A novel approach to improve detection of glucocorticoid doping in sport with new guidance for physicians prescribing for athletes

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ABSTRACT

The systemic effect of glucocorticoids (GCs) following injectable routes of administration presents a potential risk to both improving performance and causing harm to health in athletes. This review evaluates the current GC antidoping regulations defined by the World Anti-Doping Agency and presents a novel approach for defining permitted and prohibited use of glucocorticoids in sport based on the pharmacological potential for performance enhancement (PE) and risk of adverse effects on health. Known performance-enhancing doses of glucocorticoids are expressed in terms of cortisol-equivalent doses and thereby the dose associated with a high potential for PE for any GC and route of administration can be derived. Consequently, revised and substance-specific laboratory reporting values are presented to better distinguish between prohibited and permitted use in sport. In addition, washout periods are presented to enable clinicians to prescribe glucocorticoids safely and to avoid the risk of athletes testing positive for a doping test.

AIMS

The aim of this review is to analyse the current glucocorticoid (GC) antidoping regulations defined by the World Anti-Doping Agency (WADA) and to better define the prohibited or permitted routes of administration in sport based on strong scientific and medical rationale. The approach aims to reduce the risk of misuse and abuse of this class of substances by athletes and present a practical framework to allow for legitimate medical use.

INTRODUCTION

GCs have been prohibited by some routes of administration since 1985; first by the International Olympic Committee, and from 2004 by WADA under the World Anti-Doping Code. According to this Code, two out of three criteria must be fulfilled to consider the inclusion of a substance in the Prohibited List. These criteria include: (1) That the substance has the *potential* to enhance performance; (2) Its use represents an actual or *potential* health risk; (3) Its use violates the spirit of sport. When assessing a substance for the Prohibited List, the most challenging criteria to determine with any robust evidence-based approach is whether a substance actually improves performance. For many substances on the List, this is rarely demonstrated by double-blind, peer-reviewed, randomised clinical trials in athletes as this is often not permitted for safety or ethical reasons. These limitations certainly also apply to GCs, and currently there is only a small number of studies in athletes that provide an indication that these drugs may improve performance.

On this premise, and as with other substances on the Prohibited List, the concept of *potential* performance enhancement (PE) is key in the assessment of whether a drug is considered prohibited in sport; 'potential to enhance performance' is the current standing assumption that has applied to this class of medications since their inclusion on the Prohibited List in 1985, although with even less evidence then for PE than is available today. The work presented here acknowledges these limitations and refers to the concept of *potential* PE in line with the Code as the level of risk this class of drugs presents to having a meaningful physiological effect on athletic performance.

In the current International Standard of the Prohibited Substances and Methods (the Prohibited List), GCs are prohibited in-competition when administered by oral, intravenous, intramuscular or rectal routes, but are allowed by other routes of administration, where a local, non-systemic effect is required, including topical application and local injections. The ability for sports drug testing to differentiate between permitted and prohibited routes of administration through laboratory methods was needed in order to distinguish between doping and permitted and legitimate therapeutic purposes.

In 2004, a urinary concentration reporting level (RL) of 30 ng/mL was initially established as a temporary RL, based on the best but limited evidence at the time, to differentiate prohibited and permitted use through analysis of urine collected from athletes at the time of doping control. For the last 17 years until now, this temporary 30 ng/mL RL has been applied to every type of GC drug and every prohibited route of administration as a possible indicator of doping. However, since its introduction, it has been acknowledged by WADA that this single RL lacks the required specificity to ever be an accurate indicator of potential or actual doping in all cases. What was needed was a model of laboratory GC detection that took into account the vast differences in pharmacology, metabolism and excretion rates that occur with different GC compounds and when administered at different doses by a diverse range of administration routes. In addition, the most relevant marker in the urine

to best determine permitted or prohibited use needed to be specifically defined for each GC, whether that be the parent compound, or a metabolite of the drug.

After the initial introduction of the temporary RL, WADA proceeded to sponsor a number of excretion studies which aimed to provide the evidence needed to improve the specificity of the RLs for individual drugs and the various routes of administration.[1] As more data became available through these studies, it emerged that when GCs were administered by local injections in doses used for legitimate medical use, the concentrations found in the urine could reach levels similar to those of prohibited routes, indicating systemic distribution of the drug and presenting a real risk of the athlete sample being reported as an adverse analytical finding (AAF). These studies also reinforced the fact that a single RL was not suitable for all GCs and all routes of administration. The initial results were corroborated and expanded on by numerous studies published thereafter which further evidenced the systemic distribution by measuring not only urinary but also plasma concentrations of the drugs.[1–20] As a consequence, the status of local injections in the WADA Prohibited List needed to be re-evaluated.[5–7 13 19 20]

The need for reliable and practical guidance for physicians treating athletes with GCs has also been recognised by WADA since the first inclusion of GCs on the Prohibited List. When treating athletes with GCs, sports physicians are often faced with complex decisions in order to ensure the athlete does not test positive after being administered these drugs for therapeutic use. Since GCs are permitted out of competition without restrictions, physicians are often left with the difficult task of attempting to estimate the time of elimination in order for the athlete to avoid an AAF during the next in-competition period, and to assess whether a Therapeutic Use Exemption is required if the drug might still be detectable at levels above 30 ng/mL at the time of competition. With recent studies showing the vast differences in elimination times between different GCs,[1–10 13 15 16 18] the extreme difficulty for physicians to make informed treatment decisions in order to comply with the antidoping rules was evident. There was a pressing need for the establishment of clear and practical guidance on washout periods for individual drugs and their routes to empower physicians to be able to use these drugs in the athletes they treat, with the confidence to know that they are complying with the antidoping rules.

Another limitation of the current approach was that local injections of GCs can produce urinary concentrations similar to those of prohibited routes due to systemic distribution of the drug following administration. For example, permitted intra-articular and periarticular administrations of triamcinolone acetonide (TA) and betamethasone (BET) can result in similar urine and plasma concentrations as after prohibited intramuscular administration of the drug,[1 5 6 11 13 15 19] with no differences in metabolites between these routes,[6 13] making differentiation by laboratory urinalysis methods currently impossible. Side effects observed after intra-articular administration also indicate that systemic effects are possible after local injection.[21]

To undertake this evaluation WADA convened a number of expert groups to review the published literature in the field and incorporate the pertinent published and unpublished results to elaborate a novel approach that differentiates doping and acceptable medical use in sport.[22] Through this review, washout periods were also established to support the use of GCs medically, aimed to avoid risk of a positive doping test through legitimate medical use.

Therapeutic use of GCs in sports

GCs are widely used in sports medicine, mainly to treat musculoskeletal injuries and asthma. GCs administered by local injection can be an important and effective option in the treatment plan of a number of musculoskeletal conditions commonly encountered in sports medicine. For example, intra-articular GC injections are used to treat adhesive capsulitis, where it has been shown that a single GC injection provides faster pain relief and earlier improvement of shoulder function and motion compared with oral NSAIDs, and that they are effective for both short-term and long-term pain relief.[23 24] Intra-articular GC injections are also commonly used for the treatment of bursitis in athletes.

