NSAIDs and tissue healing - bone.

Sigbjørn Dimmen and Lars Engebretsen, Orthopaedic Center, Ullevaal University Hospital, Oslo, Norway
Prevalence of use of NSAIDs in sport

• Most used drug class in Olympic environment

• Sydney 2000 - 1 in 4 athletes

• Athens 2004 - 1 in 10 athletes

• Football World Cup 2002-2010 – ½ all athletes
## London 2012 Olympic Usage

<table>
<thead>
<tr>
<th>Medicine</th>
<th>% of total prescriptions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Paracetamol 500mg tablets</td>
<td>10.95%</td>
</tr>
<tr>
<td><strong>Ibuprofen 400mg tablets</strong></td>
<td>3.89%</td>
</tr>
<tr>
<td><strong>Diclofenac sodium 50mg gastro-resistant tablets</strong></td>
<td>3.17%</td>
</tr>
<tr>
<td><strong>Ibuprofen 200mg tablets</strong></td>
<td>2.30%</td>
</tr>
<tr>
<td>Strepsils lozenges</td>
<td>2.30%</td>
</tr>
<tr>
<td>Amoxicillin 500mg capsules</td>
<td>2.09%</td>
</tr>
<tr>
<td>Hydrocortisone 1% cream</td>
<td>1.90%</td>
</tr>
<tr>
<td>Amoxicillin 250mg capsules</td>
<td>1.87%</td>
</tr>
<tr>
<td>Xylometazoline 0.1% nasal spray</td>
<td>1.85%</td>
</tr>
<tr>
<td>Cetirizine 10mg tablets</td>
<td>1.75%</td>
</tr>
<tr>
<td>Loratadine 10mg tablets</td>
<td>1.73%</td>
</tr>
<tr>
<td>Omeprazole 20mg gastro-resistant capsules</td>
<td>1.51%</td>
</tr>
<tr>
<td><strong>Diclofenac 1% gel</strong></td>
<td>1.44%</td>
</tr>
<tr>
<td><strong>Diclofenac sodium 75mg modified-release tablets</strong></td>
<td>1.37%</td>
</tr>
</tbody>
</table>
Rio 2016 Formulary

- **Athlete medical room**
  - Diclofenac 50mg tablets
  - Diclofenac topical spray
  - Ketoprofen 100mg tablets
  - Ketoprofen 50mg IM injection
  - Ketorolac 10mg sublingual
  - Morphine 10mg injection
  - Paracetamol 500mg oral

- **Field of Play Medical Bag**
  - Ketorolac 10mg sublingual
  - Tramadol 50mg injection

- **Polyclinic Pharmacy**
  - Wide selection of NSAIDs and formulations
Prevalence of use of NSAIDs in sport

• Athletes use 4X more NSAIDs than age-matched controls from the general population

• Prevalence differs between sports

• Athletes in speed and power sports, more frequent users than endurance or motor skill-based sport

• International-level power and sprint disciplines in track and field, more frequent users than long distance runners
Prevalence of use of NSAIDs in sport

• Higher incidence in:
  – team sports (football, volleyball, handball)
  – sports involving extensive use of upper and lower limbs (baseball, fencing, gymnastics, rowing)

• Differences in incidence likely due to:
  – The specific injury profile (i.e. rate of acute or chronic injuries)
  – Physical demands of the sport
What are NSAIDs?

• Analgesic, anti-inflammatory, antipyretic, and antithrombotic properties

• Inhibit cyclo-oxygenase (COX) leading to:
  – Decrease synthesis of prostaglandins
  – Decrease inflammatory response

• NSAIDs categorised by their selectivity for inhibiting COX-1 & COX-2
How do they work? - NSAID v COX2

Maintenance

Arachidonic acid

Induced

COX-1

COX-2

NSAIDs

Coxibs

thromboxane / prostaglandins

prostaglandins

Primarily support platelet function

Primarily protect GI mucosa

Primarily mediate inflammation, pain & fever
Examples

NON-SELECTIVE
• Diclofenac
• Ibuprofen
• Naproxen
• Ketoprofen

COX-2 SELECTIVE
• Celecoxib
• Rofecoxib (withdrawn due to safety)
SUMMARY:

These animal data, together with the view of limited scientifically robust clinical evidence in humans, indicate that physicians consider only short-term administration of COX-2 inhibitors or other drugs in the pain management of patients who are in the phase of fracture or other bone defect healing. COX-2 inhibitors should be considered a potential risk factor for impaired fracture healing, and therefore to be avoided in patients at risk for delayed fracture healing.

