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Over-the-Counter Non-Steroidal Anti-Inflammatory Drugs in Adolescent Athletes

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Over-the-Counter Non-Steroidal Anti-Inflammatory Drugs in Adolescent Athletes

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Anne Christine Parada

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Abstract

Non-steroidal anti-inflammatory drugs (NSAIDs) are common medications used by the general population due their anti-inflammatory and analgesic properties. These are especially popular in athletes since they are not prohibited in many rules of athletic competition. Over-the-counter (OTC) NSAIDs comprise several drugs that may be purchased without a prescription. These are often over-utilized by the general population due to their accessibility and relatively low cost. The unsuspecting victims are the children, especially adolescent athletes, who deem OTC NSAIDs safe without realizing the potential adverse effects of inappropriate consumption of these medications. This article reviews the approved indications and side effects of NSAIDs as well as the literature that reveals the overuse and potential complications of NSAIDs in adolescents with recommendations to minimize injury.

Introduction

Non-steroidal anti-inflammatory drugs (NSAIDs) are often the drugs-of-choice for acute injuries (i.e. sprains and strains) due to their anti-inflammatory and analgesic properties.¹ The use of NSAIDs across a wide range of sports²⁻⁵ has been reported, and NSAIDs are touted as one of the drug classes most often used by athletes.⁵ Certain NSAIDs including aspirin, ibuprofen, ketoprofen, and naproxen are available over-the-counter (OTC) which allows the patients to obtain the medication without the need of a prescription. Over-the-counter NSAIDs are easily accessible and relatively low-cost; appearing to be a quick solution to sprains and strains experienced in athletic training. The use of these medications is legal in competition and since no prescription is required

for OTC NSAIDs, many people, including high school athletes, deem them safe to use without realizing the potential adverse effects stemming from inappropriate use of these medications.⁶ Many case reports of adolescents have been reported about the serious and possibly life-threatening effects of NSAIDs, including acute and chronic renal failure.⁷

The problem is the lack of education and understanding by adolescents about the dangers of NSAID use. Many case reports have clearly established that children can experience serious, if not sentinel, events with NSAID use. This article reviews the frequency and awareness of OTC NSAID use by athletes and reports the adverse effects from these medications in athletes and children. By providing guidelines for OTC NSAID use, adolescents will understand the appropriate and safer use of these drugs that will then be carried on into adulthood.

NSAID Overview and Mechanism of Action

NSAIDs are comprised of a wide selection of agents with different pharmacodynamics, pharmacokinetics, indications, and formulations. Over-the-counter NSAIDs are only orally administered and limited to aspirin, ibuprofen, ketoprofen, and naproxen.⁸ To achieve their desired anti-inflammatory and analgesic properties, NSAIDs work by blocking cyclooxygenase (COX) which in turn inhibits prostaglandin synthesis from arachidonic acid.⁹ As Figure 1 illustrates, NSAIDs reversibly block two isoenzymes: a constitutive form called COX-1 and an inducible form called COX-2. Inhibition of the COX-2 enzyme reduces the inflammatory response from injury while blocking the COX-1 enzyme is responsible for gastrointestinal and renal side effects of

NSAIDs. Selective COX-2 NSAIDs are agents that only block COX-2 isoenzyme, thereby theoretically avoiding mainly gastrointestinal and some kidney complications. COX-2 is also implicated in other physiologic process including renal function and tissue repair.¹⁰

FDA Approved Indications

Based on their therapeutic effects, NSAIDs are approved and labeled for an assortment of inflammatory conditions as well as mild-to-moderate pain, and fever.¹¹ The two main OTC NSAIDs used by the general public are ibuprofen (Advil® or Motrin®) and naproxen (Aleve®) and are available at lower doses than the prescription products, 200 milligrams and 220 milligrams respectively per tablet, capsule, or caplet. For conditions that require higher strength NSAIDs, a prescription is usually warranted; however, many athletes have resorted to using OTC NSAIDs for unlabeled indications and in quantities surpassing the recommended daily amount according to OTC directions.

Misuse of NSAIDs

Due to their permissible use in competition, accessibility, low-cost, and therapeutic benefit, athletes frequently take NSAIDs to continue their daily activities. They have been reported to self-medicate with OTC NSAIDs to return to their respective sport or training at an accelerated pace.⁸ As well, athletes use them as a preventive measure to avoid injury even though the drugs have not been indicated for this.

