Acetaminophen and NSAID Use in Athletes

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Objectives
• Review normal healing process and types of injuries treated with these medications
• Review risks and benefits of acetaminophen use in athletes
• Review risks and benefits of NSAID use in athletes

Types of Injuries
• Acute
  – Sprain
  – Strain
• Chronic
  – Overuse, overload
• Fractures
  – Acute/Stress

Injury → Inflammation

Acute Injuries
• What happens when tissues are acutely injured?
How Does the Body Heal? Achieve Homeostasis?

Healing Process

- Inflammatory phase (injury to 48-72 hrs)
  - Remove debris, damaged tissue.
  - Recruit cytokines and other growth factors.
  - May also be integral to muscle repair and adaptation.

- Proliferative phase (48 hrs – 6 weeks)
  - Proteolytic degradation of damaged tissue facilitated by protein-rich exudate resulting from vascular permeability.
  - Proteolysis attracts neutrophils, lymphocytes, macrophages.
  - Fibroblasts form new extracellular matrix.

- Maturation phase (6 weeks – months)
  - New extracellular matrix.
  - Functional tissue is laid down.

  - Each phase is dependent upon the preceding phase!

Inflammation

- **Good or Evil??**

- Inflammation is a necessary component in the healing process!

- "inflammation can occur without healing, but healing cannot occur without inflammation."
  - Leadbetter

Chronic/Overuse

- **Tendinitis**: "itis" = inflammatory process
  - these injuries may not be inflammatory in nature!

- **Tendinosis**: “tendon degeneration”

- **Tendinopathy**: “nonspecific tendon pathology”

Tendinopathy

- Theoretical Model of Tendinosis cycle:

  - Adequate Repair (Adaptation) → Increased Demand on Tendon → Inadequate Repair (inadequate collagen and matrix production) → Tendinosis Cycle → Further reduction in collagen and matrix production → Tenocyte Death

Acetaminophen and NSAIDs

- What do they have in Common??
  - Analgesic
  - Antipyretic
Mechanism of Action

• NSAID
  – COX inhibitor (block prostaglandin formation)

• Acetaminophen
  – “central acting”
  – Debate on mechanism of action
  – May have weak COX inhibition

Acetaminophen

• N-acetyl-p-aminophenol (APAP)
• First marketed as children’s elixir in US in 1955
• Approx 184 OTC and Rx APAP avail
• Preg risk factor B
• Safe in breastfeeding

Acetaminophen Risks

• Liver Toxicity
  – Thousands of ER visits/yr
  – Overdose is biggest issue
    • Acute liver failure (hepatic necrosis)
  • Btw 2000-2004, 1600 cases of acute liver failure in US/yr.
    – 86% attributed to intentional and unintentional APAP overdose

Acetaminophen Risks

• FDA “Boxed Warning”
  – potential for severe liver injury

• “Warning”
  – potential for allergic reactions (e.g., swelling of the face, mouth, and throat, difficulty breathing, itching, or rash)

• Increased liver toxicity risk with consumption of 3 or more alcoholic drinks per day with APAP use

Acetaminophen Risks

• January 2011:
  – FDA limited strength of acetaminophen in prescription drug products to 325 mg per tablet/capsule

• >4g/day = potentially toxic
• Advised max daily dose = 3g/day
NSAIDs

• Non-Steroidal Anti-Inflammatory Drugs (NSAIDs)
  – Analgesic
  – Anti-inflammatory
  – Antipyretic

• 17,000,000 Americans use various NSAIDs on a daily basis
  – One of most commonly used class of drugs in the world

COX-1 enzyme

• Homeostatic (constitutive enzyme; responsible for regulation of normal cell activity)

• Form prostaglandins for:
  – Protection of gastric mucosa
  – Platelet activation
  – Macrophage differentiation
  – Maintenance of some renal functions

COX 2 enzyme

• Inducible (Pathologic)

• Form prostaglandins for:
  – Inflammation
  – Pain
  – Fever

  • AND...
    – Bone formation
    – Tissue repair after injury (collagen synthesis)
    – Physiologic – reproduction and renal function
    – Healing of H. Pylori gastric ulcers

NSAIDs GI RISK

• Symptoms: dyspepsia, nausea, heartburn, constipation

• G-I bleeding: (dose-related)
  – Direct effect/irritation
  – Systemic (post-absorptive) prostaglandin inhibition of endogenous mucosal protection (cytoprotective effect)

NSAIDs GI RISK

• GI bleeding secondary to NSAID use is the 15th leading cause of death in the United States

• > 100,000 hospitalizations annually
  – 5-10% mortality rate in those hospitalized for NSAID-induced GI bleed

• Increased risk
  – Increased age (> 65), simultaneous use with another NSAID, alcohol use, corticosteroid use, anticoagulant use
**NSAIDs GI RISK**

- After 7 day use:
  - 6.7% incidence gastric ulceration
  - 1.4% duodenal ulceration

- COX-2s safer?
  - Compared to placebo, COX-2s still have 5x risk of bleeding

**NSAID GU RISK**

- Risk of acute renal failure
- 5% who use NSAIDs experience renal complications
  - Prostaglandin-induced decreased renal blood flow
  - Complicates prolonged exercise/heat-induced hypovolemia
  - Inc risk of hyponatremia
  - Electrolyte imbalance (prostaglandin inhibition)

**Hepatic Risk**

- Unusual (< 5/100,000 users per year)
- Combination with other hepatotoxic drugs increases risk
  - i.e. acetaminophen

**Cardiac Risk**

- May accelerate CHF in at-risk individuals
- Selective inhibition of antithrombotic prostaglandins (COX 2) might increase cardiovascular events??
  - Mechanism:
    - increased vascular resistance
    - interference with actions of diuretics, ACE inhibitors

**Cardiac Risk**

- Celecoxib
  - 400 mg twice daily linked to 3.4-fold increase in CV death, MI, CVA
  - 200 mg twice daily $\rightarrow$ 2.4-fold increase
- CV risk greatest after 18 months of use
  - *New data: Even shorter duration has risk!*
**Bleeding Risk**

- Interferes with platelet function/aggregation

**Specific Concern For the Sports Medicine Physician:**

- Delayed Healing??

