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British Horseracing Authority

MEDICATION CONTROL OF CORTICOSTEROIDS IN HORSERACING

What are the issues?

Tim Morris

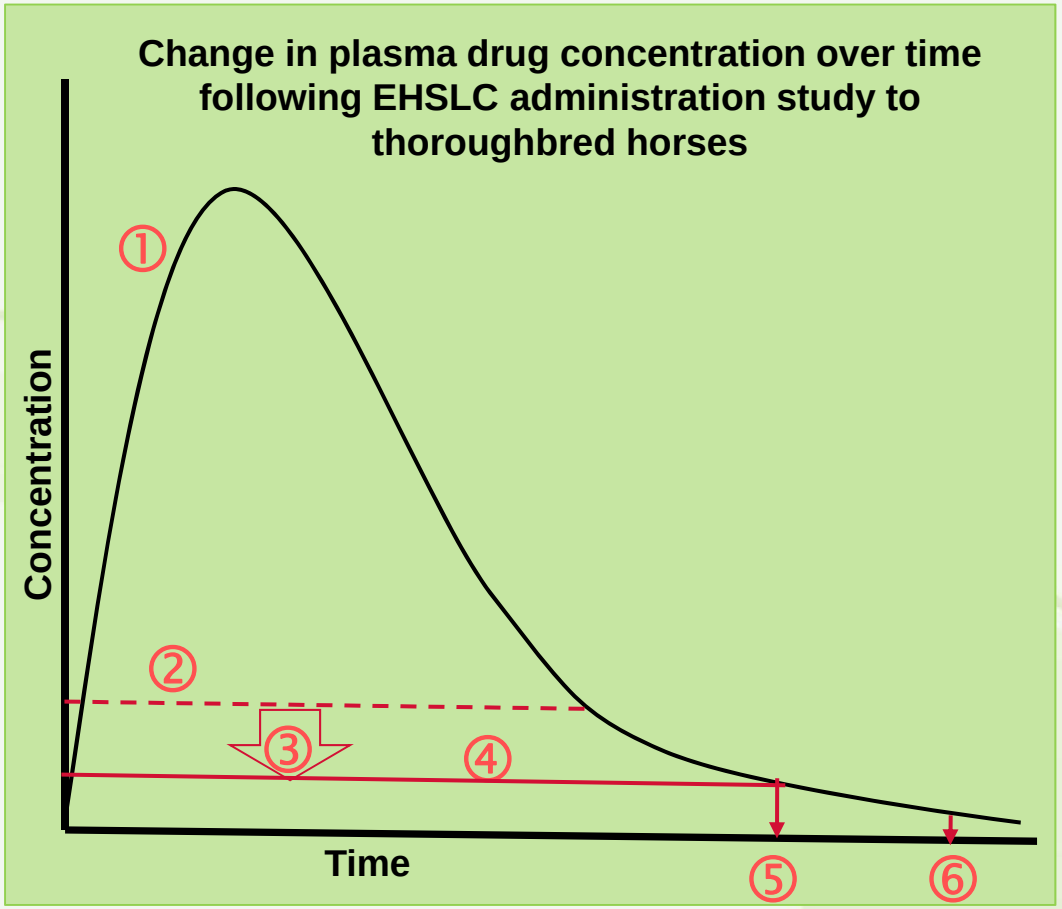
Clive Pearce

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

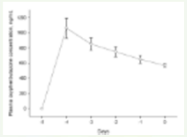
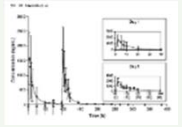
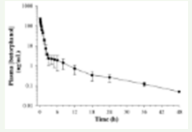
1. Perform drug time concentration study
2. Determine the irrelevant plasma concentration
3. Apply risk management by EHSLC consensus using an ordinal scale
4. Set a harmonised screening limit
5. Translate to a Detection Time and publish
6. Use Detection Time to estimate Withdrawal Time



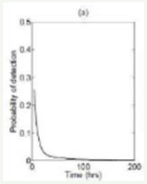
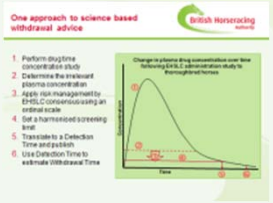
Generic framework for medication control



- Risk Assessment

- Risk Management

- Risk Communication



Generic framework for medication control

- 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?

