

# NONSTEROIDAL ANTI-INFLAMMATORY DRUG USE FOR MANAGEMENT OF JOINT DISEASE



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## MEDICATIONS

- Now tailored to influence any tissue
- Applications by a number of routes
  - Systemic
  - Topical
  - Intra-articular
  - Physical



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## CHOICES



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## AIMS OF THERAPY

- Remove inciting cause
- Decrease catabolic state (inflammation)
- Increase anabolic state
- Return to best possible use



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## GROWING COMPLEXITY OF THERAPIES

- Objective, experimental testing often lags behind development and commercialization
- Therapeutics now showing specific effects
  - SMOADS – Symptom-modifying OA Drugs
  - DMOADS – Disease-modifying OA Drugs
  - Combination

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## Methods of Action

- Symptom modifying effects
  - SMOAD - Symptom Modifying Osteoarthritic Drugs
    - Improve symptoms of disease
    - Anti-inflammatories
    - Pain modifying
- Disease modifying effects
  - DMOAD – Disease Modifying Osteoarthritic Drugs
    - Chondroprotective
    - Increase anabolic effects, decrease catabolic effects

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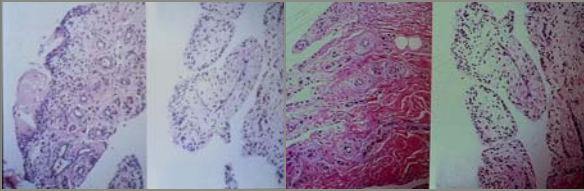
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## Synovial Membrane Histology



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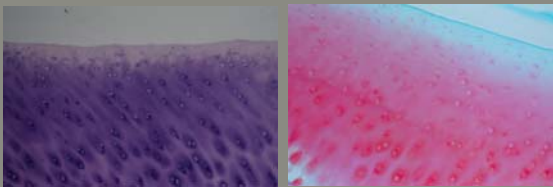
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## Articular Cartilage Histology



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## OBJECTIVES

- Mode of action of various NSAIDs
  - Pain relief
  - Clinical evidence
  - Site of action
- Role in OA
  - Role of synovitis in OA pain
  - Effects of NSAIDs on synovial fluid
- Negative effects - Toxicity

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## MODE OF ACTION

- NSAIDs developed over 100 years ago
- Inhibit enzyme systems that convert arachidonic acid into prostaglandins and leukotrienes




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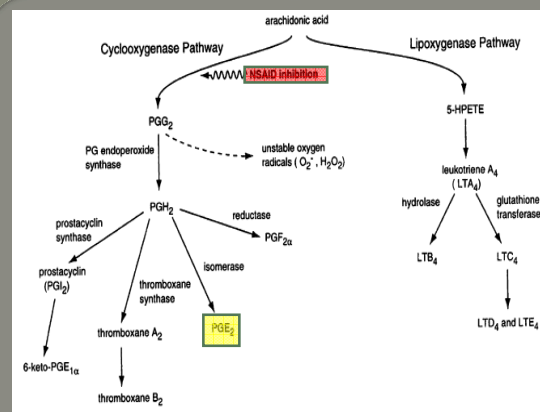
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## CYCLOOXYGENASE

- COX-1
  - Constitutive – (House-keeping COX) regulates normal cell function in some tissues
    - Gastric function
    - Renal function
    - Vascular homeostasis
    - Some hormonal regulation
- COX-2
  - Functions in converting arachidonic acid into Prostaglandins = inflammation
- Different NSAIDs have variable COX-1 and COX-2 effects

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## PROSTAGLANDINS

- Known to induce localized pain and worsening of inflammation
- Known to induce articular cartilage matrix degradation
- Goal is to reduce Prostaglandins within local tissue exudate
  - IA effects?
  - CNS effects?

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## PHENYLBUZAZONE

- Most widely used NSAID
  - Cheap
  - Easy to administer orally
- Oral absorption varies with feed within stomach. Fasted 1 hour pre and post = 6 hour absorption, hay present = 13 hours. (May and Lees, 96)
- Exudate lasts as long as 24 hours.

