Performance Enhancement and Healing: Fact or Fiction - Part 2

Toradol: Is it Safe or Effective?

Matthew J. Matava, M.D.
Professor, Orthopedic Surgery
Co-Chief, Sports Medicine Section
Washington University Orthopedics
Head Team Physician, St. Louis Rams Football Team
St. Louis, Missouri
(314) 514-3569
matavam@wudosis.wustl.edu

I. Toradol in Sports – What’s the Big Deal?
   a. “I think it should be mandatory”
   b. “It helps you get where you have to go.”
   c. “…feel like superman”
   d. “Ex-Players Suing NFL Over Use of Painkiller”
   e. “NFL PA Warns Players About Prescription Pain-Reliever”

II. History of NSAID Use in Sports
   a. 1950s: NSAIDs prescribed for athletic injuries to blunt the body’s inflammatory response to injury, control pain, and aid return to sports
   b. NSAIDs used by 30% of adults in the past 48 hrs.
   c. NSAIDs used by approximately 8% of athletes
   d. Adverse events reported in 20% of athletes using NSAIDs
   e. NSAIDs as a preventive measure:
      i. 2000 Olympic Games in Sydney: Canadian athletes used NSAIDs more than any other medication
      ii. American football survey (Ticker):
         1. 1 of 7 high school athletes took NSAIDs daily
         2. 29% of college athletes used NSAIDs prophylactically
   f. There is a perceived performance enhancement to justify taking these medications

III. Ketorolac Tromethamine (Toradol®)
   a. Released in 1989 as a non-specific NSAID with potent analgesic and anti-inflammatory properties
   b. Used principally for its analgesic properties following acute strains and sprains, overuse injuries, and as an adjunct to narcotic medication
   c. Routes of administration: oral, intravenous, intramuscular, or intranasal
   d. Only NSAID available in IM or IV form until 2009 (IV Ibuprofen, Caldolor®)
   e. Narcotic comparison:
      i. Standard dosing (30 mg IM) is comparable to 12 mg of IM morphine
      ii. Veenema et al. (2000): Single 60 mg IM ketorolac dose comparable to a single IM dose of meperidine (1mg/kg) in patients with severe back pain
IV. Ketorolac Injections in Athletes
   a. Used since the mid-90’s in the NFL (oral and injectable) to treat musculoskeletal injuries and to prevent postgame soreness
   b. “The Charleston Post and Courier”
      i. Reported that the South Carolina football medical staff administered 169 Toradol injections on game days during the 13 games in 2008
   c. Sawyer et al. (Sports Health, 2012)
      i. 19-question survey evaluating use of injectable ketorolac in athletes
      ii. 1100/6950 (16%) respondents (60% orthopedists, 40% primary care)
      iii. 49% used IM ketorolac primarily at the collegiate and professional levels
          1. Football: 88%,
          2. baseball: 26%
      iv. 76% administered the drug <6º prior to the event
      v. 96% reported effective pain control after administration
      vi. 3% reported bleeding complications; and 2% reported renal complications
      vii. Some physicians indicated that they do not administer IM ketorolac to their own athletes but are willing to inject a visiting team athlete(?)

V. Ketorolac Use in the NFL
   a. Tokish et al. (Physician and Sportsmedicine, 2002)
      i. Survey of injectable ketorolac in NFL teams during the 2001 season
      ii. 28 of the 30 teams that responded used IM ketorolac
      iii. Game day usage: 93%
      iv. Pain relief of 1 to 2 days noted in 50% to 75% of players
      v. 6 adverse reactions:
         1. 4 muscle injuries
         2. 1 gastrointestinal complaint
         3. 1 post-injection soreness
      vi. Concern by some NFL medical staffs that ketorolac injections were considered more powerful than other NSAIDs due to the IM route of administration
VI. Analgesic Modalities in Sports