Local GC injections also provide short-term pain relief and improvement in function in subacromial impingement syndrome, a condition commonly observed in overhead sports, where athletes perform frequent and quick upper limb actions causing alterations of scapular kinematics.[25]

Health risks associated with GC use

The proven or potential risk to health of the athlete is one of three criteria established by the Code to assess when determining whether a substance is prohibited. Despite their excellent therapeutic effects, GCs have a relatively high potential for triggering adverse effects, particularly when administered systemically.[26] The potential for harmful effects ultimately depends on the duration of treatment, dose, route of administration and patient-specific factors.[27 28] For these reasons, if athletes are taking GCs with the intention to improve performance, shorter periods of administration are likely to be preferred due to a lesser incidence of adverse effects such as muscle wasting, and without the need for tapering the dose at the end of the course.[29 30]

When administered as a local injection by the intra-articular or periarticular route, systemic absorption occurs to some extent due to the high vascularity of the joint and diffusion of the drug into the surrounding tissue after injection. This can lead to adverse effects including flushing of the face, blood glucose increase in diabetics, increase in blood pressure or palpitations, transient immunosuppression, and, rarely, water retention and intermittent gynaecological bleeding.

Locally occurring adverse effects after intra-articular GC injections are rare but may include reactive synovitis, local irritation and postinjection pain, septic arthritis, cutaneous depigmentation, tendinopathy and avascular necrosis.[31–34] Adverse effects following local infiltrations into periarticular structures, tendon sheaths or bursae are also rare, but may include atrophy of the subcutaneous tissue and cutaneous depigmentation.

Mechanism of the performance-enhancing effect of GCs

During exercise, there is a strong stimulation of the hypothalamic-pituitary-adrenal (HPA) axis, which results in a rise in baseline blood cortisol concentration, according to the intensity and the duration of the activity.[35 36] Administration of oral GCs has been shown to inhibit the HPA axis, resulting in a strong decrease in baseline blood cortisol concentration and an inhibition of exercise-induced cortisol secretion.[37–42] Similar effects were not observed after administration via the inhaled route.[43 44]

The response of cortisol to endurance exercise results from both the central and peripheral actions of GCs by direct and/or indirect pathways, which can lead to effects including euphoria and decrease in fatigue. In addition, GCs increase energy mobilisation via proteolysis and gluconeogenesis while maintaining the blood glucose level, and have a marked effect on reducing inflammation.[45] Any ergogenic effect produced by GCs probably

includes a local muscular effect of the drug rather than any direct link to the anti-inflammatory response, but the complexity of the central and peripheral response after GC administration makes the exact causal effects of PE difficult to identify.

Studies of GC effects on performance

A number of recent studies show that the impact of GCs on athletic performance depends on the intensity and duration of exercise, the dose and duration of treatment and the route of administration.[38–44 46–49] Results of all known studies looking at the effects of GCs on exercise performance are presented in table 1. Only the inhaled and oral routes of administration for GCs have been studied to assess their effect on PE, with evidence of PE only after oral administration.

A significant performance-enhancing effect has been demonstrated after administration of oral prednisolone (PRED) and prednisone (PSONE) at 50–60 mg/day over a 7-day period, respectively, in female and male recreationally trained subjects, during prolonged endurance exercise lasting more than 40 min.[38–40] A small improvement in performance was also observed after administration of PSONE 60 mg/day over a 7-day period during repeated exercise leading to muscle fatigue and exhaustion.[48]

However, no studies have demonstrated an improvement in performance following acute systemic GC administration (such as a single dose of 20 mg of PRED) at any intensity of exercise,[41 42] or which examine the effect on performance by combining different GCs by any route of administration. In

Table 1 Effect of GCs on exercise performance

GC molecule (*references*)	Study place (L, F)	Gender (M, F)	Type of exercise	Route (INH, PO)	Mode (A, ST)	Dose and environment	PE effects
Budesonide							
Kuipers et al[43]	L	M	VO_2 max (maximal graded exercise)	INH	ST (4 weeks)	800 µg/day	= (Watt) *GC: 375±36 vs Pla: 376±25*
Hostrup et al[44]	L	M	90% peak power output until exhaustion	INH	ST (2 weeks)	1.6 mg/day + acute terbutaline	= (second) *Post-GC: 214 vs pre-GC : 203*
Dexamethasone							
Marquet et al[37]	L	M	VO_2 max (maximal graded exercise)	PO	ST (4.5 days)	1–3 mg/day	= (VO_2 max) *values not provided*
Nordsborg et al[47]	L	M	Knee extensor exercise until exhaustion at several intensities	PO	ST (5 days)	4 mg/day	High intensity = (second) *GC: 106±10 vs Pla: 108±9* Low intensity: **+ (second)** *GC: 393±50 vs Pla: 294±41*
Casuso et al[46]	L F F	M	Knee extensor exercise until exhaustion 20 m shuttle run Yo-yo (maximal graded exercise) 30 m sprint test	PO	ST (5 days)	4 mg/day	**+ (second)** *GC: 333±30 vs Pla: 264±21* **+ (minute)** *GC:16.1±2.9 vs Pla: 13.5±2.6* = (second) *GC: 4.5±0.1 vs Pla :4.6±0.1*
Prednisolone							
Arlettaz et al[41]	L	M	80%–85% VO_2 max until exhaustion	PO	A	20 mg	= (minute) *GC: 22.0±2.5 vs Pla: 21.5±2.9*
Arlettaz et al[42]	L	M	70%–75% VO_2 max until exhaustion	PO	A	20 mg	= (minute) *GC : 55.9±5.2 vs Pla: 48.8±2.9*
Arlettaz et al[38]	L	M	70%–75% VO_2 max until exhaustion	PO	ST (7 days)	60 mg/day	**+ (minute)** *GC: 74.5±9.5 vs Pla: 46.1±3.3*
Collomp et al[40]	L	M	70%–75% VO_2 max until exhaustion	PO	ST (7 days)	60 mg/day + 2 hours training/day	**+ (minute)** *GC:107.0±20.7 vs Pla: 64.0±9.1*
Tacey et al[49]	L	M	4 × 4 min cycling bouts at 90%–95% peak heart rate	PO	A	20 mg	- (kjoule) *GC : 206 vs Pla: 217 (–5%)*
Prednisone							
Le Panse et al[39]	L	F	70%–75% VO_2 max until exhaustion	PO	ST (7 days)	50 mg/day	**+ (minute)** *GC: 66.4±8.4 vs Pla: 47.9±6.7*
Zorgati et al[48]	L	M	Hopping until exhaustion	PO	ST (7 days)	60 mg/day	**+ (peak force)**, = (second) *GC: 123.1±29.5 vs Pla: 119.9±24.7*

Bold indicates there was a positive response in PE (performance enhancement) to emphasise the finding.
=, no change in performance.
+, significant performance improvement expressed in mean±sem.

