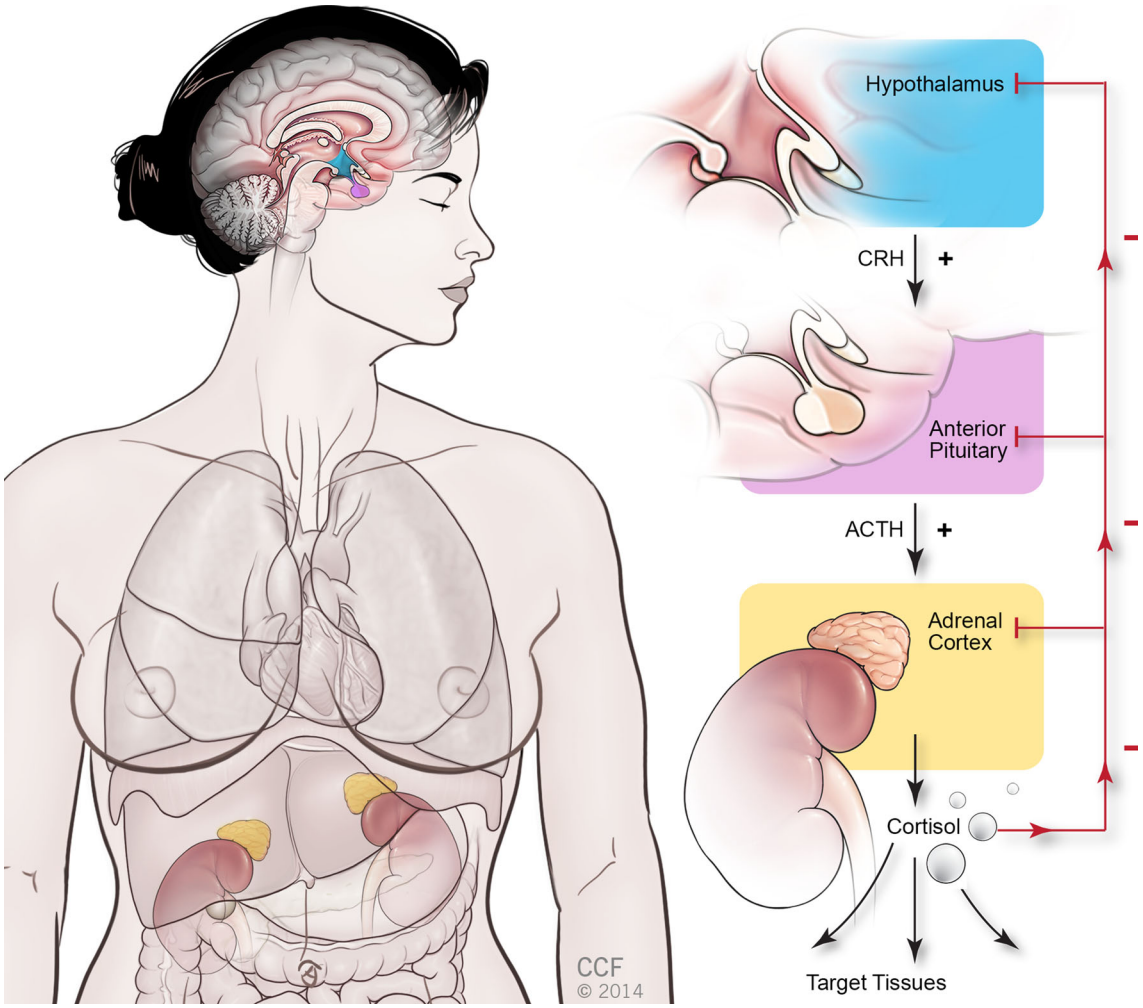

Fig. 1 The hypothalamic–pituitary–adrenal (HPA) axis—CRH produced by the hypothalamus, stimulates the pituitary to produce ACTH. ACTH signals production of cortisol from the adrenal cortex. Cortisol exhibits negative feedback on the hypothalamus and pituitary. Exogenous glucocorticoids can suppress release of ACTH and subsequent cortisol production from the adrenal cortex, leading to adrenal suppression and/or iatrogenic Cushing syndrome

themselves contribute to alterations in HPA-axis function. It is postulated that the HPA-axis plays an important role in counter-regulation of the immune-inflammatory response in rheumatoid arthritis and that deficiencies in HPA-axis function can pre-dispose individuals to severity of disease and its onset [33, 34].