RECENT FINDINGS:

Prostaglandins play an important role as mediators of inflammation and COX are required for their production. Inflammation is an essential step in the fracture healing process in which prostaglandin production by COX-2 is involved. Data from animal studies suggest that NSAIDs, which inhibit COX-2, can impair fracture healing due to the inhibition of the endochondral ossification pathway. Animal data suggest that the effects of COX-2 inhibitors are dependent on the timing, duration, and dose, and that these effects are reversible.
Biosynthesis of prostaglandins and thromboxane

Membrane-bound phospholipids

\[ \downarrow \]

Phospholipase A\(_2\)

Arachidonic acid

\[ \downarrow \]

\[ \text{O}_2 \]

\[ \text{COX-1} \]

\[ \text{COX-2} \]

\[ \text{NSAIDs} \]

\[ \text{COX-2 inhibitors} \]

\[ \text{Tissue-specific isomerase} \]

\[ \downarrow \]

\[ \text{PGG}_2 \]

\[ \downarrow \]

\[ \text{PGH}_2 \]

\[ \downarrow \]

\[ \text{PGD}_2 \]

\[ \text{PGE}_2 \]

\[ \text{PGF}_{2\alpha} \]

\[ \text{PGI}_2 \]

\[ \text{TxA}_2 \]
Parecoxib and Indomethacin Delay Early Fracture Healing

A Study in Rats

Sighjorn Dimmen MD, Lars Nordsletten MD, PhD,
Jan Erik Madsen MD, PhD

Negative effect of parecoxib on bone mineral during fracture healing in rats

Sigbjørn Dimmen¹,², Lars Nordsletten¹,², Lars Engebretsen¹, Harald Steen²,³, and
Jan Erik Madsen¹,²
NSAIDs and fracture healing.
Geusens P1, Emans PJ, de Jong JJ, van den Bergh J. JOR 2014

SUMMARY:

These animal data, together with the view of limited scientifically robust clinical evidence in humans, indicate that physicians consider only short-term administration of COX-2 inhibitors or other drugs in the pain management of patients who are in the phase of fracture or other bone defect healing. COX-2-inhibitors should be considered a potential risk factor for fracture healing, and therefore to be avoided in patients at risk for delayed fracture healing.
Nonsteroidal anti-inflammatory drugs' impact on nonunion and infection rates in long-bone fractures.

Jeffcoach DR1, Sams VG, Lawson CM, Enderson BL, Smith ST, Kline H, Barlow PB, Wylie DR, Krumenacker LA, McMillen JC, Pyda J, Daley BJ; University of Tennessee Medical Center, Department of Surgery.

LBF patients who received NSAIDs in the postoperative period were twice as likely and smokers more than three times likely to suffer complications such as nonunion/malunion or infection. We recommend avoiding NSAID in traumatic LBF.
Clinical studies

- What about clinical studies?

The Effect of Nonsteroidal Anti-Inflammatory Drug Administration on Acute Phase Fracture-Healing: A Review

Andrew P. Kurnis, BMBS, PhD, Timothy P. Kurnis, BMBS, Justin X. O’Brien, BMBS, and Tore Dalén, MD, PhD

Investigation performed at the Department of Orthopaedics, Repatriation General Hospital, Daw Park, South Australia, Australia,
Clinical studies

• Two studies on Colles’ fractures did not show any negative effects of NSAIDs.
  
  
Clinical studies

• No prospective, randomized clinical trials have been performed on the effects of NSAIDs and selective COX-2 inhibitors on long bone fractures.
Clinical studies

• One study on femoral shaft fractures.
• Retrospective study.
• There was a marked association between nonunion and the use of NSAIDs after injury.
• Delayed healing was also noted in patients who took NSAIDs and whose fractures had united.
Clinical studies

- The best clinical study in my opinion is the study published by Burd in 2003.

- Of 282 patients operated for acetabular fracture, 166 were randomized to indomethacin or localized irradiation for prevention of heterotopic ossification.
Clinical studies

112 of these patients also had a long bone fracture.
- 36 without indometacin or radiation
- 38 received radiation
- 38 received indometacin 25 mg x 3 in 6 weeks
Clinical studies

112 of these patients also had a long bone fracture.

- 36 without indometacin or radiation ⇒ 6% nonunion
- 38 received radiation ⇒ 8% nonunion
- 38 received indometacin 25 mg x 3 in 6 weeks ⇒ 29% nonunion
Clinical studies

112 of these patients also had a long bone fracture.

- 36 without indometacin or radiation $\Rightarrow$ 6% nonunion
- 38 received radiation $\Rightarrow$ 8% nonunion
- 38 received indometacin 25 mg x 3 in 6 weeks $\Rightarrow$ 29% nonunion

- No nonunions in the acetabular fractures!
Summary

• Strong evidence that cox inhibitors impaires bone healing in animals
• Weaker, but compelling evidence in humans
Summary

- Prostaglandins are necessary for fracture healing.
- COX-2 is critically involved in fracture healing the first 3 weeks after fracture.
- NSAIDs and COX-2 inhibitors impair fracture healing.
- Findings also indicate that NSAIDs and COX-2 inhibitors impair tendon-to-bone healing.
The Effect of Limited Perioperative Nonsteroidal Anti-inflammatory Drugs on Patients Undergoing Anterior Cruciate Ligament Reconstruction

Endre Soreide,*† MD, Lars-Petter Granan,‡§ MD, PhD, Geir A. Hjorthaug,‖ MD, Birgitte Espehaug,¶ PhD, Sigbjørn Dimmen,# MD, PhD, and Lars Nordsletten,† MD, PhD

Investigation performed at Oslo University Hospital, Oslo, Norway

Background: The administration of nonsteroidal anti-inflammatory drugs (NSAIDs) to patients undergoing anterior cruciate ligament reconstruction (ACLR) is controversial because it may impair tissue healing and clinical outcomes.