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## PHENYLBUZAZONE

- Significant positive clinical effects in synovitis at around 8-10 hours
  - Decrease lameness, PGE<sub>2</sub>, fluid volume.
  - effects were greater than Ketoprofen. (Owens, et al. Am J Vet Res, 1996)
- Reduce lameness 2-8 hours after administration

Foreman, J. H., Barange, A., Lawrence, L. M., Hungerford, L. L. Effects of single-dose intravenous phenylbutazone on experimentally induced, reversible lameness in the horse. *J. vet. Pharmacol. Therap.* 31, 39-44.

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**Evaluation of the analgesic effects of phenylbutazone administered at a high or low dosage in horses with chronic lameness**

Helen H. Hu, DVM; Charles G. MacAllister, DVM, DACVIM; Mark E. Payton, PhD; Ronald S. Erkert, DVM

JAVMA, Vol 226, No. 3, February 1, 2005

- 9 horses with chronic forelimb lameness (Navicular Disease +/- other)
- 4.4 vs 8.8 mg/kg vs saline IV SID for 4 days. 14 day washout in between
- NSD in peak vertical force or lameness between high dose and low dose PBZ.

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Treatment	Time (h)			
	0	6	12	24
Phenylbutazone				
High dosage	76.44 ± 2.35 <sup>a</sup>	84.20 ± 3.43 <sup>a</sup>	83.80 ± 3.67 <sup>a</sup>	84.70 ± 4.15 <sup>a</sup>
Low dosage	75.45 ± 2.53 <sup>a</sup>	84.37 ± 2.65 <sup>a</sup>	85.29 ± 2.71 <sup>a</sup>	82.19 ± 3.50 <sup>a</sup>
Saline solution	74.92 ± 2.33 <sup>a</sup>	75.78 ± 2.99 <sup>b</sup>	76.76 ± 2.34 <sup>b</sup>	77.12 ± 2.68 <sup>b</sup>

Values were obtained from force plate analyses of the more severely affected forelimb in each horse; data are given as least squares mean ± SEM.  
<sup>a,b</sup>In each column, values with different superscripts were significantly ( $P < 0.05$ ) different.

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**Effectiveness of administration of phenylbutazone alone or concurrent administration of phenylbutazone and flunixin meglumine to alleviate lameness in horses**

Kevin G. Keegan, DVM, MS; Nat T. Messer, DVM; Shannon K. Reed, DVM; David A. Wilson, DVM, MS; Joanne Kramer, DVM

AJVR, Vol 69, No. 2, February 2008

- 29 horses with forelimb or hindlimb lameness
- 2.2 mg/kg oral PBZ vs 2.2 mg/kg oral PBZ plus 1.1 mg/kg IV flunixin q 12 hours for 5 days
- Combination was significantly better for kinematic outcomes

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## FLUNIXIN

- Quick oral absorption
  - 30 min if fasted
  - 7.5 hours with feed
- Action within 2 hours
- Effect up to 30 hours
- Efficacy for visceral pain
- Questionable clinical effect on lameness

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### **Use of force plate analysis to compare the analgesic effects of intravenous administration of phenylbutazone and flunixin meglumine in horses with navicular syndrome**

Ronald S. Erkert, DVM; Charles G. MacAllister, DVM; Mark E. Payton, PhD; Cyril R. Clarke, BVSc, PhD

AJVR, Vol 66, No. 2, February 2005

- 12 horses with Navicular Disease
- Each received 1.1mg/kg flunixin, 4.4 mg/kg bute or saline IV SID for 4 days with 14 day washout
- Those treated with Flunixin and Phenylbutazone were sig improved compared to control, but NSD between each other
- Effect maintained for 24 hours

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## KETOPROFEN

- Rapidly absorbed and eliminated
  - Sequester in areas of peripheral inflammation
  - Reason that it was thought to work well for OA
- Was thought to be effective on 5-lipoxygenase
  - but no change in leukotrienes

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Effects of ketoprofen and phenylbutazone on chronic hoof pain and lameness in the horse

JANE G. OWENS\*, S. G. KAMERLING, S. R. STANTON and M. L. KEOWEN

- 7 horses with chronic laminitis
- 2.2 mg/kg vs 3.63 mg/kg Ketoprofen vs 4.4 mg/kg PBZ IV SID. 7 day washout.
- Hooftester and Obel scoring
- Ketoprofen at 3.63 mg/kg was significantly better than 2.2 mg/kg Ketoprofen and 4.4 mg/kg PBZ in alleviating pain associated with chronic laminitis.

