



MEDICATION CONTROL OF CORTICOSTEROIDS IN HORSERACING

What are the issues?

Tim Morris

Clive Pearce

Purpose of this session



- Place corticosteroid medication control in an international context
- Stimulate the issues for the discussion session
- Set a pathway to science based withdrawal advice for corticosteroids
- Enhance international cooperation and harmonisation





Just one approach to science based withdrawal advice



- 1. Perform drug time concentration study
- 2. Determine the irrelevant plasma concentration
- 3. Apply risk management by EHSLC consensus using an ordinal scale
- 4. Set a harmonised screening limit
- 5. Translate to a Detection Time and publish
- 6. Use Detection Time to estimate Withdrawal Time



Generic framework for medication control





Risk Management







ICRAV 2012

RMTC NEWS RELEASE: RMTC RECOMMENDS NEW PHENYLBUTAZONE THRESHOLD LEVEL, ANNOUNCES LAUNCH OF RECENT RULINGS DATABASE

April 15, 2010 act: Halle Lenix (859) 224-2848

Risk Communication



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Home	Wittednamat Terrina I Mitedai Flainia I
About Us Our Work	Withdrawal Times
News	The RMTC Withdrawal Times Database is a collection of withdrawal time suggestions that our office

Risk Assessment (RA)

- Are corticosteroids a concern?
- What data do we have?
- Coordination of study planning?
- Sharing study data?
- Formulation issues
- Sample matrices?
- Analytical challenges?

British Horseracing

Authority



- Commonly used in racehorse treatment
- Relatively little science based withdrawal advice
- Current reviews on balance of safety and efficacy
- Better understanding of safe use driving increased use
- Risks of use remain
- More stringent controls on NSAIDs driving increased use in some jurisdictions
- Different potencies, formulations and routes of administration all used



- Commonly used in racehorse treatment
- Relatively little science based withdrawal advice

 From a survey of ~5000 samples over 10 years from British racehorses in training corticosteroids were the only drug class in top 15 used with no science based withdrawal advice

Rank	
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- Current reviews on balance of safety and efficacy
- Better understanding of safe use driving increased use
- Risks of use remain
- More stringent controls on NSAIDs driving increased use in some jurisdictions

17.00-17.15

Musculoskeletal injury following local corticosteroid injection in Thoroughbred racehorses

<u>Whitton, C.</u>, Jackson, M., Anderson, G., Campbell, A., Parkin, T. and Boden, L.

Faculty of Veterinary Science, University of Melbourne, 250 Princes Hwy, Werribee, Victoria, 3030, Australia. Email: cwhitton@unimelb.edu.au





Ned Bonnie, a member of the KEDRC and the KHRC, said use of corticosteroids could increase should Kentucky lower the threshold testing level for phenylbutazone, a non-steroidal anti-inflammatory drug that can't be administered within 24 hours of a race.

RA: What data do we have?





RA: Coordination of study planning?



Costs

— 100,000's of \$.€,£s

Ethics

- National and Federal laws on animal experiments
 - Replication versus Duplication
- Replication an essential component of science
- Validation across worldwide TB population
- Duplication an economic ethical and legal concern
 - Dex Na Phos graphs versus PK data
 - Dex Na Phosphate iv versus TCA ia
- From agreement to process to implementation?



•What is need to share study data?

- To allow replication and problem solve
- Before final publication and protect publication
- When not published
- To see the full study data
- Protect security and confidentiality



RA: Formulation issues



Different Potencies

- Hydrocortisone 1X Prednisone 4X Dexamethasone 25X

Different formulations

Solubility, esterification, excipients, pharmacopeia specification

Different routes of administration

- Oral, iv, im, ia, intra/fascial, topical, ocular









- Advances in LC-MS technology, particularly MS/MS, have taken corticosteroids from being a difficult group of compounds to analyse to one that is relatively straight-forward
- Drug screens can be set up to detect concentrations down to 50 pg/ml routinely (every day operation)
- Some routes of administration, notably the inhaled route, require detection of concentrations close to (or even below!) 1 pg/ml – this pushes the sensitivity of even the latest LC-MS/MS systems and can be expected to require extensive sample work-up beforehand, i.e. a targeted assay rather than routine screen