The potential for glucocorticoid injections to cause adrenal suppression and/or iatrogenic Cushing syndrome appears to be under-recognized, and if both occur together confusion can arise. The true incidence of HPA-axis suppression and/or Cushing syndrome after IAGC is largely unknown as most reports are from single cases; adrenal suppression has been more commonly reported in series of patients receiving steroid injections [3, 4, 9, 10, 35]. Adrenal suppression, if not recognized, can result in increased morbidity and mortality. This may be particularly relevant for the juvenile population who may not be aware of the signs and symptoms as well as athletes, and those who participate in extreme sports who are at risk of trauma, infection, and periods of acute stress [11, 36]. A single dose may be sufficient to result in HPA-axis suppression (with or without Cushing syndrome), but the effects on the HPA-axis can be subtle and are not always clinically evident. There is also significant potential for those receiving repeated intra-articular steroid injections to develop adrenal insufficiency after withdrawal of the treatment. There is considerable variation in individual physiology including glucocorticoid receptor polymorphisms and genetic mechanisms which might explain why some patients exhibit changes in HPA-axis function while others do not, in addition sometimes patients may be unaware that the intra-articular injection they have received was actually a steroid [24, 37]. Recovery of HPA-axis to baseline normally takes 1–4 weeks but can be longer

depending on the dose and frequency of injections [7, 31, 38–43]. A single dose of intra-articular TH can suppress the HPA-axis for as long as seven weeks, this is clinically relevant as a patient's requirement to mount an appropriate 'stress response' i.e., production of sufficient endogenous cortisol, in times of stress, acute illness, or for surgical procedures could be impaired, and thus has the potential to precipitate an adrenal crisis. However, we believe that to date no cases of adrenal crisis after intra-articular steroid injections have been reported. Other potential effects of IAGC on the endocrine system include suppression of growth hormone, gonadotropins, sex hormone binding globulin, thyrotropin, and adrenal androgens [44–46].

HPA-axis suppression

Determining if and when HPA-axis suppression occurs after glucocorticoid injection can be difficult, primarily due to the variability of steroid type and cumulative dose. It has been observed that in spite of significant expertise, the injection is often delivered in the peri-articular soft tissues instead of the intra-articular space, especially when performed without imaging guidance. We will outline various methods for the assessment of HPA-axis suppression after intra-articular glucocorticoid injection, including the measurement of serum cortisol/ACTH, 1 and 250 μg ACTH stimulation tests, 24 h urine cortisol and early morning salivary cortisol [7, 36, 38–41, 43]. Less commonly used tests include the overnight metyrapone and insulin tolerance tests which can be expensive and uncomfortable for the patient. In assessing for HPA-axis suppression it is difficult to make direct comparisons between the various studies because of differences in collection protocols, laboratory analyses, injection technique, current joint disease status, and whether ultrasound guidance was used, also timing of assessment in relation to the steroid injection, the follow up time period as well as the confounding effects of inflammation, stress, and pain on cortisol levels.

Decreased twenty four hour urine cortisol (as a result of suppression of endogenous cortisol production) has been shown within 24 h after a knee joint injection of TH 20 mg in patients with rheumatoid arthritis [31]. Animal studies have shown that glucocorticoid receptor activation rapidly suppresses basal and stress induced HPA-axis activity [47]. Serum cortisol has shown a significant but reversible decrease with the earliest change seen within 4 h, and maximum response seen between days 1–2 but in some instances up to 4 days [31, 32, 36, 38, 43]. Increased suppression of serum cortisol levels have been seen when the dose of steroid is split, when higher doses have been used, and when there is more than one joint injected [7, 32, 42, 48]. Normalization of serum cortisol levels usually occurs at 1–2 weeks following the usual doses of MPA, betamethasone, TH usually takes 2–4 weeks, and TA is normally beyond 28 days [7, 9, 49].