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### NAPROXEN

- 10 mg/kg orally, sid, bid or eod
- Limited efficacy studies for OA

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### CARPROFEN

- Least understood NSAID in horses
- Accumulates in inflammatory exudates
- 0.7 mg/kg IV, or 1.4 mg/kg PO sid
- Potentially beneficial to proteoglycans, unlike some others

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## DICLOFENAC

- Nonselective COX inhibitor
- Systemic
  - Toxic
  - Short elimination half-life requiring frequent dosing
- Transdermal delivery

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## TOPICAL ANTIINFLAMMATORY

Surpass

- Good for localized therapy
- Good as adjunct to other therapies
- Good for periodic and long term use



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## Results



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## FIROCOXIB

- Selective COX-2 inhibitor
- Oral preparation at this time

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## FIROCOXIB

*J. vet. Pharmacol. Therap.* 30, 208–217, doi: 10.1111/j.1365-2885.2007.00840.x.

Pharmacokinetics and metabolism of orally administered firocoxib, a novel second generation coxib, in horses

V. KVATERNICK\*  
M. POLLMEIER†  
J. FISCHER\* &  
P. D. HANSON‡

Kvaternick, V., Pollmeier, M., Fischer, J., Hanson, P. D. Pharmacokinetics and metabolism of orally administered firocoxib, a novel second generation coxib, in horses. *J. vet. Pharmacol Therap.* 30, 208–217.

- Long half life, therefore sid treatment.
  - 5X-10X longer than phenylbutazone and flunixin
- 30% of plasma concentration penetrates into SF

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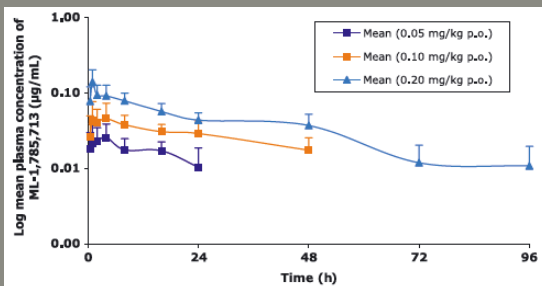
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## FIROCOXIB



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### The use of force plate measurements to titrate the dosage of a new COX-2 inhibitor in lame horses

W. BACK<sup>1\*</sup>, C. G. MACALLISTER<sup>1</sup>, M. C. V. VAN HEEL<sup>1</sup>, M. POLLMEIER<sup>2</sup> and P. D. HANSON<sup>2</sup>

- 64 horses treated with vehicle control, firocoxib at 0.05, 0.1 or 0.25 mg/kg PO
- Force plate prior to tx, and again 10 hours after treatment on days -1 (no treatment), 0, 2 and 6
- Horses treated with 0.25 mg/kg were better than control on day 0
- Horses treated with 0.1 mg/kg and 0.25 mg/kg doses were better than controls on days 2 and 6

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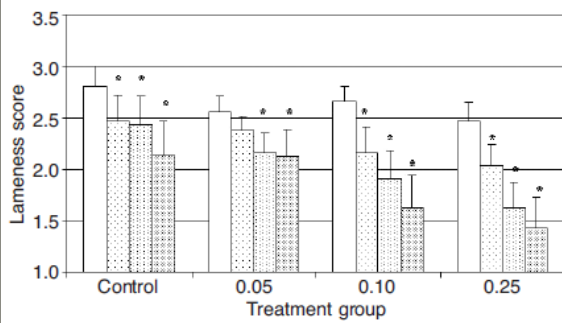
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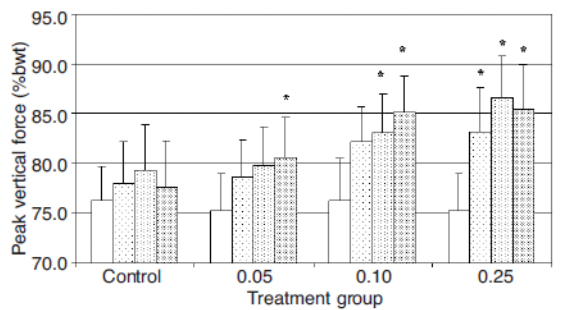
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## ROLE IN JOINT DISEASE

