Traditional/Non-traditional ’New’ Equine Orthopaedic Therapeutics - A UK Perspective

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NW Equine Referrals, UK & France
<table>
<thead>
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<th>Diagnosis</th>
<th>Treatment</th>
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<td>Broken leg</td>
<td>Shoot</td>
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<td>Infected eye</td>
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<td>Splayed hoof</td>
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<td>Runny nose</td>
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<td>Open sores</td>
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<td>Swollen belly</td>
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<td>Swayback</td>
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Like most veterinary students, Priscilla breezes through Chapter 9.
Introduction

- 60% of equine lameness problems related to osteoarthritis (OA)
- Understanding OA as a dynamic spectrum disease
- Understanding the pathophysiology of OA
- Understanding the biological effects of currently available therapeutic agents
- Appreciating advanced imaging in the evolution of joint therapies in particular, MRI
- Appreciating the contribution of diagnostic and surgical arthroscopy in the treatment of OA
Consider the joint as a highly differentiated structure:

- Normal joint structure & function
  - Synovium/Synovial fluid
  - Peri-articular soft tissues
  - Subchondral bone
  - Articular cartilage - collagen/proteoglycans/matrix proteins/chondrocytes/nutrition

Joint lubrication
(Intra-articular volume & pressure)
(Biomechanical considerations)
Joint Components

- External support structures
- Joint Capsule
- Synovial membrane
- Articular cartilage
- Subchondral bone
Synovial Membrane
Articular Cartilage 2

- Proteoglycan complex
  - Glycosaminoglycans (GAG’s)
    - repeating disaccharide units
  - The most important GAG’s in joints
    - Hyaluronic acid; non sulfated
    - Chondroitin Sulfate 4 & 6
    - Keratin Sulfate

[Image of articular cartilage]
Osteoarthritis (OA)

- Changes to structure & metabolism of the joint structures
- Equine OA is a group of disorders characterised by a common end stage: ‘progressive deterioration of the articular cartilage accompanied by changes in the bone and soft tissues of the joint’
Osteoarthritis Pathophysiology

Normal | Early | Late

Aggrecan (Proteoglycans) + Degradative Enzymes → Matrix Damage → Cartilage Erosion


Roudebush NAVC
Pain in Chronic OA

- Joint capsule, menisci, ligaments
- Increased intra-articular pressure
- Subchondral bone
- Periosteum
- ‘Central sensitisation’
- Neurogenic inflammation - neuropeptides, **substance P**
- Anxiety/depression…
At a Molecular Level…

- Role of Synoviocytes / Synovial fluid
- Role of Chondrocytes
- Role of Subchondral bone
- MMPs - collagenases, stromelysins, gelatinases
- Aggrecanase (ADAMTSs 1, 4, 5)
- Prostaglandins
- Catabolic cytokines (pro-inflammatory) - IL-1, TNF
- Modulatory (regulatory) - IL-4/6/10/13
- Anabolic (growth) - IGF-1, TGF, bFGF
- Nitric oxide
- TIMPS
Enzyme Activity
Clinical Evaluation of Joint Disease

- Joint pain
- Local signs - degrees of heat & swelling
- Synovial fluid changes (gross/cellular/TP)
- Radiography
- Ultrasonography
- Bone scan
- MRI
- (CT)
- Arthroscopy
Diagnostic Imaging 5b - CAT Scans
Smith, 2008
Aims of Joint Therapy

- Reduce pain
- Reduce symptoms (‘SMOADs’)
- Minimise/arrest progression of joint deterioration (‘DMOADs’)
- **Stimulate cartilage regeneration**

‘Good’ cartilage is functionally adapted to the loading conditions it is subjected to
Medical Treatment of OA

- Slow or arrest progression of lesions ‘Chondroprotection/Disease Modification’ (DMOADs)
- Therapeutic decision making based on:
  - Specific joint involved (‘high v low motion’)
  - Stage of OA
  - Current & intended use of horse
  - Age & type of horse
  - Competition regulations (Jockey Club/FEI)
  - Treatment cost
  - Response to initial therapy
‘Critical thinking’ is the process of evaluating the merit and reliability of a stated fact and deciding whether the fact should be accepted or rejected.

