New Research and Regulatory Issue Associated with Corticosteroids

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Introduction
The use of corticosteroids for the treatment of equine joint disease, as well as the controversy surrounding the risk–benefit ratio of their use have been reported for almost five decades. Few, if any, of the early clinical reports suggesting deleterious effects associated with intra-articular (IA) corticosteroid administration have withstood close modern-day scientific scrutiny. Specifically, most of these reports lacked an appropriate control population that would ensure the reported deleterious effects occurring in corticosteroid treated joints would not have occurred as a natural progression of the disease process that often initiated corticosteroid use in these clinical cases. Extensive reviews dealing with the benefits and controversy surrounding IA corticosteroid administration have been published, and these works will not be recreated here. Rather, a brief review of the basic pharmacology, a subjective synopsis of IA corticosteroid research, an update on research since these published reviews, a summary of the beneficial and potentially deleterious effects based on scientific evidence, and how the use of IA and systemic corticosteroids relates to issues surrounding the athletic horse (including regulatory issues) will be presented.

Basic Pharmacology
Traditionally, the duration of action associated with a drug was thought to be inversely related to its water solubility. The corticosteroids commonly used today for therapy are synthetic in nature, made by modifying various sites on the parent compound to increase the anti-inflammatory effects and reduce any effect on water or sodium metabolism. These synthetic compounds are associated with different esters that influence their solubility. Succinate and phosphate esters are thought to be associated with the shortest acting preparations. Acetate and acetonide esters are considered less water soluble and more lipid soluble, allowing preparations conjugated with these esters to be considered of moderate duration. The most lipid and least water soluble ester is hexacetonide, available as triamcinolone hexacetonide, and considered to be the longest acting corticosteroid for IA use. Celestone Soluspan® is a combination of betamethasone sodium phosphate and betamethasone acetate, a preparation designed to provide a fast acting and prolonged duration of action, but the need for this combination has been questioned. The action of corticosteroids is mediated by the activated cytoplasmic hormone-receptor complex, which interacts with the nucleus of target cells to effect a biological response. Once activated, the steroid-receptor complex can bind to DNA in the nucleus and affect mRNA and subsequent protein production in various ways.

The anti-inflammatory actions of corticosteroids spread over many physiologic and cellular systems. Historically, corticosteroids were thought to act mainly by stabilization of lysosomal membranes. Today corticosteroids have been credited with significant actions on function and movement of neutrophils, lymphocytes, eosinophils, and macrophages. Corticosteroids also have been shown to have a significant action on reducing the production of prostaglandin; this mechanism is one pathway by which corticosteroids modulate many of the inflammatory cytokines such as interleukin-1 (IL-1) and tumor necrosis factor. Extensive reviews of the action of corticosteroids may be found in other references.

Subjective Synopsis of IA Corticosteroid Research
Since the first equine report of IA corticosteroid use in 1955, many attempts have been made to define the beneficial and deleterious effects of their use. Many of the early papers were a compilation of cases in which IA corticosteroids had been used and conclusions were mainly made based on subjective clinical outcomes parameters with little attention to...
possible confounding factors. Realizing that not all joints appeared to respond favorably to corticosteroid use, experimental studies began to address differences between normal and pathologic joints treated IA with corticosteroids. It is noteworthy that many of these experimental studies used IA corticosteroids at higher dosages and frequencies compared to those used routinely in a clinical setting. These studies began to delineate the need for distinctions between specific preparations, doses, frequency of administration, as well as the exercise protocols following treatment.

Taking these distinctions into consideration shaped future research into the scientific evaluation of IA corticosteroid use in the horse. These evaluations have been carried out using in vivo and more recently, in vitro experimental models. Although controlled experimental models are good for addressing many of the questions surrounding IA corticosteroid use, they are unable, by definition, to adequately address all factors present in clinical situations where corticosteroids are used.