The 250 μg ACTH or 'standard/high dose' stimulation test is traditionally used to access HPA-axis function. The dose of ACTH used in the 250 μg ACTH stimulation test is supra-physiologic and, therefore, a potential drawback to this test in assessing secondary adrenal suppression is that it is less sensitive in detecting subtle changes in HPA-axis function that could otherwise only be observed using the 1 μg ACTH stimulation test [50]. In this regard, utilizing the 250 μg ACTH stimulation test, a normal response was seen in ten patients with rheumatoid arthritis at 1–2 weeks after knee joint injections of 20 mg of TH. A further study examining repeated injections of patients receiving MPA at 160 mg/visit showed impaired response to the standard ACTH stimulation test 5–6 weeks after the most recent steroid injection [40]. The 1 μg ACTH or 'low dose' stimulation test has been proposed as having better sensitivity than the 250 μg ACTH or 'standard/high dose' stimulation test in evaluating the pituitary−adrenal axis in non-stressed patients suspected of having secondary adrenal insufficiency. There are few studies assessing HPA-axis function after intra-articular glucocorticoid injection in which the 1 μg ACTH stimulation test was used [7, 36, 40, 43, 51–53]. The first such study was in patients with osteoarthritis and inflammatory arthropathies receiving a single dose between 20 and 160 mg of MPA into various joints, the study demonstrated short term (up to 2 weeks) adrenal suppression. HPA-axis suppression was more common in those who received a higher dose and who had an inflammatory arthropathy [43]. More recent studies assessing HPA-axis function with the 1 μg ACTH stimulation test after joint injection of MPA 80 mg ($n = 20$) by Habib et al., in patients with osteoarthritis of the knee, showed a transient adrenal suppression in about a quarter of the patients which occurred between week 2 and week 4. Interestingly in this study, one patient had adrenal suppression which recurred after 2 weeks suggesting that the systemic absorption of corticosteroids from the knee joint can be variable over time [51]. In a further study, also conducted by Habib and colleagues, simultaneous bilateral knee injections of MPA 80 mg in patients with osteoarthritis, showed that adrenal suppression was seen nearly 2 months after injections in 10 % of the patients [53]. However, a study on the effects of betamethasone at 6 mg ($n = 20$) in patients with knee osteoarthritis did not demonstrate HPA-axis suppression [52], betamethasone at 7 mg ($n = 3$) using the 1 μg ACTH stimulation test showed suppressed serum cortisol levels 30 min after injection [36]. This is relevant as advice with regard to supplemental steroid cover during periods of illness or forthcoming surgery could possibly be tailored to the specific dose and type of steroid injection given.

Morning salivary cortisol reflects the basal secretion of cortisol, it is best performed either immediately after awakening, or 2 h after awakening as the cortisol awakening response (CAR) increases cortisol concentrations during the 1st hour of awakening [54]. Cortisol exhibits circadian rhythm and is also affected by age, stress, and weight as well as seasonal differences. Cortisol peaks in the morning and is lowest around midnight. Morning salivary cortisol is a potentially useful indicator of adrenal suppression and can assess changes in HPA-axis function [55, 56]. The measurement of cortisol in saliva offers various advantages, it can be performed in a low stress environment at home, is simple to collect, and by its nature less invasive; it also performs better than plasma cortisol when there are discordant results which are related to changes in cortisol binding globulin (CBG) [57]. The cortisol concentration in saliva is independent of secretion rate and saliva volume and correlates well with total and free plasma cortisol levels. Cortisol in saliva is stable at room temperature for at least a week and can be mailed to the laboratory for analysis [58, 59]. The use of liquid chromatography-tandem mass spectrometry (LC–MS/MS) to measure salivary cortisol, avoids the problem of cross reactivity from synthetic steroids, or other interfering medications [60, 61]. Salivary cortisol determinations have been used during the corticotropin stimulation test in detecting hypoadrenal states. Although single salivary cortisol measurements do not confirm adrenal insufficiency without the use of the corticotropin stimulation testing they are nonetheless useful diagnostic predictors of HPA-axis function [62].