In other words, don’t believe everything you read and hear!

Be a critical thinker and a critical reader and listener!

Dwyer, 2010
Equine Orthopaedic Therapeutics Delegate Survey…..

- NSAIDs
- Corticosteroids (short-acting versus long-acting)
- HA - i/a versus i/v versus po
- Corticosteroids + HA
- PSGAGs (Adequan)
- Pentosan polysulphate (Cartrophen)
- Sodium tiludronate (Tildren) i/v (i/a, ivrp)
- Glucosamine +/- chondroitin / ASUs
- ACS/IRAP I & II (i/a, intra-tendinous, i/t/intra-ligamentous, i/l)
- PRP (i/a, i/t, i/l)
- Stem cells (bone marrow versus adipose derived/ i/a, i/t, i/l)
- Shock wave therapy (joints/tendons/ligaments/back)
- Physiotherapy & Rehabilitation
- Acupuncture (cf Mesotherapy)
- Homeopathy eg. Traumeel
- Manipulations eg. osteopathy, chiropractic
- Other eg. sarapin, internal blisters eg. 2%iodine in almond oil, 70% ethanol, Vit. B12, 0.9% saline, sterile water for injection, (black box, reike), other eg. Botox
NSAIDs - COX inhibitors

- Phenylbutazone (Equipalazone)
- Suxibuzone (decreased adverse effects of GI/renal systems) (Danilon)
- Flunixin (Finadyne)
- Meclofenamic acid
- Meloxicam (Metacam)
- Ketoprofen (Ketofen)
- Carprofen/Firocoxib (preferential COX-2 inhibition)
- Diclofenac sodium (topical cream)
Phenylbutazone (PBZ) v Suxibuzone (SBZ)

- Monreal et al, 2004
- Sabate et al, 2009
- SBZ is a prodrug of PBZ and converted to PBZ and oxyphenbutazone immediately after absorption from the GI tract (Mayos, 2002)
- No significant difference in alleviating lameness
- Lower gastric ulcerogenic effect than PBZ after oral administration
- SBZ better product acceptability
Meloxicam (Metacam)

- De Grauw et al, 2009
- Double blind randomised placebo controlled two-period cross-over study using a meloxicam po v morphine i/a and SF biomarker panels to measure effects on inflammation and cartilage turnover in acute synovitis model

- Improves clinical symptoms
- Reduced inflammation
- Limited inflammation-induced cartilage catabolism
Corticosteroids

- **Triamcinolone** (Frisbie, Kawcak et al, 1997)
- **Betamethasone** (Foland, McIlwraith et al, 1994)
- (Dexamethasone)
- **Methylprednisolone** (Murray, DeBowes et al, 1998; Murray, Znaor et al, 2002)
- Triamcinolone - ‘high motion joints’
- Methylprednisolone - ‘low motion joints’ ??
- + HA i/a ‘protective against steroids’ ???
Anecdotal risks of intra-articular corticosteroid use and laminitis…..

- Frisbie (2006)
  - Triamcinolone - maximum dose 18mg
  - Methylprednisolone - max 200mg
  - Betamethasone - max 30mg

- McCluskey and Kavenagh (2004) Clinical use of triamcinolone acetonide in horses (205) and the incidence of glucocorticoid-induced laminitis associated with its use

- Delegate survey…..?!
Sodium hyalurononate (HA)

- Non-sulphated GAG
- Anti-inflammatory through physical (steric hindrance) or pharmacological (inhibition of inflammatory cells and mediators) effects
- Mild analgesic/joint lubrication
- >1.0x10^6 daltons - better clinical resolution and chondroprotective events?
  (Howard & McIlwraith, 1996; Aviad & Houpt, 1994; Smith & Ghosh, 1987)
- 20mg HA i/a once weekly for 3 weeks (Frisbie, 2006)
- Intra-articular v Intra-venous use
- Oral HA / Prophylactic use ???
Adequan™