State-of-the-art knowledge of IA corticosteroid use in the horse today rests with in vivo and in vitro studies because no blinded controlled clinical studies have been published. Given the lack of defined optimal dosages, frequency of administration, exercise/rest protocols, and potential interaction with other medications, as well as indications for use of specific preparations have yet to be clearly delineated, it may be some time in the future before a useful clinical trial can be designed and completed. Until the completion of such a trial, evaluation of IA corticosteroid use should be made based on scientific evaluations with good experimental designs.

Update on IA Corticosteroid Research

As previously stated, extensive reviews of IA corticosteroid use in the horse can be found elsewhere,1,2 and this manuscript will focus on research conducted after 1995.

Normal versus Diseased Joints

In vitro differences in the response of normal cartilage to IL-1 (a potent mediator of cartilage destruction) conditioned cartilage explants have been demonstrated following treatment with triamcinolone and insulin-like growth factor-1 (IGF-1).7–9 More recently, in vivo results also confirmed similar differences comparing normal and abnormal joint tissue.6 Todhunter et al observed a different response when comparing articular cartilage from inflamed and normal joints with and without methylprednisolone treatment.10 In this study depression of GAG synthesis was observed in normal joints administered methylprednisolone while inflamed joints treated with methylprednisolone demonstrated no change compared to control joints. These findings suggest caution should be used when interpreting results of IA corticosteroids used in normal joints.

Rest versus Exercise

Although many authors have suggested an “appropriate” rest period be used after IA corticosteroid administration, a definition of this period is difficult to ascertain from the literature. The issue of exercise versus rest was specifically addressed in one controlled study and no significant differences were demonstrated.11 In this study 15 mg of betamethasone was administered twice, 14 days apart, in joints containing osteochondral fragments. The exercised group of horses followed a 5 day per week treadmill exercise protocol for a total of 8 weeks. The outcome parameters in this study were subjective lameness scores, gross postmortem changes, histologic evaluation of articular cartilage and synovial membrane, as well as histochemical staining and biochemical analysis of articular cartilage. The authors reported slightly better histochemical and biochemical parameters in articular cartilage treated with betamethasone from exercised versus rested horses, although the differences were noted not to be significant. The impression that some exercise or loading may be beneficial to cartilage following corticosteroid administration has also been substantiated in part by an in vitro study.12 Normal canine articular cartilage explants treated with Solu-Medrol® were subjected to three different loading patterns (0—none, 1—normal, and 10 Mpa—heavy). This study demonstrated that inhibition of cartilage GAG synthesis by Solu-Medrol® at 0.1 and 1 mg/ml was combated by normal loading (comparable to walking) whereas heavy loading (comparable to running) exacerbated inhibition of GAG synthesis at the 1 mg/ml dose. Murray et al. in 1998 published an in vivo study assessing he mechanical properties of articular cartilage in the horse using a routine clinical dose of Depo-Medrol®; however, the dose was repeated every 14 days for a total of 4 treatments.13 Horses were also concurrently exercising on a high-speed treadmill throughout the entire study period. The use of the opposite limb as a control is of note, as this may not be valid in light of work demonstrating significant effects on joint tissue (including articular cartilage) remote to IA corticosteroid administration.14–16 Depo-Medrol® treatment resulted in thinner, more compressible and less stiff cartilage as compared to control cartilage, no gross or clinically apparent osteochondral lesions were noted.13 These authors recommended no vigorous exercise for at least 27 days after Depo-Medrol® treatment assuming a similar dose and frequency protocol were used (27 days was the longest period assessed following Depo-Medrol administration). In another study a 21-day period was required for return of normal GAG synthesis following a single Depo-Medrol® treatment at 0.2 mg/kg in ponies.16 Chune kamrai et al. observed a greater GAG synthe-
sis 16 weeks following a single 120 mg dose of Depo-Medrol\textsuperscript{\textregistered} as compared to control cartilage, although total GAG content was still significantly lower in a similar comparison.\textsuperscript{17} It should be noted again that all but the first study\textsuperscript{14} were conducted in normal joints or using normal articular cartilage\textsuperscript{12,13,16,17} and different results may have been obtained in pathologic joints. Two additional studies\textsuperscript{14,15} have been completed in exercising horses assessing cartilage from joints containing osteochondral fragments and may be used to address some questions regarding IA corticosteroid treatment in pathologic joints with exercise. In the first study,\textsuperscript{15} GAG synthesis was significantly lower in articular cartilage about 7 weeks after the last 100-mg dose (2 total doses 14 days apart) of Depo-Medrol\textsuperscript{\textregistered}, although at a similar time point total GAG content was similar to control cartilage. The other study utilized 12 mg of Vetalog\textsuperscript{\textregistered} and observed no difference in either GAG synthesis or total GAG content compared to control cartilage at a similar time period after Vetalog\textsuperscript{\textregistered} administration.\textsuperscript{14} These results suggest a difference between corticosteroid preparations and a more normal cartilage metabolism earlier following Vetalog\textsuperscript{\textregistered} administration.