**Animal Studies: Sprains**

  - Results of animal studies show increased mechanical strength during healing, presumably due to increased collagen cross-linking.
  - Once healed, however, there were no differences between placebo and NSAID-treated ligaments.

  - Evaluated effects of COX-2 inhibitor (Celecoxib)
  - Inhibited early Healing of incised rat MCLs
  - Celecoxib-treated injured ligaments were found to have a 32% lower load to failure than untreated/injured ligaments.
  - No effect on unrelated, healthy ligaments.
  - Contradicted 1988 study.

- Negative effect on ligaments is more profound with COX-2 inhibitors

**Animal Studies: Sprains**

  - 7 groups: piroxicam, naproxen, rofecoxib, butorphanol, 2 doses of acetaminophen, and control
  - Mechanical testing on day 14 post op
  - Piroxicam group demonstrated significantly greater load to failure (27%) compared with the control
  - No sig difference with opiate analgesics, acetaminophen, and cyclooxygenase-2 inhibitors

**NSAIDs and Sprains**

- *A randomized controlled trial of piroxicam in the management of acute ankle sprain in Australian Regular Army recruits.* Slatyer MA, et al. AISM 1997
  - 364 army recruits with ankle sprains
  - Randomized to piroxicam or placebo
  - Piroxicam group: less pain & able to resume training faster
  - However some evidence of local abnormalities: instability and reduced ROM

- Unknown long term effect on tissue healing and structure

**NSAIDs and Sprains**

- Summary:
  - Contradicting results:
    - Piroxicam: stimulate collagen synthesis and early strength?
    - Some evidence of short term decreased ligament healing
    - Detrimental effect on ligaments is more profound with COX-2 inhibitors
    - Variations in cyclooxygenase enzyme selectivity by different drugs?
    - Variation in analgesic properties?
  - Unknown long term effect on tissue healing and structure
  - Animal Studies = Clinical relevance?
  - Inflammation is a necessary component in the healing process!
Animal Studies: Strains

  - Transected and sutured rat patellar tendons
  - Mechanical testing and biochemical analysis at 14 d post op
  - NSAIDs (except ibuprofen) had decreased failure loads and increased failures of suture.
  - Acetaminophen had no effect on healing strength
  - Biomechanical properties paralleled closely with total collagen content at the injury site
- Suggests agents may alter healing strength by decreasing collagen content

Strains

- NSAIDs may...
  - Delay and possibly decrease inflammation
  - Inc contractile force in early post-injury state

But

... prostaglandins have a stimulant effect on skeletal muscle protein synthesis...

- Delayed muscle regeneration?
- Dec collagen synthesis?
- Delayed effect on tissue level healing?

Fracture Healing

- Prostaglandins important in the regulation of osteoblast and osteoclast functions
  - Important for bone formation, healing, and remodeling
  - Inhibition of prostaglandin production retards bone formation

- NSAIDs used to prevent ectopic bone formation (heterotopic ossification)
  - Documented in controlled clinical trials

Fracture Healing

- Bone fracture healing
  - Oral application of diclofenac significantly delayed fracture healing in rats*
  - Animal studies show inhibition or deficiency of COX-2 impairs the bone healing process
    - Mice with COX-2 knockout gene
      - Reduced endochondral ossification and greater delayed union

- Limited clinical data supports assumption that inhibition of COX-2 by non-selective or COX-2-selective NSAIDs delays fracture healing


NSAIDs and Fracture Healing

- Benefits
  - Pain relief
  - Inhibition of ectopic bone formation

- Risk
  - Non-union
  - Delayed union

NSAIDs in MSK Injuries

- Animal studies show delayed fracture healing and delayed tissue regeneration
- Cox-2 inhibitors have an adverse effect on bone healing and may have an adverse effect on ligament healing

- Further investigation needed to confirm traditional NSAIDs preferable for the healing of collagenous tissues?

- Need for studies on the effects of NSAIDs on clinical level tissue repair
Prophylactic Use?

- Impair normal biofeedback – injury risk
- Impair normal healing response – Collagen synthesis
- Acute GI Risk – GI mucosal damage
- Acute Renal risk – Hyponatremia
- Increased bleeding risk

Summary

- Acute Analgesia is Important in Injury Treatment – Earlier mobilization and return to function
- Consider Risks and Benefits in Acute Injuries – Screen for comorbidities – Further research needed
- Avoid NSAID Use in Fracture Care
- Counsel on Risks of Prophylactic NSAID Use
- Avoid Prolonged NSAID Exposure – GI, Cardiac Risk
- Counsel on proper dosing of APAP – Increase risk of overdose with EtOH

References