Survey studies have reported participants' responses point toward NSAID overuse. For example, Canadian athletes used NSAIDs more than any other medication in the 2000 Sydney Olympic Games.⁹ Huang et al.¹² also surveyed Canadian athletes in the

1996 and 2000 Olympic Games for NSAID use and found that it was reported by 33% and 38% of the athletes, respectively.

Gorski et al.¹ surveyed the 2008 Brazil Ironman triathletes for NSAID use and awareness of the drugs' effects. Of the 1250 participants, 327 athletes were enrolled in the study. Of the enrolled subjects, over half (59.9%) reported NSAID use in the previous three months. Pain prevention during the race was the main reason cited for taking NSAIDs one day prior to race day, immediately before the race, and during the competition. When awareness of NSAID effects was assessed, the authors discovered the majority of athletes were generally unknowledgeable of adverse effects. Gastrointestinal complications were the most familiar side effect with 58.7% (n = 192) of respondents listing it as a concern while kidney failure was identified as a possible consequence in only 18.3% (n = 60) of the athletes.

Animal studies have shown some benefit of the use of NSAIDs prior to artificially-induced muscle insult, but have not suggested any evidence for benefit for prophylaxis to muscle injury owing to physical activity.¹³ Even in human studies, results remain ambiguous for prophylactic NSAID use and only conclude that further studies are needed in athletes to fully assess NSAID potential in preventative care.¹³

In Table 1, Warden et al.¹³ provides a comparison of the risks versus benefits for the prophylactic use of NSAIDs by athletes. This unsupported use of NSAIDs occurs not only in elite athletes, but also in young athletes. Tscholl et al.² investigated the use and possible abuse of analgesics with adult female and male youth soccer players in six Fédération Internationale de Football Association (FIFA) tournaments. Surprisingly,

approximately one in six (17.3%) players under 17 years, one in five (21.4%) players under 20 years, and one in three (30.7%) female players took NSAIDs before a match. Of all the players combined, 8.9% (209 of 2340) used at least two formulations of NSAIDs. The topical route was the least popular preparation with use at 0.6% even though topical applications have the least amount of systemic adverse reactions.

Warner et al.⁶ assessed NSAID use and attitude among high school athletes. The authors provided a self-administered questionnaire to 681 high school football players with a mean age of 15.8 years. Their answers revealed that nearly one in seven of these adolescent athletes used NSAIDs daily, and 75% (n = 432) had used NSAIDs within the past three months. The majority of daily users (91%) believed NSAIDs improved their performance even though the drugs are not considered performance enhancers. The authors concluded that the adolescents that were most likely to use NSAIDs daily were those who believed they performed better with the medications, those who decided on their own when to take NSAIDs, and those who used the drugs to block pain as a preventative measure instead of treating the pain that was inflicted. The survey did not assess the athletes' awareness of either therapeutic benefits or side effects of NSAIDs.

Adverse Effects

Besides underlining the overuse of NSAIDs, the above surveys also highlight the observation that athletes are unaware of the potential adverse effects from NSAIDs. The most common, and well-known, side effects involve the gastrointestinal (GI) tract to inhibition of GI protective prostaglandins.¹ Minor insults affecting anywhere between 10 to 60% of users include nausea, dyspepsia, flatulence, anorexia, abdominal pain, and

diarrhea.¹⁰ These effects can be reduced if NSAIDs are taken with food or milk or with enteric coated NSAIDs, which should not be taken with milk or antacids. More serious GI problems consist of gastric or duodenal bleeding or ulceration, perforation, and gastric outlet obstruction. These occur in 1.5 to 4% of persons per year which amounts to substantial morbidity and mortality considering NSAIDs' widespread use.¹⁰ The risks increase in the geriatric population, those with a history of ulcers or GI bleeding, smokers, frequency of alcohol consumption, and comorbid conditions like cardiovascular disease.¹¹ Long duration of NSAID use, large NSAID dose, and number of agents concomitantly administered also augment the risk for GI side effects as well as other adverse reactions.

Non-steroidal anti-inflammatory drugs also increase the risk of cardiovascular-related events, including myocardial infarction. Although these cardiovascular (CV) risks were considered to be more associated with COX-2 selective NSAIDs, new Food and Drug Administration (FDA) guidelines have mandated new labeling on all NSAIDs. Newer studies have indicated a possible increase in CV events with more widely used NSAIDs such as ibuprofen.¹⁴ Even though these risks are more related to older age, Fosbøl et al.¹⁵ demonstrated an increase in myocardial infarction in young healthy individuals aged 30 to 50 years with NSAID use. Although the risk was low (63 deaths per 1,000,000 person-years), the outcomes were serious, creating more controversy on the prophylactic use of NSAIDs in athletes.