RA: Are corticosteroids a concern?

- 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

RA: Are corticosteroids a concern?

- 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

Drug	Rank
Oxy and Phenylbutazone	1
Omeprazole metabolite(s)	2
Trimethoprim	3
Dantrolene metabolite(s)	4
Acepromazine metabolite(s)	5
Flunixin	6
Morphine	7
Caffeine	8
Clenbuterol	9
Dembrexine	10
Meloxicam	11
Beta/Dexamethasone	12
Theobromine	13
Mepivicaine	14
Xanthines	15

RA: Are corticosteroids a concern?

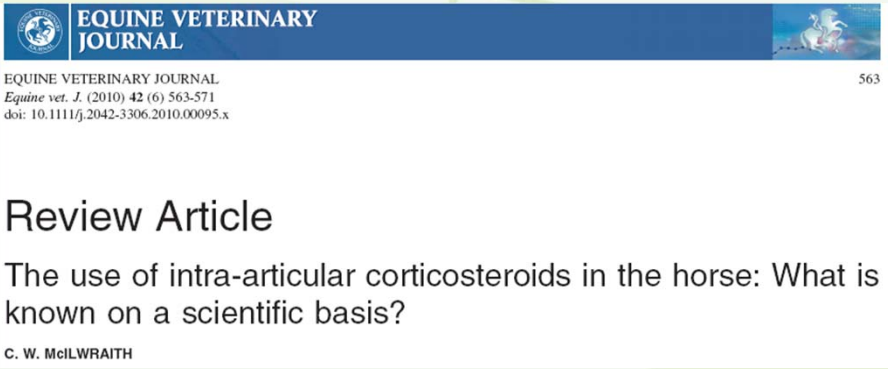
- Current reviews on balance of safety and efficacy
- Better understanding of safe use driving increased use
- Risks of use remain
- More stringent controls on NSAIDs driving increased use in some jurisdictions

17.00–17.15

Musculoskeletal injury following local corticosteroid injection in Thoroughbred racehorses

Whitton, C., 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



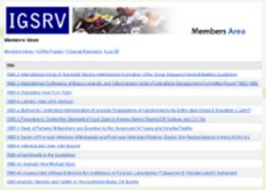
Ned Bonnie, a member of the KEDRC and the KHRC, said use of corticosteroids could increase should Kentucky lower the threshold testing level for phenylbutazone, a non-steroidal anti-inflammatory drug that can't be administered within 24 hours of a race.

RA: What data do we have?

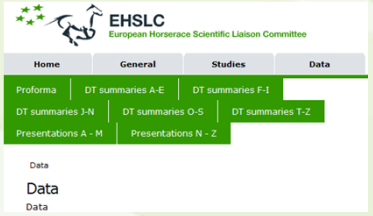
- Published studies

  - Published reports

    - ICRAV proceedings



      - Unpublished

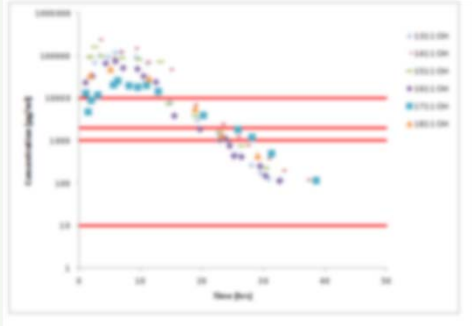


RA: Coordination of study planning?

- 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?