A, acute; F, field; F, female; GC, glucocorticoid; INH, inhalation; L, laboratory; M, male; PE, performance enhancement; PO, oral; ST, short-term.

addition, an impaired cycling performance has been demonstrated 12 hours after acute PRED administration, suggesting that any ergogenic effect obtained in the 2–3 hours after initial administration may be reversed with GC elimination.[49]

A significant PE effect has been confirmed after oral dexamethasone (DEX) administration of 4 mg/day over a 5-day period during knee extensor and maximal graded exercises,[46 47] and a small improvement in performance observed with the same doses during repeated exercise leading to muscle fatigue and exhaustion.[47] However, no PE was observed at lower doses of oral DEX of 1–3 mg/day over 4.5 days.[46 47]

No PE has been demonstrated after inhaled GCs have been administered. Although only inhaled budesonide has been studied, this finding is expected to apply to all inhaled GCs at recommended therapeutic doses due to their relatively low systemic exposure compared with oral administration.[43 44]

These few studies demonstrate that under certain conditions and routes of administration GCs can enhance sport performance, while under other conditions no PE effect could be measured. It is conceivable that in certain circumstances, other GCs in other doses or other sports could also potentially influence performance in a positive way. This concept of *potential* PE is the basis for defining the status of these drugs on the Prohibited List.

Novel approach for defining permitted and prohibited GC use

The naturally occurring GC hormones and their synthetic analogues possess a wide range of potencies and pharmacokinetic properties.[50] The body produces a daily output of endogenous GC (cortisol), typically 18–22 mg/day[51] and hence this amount of GC should be regarded as the normal physiological baseline for cortisol levels in the body. The upper end of this basal physiological range can be defined as 26.4 mg/day which is 20% above the upper typical output of 22 mg/day. The supraphysiological threshold can be defined as >32 mg/day which is >20% above the 26.4 mg/day upper basal physiological range. Although there is no reference range for daily cortisol production, these ranges are similar to that seen for morning serum cortisol levels. The 20% margins allow for additional variability recognising that less than a 20% difference in exposure is not usually considered clinically relevant compared with expected biological variability.

Administering GC drugs can result in a total GC exposure (exogenous + endogenous) that exceeds the supraphysiological threshold for daily physiological GC exposure when expressed in cortisol equivalents. Based on the studies presented above it is generally accepted that GCs have PE potential, but it is not known exactly at what level total GC exposure is required to elicit a meaningful PE effect as there are insufficient data to construct a dose-response relationship. However, like other pharmacological actions of GCs, PE is not expected to be an all-or-nothing effect but rather gradually increase with increasing GC exposure, following a non-linear sigmoid dose-response curve. On this basis, PE, even though initially very small, may occur once the supraphysiological threshold for daily physiological GC exposure is exceeded. Whereas GC drug use that does not exceed the supraphysiological threshold of 32 mg/day, in cortisol equivalents, can reasonably be regarded as not having significant PE potential. This gradual onset of effect is represented by the gradual shading from green to red in figure 1.

For any exogenous GC dose or route of administration, where the estimated systemic exposure exceeds these limits, there is an increased risk of inducing PE effects (figures 1 and 2). Using this approach, two categories were defined:

1. Low-risk GC use

Low-risk use is defined as a dose of exogenous GC (cortisol equivalent dose ≤5.28 mg/day) that when added to normal physiological daily GC exposure (26.4 mg/day) results in a total exposure (endogenous + exogenous) that does not reach supraphysiological levels (cortisol equivalent dose >32 mg/day) (figure 1). In terms of adverse effects on health the extent of HPA-axis suppression is expected to result in <50% cortisol suppression.

2. High-risk GC use

High-risk use is defined as a dose of exogenous GC that is equivalent to or greater than a dose demonstrated to be performance enhancing (eg, DEX 4 mg, equivalent to 32.6 mg cortisol) (figure 1). This is also ≈6 times the 5.28 mg/day acceptable dose defined above and results in a total GC exposure (26.4 mg endogenous + 32.6 mg exogenous) of ≈60 mg/day. In terms of adverse effects on health the extent of HPA-axis suppression is expected to result in ≥80%–90% cortisol suppression.

Between these two categories, there is an intermediate risk of adverse health effects but there are insufficient data to experimentally derive the potential for PE. However, the level of risk is anticipated to be on a continuous dose-response scale, starting with little or no PE effects rising to a high and known PE risk. Despite these limitations, this framework still allows clear guidance on acceptable low-risk use versus unacceptable high-risk use since many of the widely used GC doses and formulations fall into one of these categories.

Applying the approach to GC doses with known performance-enhancing effects

Clinical data confirming PE are only available for 4 mg oral DEX, and 50 mg and 60 mg oral PRED when given over 5–7 days, based on published data as described above.[38–40 46 47] Using the methodology described in this article (see below) the corresponding cortisol equivalent doses were estimated to correspond to 32.6 mg, 80 mg and 96 mg, respectively (figure 1), all of which exceed the 32 mg/day threshold set to determine low-risk versus high-risk use of a GC drug in sport. These results validate that the new framework to determine acceptable or unacceptable GC use in sport applies appropriately to drugs and doses with known PE effects and corroborates that their use is high risk and therefore unacceptable in sport.

Methodology for determining cortisol equivalent doses

For any GC the dose can be expressed in terms of a cortisol-equivalent dose and thereby the dose which exceeds 32 mg/day total cortisol-equivalent exposure for any GC and route of administration can be determined. This approach was applied to define the GC doses and routes of administration that should be prohibited, or not prohibited in sport.

To make this assessment it is first necessary to convert the administered exogenous GC dose into a cortisol-equivalent dose (figure 1). This was calculated as follows:[52]

Equation 1: Cortisol equivalent dose = CL_{cort} . (P_r . ((F_{GC} . $Dose_{GC}$) / CL_{GC}))),

where, F=the bioavailability of the systemically absorbed fraction of the dose for the route of delivery and formulation; P_r=relative GC potency in terms of the GC-receptor binding or GC activity (cortisol=1); CL=the rate at which active GC is