Unfortunately, many of the experimental studies carried out in “diseased joints” even with 2 doses of corticosteroids 14 days apart exceed clinically utilized doses\textsuperscript{16} making the selection of an “adequate” rest period after corticosteroid administration based on current scientific evidence problematic. Further research specifically addressing this question is needed, although first an outcome parameter that predicts the long-term consequences of exercise after IA corticosteroid administration must be defined. In the interim, I use 10–14 days of stall and run confinement followed by a gradual return to full work during the subsequent week, as a post-IA corticosteroid exercise protocol (assuming a single clinical dose).

Controller In Vivo Comparison of 3 Commonly Used Preparations in Joints with Disease

Three of the most commonly used IA corticosteroid preparations (Betavet\textsuperscript{\textregistered},\textsuperscript{11} Vetalog\textsuperscript{\textregistered},\textsuperscript{14} Depo-Medrol\textsuperscript{\textregistered}\textsuperscript{\textregistered15}) have been evaluated using a similar osteochondral fragment exercise model. The dose of Betavet\textsuperscript{\textregistered} (15 mg) and Vetalog\textsuperscript{\textregistered} (12 mg) were chosen based on clinical experience and an estimated 10 ml volume of the midcarpal joint. After the completion of the Betavet\textsuperscript{\textregistered} and Vetalog\textsuperscript{\textregistered} in vivo studies the same authors conducted in vitro dose studies\textsuperscript{8} to confirm the Vetalog\textsuperscript{\textregistered} and choose a Depo-Medrol\textsuperscript{\textregistered} (100 mg) dose to be tested using the same in vivo model. Interestingly, the doses chosen based on the in vitro studies were similar to the clinically utilized doses, although the frequency of dosing was not addressed. All preparations were given twice, 14 days apart, and the horses followed a similar exercise pattern throughout the study. Corticosteroid treatment was repeated 14 days apart followed by immediate exercise without a rest period. Because of the temporal pattern of these studies, more sophisticated parameters were measured in the most recent studies so direct comparisons between all preparations was not feasible.

A summary of the results from the Betavet\textsuperscript{\textregistered} study indicate that no deleterious effects were observed with this preparation, although no significant beneficial effects were seen either. The results of this study did suggest no deleterious effects associated with Betavet\textsuperscript{\textregistered} at the tested dose and frequency. The lack of beneficial effects in the model was in contrast to the perception of clinical improvement when Betavet\textsuperscript{\textregistered} was used in the field. However, it is possible that the low level of pathology induced with the experimentally created fragment potentially masking an improvement that was not statistically documented. Therefore, in subsequent studies a small portion of the parent bone from which the fracture was created was removed using a burr (the debris created from the burring process was left within the joint). This change in the model did create more inflammation and probably more closely mimicked a clinical case with osteochondral fragmentation.