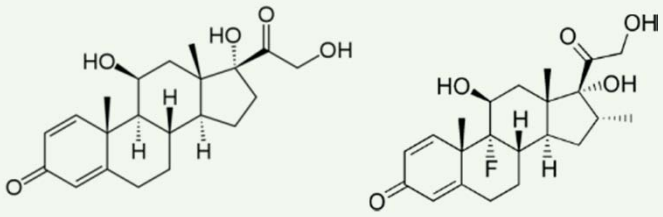
RA: Sharing study data?

- 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



RA: Analytical challenges

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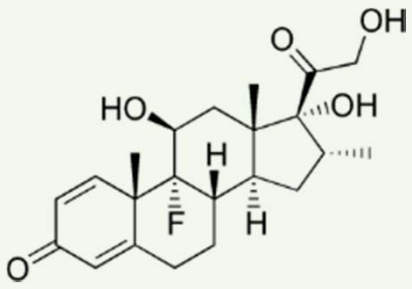
- Advances in LC-MS technology, particularly MS/MS, have taken corticosteroids from being a difficult group of compounds to analyse to one that is relatively straight-forward
- Drug screens can be set up to detect concentrations down to 50 pg/ml routinely (every day operation)
- Some routes of administration, 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

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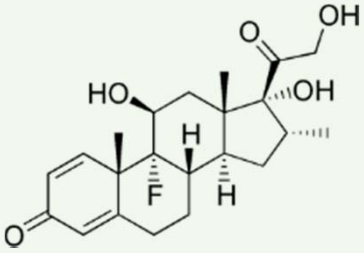
- Corticosteroids have been a concern for racing jurisdictions in Europe and Asia for 30 years, and for several years in the US, but until relatively recently the prospect of enforcing drug withdrawal through laboratory detection has not been feasible technically
- For most routes of administration it 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

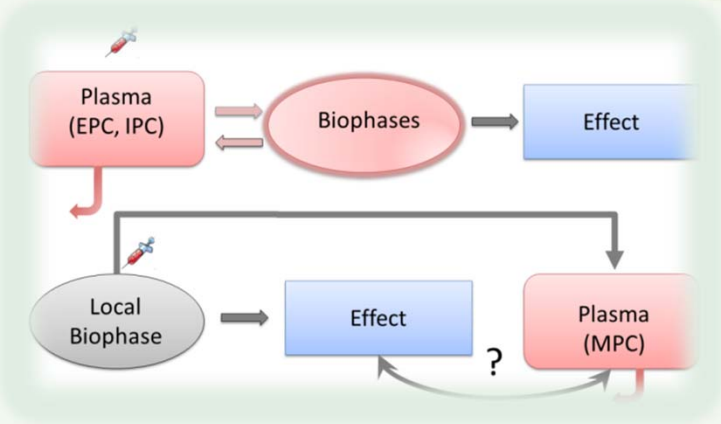


Generic framework for medication control

- Risk Management (RM)
  - Understanding biological effects and endpoints
  - Managing biological effect and defining endpoints
  - Different approaches to risk management
  - Targeted and routine analytical capability

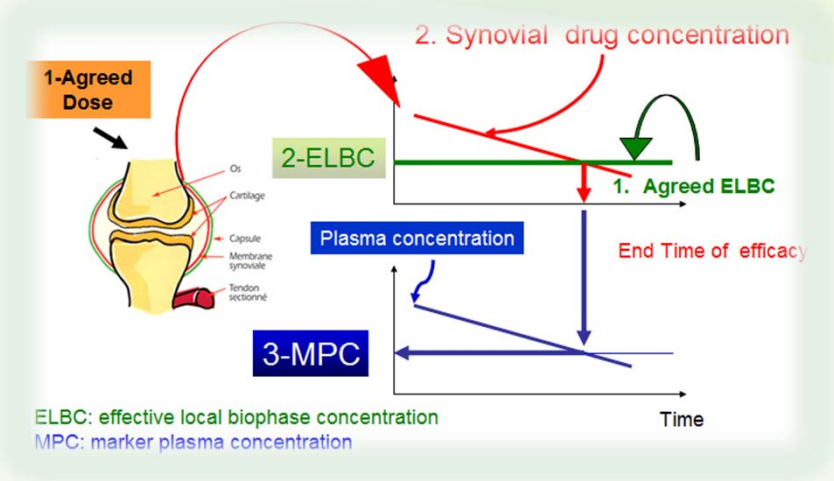
RM: Understanding biological effects and endpoints