<table>
<thead>
<tr>
<th>Modality</th>
<th>Pro</th>
<th>Con</th>
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<tbody>
<tr>
<td>OTC NSAIDs</td>
<td>Accepted by public</td>
<td>Bleeding risk</td>
</tr>
<tr>
<td></td>
<td>Well-tolerated</td>
<td>Renal risk with dehydration</td>
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<tr>
<td></td>
<td>GI symptoms</td>
<td>? effective</td>
</tr>
<tr>
<td>Prescription NSAIDs</td>
<td>Well-tolerated</td>
<td>Bleeding risk</td>
</tr>
<tr>
<td></td>
<td></td>
<td>GI symptoms</td>
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<tr>
<td></td>
<td></td>
<td>Renal risk with dehydration</td>
</tr>
<tr>
<td>Tramadol (Ultram®)</td>
<td>Well-tolerated</td>
<td>Sedation</td>
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<tr>
<td></td>
<td>Narcotic strength</td>
<td>Dizziness</td>
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<tr>
<td></td>
<td></td>
<td>Psychological dependence</td>
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<tr>
<td>Narcotics</td>
<td>Highly effective</td>
<td>Physical dependence</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Sedation</td>
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<tr>
<td></td>
<td></td>
<td>Dizziness</td>
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<tr>
<td></td>
<td></td>
<td>Nausea</td>
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<tr>
<td></td>
<td></td>
<td>Public perception</td>
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<tr>
<td>Local Injection</td>
<td>Highly effective</td>
<td>Exacerbation of injury</td>
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<tr>
<td></td>
<td>No systemic effects</td>
<td>Risk of infection</td>
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<tr>
<td></td>
<td></td>
<td>Inadvertent N/V effects</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Public perception</td>
</tr>
</tbody>
</table>

VII. Benefits of Ketorolac in the Athletic Setting
a. Well-tolerated with less side effects than opioids
b. Effective pain killer with potency similar to some opioids
c. Decreases need for opioids when combined
d. Multiple routes of administration
e. Proven efficacy in athletes
f. Perceived “day after” effects
g. Dosage independent of body habitus
h. Short half-life (6.5 hours)

VIII. “Issues” with Ketorolac in the Athletic Setting
a. Similar side effect profile to other NSAIDs
b. Use limited to 5 days (renal effects)
c. Prophylactic use contraindicated in collision sports
d. Increased renal risk with dehydration
e. GI side effects exacerbated by empty stomach
f. Athletes not always admit to other NSAID use
g. Psychological dependency with IM injection
h. Locker room gossip: veterans pressure rookies
i. NFL law suit linking ketorolac with concussions
j. **Player perception: “The needle is mightier than the pill”**
IX. Mechanism of Action of NSAIDs

Phospholipids

Phospholipase A2
(Inhibited by Corticosteroids)

Arachidonic Acid

Ketorolac NSAIDs

Cyclooxygenase – 1
Constitutitive

Cyclooxygenase – 2
Inducible

Coxibs NSAIDs

*Questionable dose-response relationship between pain relief and anti-inflammatory effects*
XI. Formulations of Ketorolac
   a. Available in oral, IM, IV, intranasal, and ophthalmologic routes
   b. Oral ketorolac was originally approved by the FDA only after IM or IV use
   c. The drug is now most commonly given alone in its oral form, which is considered an “off-label” usage
   d. Intranasal route must be refrigerated for single patient use
      i. Bioavailability of IN compared to IM dosing is between \( \frac{1}{3} \) and \( \frac{1}{4} \) of the IM dose
      ii. IN dosage of 30 mg produces a plasma level equal to the 20 mg IM dose
   e. Bioavailability is dependent upon plasma volume rather than body mass. The same dose can be administered to a 300 lb lineman as would be given to a 200 lb wide receiver

XII. Dosing of Ketorolac
   a. Oral formulation:
      i. 10 mg tablets
      ii. Usual oral dosage is 10 mg every 6 hours
      iii. Maximum of 40 mg/day in healthy adults
   b. IM and IV formulations:
      i. 15 mg/ml and 30 mg/ml
      ii. Usual dose is 30 mg or 60 mg
      iii. Maximum parenteral dosage not to exceed 120 mg/day
   c. Intranasal formulation:
      i. 15.75 mg/spray
      ii. The IN dosage is 1 spray in each nostril (31.5 mg) every 6-8 hours
      iii. Maximum daily IN dose is 4 sprays per day (126 mg)
   d. Higher doses of ketorolac do not appear to confer increased pain relief over the lesser dose, though the risk of side effects is higher

XIII. Pharmacologic Properties of Ketorolac
   a. Peak plasma concentration within 20 minutes when taken orally and within 45 minutes when administered IM
   b. Half-life: 6.5 hours in young, healthy adults; oral bioavailability: 100%
   c. 99% protein bound, metabolized in the liver through glucuronidation and oxidation, and excreted by the kidneys
   d. 90% of the drug clears the plasma within 1 day (rapid turnover)
   e. No gender differences in pharmacokinetics
   f. Plasma clearance is decreased in renal failure with a mean half-life of 9-10 hrs. due to accumulation of the glucuronide metabolite that decomposes in plasma back to the parent drug – “futile cycling”
XIV. Comparison of Oral to IM Dosing

\[ \text{a. Direct proportionality in plasma concentration (Cmax) and area under the plasma-concentration time curve (AUC) between 10 mg oral and 30 mg IM} \]