- 17 million use NSAIDs daily, and over 60 million prescriptions per year
- What evidence is there that OA is an inflammatory disease, and how much of pain is due to synovitis?
  - Evidence linking synovitis and oa is inconsistent. Ex = dog acl model
- Variable effects on proteoglycan production in articular cartilage

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## NSAIDs and OA – Positive Effects

- Most studies show NSAIDs to help in reducing articular cartilage catabolism
- Some studies also show:
  - different NSAIDs have different effects on AC in vitro
  - Pirprofen reduced articular cartilage degeneration in rabbits
  - Tiaprofenic acid reduced medial femoral condyle erosion in ACL-deficient dogs
  - Tiaprofenic acid showed chondroprotective effects both with treatment and prophylactically

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## NSAIDs and OA – Negative Effects

- Rapid destructive OA with indomethacin
- Some studies show:
  - Acceleration of degeneration in spontaneous OA model in rats
  - Depletion of proteoglycans in dogs
  - Increased water content in AC of ACL dogs given naproxen
  - Increased AC degeneration and increased chondrocyte death

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**Is there preliminary in-vivo evidences of an influence of  
nonsteroidal antiinflammatory drug treatment on osteoarthritis  
progression? Part I**

By MICHEL G. LAQUENNE  
Hôpital Leopold Bellan, 31-33 rue Guilleminot, 75014 Paris, France

- No DMOADS effects, some negative effects on joints
- Analgesia and overuse?

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**Is there preliminary in-vivo evidence for an influence of  
nonsteroidal antiinflammatory drugs on progression in  
osteoarthritis? Part II—evidence from animal models**

By URSBERT REIN, ALVARO MARRAS AND MARCO BELLUCCI

“... In that there are no therapies without inherent risk to some patients, it is critical to understand the impact of that potential risk in the context of what clinical improvements can be expected by exposure to the therapy. The difficulty in measuring competing risks vs benefit continues to be challenging.”

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Editorial  
**Coxibs and NSAIDs — Is the air any clearer? Perspectives  
from the OARS/International COX-2 Study Group Workshop 2007**  
R. W. Moskowitz M.D.<sup>1</sup>, S. B. Abramson M.D.<sup>1</sup>, F. Berenbaum M.D.<sup>2</sup>,  
L. S. Simon M.D.<sup>3</sup>, M. Hochberg M.D., M.P.H.<sup>4</sup>

- “... there were no clinically significant differences in efficacy between the various non-aspirin NS NSAIDs and coxibs when used in comparable doses. Several additional studies and a review published after July 2005 have demonstrated that the COX-2 selective NSAIDs etoricoxib and lumiracoxib have similar efficacy to NS NSAIDs”
- “Choice of a NS NSAID or a coxib in the individual patient with OA is predicated more on differences in safety and cost rather than efficacy.”

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## Evaluation of topically administered diclofenac liposomal cream for treatment of horses with experimentally induced osteoarthritis

David D. Frisbie, DVM, PhD; C. Wayne McIlwraith, BVSc, PhD; Chris E. Kawcak, DVM, PhD; Natasha M. Werny, DVM; Gregory L. Pearce, MStat

AJVR, Vol 70, No. 2, February 2009

- 24 horses each with unilateral osteochondral fragment
  - 8 horses – 7.3 g Diclofenac (DLC) bid
  - 8 horses – 2 g phenylbutazone (PBX) sid
  - 8 horses – no treatment
- Evaluation of SMOAD and DMOAD outcomes

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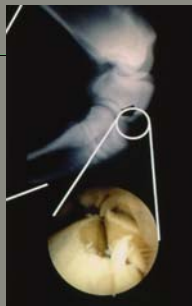
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## Middle Carpal Joint



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- Significant improvement in lameness in PBZ and DLC groups compared to controls
  - Improved in both forelimbs in PBZ group
  - Improved in only the treated joint of DLC group
- PBZ group had significantly less PGE2 in synovial fluid than other groups
- Barely detectable amounts of DLC in synovial fluid
- Significantly lower total articular cartilage erosion score in DLC treated than PBZ and control treated groups
- Significantly better safranin-O staining in DLC treated than PBZ and control treated groups

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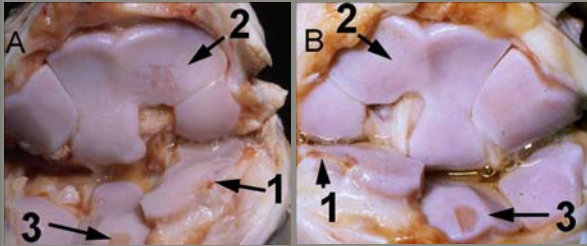
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## Gross Lesions



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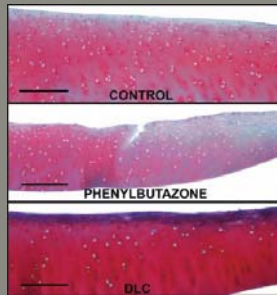
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- Therefore, DLC did not lower PGE<sub>2</sub>, but had DMOAD effect
- Significance of inflammation in OA and lameness?
- Capsular pain effect?
- How did DMOAD effect occur?



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## ROLE IN JOINT DISEASE

### ANTI-INFLAMMATORY DRUG THERAPY AFTER ARTHROSCOPY OF THE KNEE

A PROSPECTIVE, RANDOMISED, CONTROLLED TRIAL OF DICLOFENAC OR PHYSIOTHERAPY

NICHOLAS C. BIRCH, CAROLINE SLY, STUART BROOKS, DAVID P. POWLES  
*J Bone Joint Surg [Br]* 1993; 75-B:650-2

- NSD in knee function at 42 days after knee arthroscopy between diclofenac acid, physiotherapy and control.
- 9.6% of diclofenac group had side effects.

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Equine Practice  
30(10):155-167

**Preliminary Investigations of Pain and Analgesia Assessment in Horses Administered Phenylbutazone or Placebo After Arthroscopic Surgery**

M. RAERKALLO, DVM, PhD, FPM, FMTaylor, MA, VMD, PhD, DVM, Diplomate ACV, MRCV, MRCVS, and R.C. BENNETT, MA, VMD, CVMA, MRCVS

- Significant reduction in post-operative pain compared to control

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**Comparison of efficacy and safety of paste formulations of firocoxib and phenylbutazone in horses with naturally occurring osteoarthritis**

Michele Y. Doucet, DVM, DVM, DACVIM, DACVCP; Alicia L. Bertone, DVM, PhD, DACVIM; Dean Hendrickson, DVM, MS, DACVIM; Faith Hughes, DVM, DACVIM; Charles MacAllister, DVM, DACVIM; Scott McClure, DVM, PhD, DACVIM; Craig Reinemeyer, DVM, PhD; Yves Rossier, DVM, DACVIM; Roger Sifferman, DVM; André A. Vriens, DVM; Gary White, DVM; Bruce Kunkle, DVM, PhD; Roberto Alva, DVM, PhD; Davida Romano, MPH; Peter D. Hanson, DVM, PhD, DACVIM

JAVMA, Vol 232, No. 1, January 1, 2008

- 253 horses
  - treated with either 0.1 mg/kg PO q 24 hours firocoxib or 4.4 mg/kg phenylbutazone q 24 hours for 14 days
  - PE and LE days 0,7,14
- NSD on day 7, NSD in le on day 14
- Firocoxib significantly better on ROM, pain on palpation and joint circumference
- No adverse effects

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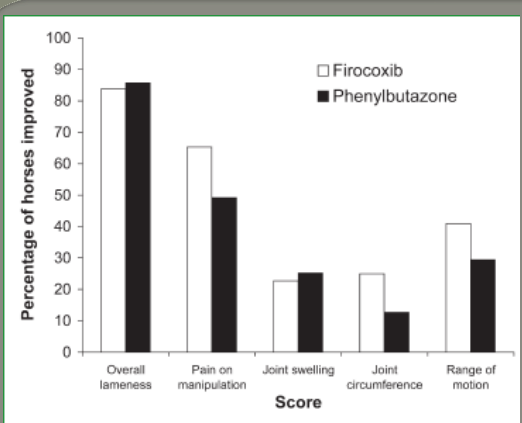
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**Preferential and non-selective cyclooxygenase inhibitors reduce inflammation during lipopolysaccharide-induced synovitis**  
 Alison J. Morton, Nigel R. Campbell, Fimai M. Gayle, W. Rich Redding, Anthony T. Björklager \*

- 18 horses – each with unilateral middle carpal joint LPS
  - 6 horses – 4.4 mg/kg PBZ IV q 24 hours
  - 6 horses – 23 mg/kg etodolac IV q 12 hours
  - 6 horses control
- PBZ and etodolac reduced synovial fluid WBC 6 and 24 hours post LPS injection
- Both reduced synovial fluid PGE<sub>2</sub> 6 hours post LPS injection

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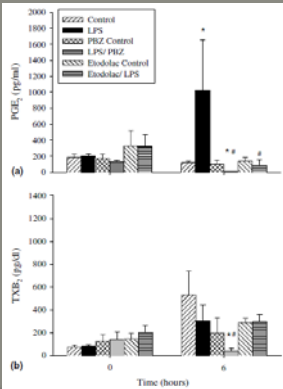
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- Thromboxane reduced by PBZ
- Probable COX-1 factor

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**Differential direct effects of cyclo-oxygenase-1/2 inhibition on proteoglycan turnover of human osteoarthritic cartilage: an *in vitro* study**

Simon C Maestbergen, Nathalie WD Jansen, Johannes WJ Bijlma and Floris PJG Lafeber

Rheumatology & Clinical Immunology, University Medical Center Utrecht, Utrecht, The Netherlands

Corresponding author: Simon C Maestbergen, s.maestbergen@azu.nl

Received: 7 Jul 2005; Revision accepted: 2 Aug 2005; Revision received: 28 Sep 2005; Accepted: 10 Oct 2005; Published: 9 Nov 2005

Arthritis Research & Therapy 2005, 8(R2):10.1186/arthritis

- Evaluated NSAIDs on OA explants
- Conventional NSAIDs reduced proteoglycan synthesis and content
- COX-2 inhibitors increased proteoglycan synthesis and content
- COX-2 could be protective

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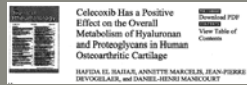
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- In Vitro study evaluating effects of NSAIDs on proteoglycan and HA synthesis
  - Diclofenac had no effect on proteoglycan or HA depletion in OA explants
  - Celecoxib increased HA and proteoglycan synthesis

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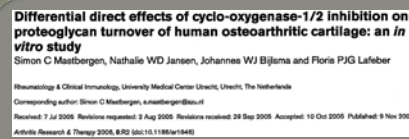
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- Compared indomethacin, naproxen, aceclofenac and celecoxib on articular cartilage from OA joints
- Higher COX-2/COX-1 resulted in:
  - Higher proteoglycan synthesis and content
  - Larger reduction in PGE<sub>2</sub>

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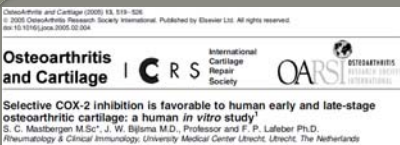
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- Evaluated celecoxib using OA, acutely degenerated and normal articular cartilage
- Celecoxib increased proteoglycan synthesis and normalized release of newly formed and resident proteoglycans

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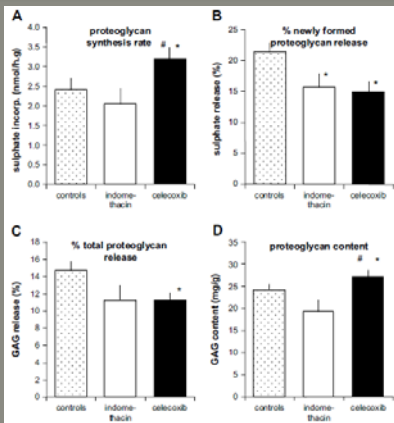
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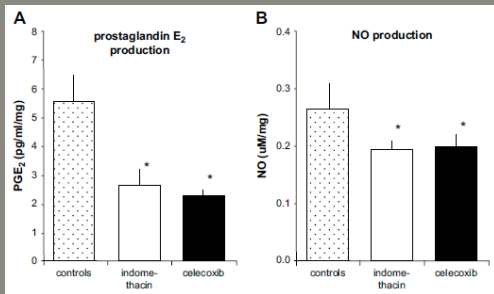
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CLINICAL RESEARCH STUDY



**Do NSAIDs Affect Longitudinal Changes in Knee Cartilage Volume and Knee Cartilage Defects in Older Adults?**

Changshai Ding, MD,<sup>1,2</sup> Flavia Cicuttini, PhD,<sup>2</sup> Graeme Jones, MD<sup>1</sup>  
<sup>1</sup>Medical Research Institute, University of Tasmania, Hobart, Australia; <sup>2</sup>Department of Epidemiology and Preventive Medicine, Monash University Medical School, Melbourne, Australia

- Followed 395 patients over 2.9 years and measured cartilage volume and defect size
- COX-2 users = less defects compared to non-NSAID users
- NS NSAID users = increased defects and decrease cartilage volume

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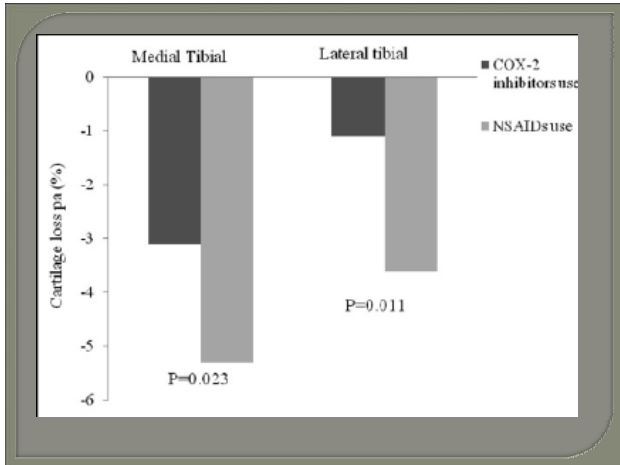
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## TOXICITY

- Phenylbutazone - Toxicity - >4.4 mg/kg BID for 2 days, then 2.2 mg/kg bid.
- Leads to:
  - Anorexia
  - Neutropenia
  - Hypoproteinemia
  - GI ulcer
  - Renal papillary necrosis
  - Vascular thrombosis
- Oral lesions with oral administration

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### Pathophysiologic effects of phenylbutazone on the right dorsal colon in horses

Rebecca S. McConnico, DVM, PhD; Timothy W. Morgan, DVM, PhD; Cathleen C. Williams, PhD; Jeremy D. Hubert, BVSc; Rustin M. Moore, DVM, PhD

AJVR, Vol 69, No. 11, November 2009

- 8.8 mg/kg sid for 21 days
- 12 horses but only 8 were evaluated vs placebo
- Decreased albumin from 10-21 days
- Neutropenia
- 2 horses developed colitis
- NSD in histologic changes between pbz and control colons for histo, PGE2, etc
- Significant increase in RDC arterial blood flow in pbz compared to control

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## OTHER NSAIDs

- Flunixin
  - Myonecrosis with IM.
  - Toxic at around 5.5 mg/kg sid
- Ketoprofen
  - Low toxicity compared to PBZ and flunixin due to peripheral tissue accumulation at sites of inflammation and rapid clearance
- Naproxen
  - Wide safety margin

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## CONCLUSIONS

- Convincing evidence for efficacy
  - Phenylbutazone
  - Flunixin
  - Diclofenac
  - Firocoxib
- Selective COX-2 inhibitors
  - Reduced toxicity
  - Objective evidence for positive articular cartilage effects
  - Untested in objective model of equine OA

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