- 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

RM: analytical capability

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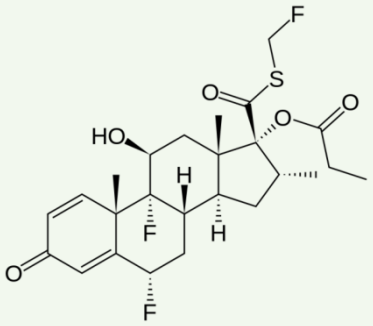
- Different analytical focus for RA and RM (screening) stages but outcomes are intimately linked, e.g. use of validated, high sensitivity methodology to model beyond the IPC/IUC might only be necessary for the RA stage, whereas choices of target analyte or whether or not to hydrolyse necessitate decisions 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



RM: analytical capability

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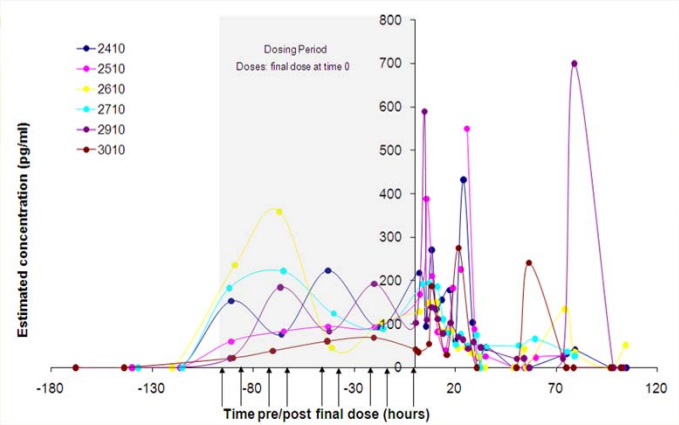
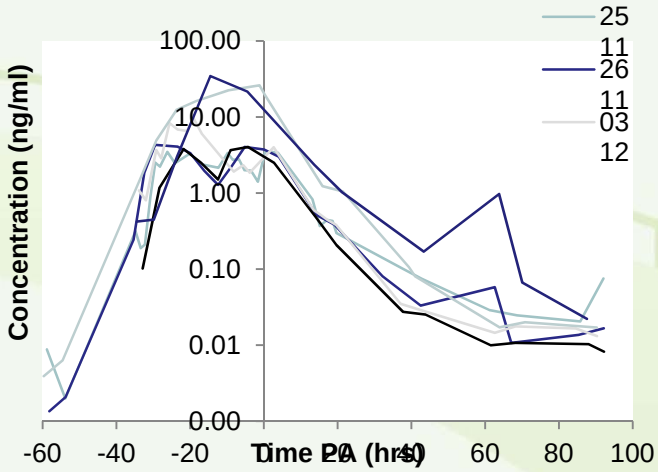
Inhaled corticosteroid steroid drugs, such fluticasone propionate, have very low and variable systemic presence - consequences for blood and urine detection (more challenging than other inhaled drugs)





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


DETECTION OF THERAPEUTIC SUBSTANCES IN RACING HORSES

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continuing education

Doping and drug detection times in horses:
New data for therapeutic agents

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!

RC: International

- 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)
  - Are corticosteroids a concern?
  - What data do we have?
  - Coordination of study planning?
  - Sharing study data?
  - Formulation issues?
  - Analytical challenges?
- Risk Management
  - Understanding biological effects and endpoints
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  - 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 now to create, share and understand data to help others 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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