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Young Volunteers (n = 10)</th>
<th>Elderly Volunteers (n = 12)</th>
<th>Patients With Renal Impairment (n = 10)</th>
<th>Patients With Hepatic Impairment (n = 7)</th>
</tr>
</thead>
<tbody>
<tr>
<td>AUC, mg/L × h</td>
<td>2.84</td>
<td>11.3</td>
<td>4.16*</td>
<td>15.7</td>
</tr>
<tr>
<td>C_{max}, mg/L</td>
<td>0.86</td>
<td>2.99</td>
<td>0.93</td>
<td>2.51</td>
</tr>
<tr>
<td>t_{1/2}, h</td>
<td>0.33</td>
<td>0.75</td>
<td>0.73*</td>
<td>1.03</td>
</tr>
<tr>
<td>t_{1/2}, h</td>
<td>4.69</td>
<td>4.45</td>
<td>6.21*</td>
<td>7.01*</td>
</tr>
<tr>
<td>CL, L/h/Kg</td>
<td>0.033</td>
<td>0.027</td>
<td>0.023*</td>
<td>0.019*</td>
</tr>
</tbody>
</table>

PO, orally; IM, intramuscularly; AUC, area under the plasma concentration-time curve; $C_{max}$, maximum plasma concentration; $t_{1/2}$, time to $C_{max}$; $t_{1/2}$, terminal elimination half-life; CL, total plasma clearance.

*P < 0.05, compared with young or healthy subjects.

From: Buckley et al., Drugs, 1990

XV. Pharmacokinetic Properties of Ketorolac

\[ \text{a. Mean plasma-concentration time curves are nearly identical} \]

From: Jung et al., Eur J Pharmacol, 1988
XVI. Contraindications to Ketorolac ("Physicians Desk Reference")
   a. Contraindicated in patients with active or prior peptic ulcer disease, GI bleeding, or perforation
   b. Contraindicated for the treatment of peri-operative pain in the setting of coronary artery bypass graft surgery, in patients with advanced renal impairment and in patients at risk for renal failure due to volume depletion
   c. Contraindicated in patients with suspected or confirmed CNS bleeding, patients with hemorrhagic diathesis, and those at risk of bleeding
   d. Contraindicated as a prophylactic analgesic before any major surgery, in patients currently receiving aspirin or other NSAIDs because of the increased risk of bleeding
   e. Ketorolac is not indicated for use in pediatric patients and is not indicated for minor or chronic painful conditions

XVII. Side Effects of Ketorolac
   a. Gastrointestinal
      i. GI symptoms such as heartburn, nausea, diarrhea, and occult fecal blood loss are among the most common side effects of NSAIDs
      ii. Data:
          1. 10% to 30% of NSAID users develop dyspepsia
          2. 30% show endoscopic abnormalities
          3. 1% to 3% develop symptomatic gastroduodenal ulcers
          4. 1% to 3% risk of GI bleeding requiring hospitalization
      iii. Risk of GI side effects increase in a linear fashion with dose and duration
      iv. GI side effects occur via both a systemic mechanism from the inhibition of prostaglandin synthesis, as well as through irritation of the GI mucosa
   v. Preventive strategies to reduce the risk of GI toxicity with NSAID use include short dosing intervals, taking the medication with food, and use of a concurrent proton-pump inhibitor or Cytotec
   b. Renal
      i. Prostaglandin E₂ decreases Na⁺ reabsorption and prostacyclin increases K⁺ excretion that results in Na⁺ retention, hypertension, edema, and hyperkalemia
      ii. Prostacyclin I₂ also functions as a potent vasodilator and is critical to preservation of renal blood flow and glomerular filtration rate
      iii. Risk of renal failure between ketorolac and opioids (Feldman et al.):
          1. Risk of renal failure was 1.1% with either ketorolac or opioids
          2. Multivariate adjusted rate ratios were 1.00 for less than 5 days, and 2.08 for more than 5 days of therapy of ketorolac
   iv. Inhibition of COX activity in the kidney by NSAIDs, including ketorolac, has relatively mild consequences in healthy athletes
   c. Hemostatic
      i. Increased risk of internal bleeding related to its temporary inhibitory effects on platelet function
      ii. Mynster and Singer (2001):
1. A single 60 mg injection of ketorolac was associated with a 50% prolongation of the bleeding time 4 hours following injection