Proven to stimulate cartilage synthesis
Polysulphated glycosaminoglycans (PSGAGs)

- Principal GAG - chondroitin sulphate
- Chondroprotective/DMOAD
- Prevention, retardation, reverse signs of cartilage degeneration via effects on proteoglycan synthesis
- Intra-muscular (500mg q4d for 5-7 Tx)
- Intra-articular (250mg + 125mg amikacin)
- Post-op esp where notable loss of articular cartilage (McIlwraith, 2005)
- Licensed for horses
CARTROPHEN VET

A Disease Modifying Osteoarthritis Drug

CARTROPHEN VET (pentosan polysulfate) is a treatment for osteoarthritis that provides pain relief by acting on the pathology within the joint that causes the pain. It also protects and supports the recovery of joint cartilage that is damaged by the arthritic process. CARTROPHEN VET has therefore been classified as a disease modifying osteoarthritis drug (DMOAD) and represents the rational approach to the medical treatment of osteoarthritis in dogs.

www.arthritis.au.com

* Biopharm Australia Pty Ltd – September 2006
Pentosan polysulphate (PPS)

- Heparanoid compound/beechwood hemicellulose derivative
- Considered a disease-modifying OA drug
- No analgesic effects
- Correct pathological imbalances in OA joint
- 3mg/kg once weekly for 4 weeks or once every 5 days for 7 injections for early/mild OA
- Unlicensed for horses in UK
- (Glucoronoxlan sulphate, GXS)
Glucosamine +/- Chondroitin sulphate

- Oral joint supplements/’Nutraceuticals’ - definition?
- None licensed
- Common, easy, benign…..?!?
- Proof of efficacy lacking
- Bioavailability questioned
  (oral glucosamine 2-5%, Laverty, 2005)

However,
- Higher glucosamine level in inflamed joints (Meulyzer et al, 2008)
- Improve proteoglycan synthesis/anti-inflammatory effects in vitro
  (Chane et al, 2007; Byron et al, 2008)
- Sulphate > hydrochloride?
- Glucosamine & Chondroitin sulphate SMOAD?
  (Forsyth et al, 2006)
Avocado-soybean unsaponifiables (ASUs)

- Oral nutraceutical supplement (avocado/soybean oil phytosterols 1:2 ratio) under investigation
- In vitro studies when combined with glucosamine & chondroitin may be anti-inflammatory effects (Au et al, 2007)
- Significant anabolic effect (increased cartilage matrix proteoglycan synthesis) in articular cartilage from OA joints - disease-modifying effects and greater than parenteral PSGAGs, i/v HA and oral HA (Kawcak, 2007)
- Partial chondroprotection? (Changes only at molecular level and not histologically/grossly) (Cake, 2000)
Autologous Conditioned Serum (ACS/IRAP I & II)

- Proinflammatory cytokine interleukin-1 (IL-1) induces cartilage destruction in OA
- IL-1 balance with IL-1Ra
- Glass beads stimulate anti-inflammatory cytokines including IL-1Ra (humans up regulated 140-fold/horse 2-fold...)
- Significant improvement in lameness at 70d and synovial mb histopath score (4 weekly i/a injs of 5ml)/no protective effects on articular cartilage (Frisbie et al, 2007)
- Symptom modifying rather than disease modifying?
- (Gene therapy - mRNA vector for IL-1Ra? Frisbie, 2002)
ACS/IRAP

ACS production
Stem cells

- Intra-articular bone marrow and fat-derived stem cells under investigation for early OA (Frisbie et al, 2006)
- No improvement in lameness, inflammation parameters or cartilage degeneration on histological assessment
- However…..
Impinging DSP treatment

Intralesional corticosteroids/other

- 40mg MPA/site <200mg total
- Dilute with local up to 5-10ml per site
- Radiographic control
- 18g 9 cm needle
- Work when comfortable
- Repeat as necessary
Tildren
500 mg
Lyophilisate for solution for infusion
1 vial
Sodium tiludronate