To date, only two studies have been performed utilizing salivary cortisol measurements to assess for HPA-axis suppression after glucocorticoid injection. In the first study, salivary cortisol levels were suppressed for a median of 16 days in 22 children with chronic arthritis who received an intra-articular injection of TH 20–60 mg (mostly administered in the knee joint) [39]. No patients in this study developed Cushing syndrome, and normalization of salivary cortisol levels was seen before 28 days in the majority of patients. More recently, a pilot study of salivary cortisol concentrations (in 8 subjects) by Chon et al., demonstrated that after a single glucocorticoid injection of triamcinolone acetate 40 mg, all subjects demonstrated HPA-axis suppression for 19.9 $\pm$ 6.8 days [63], although the injection administered in this study was epidural and not intra-articular. This study also found that baseline salivary cortisol did not correlate with the period of HPA-axis suppression.

Cushing syndrome

The clinical features of Cushing syndrome can include moon shaped face, centripetal adiposity, supraclavicular fat pad accumulation, bruising, striae, and proximal myopathy but can be subclinical or overlap with other medical conditions. There is an increased risk of developing diabetes, hypertension, and a predisposition to opportunistic infections [64]. Cushing syndrome is typically demonstrated by elevations in serum or urine cortisol, sequential midnight salivary cortisol as well as dexamethasone suppression testing [65, 66]. After the administration of intra-articular glucocorticoid it is important to note, however, that hypercortisolemia is generally not observed, as even though the patient can appear cushingoid, HPA-axis suppression will result in low cortisol levels. This can cause confusion and result in the patient being erroneously diagnosed as having adrenal insufficiency or labeled as having 'Addison's' based on these findings. Although their use is widespread, the true incidence of iatrogenic Cushing syndrome occurring in the context of intra-articular glucocorticoid injection is unknown. Various cases of Cushing syndrome occurring after intra-articular injections have been reported, with florid Cushing syndrome present even after a single injection. However, it is more common after repeated injections and associated with HPA-axis suppression or in patients who are taking other medications that can alter the pharmacodynamics of glucocorticoids and potentiate their effects [24, 32, 36, 39, 41, 42, 67–75]. A retrospective study in children with juvenile idiopathic arthritis by Gondwe et al. demonstrated that 5 % developed a Cushingoid appearance after injection with the less soluble preparation TA, this was not seen in the children who received TH [69]. The clinical effects of Cushing syndrome can remain for 6 months [68, 69], and even up to 12 months in some cases [39].

Conclusions

IAGC can result in a sharp decline in cortisol to low or undetectable levels within the first days after administration. HPA-axis suppression can typically last up to four weeks after a single injection, although recovery of HPA-axis to baseline can take longer depending on the dose and frequency of injections. Considering the widespread use of intra-articular steroid injections and their clinical effectiveness, physicians who administer these need to be aware of the potential risks of HPA-axis suppression and/or iatrogenic Cushing syndrome. Guidelines for the frequency of dosing in addition to defined time intervals between each injection should be clear. High risk populations have the potential to be screened for adrenal suppression and could include those who receive high doses and multiple injections particularly within the previous six months. Patients who are undergoing scheduled surgery and who have received an intra-articular glucocorticoid injection within

the previous month could potentially undergo testing for adrenal suppression, and if present supplemented with oral steroids as a bridging measure. The potential use of the measurement of morning salivary cortisol in identifying patients who have subtle changes in HPA-axis function remains to be seen.

Acknowledgments We would like to thank Amanda Mendelsohn for providing the illustration from the Center for Medical Art and Photography, Cleveland Clinic Foundation.

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