The results of the study evaluating Vetalog\textsuperscript{\textregistered} indicated this preparation to be a very effective anti-inflammatory drug without negative side effects on the articular cartilage and indeed there were some suggestions of chondroprotective effects seen in measured parameters. Additionally, significant improvement in the clinical parameter of degree of lameness in the limb containing the osteochondral fragment was also observed with the treatment of Vetalog\textsuperscript{\textregistered}. Furthermore, after all three studies were completed Vetalog\textsuperscript{\textregistered} was the most beneficial based on the measured parameters.

The study evaluating Depo-Medrol\textsuperscript{\textregistered} was less consistent in its beneficial effects and although some improvement in the lameness scores in limbs treated directly with Depo-Medrol\textsuperscript{\textregistered} was seen, it was not statistically significant as compared to the placebo-treated controls. Other parameters that have been associated with joint pain, such as prostaglandin E\textsubscript{2} (PGE\textsubscript{2}) levels within the synovial fluid, were significantly improved with Depo-Medrol\textsuperscript{\textregistered} treatment (PGE\textsubscript{2} was not measured in the other studies). However, there were deleterious effects seen in articular cartilage following treatment with Depo-Medrol\textsuperscript{\textregistered} similar to those previously reported by other researchers, causing some reason for concern.

In summary, the three preparations tested using a relatively similar osteochondral fragment model indicated the most beneficial effects were seen with Vetalog\textsuperscript{\textregistered} and in fact some protective effects were associated with this preparation. Although Depo-Medrol\textsuperscript{\textregistered} did have some measured effects that would be considered beneficial, detrimental effects to the articular cartilage were also demonstrated. Lastly, Betavet\textsuperscript{\textregistered} had no significant effects and may suggest that this preparation has a less potent effect on joint
tissues as compared to Vetalog® and Depo-Medrol® (although lack of differences may be due to the slight differences in the experimental models). In vitro studies have also shown the ability of methylprednisolone to inhibit specific mediators associated with cartilage degeneration while betamethasone failed to inhibit similar molecules. Interpreting these experimental results in light of clinical use suggests that Betavet® (or more recently Celestone Soluspan®) has a shorter acting treatment period or less potency with no detected negative side effects. Depo-Medrol®, while having clinically the most potent and longest acting effect of the three preparations, was not associated with the best clinical response in an experimental situation, and can be associated with cartilage degeneration. Based on the research presented in the comparisons of these three preparations the use of Vetalog® at recommended doses may provide more beneficial and less deleterious effects on the long-term health of joint tissues as compared to Depo-Medrol®, while providing a longer duration of action as compared to the betamethasone products.

Combination Therapy

Combination treatment regimes have also been studied recently, in hopes that a pro-anabolic substance might counteract the anti-anabolic effects seen on cartilage matrix metabolism following corticosteroid administration. Specifically, recently published in vitro studies using equine cartilage explants have assessed insulin-like growth factor-1 (IGF-1), a substance known to stimulate cartilage metabolism, in combination with Vetalog®. To date, this research has encompassed proof of principle experiments, which began by demonstrating that at single concentrations of corticosteroid (Vetalog®) and IGF-1, beneficial effects on cartilage metabolism were seen. This work was followed by separate dose titrations of each agent individually and then in combination. The final concentration of IGF-1 (500 ng/ml) and Vetalog® (1.2 mg/ml) were shown to block the anti-anabolic effects seen with Vetalog® alone and the catabolic effects seen with IL-1 exposure. Further studies evaluating this and other combination therapies are needed using in vivo designs.

Although many therapeutic substances have been combined with IA corticosteroid treatment clinically, little controlled experimental work has been published. This work is needed to validate the optimal combination and correct doses of these therapeutic agents.

Laminitis and IA Corticosteroids

One must consider the reported incidence of corticosteroid-induced laminitis when comparing corticosteroid preparations. Cases of laminitis have been associated with various corticosteroid preparations and one must remember all corticosteroids possess the ability to induce laminitis. Furthermore, the therapeutic index may not be the same for all preparations. Anecdotal reports certainly suggest a narrower therapeutic index with Vetalog® as compared to Depo-Medrol® and Betavet®/Celestone Soluspan® when it comes to laminitis as a secondary complication with joint injections. It has been suggested that the total body dose of Vetalog® not exceed 18 mg, Depo-Medrol® 200 mg, and Betavet® 30 mg, and while these numbers are based on some fact and some fiction one of the main goals is to eliminate corticosteroid-induced laminitis.