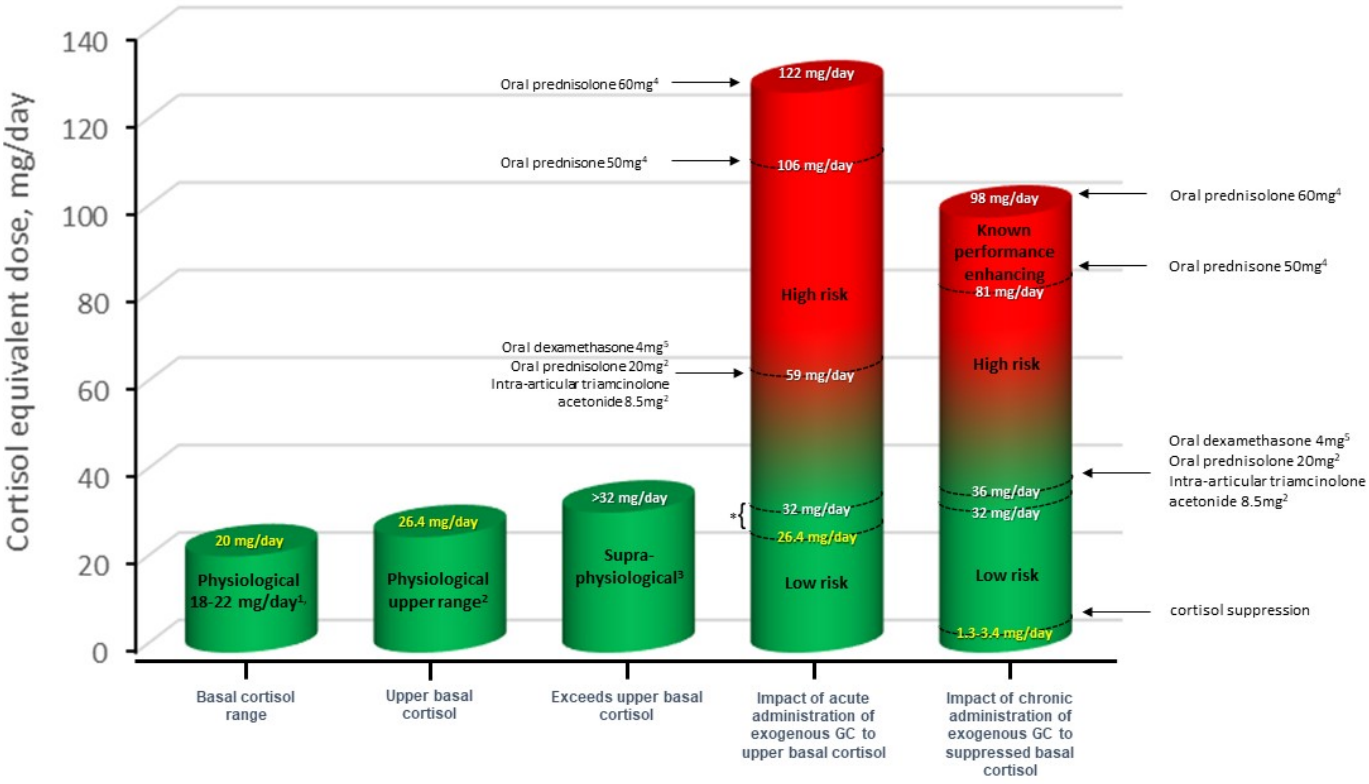

Figure 1 Physiological, supraphysiological and GC exposure with low risk and high risk of performance-enhancing effects in mg/day shown in cortisol equivalents. Column 1 shows the physiologically normal basal cortisol daily production rate typically 18–22 mg/day. Column 2 shows the upper end of basal physiological range defined as 26.4 mg/day which is 20% above 22 mg/day. Column 3 depicts the supraphysiological range of >32 mg/day which is defined as >20% above the 26.4 mg/day upper basal physiological range; exceeding this represents a continuum for increasing the risk for performance-enhancing and adverse health effects as shown in columns 4 and 5. The 20% margins (indicated with an asterix * in column 4) allow for additional variability recognising that a 20% difference in exposure is not usually clinically relevant compared with biological response variability. Column 4 shows the impact of acute administration of exogenous GC to upper basal cortisol (26.4 mg/day) exceeding the supraphysiological range of >32 mg/day in the acute administration scenario (eg, oral dexamethasone 0.65 mg, oral prednisolone 3.3 mg, intra-articular triamcinolone acetonide 8.5 mg). Column 5 shows the impact of the same exogenous GC doses shown in column 4 but in a chronic administration scenario where basal endogenous GC levels are suppressed by chronic administration of high doses of exogenous GC. GC, glucocorticoid.

cleared from the body via metabolism and/or excretion; CL_{cort} is the plasma clearance of cortisol (L/h); and CL_{GC} is the plasma clearance of the exogenous GC (L/h).[50]

These parameters are mostly available for commonly used GC formulations and routes of administration.[50 52–77] Although the bioavailability for some less common topical delivery routes (eg, skin, eye, ear) and older molecules is not known, this was not a significant issue since even when hypothesising 100% bioavailability the upper physiological exposure threshold was not exceeded within the approved therapeutic dose ranges (figure 2). Similarly, for parenteral injections other than intravenous, for example, intradermal, periarticular and intralesional, bioavailability was assumed to be 100%.

For intra-articular injections the situation is more complex since they can be absorbed slowly from the injection site. Although 100% bioavailability may eventually be achieved, we estimated the fraction absorbed in each 24-hour period postdose from the absorption half-life which is known in most cases. A sensitivity analysis was also performed using different bioavailability scenarios (figure 2).

The approved dose ranges for all the commonly used GC drugs, formulations and routes of administration[78] were converted into cortisol equivalents using equation 1. These were compared with the cortisol-equivalent doses corresponding to normal and supraphysiological GC thresholds (figure 1). These values are not based on circulating cortisol concentrations, which can vary widely throughout the day due to the pulsatile nature of cortisol secretion, but nevertheless they still reflect the variability seen in morning serum cortisol concentrations (5–25 µg/dL) that are used in clinical chemistry.

Higher or lower cortisol production or secretion rates and circulating concentrations can occur during stress, disease or exercise. Consequently, some athletes may have elevated circulating cortisol levels during exercise,[79 80] but there is no evidence that this alters the daily cortisol production rate and therefore was not considered relevant to the argument for using a single supraphysiological threshold of >32 mg/day for total GC exposure (endogenous + exogenous). This is a conservative position, because if an athlete generates increased cortisol levels during extreme exercise and has higher endogenous GC exposure, taking exogenous GC will only result in a higher risk of PE.

Consideration of cortisol suppression

We also considered that cortisol suppression can occur following exogenous GC administration. With acute and single doses, this is not important because although the body immediately starts to reduce cortisol production/secretion the amount of cortisol