- Bisphosphonate
- Inhibits osteoclast action reducing bone resorption leading to improved bone remodelling, decreased bone mineral loss and alleviation of pain induced by abnormal osteolysis
- 500mg intravenous in 1l 0.9% saline 500kg horse
- Recommended for bone spavin specifically in the UK
- In France, navicular syndrome, DSPs, subchondral bone cysts, OA in general (& used intra-articular eg. 3rd carpal bone sclerosis)
Shock Wave Therapy

- Extracorporeal shock wave therapy (ESWT)
- Radial pressure waves (RPWs)
- Dose dependent
- Frequency (pulses/s) unimportant?
Many applications…

- Proximal suspensory desmitis
  - 0.15mJ/mm² 2000 pulses
  - 40% improvement hindlimbs at 6 mths
  - 60% improvement forelimbs at 6 mths
- Osteoarthritis
  - 0.89mJ/mm² 2000 pulses
  - 80% improvement in bone spavin at 90 days (McCarroll, & McClure, 2002)
- Sacroiliac desmitis
- Navicular/DIP collateral desmitis/
- Impinging DSPs/Articular facet disease
- Other
Sacroiliac joint injection

Only infiltration into region of joint is possible
Sacroiliac joints, cranial view
Location of sacroiliac joint, viewed from cranial

Diagnosis difficult, often by rule-out of other conditions causing hindlimb lameness

Injection into joint in live horse not possible
Sacral surface of SI joint (hyaline cartilage)

Ilial surface of SI joint (fibrocartilage)
Outcome of 50 cases of sacroiliac joint region pain in horses
Bathe et al, 2010 ECVS 19th Congress, Helsinki, Finland

- Represented 6% of orthopaedic cases referred
- Warmbloods/ThoroughbredX over-represented in SI group
  Thoroughbreds under-represented
- Showjumpers & Dressage over-represented in SI group
  Eventers & GP under-represented
- History of poor performance rather than back/hindlimb problems
- 34% pelvic asymmetry/44% pain on palpation of SIJR
- All horses lame behind/54% bilateral
- Positive response to diagnostic analgesia
- 68% blocked bilaterally
- 18g 9cm 10ml local midline cranial TS axial to opposite ilial wing + 10ml caudal 10°
Scintigraphy 64% increased uptake
Ultrasound per rectum - no significant abnormalities in 12 horses
Concurrent diagnoses
86% HLPSD
38% TMT/DIT OA
28% DSPs
Only 4 horses (8%) with sacroiliac pain alone.....
- Longterm follow-up (max 18 mths)
  - 72% return to work
  - 10% lower level
  - 10% retired for HLPSD/SI
  - 8% retired other reasons
- Treatment Sx HLPSD with no Tx of SI 89% return
- Treatment Sx HLPSD and Tx of SI 65% return

- Overall prognosis good.....
Other.....

- Methylsulfonylmethane (MSM)
- Fatty Acids
  n-3 (omega-3) polyunsaturated fatty acids (PUFAs)
- HA + Chondroitin Sulphate (C4 + C6) as a post-arthroscopic lavage solution or i/a use but has been used i/v at 5ml weekly or every other week in performance horses
- Doxycycline - inhibition of MMPs?
  Schnabel et al, 2010
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After Years Of Botox
Botox

Capsular v Phalangeal Rotation:

Capsular rotation
= hoof capsule diverges from the dorsal surface of P3
= alignment with P2/P1 relatively normal

Phalangeal rotation
=P3 displaced in relation to P2/P1
= abnormal DIP flexion + DDF functional shortening
Surgical Treatment:

- Why & When?
- Inferior check ligament desmotomy/resection
- DDF tenotomy
  Mid-metacarpal
  Mid-pastern

??SALVAGE ONLY??
Conclusions

- Objective & subjective considerations
- Generalised recommendations for every situation not really possible
- Therapeutics still based on general scientific principles, past experience, peer experience, economics, therapeutic response
- Current trends & recommendations…
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