Regulatory Issues Related to the Athletic Horse

Is IA Corticosteroid Administration

Performance-enhancing?

Based on the Association of Racing Commissioners International (ARCI) classification, corticosteroids fall into a category of drugs defined as performance restoring and are considered to normalize behavior and relieve symptoms of performance-impairing disorders. The ability of IA corticosteroids to reduce pain in diseased or “inflamed” joints is with few exceptions globally accepted in the scientific community as well. Therefore for the purposes of this manuscript the ARCI definition will be accepted as accurate. The systemic administration of corticosteroids also has questionable performance-enhancing properties that will be discussed in a following section of this paper.

Three governing bodies oversee most of the sanctioned equine competition in the United States, American Horse Shows Association (AHSA), Federation Equestre Internationale (FEI), and the ARCI. Although stated in different terms, these organizations attempt to limit drug use for the purpose of altering a horse’s performance while competing in sanctioned events. Based on this intent, IA corticosteroids may not be in complete compliance with drug policies drafted by these organizations. A closer inspection of how IA corticosteroid administration relates to policies from each organization is required.

Policies Governing Equine Competitions with Respect to IA Corticosteroids

The ARCI passed a model rule on Drug Classification and Penalties that includes the specifications for Uniform Classification Guidelines of Foreign Substances, which classifies many different drugs into five classes. The classes are then used to determine severity of the penalization if a horse tests positive with a drug in a particular class; detection of class 1 drugs is punished most severely and class 5 least severely. Corticosteroids are considered class 4 substances and are therefore associated with guidelines set forth by the ARCI for penalization of that class substance. Because horses participating in events sanctioned by the ARCI are not allowed to test positive for corticosteroids, the equine veterinarian should be aware after
what time period following IA corticosteroid administration a horse will no longer test positive (withholding time), this question will be discussed in a subsequent section of this paper.

The AHSA has a Drug and Medication Program that enforces the AHSA Drugs and Medications Rule. Articles 410–412 are the Therapeutic Substance Provisions of the rules, under which most horses compete. These articles define a forbidden substance as a drug which might affect the performance of a horse and/or pony as a stimulant, depressant, tranquilizer, local anesthetic or psychotropic substance, or one which might interfere with the detection of the above (a masking substance). Corticosteroids administered by any route including IA have primarily anti-inflammatory effects. Articles 410–412 permit the therapeutic use of corticosteroids. The Endurance Riding Division of the AHSA is subject to the No Foreign Substance Provisions (Article 409), under which corticosteroids are forbidden. The American Quarter Horse Association (AQHA) classifies corticosteroids as forbidden and imposes the same requirements on their use as for a forbidden substance under either AQHA or ASHA Rules, specifically, that they be used only for a therapeutic purpose, that the animal must be withdrawn from the competition for a period of not less than 24 hr after the medication is administered and that proper documentation must be completed and provided to a Steward/Technical Delegate within one hour. Guidelines issued by the AHSA regarding the length of time before returning to competition pertain to the No Foreign Substance Provisions of the AHSA Rules (Article 409). For most drugs the AHSA suggests a generic 7–14 day period elapse prior to competition, but for a few drugs the time is longer (e.g., reserpine and fluphenazine, 45 days).

FEI-recognized events are subject to the FEI Veterinary Regulations, which are a no foreign substance rule. This includes reporting requirements for the treatment of illness and injury and would therefore include the use of IA corticosteroids, again raising questions of withholding times.

How Long Will a Horse Test Positive After IA Corticosteroid Administration?