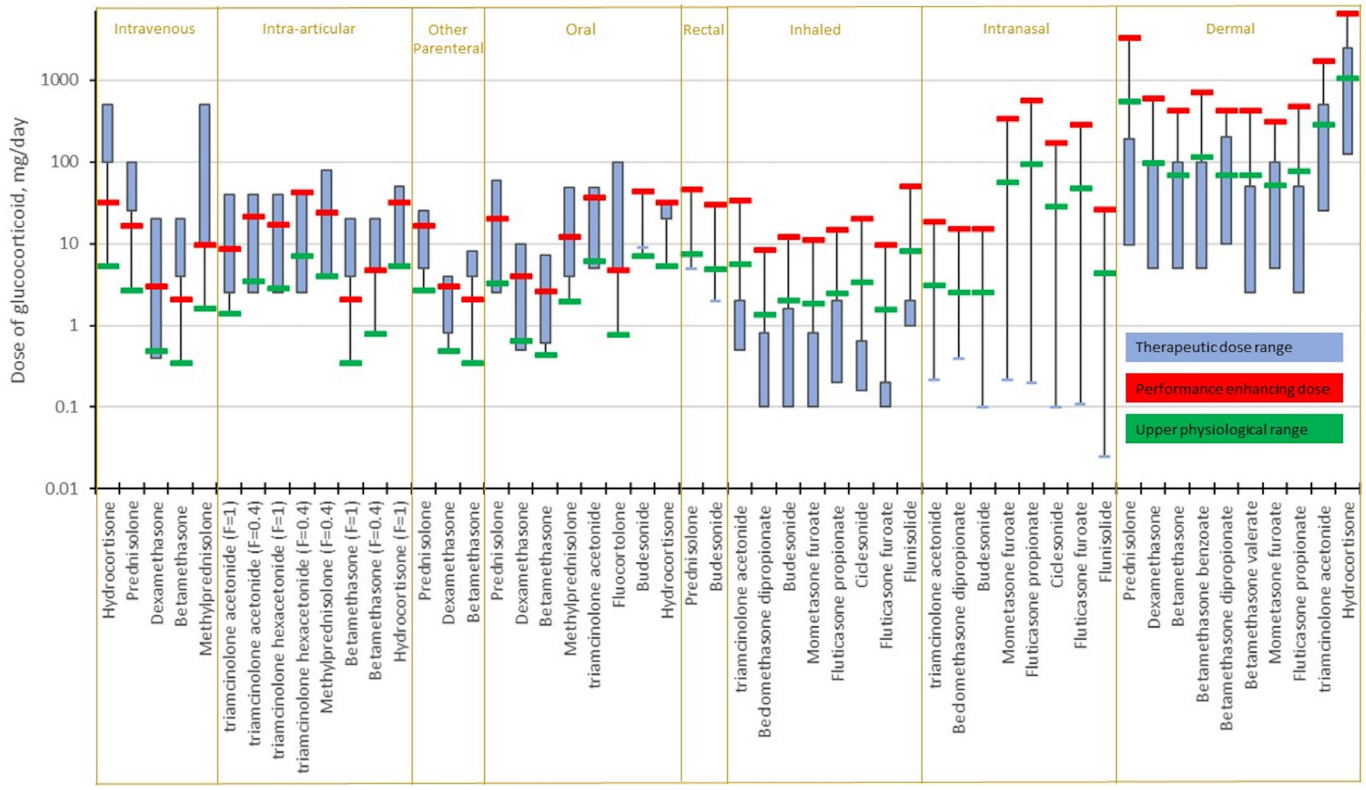

Figure 2 Relationship between approved therapeutic dose ranges (blue bars) for various GC drugs and their corresponding doses estimated to either produce systemic exposures above the upper physiological range for GC exposure (green bars) or estimated to have a high risk of performance-enhancing effects (red bars) during acute administration.* *For the intra-articular route of administration different extents of systemic absorption in 24 hours were assumed where F is the fraction of the dose absorbed. GC, glucocorticoid.

already present in the body is not immediately removed and hence is added to exogenous dose (figure 2). With chronic administration cortisol suppression is relevant, but not in the range that has a high risk of PE because the contribution of the endogenous cortisol to the total GC exposure is very small (figure 2). For example, chronic administration of 20 mg/day PRED or 4 mg/day of DEX results in 80%–90% cortisol suppression and the 32 mg/day total GC threshold is still exceeded with 20 mg/day PRED and 4 mg/day DEX despite cortisol suppression (figure 2).

Results of the application of the new methodology

Oral and injectable routes (eg, intravenous, intramuscular, subcutaneous, intra-articular) when used at their approved doses are likely to produce total GC exposures in excess of 32 mg/day except at the lowest doses that are seldom used clinically (figure 1). For example, doses of oral PRED (3.3 mg) and oral DEX (0.65 mg) and intra-articular triamcinolone acetonide (TA, 1.4 mg) are estimated to produce total GC exposures at the threshold of 32 mg/day (figure 2).

However, none of the inhaled, intranasal, dermal or other topical GCs, when used at their maximum licensed approved doses, would exceed the 32 mg/day threshold.

Using this new methodology, the dose that corresponds with unacceptable use in sport was determined for most routes of known licensed GCs. This formed the basis by which the revised specific RLs were set, which subsequently guided the establishment of washout periods.

Establishing improved urinary RLs for GC use

Up to now, a general urinary RL of 30 ng/mL was used to differentiate between permitted and prohibited administrations of all GCs. However, different studies have shown the need to establish compound-specific RLs given the diversity of administration routes and doses, as well as pharmacokinetic and pharmacodynamic properties between the different GCs.[1–20]

The ideal RL should not produce AAFs after permitted administrations or negative results after prohibited use. When testing athletes, the potential for AAFs after permitted administrations for therapeutic purposes have to be precluded, therefore the RL must be based on concentrations obtained after permitted administrations.

The compound-specific RL needs to be based on urinary concentrations obtained after administration studies and so the RLs for GCs for which these data are available were reviewed. All relevant studies are presented in table 2.[1–20] For other GCs, with limited or no data available, the RL has been maintained at 30 ng/mL until further data are generated in the future.

In most of the studies, concentrations obtained after enzymatic hydrolysis (free and glucuronide fractions) were described. The distribution of concentrations and the maximum concentrations in urine (Cmax) after permitted administrations, obtained after the maximum daily doses recommended by manufacturers, were the most important data taken into consideration to define the compound-specific RLs. When studies at those doses were not available or the number of volunteers was low, a conservative value was applied to the highest individual urinary concentration. The proposed RLs are summarised in table 3.

Table 2 Administration studies of GCs reviewed to establish the compound-specific reporting levels and washout periods†

Ref.	Glucocorticoid	Administration protocol				MF	Results in urine samples			
	Reference	GC	Route	Dose, administration	Volunteers		Marker	Cmean±sd (ng/ml)	Cmax (ng/ml)	Detection time
	Budesonide (BUD)									
2	Matabosch *et al*[2]	BUD	Inhaled	400 ug × 3 days	8 M	F+G	6β-OHBUD	3.0±2.1	10.6	none
3	Coll *et al*[3]	BUD	Inhaled	800 ug × 3 days	4 M + 4 F	F+G	6β-OHBUD	5.8±6.5	35.4	none
3	Coll *et al*[3]	BUD	Inhaled	1600 ug × 3 days	4 M	F+G	6β-OHBUD	9.0±8.7	31.0	none
3	Coll *et al*[3]	BUD	Intranasal	256 ug × 3 days	4 M + 4 F	F+G	6β-OHBUD	1.3±1.9	7.1	none
2.3	Matabosch *et al*; Coll *et al*[2 3]	BUD	Oral	3 mg	10 M + 8 F	F+G	6β-OHBUD			24 hours
4	Athanasiadou *et al*[4]	BUD	Oral	9 mg (different hydration protocols)	7 M × 3	F+G	6β-OHBUD			48 hours
	Triamcinolone acetonide (TA) and hexacetonide (THA)									
5.6	Matabosch *et al*; Coll *et al*[5 6]	TA	Intranasal	220 ug × 3 days	8 M + 6 F	F+G	TA	0.8±0.9	3.6	none
11	Avois *et al*	TA	Intranasal	220 ug	5	F+G	TA	na*	7.0	none
11	Avois *et al*	TA	Intranasal	220 ug × 5 days	6	F+G	TA	na	7.0	none
5	Matabosch *et al*[5]	TA	Dermatological	10 mg × 5 days	8 M	F+G	TA	0.4±0.4	1.8	none
12	Wicka *et al*[12]	TA	Dermatological	4.4 mg once a day × 3 days + 4.4 mg twice a day × 3 days	4 M	F+G	TA	na	0.8	none
5	Matabosch *et al*[5]	TA	Intramuscular	20 mg	10 M	F+G	TA			8 days
6	Coll *et al*[6]	TA	Intramuscular	40 mg	4 M + 4 F	F+G	TA			11 days
6	Coll *et al*[6]	TA	Intramuscular	80 mg	4 M	F+G	TA			23 days **
11	Avois *et al*	TA	Intramuscular	80 mg	6	F+G	TA			28 days ***
7	Coll *et al*[6]	THA	Intra-articular	40 mg	4 M + 4 F	F+G	TA			8 days
13	Ventura *et al*[13]	TA	Intra-articular	40–80 mg	1 M + 3 F	F+G	TA			3 days
1.11	Avois and Saugy; Avois *et al*	TA	Intra-articular	40 mg	6	F+G	TA			4 days
13	Ventura *et al*[13]	TA	Periarticular	40–80 mg	4 F	F+G	TA			8 days
	Triamcinolone (T)									
18	Chen *et al*[18]	T	Oral	4 mg	4 M+8 F	F+G	T			>24 hours
1	Avois and Saugy	T	Oral	16 mg	6	F+G	T			48 hours
1	Avois and Saugy	T	Oral	16+16, 16+8, 16+0, 8+0, 8+0 (mg)	6	F+G	T			48 hours ****
	Betamethasone (BET)									
14	Bakkene *et al*[14]	BET	Dermatological	3 mg	8	F	BET	na	1.3	none
15	Coll *et al*[15]	BET	Dermatological	10 mg once a day × 5 days	6 M	F+G	BET	1.0±1.4	6.6	none
15	Coll *et al*[15]	BET	Intranasal	320 ug × 3 days	4 M+4 F	F+G	BET	11.6±6.7	32.0	none
15	Coll *et al*[15]	BET	Oral	0.5 mg	8 M	F+G	BET			36 hours
1	Avois and Saugy	BET	Oral	2 mg	6	F+G	BET			40 hours
1	Avois and Saugy	BET	Oral	2+2+2, 2+2+1, 2+2+0, 2+0+0, 1+0+0 (mg)	5	F+G	BET			48 hours ****
14	Bakkene *et al*[14]	BET	Intramuscular	5.7 mg	8	F	BET			48 hours
15	Coll *et al*[15]	BET	Intramuscular	6 mg	6 M	F+G	BET			72 hours
1	Avois and Saugy	BET	Intramuscular	7 mg	6	F+G	BET			50 hours

Continued

Table 2 Continued

Ref.	Glucocorticoid	Administration protocol				MF	Results in urine samples			
15	Coll *et al*[15]	BET	Intramuscular	12 mg	4 M+4F	F+G	BET			96 hours
13	Ventura *et al*[13]	BET	Intra-articular	3–12 mg	10 F	F+G	BET			48 hours
1	Avois and Saugy	BET	Intra-articular	7 mg	3	F+G	BET			45 hours
13	Ventura *et al*[13]	BET	Periarticular	6–12 mg	3 M+11 F	F+G	BET			72 hours
	Dexamethasone (DEX)									
1	Avois and Saugy	DEX	Intramuscular	7 mg	6	F+G	DEX			57 hours
	Prednisolone (PRED) and prednisone (PSONE)									
8	Mazzarino *et al*[8]	PRED	Intranasal	2 mg (two sprays three times a day)	1 M+1 F	F+G	PRED, PSONE	na	40, 120	none, none
14	Bakkene *et al*[14]	PRED	Intraocular	0.9 mg	8	F	PRED *****	na	19, na	none, na
8	Mazzarino *et al*[8]	PRED	Intraocular	1 mg (four drops twice per day)	1 M+1 F	F+G	PRED, PSONE	na	50, 45	none, none
17	Coll *et al*[17]	PRED	Dermatological	5 mg × 5 days	6 M	F+G	PRED, PSONE	3.5±3.5; 3.7±3.9	12,1; 18, 0	none, none
8	Mazzarino *et al*[8]	PSONE	Oral	1 mg	2 F	F+G	PRED, PSONE			12 hours, 12 hours
8	Mazzarino *et al*[8]	PRED	Oral	5 mg	2 M	F+G	PRED, PSONE			24 hours, 12 hours
17	Coll *et al*[17]	PRED	Oral	5 mg	6 M	F+G	PRED, PSONE			8 hours, 8 hours
8	Mazzarino *et al*[8]	PSONE	Oral	5 mg	2 M	F+G	PRED, PSONE			24 hours, 12 hours
17	Coll *et al*[17]	PSONE	Oral	5 mg	2 M	F+G	PRED, PSONE			8 hours, 8 hours
14	Bakkene *et al*[14]	PRED	Oral	10 mg	8	F	PRED *****			24 hours, na
17	Coll *et al*[17]	PRED	Oral	10 mg	2 M	F+G	PRED, PSONE			24 hours, 24 hours
9	Ahí *et al*[9]	PRED	Oral	20 mg	1 M	F+G	PRED, PSONE			9 hours, none
17	Coll *et al*[17]	PSONE	Oral	30 mg	2 M	F+G	PRED, PSONE			8 hours, 24 hours
9	Ahí *et al*[9]	PRED	Oral	40 mg	1 M	F+G	PRED, PSONE			14 hours, 20 hours
1	Avois and Saugy[1]	PRED	Intramuscular	25 mg	6	F+G	PRED, PSONE			10 days, 7 days
	Methylprednisolone (MP)									
10	Matabosch *et al*[10]	MP	Dermatological	10 mg × 5 days	2 M	F+G	MP	0.5±0.3	2.0	none
10	Matabosch *et al*[10]	MP	Oral	4 mg	2 M	F+G	MP			12 hours
16	Simoes *et al*	MP	Oral	4 mg	1 M	F+G	MP			10 hours
10	Matabosch *et al*[10]	MP	Oral	40 mg	2 M	F+G	MP			24 hours
1	Avois and Saugy	MP	Intra-articular	80 mg	4	F+G	MP			48 hours

*, data not available.
**, last sample collected at 23 days.
***, concentrations between 10 and 15 ng/ml up to 56 days.
****, after the last dose.
*****, only concentrations of PRED reported.
F, female; F, free fraction; G, glucurono conjugated fraction; GC, glucocorticoid; M, male; MF, metabolic fraction; 6β-OHBUD, 6β-hydroxy-budesonide.

Table 3 Reporting levels proposed and washout periods recommended after administration of GCs by different routes

Reporting level (ng/ml)	Marker	
15	Triamcinolone acetonide	
30	Methylprednisolone	
30	All other GCs	
45	6β-hydroxy-budesonide	
60	Betamethasone, dexamethasone	
100	Prednisolone	
300	Prednisone	
Administration route	**GC**	**Washout period**
Oral	All GC	3 days
	Except: triamcinolone	10 days
Intramuscular	Betamethasone, dexamethasone, methylprednisolone	5 days
	Prednisolone, prednisone	10 days
	Triamcinolone acetonide	60 days
'Local' injections (intra-articular, periarticular, peritendinous…)	All GCs	3 days
	Except: triamcinolone acetonide, triamcinolone hexacetonide, prednisolone, prednisone	10 days

GC, glucocorticoid.

Regarding the marker of discrimination, the parent drug was suitable for the majority of GCs studied,[5 6 13 15 17] except for budesonide and triamcinolone hexacetonide (THA). For budesonide, the metabolite 6β-hydroxy-budesonide (6β-OHBUD) showed better balance between specificity and sensitivity compared with the parent drug or other metabolites.[2 3] THA, a pro-drug of TA, was not detected in urine after administration and the active drug was selected as the marker of discrimination.[7]

For all GCs, urinary concentrations after dermatological applications were very low (table 2) and, in general, data obtained after inhaled or intranasal administrations were used to define the RLs.

For 6β-OHBUD, data after intranasal and inhaled administrations were available (table 2). Concentrations after intranasal administration were very low. However, concentrations obtained after inhalation steered the decision to increase the RL to 45 ng/mL to reduce the possibility of an AAF after inhalation at high doses.

For TA, dermatological and intranasal administrations were studied. After the maximum daily intranasal dose, the mean and median concentrations were very low, however a Cmax of 7 ng/mL was obtained. Due to these results and because concentrations of TA after intramuscular administrations were very low, especially after low doses,[5 6] a reduction of the RL to 15 ng/mL was proposed to increase the sensitivity of detection after intramuscular use.

For BET, dermatological and intranasal studies were available. The Cmax obtained after repeated intranasal administration at doses below the maximum recommended daily doses suggested an increase of the RL to 60 ng/mL to avoid an AAF after higher intranasal doses. For DEX, the same criterion was proposed due to the similar pharmacological and pharmacokinetic properties with BET.

For PRED and PSONE, dermatological, intraocular and intranasal studies were available. The Cmax obtained after repeated intraocular or intranasal administration using doses below the maximum daily dose suggested an increase of the RL of PRED and PSONE to 100 ng/mL and 300 ng/mL, respectively, to avoid an AAF after these administration routes at higher doses.

For methylprednisolone (MP), only studies after dermatological application were available. Despite the low concentrations obtained after dermatological application, the RL was maintained at 30 ng/mL because the sensitivities after oral, intramuscular and intra-articular administrations and the washout periods did not significantly change using lower RLs.

Establishing washout periods following administration of GCs

After GCs administration, urinary concentrations which could result in an AAF can be reached for different periods of time after administration depending on the GC administered and the dose.

Guidance relating to clinical use according to the manufacturer's licensed doses was deemed necessary to reduce the risk of AAF after medical use during an out-of-competition period and, therefore, washout periods for oral and injectable routes were defined. The washout period refers to the time taken from the last dose to the time of the in-competition period (midnight beginning the evening of the in-competition period) in order to reduce the GC concentration in the urine below the RLs. The washout periods were established taking into account the time of detection of the drugs using the new RLs established for each. The maximum detection times obtained in each study are indicated in table 2.

It is worth highlighting the long detection times obtained after intramuscular use of TA (table 2). For triamcinolone, the recommended washout period is 10 days to ensure specificity after the maximum oral dose (table 2).

In order to simplify the recommendations and facilitate the therapeutic use of GCs in out-of-competition periods, the washout periods were unified by administration routes and the recommended values are described in table 3.

DISCUSSION

Oral, intramuscular, rectal and intravenous routes have been prohibited for some time because there is clear evidence of systemic effects which could potentially enhance performance and be harmful to health. The same GC systemic concentrations as existing prohibited routes can be achieved after administration by local injection (including periarticular, intra-articular, peritendinous and intratendinous) at licensed therapeutic doses.[5–7 11 13 15 19 69 81]

The plasma and urinary concentrations of GCs obtained after administration by local injection using normal licensed therapeutic doses are consistent with those obtained after other existing prohibited routes that were shown to have the potential to improve performance in clinical studies.

The systemic effect of GCs following local injectable routes of administration may therefore present a potential to both improve performance and cause harm to health. Consequently, all injectable routes of administration were approved for inclusion on the 2022 WADA Prohibited List as prohibited routes of administration for GCs during the in-competition period.

In addition, revised and substance-specific laboratory RLs based on excretion studies were recommended to be introduced to better reflect the proposed approach (table 3). Revised RLs were proposed for the seven GCs most frequently reported as AAFs by antidoping laboratories up to now (table 4).

Table 4 Adverse analytical findings (AAFs) reported for glucocorticoids 2010–2018

Year	Number of AAF	% of total AAF	Substance	Occurrences	% within drug class
2010	234	4	Budesonide*	111	47.4
			Prednisolone+prednisone	39	16.7
			Betamethasone	27	11.5
			Prednisolone	16	6.8
			Prednisone	9	3.8
			Dexamethasone	8	3.4
			Methylprednisolone	7	3.0
			Triamcinolone acetonide	7	3.0
			Triamcinolone	6	2.6
			Deflazacort	3	1.3
			Fluticasone propionate	1	0.4
2011	274	5	Budesonide*	113	41.2
			Prednisolone+prednisone	40	14.6
			Betamethasone	25	9.1
			Dexamethasone	21	7.7
			Prednisolone	19	6.9
			Prednisone	19	6.9
			Methylprednisolone	16	5.8
			Triamcinolone acetonide	16	5.8
			Triamcinolone	2	0.7
			Fluticasone propionate	2	0.7
			Deflazacort	1	0.4
2012	365	8	Budesonide*	157	43.0
			Prednisolone	67	18.4
			Prednisone	60	16.4
			Betamethasone	30	8.2
			Dexamethasone	18	4.9
			Triamcinolone acetonide	16	4.4
			Methylprednisolone	15	4.1
			Triamcinolone	1	0.3
			Fluticasone propionate	1	0.3
2013	330	6	Budesonide*	135	40.9
			Prednisolone	58	17.6
			Prednisone	55	16.7
			Betamethasone	35	10.6
			Dexamethasone	18	5.5
			Methylprednisolone	14	4.2
			Triamcinolone acetonide	12	3.6
			Fluticasone propionate	2	0.6
			Triamcinolone	1	0.3
2014	252	8	Budesonide*	74	29
			Prednisolone	56	22
			Prednisone	44	17
			Betamethasone	34	13
			Triamcinolone acetonide	16	6
			Methylprednisolone	14	6
			Dexamethasone	12	5
			Deflazacort	1	0.4
			Triamcinolone	1	0.4
2015	215	6	Prednisolone	60	28
			Prednisone	52	24
			Betamethasone	31	14
			Dexamethasone	19	9
			Methylprednisolone	19	9
			Triamcinolone acetonide	17	8
			Budesonide*	7	3

Continued

Table 4 Continued

Year	Number of AAF	% of total AAF	Substance	Occurrences	% within drug class
			Deflazacort	4	2
			Fluticasone propionate	3	1
			Fluticasone	2	1
			Triamcinolone	1	0.5
2016	184	4	Prednisolone	51	28
			Prednisone	48	26
			Betamethasone	29	16
			Triamcinolone acetonide	18	10
			Dexamethasone	13	7
			Methylprednisolone	11	6
			Fluticasone propionate	9	5
			Deflazacort	2	1
			triamcinolone	2	1
			Budesonide*	1	0.5
2017	224	5	Prednisolone	70	31
			Prednisone	56	25
			Triamcinolone acetonide	31	14
			Betamethasone	23	10
			Dexamethasone	20	9
			Methylprednisolone	13	6
			Fluticasone propionate	4	2
			Deflazacort	3	1
			Budesonide*	2	1
			Triamcinolone	1	0
2018	284	7	Prednisolone	77	27
			Triamcinolone acetonide	72	25
			Prednisone	70	25
			Betamethasone	34	12
			Dexamethasone	15	5
			Methylprednisolone	8	3
			Budesonide*	5	2

MRL revised to lower values are highlighted in pink; MRL revised to higher values are highlighted in orange.
*Note that the change in prevalence is due to change in target analyte from budesonide to N6β-hydroxy-budesonide in 2014.

Practical implications of new RLs for laboratories

The combination of RLs and washout periods enables better differentiation between routes of administration and provides a margin of safety to avoid reporting an AAF for therapeutic use during in-competition and out-of-competition periods.

Antidoping laboratories will need to update their procedures to incorporate the new RLs. Analytical difficulties are not foreseen because the new values are of the same order of magnitude, although validation assays will be required.

The new RLs will avoid problems of results interpretation of some specific GCs. In particular, the problem of the endogenous production of PRED and PSONE at low concentrations due to microbial activity in the urine samples which involved sophisticated confirmatory procedures including isotope-ratio mass spectrometer (IRMS) analysis[82] is solved with the new RLs.

Impact of change in urinary concentration RLs on AAFs

The total number of GC AAFs in the Anti-Doping Administration & Management System (*ADAMS*) database from 2010 to 2018 is reasonably consistent (table 4), constituting 4%–8% of total AAFs annually.

It is difficult to estimate precisely the true impact of these changes on the annual number of GC AAFs, as the estimated concentrations are not systematically reported. However, the new RLs were defined taking into account urinary concentrations obtained after allowed administrations so they ensure high specificity for these administration routes. In addition, five out of the six revised RLs are higher than 30 ng/mL. For those reasons, the number of in-competition AAFs due to allowed therapeutic administrations is expected to be drastically reduced.

In summary, the refinement of the criteria of discrimination between allowed and prohibited GC use is expected to produce a reduction in the number of AAFs. This has previously been observed with budesonide where the number of AAFs was drastically reduced from 2014 when 6β-hydroxy-budesonide was introduced as a marker of oral budesonide administration by all laboratories.[83]

Impact of prohibiting local injections on AAFs

The combination of the increase of RLs with defined washout periods that take into account their elimination time of these injections should diminish the number of AAFs, provided that those washout periods are respected. If the athlete needs an injection during a period of 3–10 days before the competition (depending on the GC) they may apply for a retroactive Therapeutic Use Exemption (TUE) in the event of an AAF, as per the International Standard for TUE and if granted, the presence of GC will not be prosecuted.[84]

In addition, data from the WADA Monitoring Programme reporting out-of-competition GC use at values greater than 1 ng/mL showed an incidence of less than 2% of urine samples tested (unpublished WADA data) confirming that there should not be a marked increase in the number of AAFs.

Implications for therapeutic use exemptions in sport

Under the current regulation, TUEs granted for GC use by prohibited routes in competition represent a third of all the TUE applications granted and entered into *ADAMS* in 2019. This is the most requested class along with stimulants or hormone and metabolic modulators, with 22% and 13% of all TUE applications, respectively.

Based on the prohibition of all injectable routes and the imposed washout periods before a return to competition requiring application for a TUE, it is anticipated that the number of TUE applications for GCs will increase. However, studies in this field conducted at the recent Olympic Games suggest a rather restricted medical need for in-competition use of injectable GCs.[85–87] However, the 2019 WADA Monitoring Programme revealed comparable use of GCs in competition and out of competition (unpublished WADA data) suggesting that TUE applications for GCs may double in number.

Beyond the number of TUEs, the concern that some physicians or athletes might misinterpret or ignore the new rules leading to unintentional antidoping rule violation is mitigated by clearer rules supported by a proactive information and education campaign launched by WADA and the antidoping organisations around the world.

Implications for medical treatment

With the existing framework of the TUE system in place, use for any legitimate and necessary medical treatment could still be applied for through the existing TUE application process.

However, the prohibition of GCs by local injection during the in-competition period, coupled with the introduction of new washout periods, will potentially shift the preferred selection of type of locally injected GC when administered near to the time of a competition event. Those GCs with the lowest washout time after medical treatment may be preferred in the immediate days before the competition period to avoid the need to apply for a TUE. For example, triamcinolone by intra-articular route is currently listed on the *2019 Olympic and Paralympic Model Formulary* as an essential medicine to have available at the Olympic and Paralympic Games for prescribing to athletes.[88] But with a washout period of 10 days, the shift to such drugs as hydrocortisone or MP with a 3-day washout period might be observed. This potential shift in preference to GCs with a shorter washout period should be considered when selecting medicines for formularies for teams and major events.

CONCLUSION

This novel approach completely redefines how GCs are tested for in sport, and presents a framework to allow for better management of the medical use of these drugs while maintaining a level playing field for competing athletes. Fundamentally, the methodology addresses the fact that the systemic effect of GCs following local injectable routes of administration previously presented a potential to both improve performance and cause harm to health.

The approach presents a vast improvement in the specificity of the urinary concentration RLs, to better reflect the unique pharmacological properties of each drug, and to more accurately distinguish between prohibited and permitted use in sport. Ultimately, the implementation of the new RLs will create efficiencies in the analysis process and rationalise the analysis by laboratories and will improve the management of AAFs reported for GCs. The model should overall decrease the number of AAFs reported, but better detect the actual potential for abuse of GCs by athletes.

With the implementation of new guidance on washout periods following medical use of GCs, clinicians should be better informed to be able to manage the athlete's treatment plan and minimise any risk to the athlete of failing a doping test after legitimate medical use.

What is already known

- The systemic effect of glucocorticoids following injectable routes of administration presents a *potential* to both improve performance and cause harm to health in athletes.

What are the new findings

- All injectable routes of administration of glucocorticoids will be prohibited in sport by the World Anti-Doping Agency from 1 January 2022.
- New washout periods are presented to enable clinicians to use glucocorticoids safely and to avoid the risk of athletes testing positive for a doping test.
- New substance-specific laboratory reporting values will better distinguish between prohibited and permitted use in sport.

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