RA: Analytical challenges

- Corticosteroids have been a concern for racing jurisdictions in Europe and Asia for 30 years, and for several years in the US, but until relatively recently the prospect of enforcing drug withdrawal through laboratory detection has not been feasible technically
- For most routes of administration it is now feasible to put screening methods in place to support detection times (DTs) derived from science-based risk assessment
- PK/PD and DT studies often serve to underpin the RA process and require fully quantitative methods to establish parameters such as IPC and IUC; given an goal of implementing a routine screen capable of 50 pg/ml sensitivity, the quantitative methods used in the prior RA work need LOQs comfortably below 50 pg/ml
- Fully modelled RA studies for locally-acting administrations such as IA may require examination of a number of matrices, e.g. synovial fluid, blood and urine



Risk Management (RM)

- Understanding biological effects and endpoints
- Managing biological effect and defining endpoints
- Different approaches to risk management
- Targeted and routine analytical capability

British Horseracing

Authority

RM: Understanding biological effects and endpoints



 Are models for drugs given intravenously with first order excretion valid for all drugs by all routes?



RM: Managing biological effect and defining endpoints



 Is detection of parent drug in plasma, or parent or metabolite in urine always appropriate and/or possible for medication control?



RM: Different approaches to risk management



-Americas and Rest of World different

- ARF and EHSLC *not* identical
- North and South America not identical
- Rest periods by records control
 - May be needed for intra-articular or pulmonary administrations
 - Especially corticosteroids?
- -14 days rest under discussion and use in Europe
 - US similar approach?
 - Difficult to enforce



- Different analytical focus for RA and RM (screening) stages but outcomes are intimately linked, e.g. use of validated, high sensitivity methodology to model beyond the IPC/IUC might only be necessary for the RA stage, whereas choices of target analyte or whether or not to hydrolyse necessitate decisions at both stages
- Ideally, international harmonisation of RA methodology would result in subsequent harmonisation during RM and RC stages
- Methods may not need to be as sensitive as during the RA stage and could use surrogates (e.g. metabolites) if these have been appropriately modelled
- Inhaled (nebulised) corticosteroids, e.g. fluticasone propionate, likely to require more extensive sample work up and greater instrument sensitivity than is practicable for routine (every day) screening



Inhaled corticosteroid steroid drugs, such fluticasone propionate, have very low and variable systemic presence - consequences for blood and urine detection (more challenging than other inhaled drugs)



flucicasone propionate (9 doses over 4 days – total 5 mg)

salbutamol (8 doses over 2 days - total 4 mg)

Generic framework for medication control



Risk Communication (RC)
 –National
 –Regional

-International



RC: National



- •Laws
- Culture
- Politics
- Inertia
- Communication

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Doping and drug detection times in I	iorses:
New data for therapeutic agents	
Dr Tum Barragry	
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DETECTION OF THERAPEUTIC SUBSTANCES IN RACING HORSES

RC: Regional









- ARF working with EHSLC on harmonisation at RM and RC stage
- RMTC working with EHSLC at RA stage
- •None of the above are primary regulators!



- IFHA working with ARF and EHSLC at RM stage
 The International Agreement is not mandatory
- Is what trainers, owners and vet want consistent withdrawal time advice consistently applied ?
- Is this what is being delivered?



Possible topics for Discussion?



- Risk Assessment (RA)
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 - Sharing study data?
 - Formulation issues?
 - Analytical challenges?
- Risk Management
 - Understanding biological effects and endpoints
 - Managing biological effect and defining endpoints
 - Different approaches to risk management
 - Targeted and routine analytical capability
- Risk Communication
 - National
 - Regional
 - International

Focus for Discussion



- Risk Assessment (RA)
 - Are corticosteroids a concern?
 - What data do we have?
 - Coordination of study planning?
 - Sharing study data?
 - Formulation issues?
 - Analytical challenges?
- Risk Management
 - An abstract exercise without data
 - A source of hours of distraction!
- Risk Communication
 - Ultimately a matter for each Racing Authority

The real question?



 In the context of the use and importance of corticosteroid medications in horseracing

— "What can we do <u>now</u> to create, share and understand data to help <u>others</u> to manage and communicate the risks of their use?" With thanks to all the contributors to this session who by example have led the way to answering that question

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