The answer to this question is dependent on enough variables that it is impossible to definitively answer; however, guidelines can be found using defined circumstances including specific doses of certain preparations and defined methods currently available to test for these preparations and/or their derivatives. Many authors have published on factors associated with “doping” or positive drug tests and as a result many different terms have evolved. For the purposes of this article the term “withholding time” will be used to mean the time from drug administration until the drug is undetectable or until the drug concentration is below the regulatory limit for that drug in blood or urine samples as defined by Gerken and Sams in 1993. Three other terms are worth defining prior to further discussion.

1) Lower limit of detection: The lower limit of detection is the lowest concentration (or amount) of a drug that can be detected by an analytic method. The limit of detection is often defined as that drug concentration that gives rise to an electric signal (detection device) that is three times the background noise level. Specific statistical methodology between laboratories can also introduce variance into this definition.

2) Limit of quantitation: The limit of quantitation is the lowest concentration of a drug that can be measured by a method and is often defined as that concentration that gives rise to a signal that is ten times the background noise levels.

3) No effect points: The specific pharmacologically defined concentrations in biological fluids at or below which the residues of the agents in question are “pharmacologically insignificant.”

In practice, equine veterinarians are often asked to provide withholding time estimates for specific medication including corticosteroids. Each individual bases their estimates on experience or research conducted under specific experimental conditions; the latter will be the focus of further discussion in this paper. Factors that should be defined and considered in conducting and interpreting the experimental conditions are the number of animals tested, the frequency, dose and route of administration, as well as the specific analytic method and lower limit of detection used in determining concentrations of a substance. Exact experimental conditions and analytic methods may differ from one individual or laboratory to another and should also be considered in withholding-time estimates.

Methylprednisolone

Based on current published scientific information methylprednisolone administered IA is associated with the longest withholding period. In one study five horses each received a 111.2 mg dose of Depo-Medrol® IA followed by blood and synovial fluid collection. Samples were analyzed using high performance liquid chromatography (HPLC). The authors quoted a lower level of sensitivity for the assay at 2–3 ng/ml in plasma and 10–20 ng/ml in synovial fluid. The factors associated with determination of sensitivity were not discussed in the publication, although for the purpose of discussion here, this term will be taken to mean lower limit of detection. The parent compound methylprednisolone acetate (MPA) was not detected in plasma samples at any time period, however; the hydrolysed active product of MPA, methylprednisolone (MP) was detected at levels less than 5 ng/ml only for the
first 24 hr following IA administration. MP was also detected in synovial fluid for 5–39 days depending on the horse. The authors also discussed the rapid conversion of MPA to MP suggest MPA is “rapid acting” when administered IA even though MPA is associated with the “long-acting/slowly-absorbed” acetate ester.

A more recent study assessed plasma, synovial, and urine fluid samples for MPA and MP concentrations. This study used 4 horses to assess a 100 mg IA dose of Depo-Medrol quantified using both enzyme linked immunosorbent assay (ELISA) and HPLC methods. The authors reported a lower limit of detection for the ELISA to be 2.5 ng/ml and 10 ng/ml for HPLC. Plasma values of MPA and its derivatives were detected until 12 hr after administration using the ELISA, while HPLC methods in this study did not detect MPA or MP at any time point using plasma samples. Using the ELISA, MPA, or its derivatives were detected until 72 hr after IA MPA administration. Synovial fluid samples analyzed using HPLC had MP detected in one horse 10 days after administration. Interestingly, joint fluid from the opposite untreated joint was also subjected to analysis and found not to contain detectable limits of MPA or MP. This finding led the authors to conclude concentrations sufficient to induce a physiologic effect are not reached in non-treated joints. Based on other authors and subsequent research, these conclusions may be questioned.

Differences between methodology and horse-to-horse variation are cited as an explanation for differing results between these two studies. Synovial fluid, urine, and plasma samples have a sequentially decreasing time in which MPA or MP can be detected. Given that only urine and blood samples are collected in current drug testing protocols, a single 100 mg dose of Depo-Medrol should be administered at least 72 hr prior to a sanctioned event to avoid a positive blood or urine result. It is important to note many physiologic factors such as urine flow rate, intra-horse and inter-horse variability, feeding, disease, and exercise, as well as pharmacologic factors such as dosage, frequency and route of administration, drug interactions, and various formulation can significantly affect plasma and urinary detection of various substances. Tobin uses a dramatic example to make this point in his book Drugs and the Performance Horse, where he cites a rather mind-boggling 9,000-fold possible range in urinary procaine concentrations, given a single, fixed plasma level of the drug. This range is possible because of the log scale used in measuring urine pH, the wide pH range of equine urine, and procaine’s propensity to concentrate more in acidic urine.  

Similar ranges have not been published for IA corticosteroid administration, but Gerken and Sams offer some generic guidelines that doubling the dose doubles the peak plasma and urine concentration and increases the time that the drug will be detected by one half-life of the drug. Although Lillich reported detection results for urine, half-life values were only calculated for synovial fluid data. Based on both published reports the mean half-life of synovial fluid MPA or MP is between 10.4 and 115.5 hours depending on the study. Therefore, the withholding time would be 7.8 days following a single 200 mg IA dose of Depo-Medrol based on the previous assumption and using the longer synovial fluid half-life of MPA and MP. In a recent publication Tobin et al. compiled a table of the shortest and longest detection times for therapeutic medications in racehorses, although variability due to different routes of administration, doses, preparations and detection methods were not considered MPA was associated with a 96 hour–44 day detection period in urine.

Triamcinolone

Two scientific studies have been published assessing the body fluid concentration of triamcinolone (TA) following IA administration of Vetalog. The first study utilized seven horses and administered 6 mg to each of three joints. Serum and synovial fluid TA concentrations were estimated using a radioimmunoassay with a sensitivity of 10 pg/tube; the determination of the sensitivity was not specifically detailed although the standard curve indicated that 10 ng/ml was the lowest concentration tested. Serum TA levels peaked 4 hr after IA administration and was undetectable at 3 days. Fifteen days following the 18 mg dose of TA (total dose per horse), TA levels were undetectable in synovial fluid. Similar to studies assessing Depo-Medrol administration, a high variability among horses was observed with TA; five of the seven horses had very low levels of synovial fluid TA on the fourth day while 2 horses had small but detectable amounts up to the fourteenth day following IA TA administration. Another study utilized four horses and 30 mg of IA Vetalog, and TA quantification was performed using HPLC at a detection limit of 0.1 ng/ml. Mean peak concentrations of TA were seen at 12 and 22 hours in serum and urine samples respectively after IA TA administration. Triamcinolone was undetectable in serum by 120 hr and in urine by 200 hr after administration. In the previously mentioned publication by Tobin et al, the detection limit was reported as 24 hr for TA. Based on published studies, Vetalog is still detectable almost 9 days after administration following a 30 mg dose (note this total body dose is higher than recommended).

Betamethasone

Similar studies using IA Betavet or Celestone were not identified in either a Medline or CABI search. Tobin et al. did report the detection time for betamethasone in urine to be 24 hr; however, many variables are involved including route of administration and dose were omitted. Another ref-

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Stimulation of appetite, which in humans has been providing an increase in available energy, and 2) the stimulation of fat utilization and amino acids leading to defining a definitive testable biologic effect of IA corticosteroids does not appear to exist. Other studies not seeking to define pharmacologic effects have indicated IA corticosteroids have significant measurable actions weeks after current detection methods indicate an absence of the parent compound or metabolites. This and a lack of a definitive pharmacologic effect for regulatory purposes may slow down the need to be completed before a better guide for the equine practitioner can be recommended. The previously outlined scientific studies have provided some scientific guidelines to be used in estimating withholding times after IA corticosteroid administration of Depo-Medrol® or Vetalog®.

Systemic Corticosteroids
In 1988 a report was published that specifically addressed the influence of systemically administered synthetic corticosteroids on racing performance. All 87 Standardbred horses entered in the study were administered dexamethasone (10–40 mg), flumethasone (5–10 mg) or prednisolone (75 mg) intravenously (IV) once, at least 2 to 8 hours prior to a race. Race results were collected for each horse entered in the study on days when corticosteroids were and were not administered; only results from an individual horse were compared (with or without corticosteroids pre-race). When the race results of an individual horse receiving corticosteroids pre-race had an average race time that fell one-fifth of a second outside (either below or above) one standard deviation of its average, it was considered to have had its performance affected. It should be noted statistical analysis of the data, excluding calculation of averages and standard deviations, was not performed in this study. This study reported 44% of the horses studies showed no significant change in racing performance when pre-race corticosteroids were administered. In contrast, 18% of the horses showed decreased performance and the remaining 38% of the horses demonstrated increased performance when assessed as described previously. This report concludes that half of the horses administered systemic corticosteroids will have their performance affected in either a positive or negative manner, although more rigorous analysis of the data should be conducted prior to definitive conclusions being reached.

Reports have speculated potential mechanisms for performance altering effects following systemic corticosteroid administration that include 1) stimulation of fat utilization and amino acids leading to increased blood glucose levels, potentially providing an increase in available energy, and 2) the stimulation of appetite, which in humans has been associated with euphoriants or stimulant effects and even dependency. These proposed effects have lead to the use of systemic corticosteroids prior to equine events when increased energy is desired. It has also been reported that large doses of systemic corticosteroid have been associated with calming or tranquilizing effects and may be utilized in some show horses for this purpose.

Numerous reports have been published regarding detection times following systemic administration of corticosteroids. Because the systemic administration of corticosteroids to alter performance typically occurs within 8 hr of the horse competing in the event and corticosteroids can be detected in urine in most reports for at least 24 hr, current assays are sufficient for “anti-doping” prevention. Because screening assays for corticosteroids (thin-layer chromatographic) being used by many laboratories in the United States have a low sensitivity, positive results rarely occur more than 24 hr after dosing. Equine veterinarians should be cautioned, however, because through use of more sensitive techniques many of the corticosteroid preparations can be detected for many days. As an example, following a 5 mg IV dose of dexamethasone, urine dexamethasone levels were detectable for 7 days using an ELISA or RIA. Further examples of withdrawal time in relation to specific systemic doses can be found in published references.

What Should be the Future of Corticosteroid Regulation?
Most studies that publish data on positive doping tests, including corticosteroids, do not separate its use for systemic or musculoskeletal effects. Because the number of samples reported to be positive for corticosteroids is low this may not be a limiting factor. In fact, a study that reviewed positive Jockey Club “dope tests” during 1975–1981 in the United Kingdom reported no positive corticosteroid samples. In another study 4 horses tested positive for corticosteroids and in 1999 an “in-house” AHSA survey revealed less than 5% of all urine samples (3000 samples tested for the AHSA, FEI, and AQHA) tested positive for corticosteroids and thus appeared not to represent a serious problem as viewed by the AHSA. Furthermore, as previously mentioned, chemists at the AHSA testing laboratory currently consider corticosteroid administration difficult to confirm after 24 hr, although the route, preparation and dose were not specified.

The lack of ‘no effect points’ for IA corticosteroids poses a problem in evaluating regulatory issues associated with their use. Although other therapeutic substances have no effect points defined based on accepted pharmacologic effect studies, work specifically aimed at defining a definitive testable biologic effect of IA corticosteroids does not appear to exist.
definition of no effect points associated with IA corticosteroid administration leaving the U.S. equine practitioner without solid guidelines. The U.S. regulatory bodies governing equine events should therefore consider following the lead set forth by Canada, Australia, and Western Europe where withholding times are based on standardized testing methods that eliminate the inter-laboratory variability based on changes in detection method or intra-laboratory variability. This would at least provide U.S. equine practitioners with solid guidelines on which to base their therapeutic protocols, until then this paper provides some scientific guidelines for use of corticosteroids in the athletic horse.

References and Notes


a Frisbie DD. Unpublished data. 1999.

b Lengel JG. (Hilliard, OH) Personal communication. 2000.