Purpose: To assess the effect of NSAID administration on patients undergoing ACLR.

Study Design: Cohort study; Level of evidence, 3.

Methods: Included patients were aged >15 years and were registered in the Norwegian Knee Ligament Registry from 2008 until 2013 after the primary ACLR. Patients with insufficient data regarding administration of NSAIDs and those with associated knee ligament injuries requiring surgical treatment were excluded from this study. Graft survival was estimated using Kaplan-Meier survival curves, and hazard ratios (HRs) for revision were evaluated using Cox regression analysis. Logistic regression analysis was used to calculate the odds ratio (OR) for a Knee Injury and Osteoarthritis Outcome Score (KOOS)–quality of life (QOL) subscale score <44 at 2-year follow-up.

Results: A total of 7822 patients were included in the analysis for graft survival and assessment for risk of revision. Of these, 4144 patients were administered NSAIDs postoperatively. The mean duration of follow-up was 2.8 years (range, 0-5.9 years). Administration of NSAIDs did not influence graft survival (P = .568). Adjusted Cox regression analyses demonstrated the same finding regarding risk of revision (HR, 1.0; 95% CI, 0.8-1.3). ACLR using a bone–patellar tendon–bone autograft showed a reduced risk of revision (HR, 0.3; 95% CI, 0.1-0.8) among patients administered NSAIDs. In subgroup analyses of 3144 patients, administration of NSAIDs demonstrated a beneficial effect on the risk of a KOOS-QOL score <44 at 2-year follow-up (OR, 0.8; 95% CI, 0.6-0.9).

Conclusion: Administration of NSAIDs to patients after ACLR does not have a negative effect on graft survival, risk of revision, or risk of a KOOS-QOL score <44 at 2-year follow-up. We emphasize using caution when administering NSAIDs by keeping the duration and dosage of NSAIDs as short and low as possible to ensure sufficient pain relief while limiting unwanted exposure to any known and unknown adverse effects of these drugs.
International Olympic Committee consensus statement on pain management in elite athletes

Brian Hainline,1 Wayne Derman,2 Alan Vernej,3 Richard Budgett,4 Masataka Deie,5 Jiří Dvořák,6 Chris Harle,7 Stanley A Herring,8 Mike McNamee,9 Willem Meeuwisse,10 G Lorimer Moseley,11 Bade Omololu,12 John Orchard,13 Andrew Pipe,14 Babette M Pluim,15 Johan Ræder,16 Christian Siebert,17 Mike Stewart,18 Mark Stuart,19 Judith A Turner,20 Mark Ware,21 David Zideman,22 Lars Engebretsen4

ABSTRACT
Pain is a common problem among elite athletes and is frequently associated with sport injury. Both pain and injury interfere with the performance of elite athletes. There are currently no evidence-based or consensus-based guidelines for the management of pain in elite athletes. Typically, pain management consists of the provision of analgesics, rest and physical therapy. More appropriately, a treatment strategy should address all contributors to pain including underlying pathophysiology, biomechanical abnormalities and psychosocial issues, and should employ therapies providing optimal benefit and minimal harm. To advance the development of a more standardised, evidence-informed approach to pain management in elite athletes, an IOC Consensus Group critically evaluated the current state of the science and practice of pain management in sport and prepared recommendations for a more unified approach to this important topic.

This consensus paper fulfils the IOC charge by addressing the multifaceted aspects of pain physiology and pain management in elite athletes through the lenses of epidemiology, sports medicine, pain medicine, pain psychology, pharmacology and ethics.

PREVALENCE OF USE OF PHARMACOLOGICAL AND NON-PHARMACOLOGICAL TREATMENTS TO MANAGE PAIN IN ELITE ATHLETES
Elite athletes commonly use prescription and over-the-counter analgesics to prevent or relieve pain.1–18 These have typically included: oral non-steroidal anti-inflammatory drugs (NSAIDs),2 4 6 16 17 injectable NSAIDs,5 other non-opioid analgesics,1 4 8 9 opioid analgesics,1 3 4 7 8 10 18 injectable and transdermal anaesthetics11 and other medications and over-the-counter supplements.1 3 12–15

Despite the perception that the use of medications and non-pharmacological strategies to relieve
The Oslo Sports Trauma Research Center has been established at the Norwegian School of Sport Sciences through generous grants from the Royal Norwegian Ministry of Culture, the South-Eastern Norway Regional Health Authority, the International Olympic Committee, the Norwegian Olympic Committee & Confederation of Sport, and Norsk Tipping AS.