iii. Garcia Rodriquez et al. (1998):
   1. Ketorolac users had a R.R. of 5 compared with nonusers for hospitalization for GI bleeding

iv. Strom et al. (1996):
   1. Risk of GI and operative site bleeding with ketorolac postoperatively
   2. Risk of bleeding was dose- and duration-dependent
   3. Patients treated for more than 5 days showed the highest risk of bleeding

v. There have been no studies documenting a bleeding complication related to ketorolac use following contact or collision sports

d. Cardiovascular
   i. CV toxicity related to non-salicylated NSAID use is generally not of concern in otherwise healthy young adults
   ii. Current data suggest that selective non-salicylated NSAIDs may increase the CV risk, but these data are conflicting
   iii. 2005: the FDA requested the makers of prescription and over-the-counter non-salicylated NSAIDs to include a “black-box” warning highlighting the increased risk for cardiovascular events
   iv. “...May cause an increased risk of cardiovascular thrombotic events, myocardial infarction, and stroke. Contraindicated in perioperative pain in coronary artery bypass graft (CABG) surgery and in pediatric patients”

e. Systemic
   i. Headache, asthma, and weight gain due to fluid retention
   ii. Possible NSAID-associated delay in healing of tibial fractures, humeral shaft fractures, and other various long-bone fractures
   iii. Animal and human trials suggest that NSAIDs such as ketorolac negatively impact fracture healing
   iv. Glassman et al. (1998) and Reuben et al. (2005):
      1. Postoperative ketorolac use significantly increased the risk of nonunion after spinal fusion

v. Avoidance of NSAIDs in the setting of acute traumatic fractures or stress fractures at higher risk for nonunion is recommended

XVIII. Ketorolac Use and the NFL
a. Ketorolac has been safely used for years for the temporary relief of moderate to severe pain and inflammation
b. NFL players are superbly fit and healthy with little risk of experiencing any of the known complications associated with the use of NSAIDs
c. Professional football possesses unique issues:
   i. Risk of traumatic injury
   ii. Temporary dehydration
   iii. Concurrent use of other pain medications
   iv. Lack of job security – no guaranteed contracts
d. **Concern regarding the perceived increase in NFL players requesting IM ketorolac injections as a prophylactic medication to reduce the anticipated pain during, as well as after competition**

XIX. Rationale for “Toradol Task Force” of the NFLPS
a. Given FDA recommendations, it is logical to avoid *prophylactic* ketorolac prior to collision sports
b. The use of IM ketorolac, though safe, has been unfavorably viewed by the media and public as a necessary adjunct to pregame preparation
c. The perception of NFL players getting “shot up” in “cattle call” line up before competition has shed an unfavorable light on the NFL
d. Team physicians are perceived as being complicit with the players’ desire to play at all costs, irrespective of the medical consequences
e. **The goal of the Task Force was to provide NFL physicians with therapeutic guidelines on the use ketorolac in order to decrease the potential risk of severe complications resulting from significant trauma**

XX. Recommendations of the Toradol Task Force of the NFLPS (*Sports Health*, 2012)

a. Ketonolac should only be administered under the direct supervision and order of a team physician
b. Ketonolac should not be used prophylactically as a means of reducing anticipated pain either during or after participation in NFL games or practices
c. Ketonolac use should be limited to those players diagnosed with an injury or condition and listed on the teams’ latest injury report, or following a physician-diagnosed injury or condition that occurs after the last injury report has been submitted to the NFL prior to competition
d. Ketonolac should be given in the lowest effective therapeutic dose and should not be used in any form for more than 5 days
e. Oral ketorolac should be given under typical circumstances since the oral form:
   i. 1) has a faster onset of action
   ii. 2) has a duration of action that is equivalent to the IM and IV forms
   iii. 3) has a plasma concentration-time curve that is nearly identical to IM
f. IM and IV ketorolac should not be used except following an acute, game-related injury where significant visceral or CNS bleeding is not expected and where other oral or IN pain medications are inadequate or not tolerated
g. Ketonolac should **not** be taken concurrently with other NSAIDs
h. Ketonolac should **not** be taken by players with a history of allergic reaction to NSAIDs, GI bleeding, renal compromise, or complications related to NSAIDs
i. **Each team physician is ultimately free to practice medicine as he or she feels is in the best interest of the patient**
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