Athletes often take NSAIDs so as to be able to continue training in their respective field, but another potential side effect of continual NSAID use is delay in musculoskeletal tissue healing. Prostaglandins mediated by COX-2 are required for

muscle regeneration.¹⁶ Short-term use of NSAIDs will provide anti-inflammatory, analgesic properties that will promote return of function of injured tissue. However, prolonged use may delay tissue-level healing.¹⁷ Trappe et al.¹⁸ studied post exercise (24 hours) skeletal muscle fractional synthesis rate (FSR) in male subjects. Over-the-counter doses of ibuprofen compared with placebo showed unchanged FSR while the placebo group had increased FSR. The potential for reduction in muscle hypertrophy following injury or exercise challenges the basis of athletes for prophylactic use of NSAIDs.

NSAIDs may also cause kidney injury such as acute or chronic renal insufficiency, hyperkalemia, renal papillary necrosis, and interstitial nephritis.¹⁰ These insults are from direct toxicities of NSAIDs and their inhibition of prostaglandins that promote vasodilation of renal blood vessels thereby, decreasing perfusion throughout the kidneys. Although the people most at risk are the elderly, certain comorbidities are associated with decreased renal blood flow such as in congestive heart failure and chronic renal insufficiency, and potentially nephrotoxic drugs, such as diuretics, aminoglycosides, angiotensin-converting enzyme inhibitors and ethanol.¹¹ Healthy athletes, especially adolescents, probably do not have these risk factors, but they are frequently dehydrated due to fluid losses during intense exercise. Volume depletion along with stress from strenuous activities promotes the development of renal diseases while on NSAIDs.¹³ Renal injuries from NSAIDs are becoming more common in children and adolescents and the following case studies indicate that proper education needs to be implemented to ensure safe use of accessible OTC NSAIDs.

Case Studies

Renal complications are a growing concern among children and adolescents. Acute kidney injury (AKI) occurring in healthy adolescents leads to the conclusion that NSAIDs are not as safe as the general public perceives. Table 2 summarizes case studies involving children and adolescents with renal complications due to NSAIDs.

Nakahura et al.⁷ reported a 16-year-old female who took ibuprofen periodically for headaches. She was admitted to the hospital for persistent flank pain and fever, unresponsive to intravenous antibiotics. Interstitial nephritis was determined upon a kidney biopsy. She was treated with oral steroids for 2 months and discontinuation of the ibuprofen was recommended. One year later, she was asymptomatic and her serum creatinine decreased from 2.6mg/dl initially to 1.2mg/dl. However, two years after initial treatment, her serum creatinine increased to 2.8mg/dl and chronic renal failure ensued when interstitial fibrosis was discovered on her repeat kidney biopsy.

Becker-Cohen et al.¹⁹ described a rare occurrence of naproxen-associated acute interstitial nephritis (AIN) developing into severe reversible renal failure. AIN occurred in a 10-year-old girl who took one month of naproxen followed by diclofenac for juvenile rheumatoid arthritis. After discontinuation of naproxen and diclofenac, administration of methylprednisolone and tapering prednisone therapy, her 6th month follow-up showed resolution of AIN.

Ulinski et al.²⁰ reported six children aged 4 to 15 years who presented with diarrhea and/or vomiting and fever. They were treated for their fever with therapeutic doses of ibuprofen before developing AKI. This case review emphasized the potential

danger of NSAIDs in instances of even mild volume depletion. These case studies stress the importance of education about the toxicity of OTC NSAIDs, even in small amounts.

Recommendations

Over-the-counter NSAIDs can be safely administered if used for short periods of time and with proper dosing according to their labeling. These medications should be taken with food to avoid GI upset and with fluids to avoid dehydration and renal complications. Appropriate indications should be followed and prophylactic doses should be avoided. If possible, oral NSAIDs should be substituted for topical products to avoid systemic adverse effects. A non-pharmacologic therapy to be considered is the RICE protocol. RICE stands for rest, ice, compression, and elevation and tries to prevent injury-induced bleeding into the muscle so to minimize the extent of an injury. If an acute injury occurs, taking time off from activities, icing the area on and off for 20 minutes, wrapping the affected area in a compression bandage, and keeping the area above heart level might prove beneficial.²¹

Conclusion

Over-the-counter NSAIDs are a frequently used medication for athletes, especially adolescents due to their anti-inflammatory and analgesic therapeutic properties. They are easily accessible and are generally safe and effective when used as directed for short durations. Overuse of NSAIDs is a frequent occurrence across sports, gender, and age. Even with existing evidence in adults and children of the detrimental effects of NSAIDs, serious complications are overlooked. To prevent adverse effects and promote healthy healing in athletes, education on NSAID complications and appropriate

use needs to be encouraged and supported by all athletes, healthcare professionals, and role models to adolescents.

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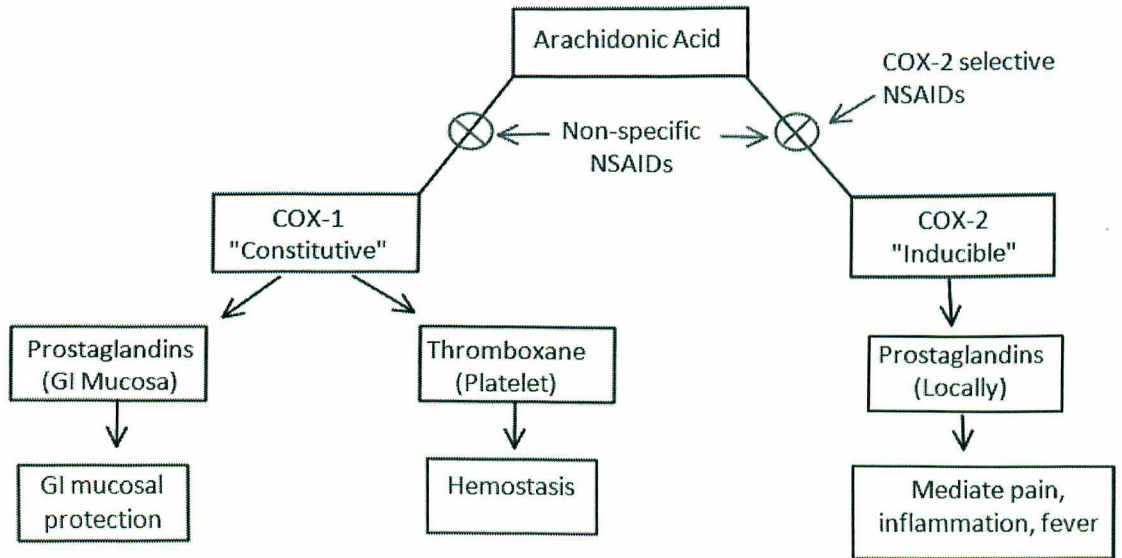
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Figure 1

Mechanism of Action of NSAIDs²²



Adapted from *Inflamm Res.* 1995;44(1):1-10

Table 1 Perceived Benefits and Potential Risks of Prophylactic and Frequent Use of NSAIDs by Athletes¹³

Perceived Benefits^a	Potential Risks
Reduced pain and tissue damage during activity	Serious gastrointestinal, renal, and cardiovascular side effects
Reduced soreness and hastened recovery following activity	Injury progression due to "masking" of pain
	Increased injury risk due to drug-induced reductions in musculoskeletal tissue adaptation
	Elevated injury risk due to drug-induced delays in tissue-level healing

^aThese benefits are anecdotal, with evidence for their existence in athletes being equivocal

Table 2 NSAID-Associated Adverse Events in Children

	Number of Cases	Age (years)	NSAID Therapy	NSAID Duration	NSAID-associated Outcome
<i>Nakahura et al.</i> ⁷	3	16	Naproxen indefinite amount	9 months	Acute kidney injury leading to chronic interstitial fibrosis Proteinuria with flank pain Positive eosinophils in urine with abdominal and bilateral flank pain
		15	Ibuprofen 400mg every other day	6 months	
		19	Ibuprofen indefinite amount (at least 2 doses/day)	Several weeks	
<i>Becker-Cohen et al.</i> ¹⁹	1	10	Naproxen 250mg twice daily Naproxen 250mg three times daily Diclofenac* 25mg three times daily	1 week 3 weeks 3 days	Acute kidney injury due to acute interstitial nephritis
<i>Ulinski et al.</i> ²⁰	6	4-15	Ibuprofen 11.5 to 32mg/kg/day	1-5 days	Acute kidney injury
<i>Krause et al.</i> ²³	2	13	Naproxen 500mg max of 1000mg/day	4 days	Acute kidney injury
		16	Ibuprofen 1200mg max of 2400mg/day Naproxen 500mg max of 1000mg/day	4 days	

* