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Original Article

Clearance of corticosteroids following intra-articular administration of clinical doses to racehorses

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Summary

Over the last few years there has been a nationwide cooperative effort to establish threshold concentrations and withdrawal time guidelines for corticosteroid use in racehorses. As dosing regimens are specific to individual horses and highly variable, it is not possible to establish regulatory guidelines for every dosing scenario and therefore they are often based on single dose administration studies. The goal of the study described here was to assess the applicability of current regulatory recommendations for intra-articular corticosteroids based on clinical protocols used by practitioners. A total of 58 Thoroughbred and 82 Quarter Horse racehorses received varying doses of triamcinolone acetonide, methylprednisolone acetate, isoflupredone or betamethasone intra-articularly in various joints by the treating practitioner. Blood samples were collected at 0, 7, 10, 14, 21, 28 and 35 days post drug administration and serum samples analysed by liquid chromatography mass spectrometry for quantitation of drug concentrations. Serum elimination varied depending upon the dose and the number and specific joints treated. Serum concentrations fell below the ARCI threshold guidance by Day 7 (100 pg/ml) for both triamcinolone acetonide (2–40 mg dose) and isoflupredone acetate (4–30 mg dose) and Day 21 (100 pg/ml) for methylprednisolone acetate (20–600 mg dose). Betamethasone fell below the regulatory threshold (10 pg/ml) by 7 days for all Quarter Horses and for 7/10 Thoroughbreds studied. Drug concentrations were below the regulatory threshold by Day 10 in the remaining 3 horses receiving betamethasone.

Introduction

The goal of a medication control programme is to: 1) assure the health and welfare of animal and human participants, 2) assure a fair and level playing field for all competitors and 3) safeguard the public interest with anti-doping regulations wherever sanctioned wagering is involved. Over the last few years, there has been an international effort to address the use of therapeutic medications commonly used in racing, including corticosteroids. Historically, regulation of horse racing in the United States (US) was on a state-by-state basis and it was up to specific jurisdictions to establish regulatory recommendations. Additionally, most regulations were established well before simulcasting and interstate wagering was legal. In spite of sporadic efforts at uniformity over the last several years, there were considerable variations between state medication and drug regulations and how those regulations are administered. In 2001, a meeting of national industry stakeholders, sponsored by the American Association of Equine Practitioners, led to the establishment of the Racing Medication and Testing Consortium (RMTC). The RMTC was tasked with promoting national uniformity with respect to medication regulations. The result has been a cooperative effort within the racehorse industry to develop a national uniform medication programme (NUMP) by establishing regulatory thresholds and withdrawal time guidance for a limited number of therapeutic medications. Whenever feasible, the preference in the US is to regulate therapeutic medications in blood (serum or plasma). This effort has been spearheaded by the RMTC through drug administration research and subsequent recommendations to the Association of Racing Commissioners International (ARCI). The ARCI represents the majority of the 38 separate racing authorities in the US and maintains the Model Rules for racing in the US (ARCI Model Rules, https://ua-rtip.org/industry_service/download_model_rules). All states in which racing occurs are encouraged, but not required, to adopt the Model Rules.

Corticosteroids are potent anti-inflammatory agents and, as such, are commonly used to treat performance-related musculoskeletal injuries and other inflammatory conditions in equine athletes. In the US, they are currently classified by the ARCI as Class 4 foreign substances with a penalty category C (ARCI Model Rules). Due to their potent anti-inflammatory effects, corticosteroid use close to competition is of particular concern to regulatory authorities because of the potential to mask injuries that may otherwise keep a horse from racing. Regulatory thresholds and withdrawal time guidance are typically based on carefully controlled studies, utilising a single dose commonly used by veterinary practitioners. While necessary for establishment of regulatory guidance, this type of study does not necessarily reflect how corticosteroid drugs are typically used in clinical racecourse practice. In the case of corticosteroids, selection of a 'common dose' becomes more problematic, as the use pattern of this class of drugs is highly variable between practitioners (Ferris *et al.* 2011). Current NUMP regulatory thresholds for triamcinolone acetonide (TCA) and methylprednisolone acetate (MPA) are

100 pg/ml, based on a single intra-articular dose of 9 mg TCA (Knych *et al*. 2013) and 100 mg MPA (Knych *et al.* 2014). The corresponding withdrawal time guidance is 7 and 21 days for TCA and MPA, respectively. For betamethasone, the regulatory threshold concentration and withdrawal time guidance is 10 pg/ml and 7 days, respectively based on a single intra-articular dose of 9 mg (Anon 2014). For isoflupredone acetate (IPA), a regulatory threshold concentration of 100 pg/ml, with a withdrawal time guidance of 7 days, is recommended (Benson *et al.* 2014). These recommended regulatory thresholds were established based on practical horseracing and racehorse management and not necessarily based on pharmacodynamic or therapeutic considerations. Since the withdrawal time guidance for each drug was based on single dose studies and in the majority of cases practitioners use combination corticosteroid therapy, widely varying doses and treat multiple joints to most effectively treat their patients, the goal of the study described here was to assess the applicability of the ARCI regulatory guidance for each corticosteroid following intra-articular (IA) administration of various clinical protocols employed by racecourse practitioners.

Materials and methods

Horse selection

Fifty-eight Thoroughbred (TB) and 82 Quarter Horse (QH) racehorses were studied. Horse selection as well as the specific corticosteroid, doses administered and joints to be treated were determined by the treating practitioner as part of their clinical evaluation of each animal. For the TB portion of the study, 18 horses received TCA (Vetalog; Kenalog)[1,2], (maximum cumulative dose of 9–18 mg), 21 horses received MPA (Depo-Medrol)[3] (maximum cumulative dose of 40–600 mg), 7 horses received IPA (Predef 2X)[3] (maximum cumulative dose of 4–18 mg) and 12 horses received betamethasone (Celestone; Betamethasone Sodium Phosphate and Betamethasone Acetate)[4,5], (maximum cumulative dose of 12–60 mg) IA in various joints. Quarter Horses received varying combinations of corticosteroids IA into various joints including: 1) betamethasone (12–24 mg), 2) IPA (4–26 mg) + betamethasone (12–42 mg), 3) MPA (40 mg) + betamethasone (24 mg), 4) TCA (10–20 mg) + betamethasone (6–12 mg), 5) TCA (10-24 mg) + IPA (2-20 mg) + betamethasone (6–36 mg), 6) MPA (20–40 mg) + IPA (5-30 mg) + TCA (10–40 mg) + betamethasone (6–30 mg), 7) TCA (2–20 mg) + MPA (20–40 mg) + IPA (8–25 mg) and 8) TCA (20–40 mg) + MPA (20–40 mg) + betamethasone (18–30 mg). Details regarding the specific drug administered, manufacturer, dose, joints treated, dose time, concurrent IA administration of other compounds as well as treatment with IA or intramuscular (i.m.) corticosteroids in the preceding 30 or 60 days, respectively were recorded. All drug administrations were conducted by the treating practitioner.

Blood samples were collected by direct venipuncture at 0, 7, 10, 14, 21, 28 and 35 (MPA only) days post drug administration from TBs and 0, 7 and 10 days post administration from QH. All samples were collected by the treating practitioner into serum separator tubes[6]. Sample collection, storage at the racetrack and shipping procedures were comparable to the processes for post race sample collection. Samples were centrifuged at the racetrack at 3300 revolutions/min (RPM) and refrigerated prior to being shipped to the laboratory. Upon receipt at the laboratory, samples were centrifuged again at 3000 RPM for 10 min and serum immediately transferred into storage cryovials.[7] All samples were stored at −20°C (approximately 2 weeks) until analysed by tandem liquid chromatography mass spectrometry (LC-MS/MS) for quantitation of serum methylprednisolone (MP), TCA, isoflupredone (IP) and betamethasone concentrations using previously validated assays used for post race drug testing (Knych *et al.* 2013, 2014, 2015).

Results

Thoroughbred study

Of the 58 TBs included in the study, 6 received MPA, 3 received isoflupredone and one received TCA IA within 30 days prior to enrolment in the study. Of these, only one horse that had received MPA had a baseline concentration (520 pg/ml) exceeding the regulatory threshold. Three horses received TCA and 3 horses received MPA as an i.m. injection within 60 days of commencement of the study. Serum baseline concentrations were below the regulatory threshold for all 3 horses. **Table 1** lists the time at which serum concentrations of TCA, MP, IP and betamethasone fell below the ARCI regulatory threshold in the TB horses. The elimination time varied based on the maximum dose administered, specific joints injected as well as the total number of joints treated. Methylprednisolone acetate concentrations were below the regulatory threshold concentration in all horses by Day 21 post administration. Serum concentrations fell below the ARCI regulatory threshold by Day 7 (100 pg/ml) for both TCA (9–18 mg dose) and IPA (4–18 mg dose). For betamethasone, 7 of 10 horses had serum concentrations below the regulatory threshold (10 pg/ml) by 7 days post administration. Serum betamethasone concentrations in the remaining 3 horses fell below the regulatory threshold by Day 10 post drug administration. Concurrently administered IA medications included hyaluronic acid (HA) (17 horses) and a HA, sodium chondroitin sulfate and N-acetyl-D-glucosamine combination product (Polyglycan)[8] (7 horses) (**Table 2**). Of the 3 horses in which betamethasone concentrations exceeded the regulatory regulatory threshold at 7 days post administration, one had received 30 mg and 2 had received 60 mg of betamethasone. All 3 horses also received IA Polyglycan (2.5–5 ml) concurrent with betamethasone administration (**Table 2**).

Quarter Horse study

Of the 82 QHs studied, 57 received MPA, 2 received betamethasone, 2 received TCA and one received IPA IA within 30 days of commencement of the study. Nineteen of the 57 that received an IA MPA injection in the previous 30 days had serum MP concentrations at or above the regulatory threshold (100 pg/ml). No TCA or IP was detected in baseline samples from horses reported as receiving either drug in the preceding 30 days. A total of 13 horses received an i.m. injection of either MPA (10 horses), TCA (2 horses) or IPA (one horse) within 60 days prior to enrolment in the study. Of these horses, 5 had MP serum concentrations that were ≥100 ng/ml in baseline samples with 4 of these animals also having received an IA injection of MPA within the preceding 30 days. The time at which concentrations fell below the ARCI regulatory threshold for combination IA corticosteroid

TABLE 1: Time at which corticosteroid concentrations fell below the ARCI regulatory threshold following administration of various clinical doses of triamcinolone acetonide, methylprednisolone acetate, isoflupredone acetate and betamethasone to a total of 58 Thoroughbred racehorses

			Time until below ARCI regulatory threshold				
Drug	Dose range (mg)	No. joints	Day 7	Day 10	Day 14	Day 17	Day 21
Methylprednisolone acetate (n = 24)	80	1	1/1				
	40–200	2	6/11	10/11			11/11
	300–400	3		3/4		4/4	
	160–600	4		3/8	5/8		8/8
Trimacinolone acetonide (n = 17)	9–12	1	5/5				
	12–18	2	12/12				
Isoflupredone acetate (n = 7)	10–18	2	3/3				
	12	3	2/2				
	10–16	4	2/2				
Betamethasone (n = 10)	30–60	2	7/10	10/10			

TABLE 2: Time at which corticosteroid concentrations fell below the ARCI regulatory threshold when administered in combination with other noncorticosteroid intra-articular medications to Thoroughbred racehorses

	Corticosteroid	No. joints	Dose (mg)	Time when below RCI proposed threshold
Hyaluronic acid (22 mg)	MPA	2	40–80	Day 7 (4/4)
		4	160	Day 10 (1/1)
	TCA	2	12	Day 7 (9/9)
	Betamethasone	2	12	Day 7 (3/3)
Polyglycan (2.5–3 ml)	Betamethasone	2	30	Day 7 (3/4)
				Day 10 (4/4)
Polyglycan (5 ml)	Betamethasone	2	60	Day 10 (2/2)
Polyglycan (3–4 ml)	TCA	1	9	Day 7 (1/1)
		2	18	Day 7 (1/1)

TABLE 3: Time at which corticosteroid concentrations fell below the ARCI regulatory threshold following administration of various combinations of clinical doses of triamcinolone acetonide, methylprednisolone acetate, betamethasone and isoflupredone acetate to a total of 82 Quarter Horse racehorses

		Time until below RCI regulatory threshold	
Drugs	Dose range (mg)	Day 7	Day 10
Betamethasone (n = 3)	12–24	3/3	
Isoflupredone + Betamethasone (n = 29)	4–26	29/29	
	12–42	29/29	
MPA + Betamethasone (n = 1)	40	1/1	
	24	1/1	
TCA + Betamethasone (n = 3)	10–20	3/3	
	6–12	2/3	3/3
TCA + Isoflupredone + Betamethasone (n = 24)	10–24	24/24	
	2–20	24/24	
	6–36	24/24	
MPA + Isoflupredone + TCA + Betamethasone (n = 17)	20–40	16/17	17/17
	5–30	17/17	
	10–40	17/17	
	6–30	17/17	
TCA + MPA + Isoflupredone (n = 3)	2–20	3/3	
	20–40	3/3	
	8–25	3/3	
TCA + MPA + Betamethasone (n = 2)	20–40	2/2	
	20–40	2/2	
	18–30	2/2	

administration to QH, are listed in **Table 3**. Serum concentrations fell below the threshold (100 pg/ml) by Day 7 for both TCA (2–40 mg dose) and IPA (2–30 mg dose) administration. For betamethasone (12–42 mg), all horses had serum concentrations below the regulatory threshold (10 pg/ml) by 7 days post administration. Following administration of MPA (9–40 mg), serum concentrations were below the regulatory threshold (100 pg/ml) by Day 10 post administration.

Discussion

The goal of the current study was to assess the applicability of current regulatory thresholds and withdrawal time guidance for the most commonly administered IA corticosteroids following the use of a variety of clinical dosing regimens. Current regulatory guidance for the use of IA corticosteroids in racehorses are based upon studies of a single dose administered in a single joint. It is not possible to study every corticosteroid dosing regimen employed by veterinary practitioners, but this study provides veterinary practitioners with threshold compliance information on a broad and clinically relevant variety of corticosteroid treatments.

In the presently reported study, TCA serum concentrations fell below the regulatory threshold (100 pg/ml) by 7 days post intra-articular administration at all doses studied. This was true whether TCA was administered as the sole treatment or in combination with other corticosteroids. This is in agreement with previous studies (Soma *et al.* 2011; Knych *et al.* 2013) describing the administration of 9 mg (Knych *et al.* 2013) or 20–30 mg (Soma *et al.* 2011) of TCA into a single antebrachiocarpal joint. Similarly, following administration of 6 mg of TCA into both tarsometatarsal joints (total dose of 12 mg), serum concentrations were less than 100 pg/ml by 7 days post administration (Knych *et al.* 2011).

Although its use is somewhat controversial (McIlwraith 2010), MPA is arguably one of the more commonly used

corticosteroid formulations in performance horses (Ferris *et al.* 2011). While the high lipid solubility of this formulation provides a prolonged local anti-inflammatory effect, it also leads to an increased residence time within the joint and a longer serum or plasma detection time, relative to more soluble compounds (Knych *et al*. 2014). Similar to previous reports (Autefage *et al.* 1986; Lillich *et al.* 1996; Soma *et al.* 2006; Menendez *et al.* 2012; Knych *et al*. 2014), in the current study, higher systemic concentrations were observed with increasing doses of MPA, including one horse receiving 600 mg which was 200 mg more than the next highest MPA cumulative dose (400 mg). However, in all studies, including the presently reported one, systemic concentrations fell below the regulatory threshold by 21 days post drug administration. In order to avoid inadvertent positive regulatory findings, it is prudent to be sensitive to previous corticosteroid administration. As was demonstrated in the current study, this is especially necessary in the case of previous MPA administration, as serum concentrations exceeded the regulatory threshold in a number of QHs previously treated with MPA. This is likely due to the longer residence time of this drug compared with other commonly used IA corticosteroids in horses.

There are limited published reports describing the clearance of isoflupredone following IA administration to horses (Lillich *et al.* 1996; Benson *et al.* 2014; Knych *et al.* 2015). In the study by Lillich *et al.* (1996), detectable concentrations of IP and IPA equivalents were reported for only 12 and 72 h, respectively following IA administration of 4 mg. More recent studies utilising more sensitive LC-MS/MS methods, reported that plasma isoflupredone concentrations fell below the regulatory threshold by 36 (Knych *et al.* 2015) and 72 h (Benson *et al.* 2014) post IA administration of 8 and 20 mg of IP, respectively. In the current study, regardless of the dose administered or the joint treated, serum IP concentrations fell below the ARCI regulatory threshold by the suggested withdrawal time guidance of 7 days. The results of previous studies as well as the presently reported one suggest that a 7 day withdrawal time guidance is adequate for IA administration of IPA at doses up to 30 mg.

The most commonly used intra-articular betamethasone product in horses is a combination betamethasone sodium phosphate/betamethasone acetate formulation. Current regulatory recommendations are based on an unpublished administration study whereby 20 horses received a single IA dose of 9 mg of betamethasone sodium phosphate/ betamethasone acetate (Anon 2014). The position statement reports plasma concentrations below the limit of quantitation (5 pg/ml) by 5 days post administration. Based on this, a regulatory recommendation of a 10 pg/ml threshold concentration with a corresponding 7 day withdrawal time was made. To the best of the authors' knowledge, there is only one published report describing the pharmacokinetics of betamethasone following IA administration to horses (Menendez *et al.* 2015); however, the LOQ (50 pg/ml) in that study is well above the current regulatory threshold (10 pg/ ml) and therefore it is difficult to use this study in the assessment of the ARCI withdrawal time guidance. In the current study, the dose of betamethasone administered ranged from 6–60 mg. The majority of the horses studied had serum concentrations below 10 pg/ml by 7 days; however, 3 of the TB horses had levels above 10 pg/ml until 10 days post administration (the next time point sampled). These 3 horses were at the upper end of the dose range (30 mg [one horse]; 60 mg [2 horses]) and interestingly all had received IA Polyglycan. It is not possible from the data in this study to make any inferences as to whether the prolonged detection is due to concurrent Polyglycan administration or simply high dose betamethasone administration, as a limited number of horses received this combination. However, until this potential interaction is more extensively studied, it may be prudent to observe an extended withdrawal time when administering high doses of betamethasone, whether in combination with Polyglycan or by itself.

It is important to note that the ARCI recommended withdrawal time guidance, as well as the results presented here apply only to IA corticosteroid administration and not administration by other routes. Other routes of administration, intramuscular in particular, necessitate a prolonged withdrawal time. As an example, Soma *et al.* (2011) have reported systemic concentrations of TCA above the regulatory threshold for upwards of 10 days, following i.m. administration of a 0.04 mg/kg dose. Higher doses and other non-IA routes of any of the corticosteroids studied here may require an even more prolonged withdrawal time to avoid inadvertent positive regulatory findings. Veterinarians should be aware that extravasation into subcutaneous tissues or inadvertent extra-articular injection during an intended IA injection may also necessitate a prolonged withdrawal time.

Although serum elimination varied depending on the dose and number of joints treated, based on the results of this study, maximum IA cumulative doses of 40 mg of TCA, 600 mg of MPA and 30 mg of IPA, either by themselves or in combination with other corticosteroids, should not result in positive regulatory findings if the ARCI withdrawal time guidance is followed for each drug. In the case of IA betamethasone administration, results of this study suggest that doses less than 30 mg should not result in excess of the regulatory threshold, when following the ARCI recommended withdrawal time guidance. However, based on the findings reported here, doses of 30 mg or greater may necessitate an extended withdrawal time as serum concentrations did not fall below the regulatory threshold until 10 days post administration. It should be noted that as the present study examined corticosteroid serum levels only and did not assess urine levels that extrapolating withdrawal time guidance in racing authorities where corticosteroids are regulated in urine may not be appropriate.

Authors' declaration of interests

No conflicts of interest have been declared.

Ethical animal research

Horses used in this study were under the care of private practitioners. Drugs were administered following a thorough examination and at the discretion of the treating practitioner.

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Authorship

H. Knych and R. Arthur contributed to study design, study execution, data analysis and interpretation and preparation of the manuscript. J. Blea and L. Overly contributed to study design and study execution. W. McIlwraith contributed to study design, data analysis and interpretation. All authors gave their final approval of the manuscript.

Manufacturers' addresses

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[4]Merck & Co, Inc, Whitehouse Stations, New Jersey, USA.
[5]American Regent, Inc, Shirley, New York, USA.
[6]Kendall/Tyco Healthcare, Mansfield, Massachusetts, USA.
[7]Phenix Research Products, Chandler, North Carolina, USA.
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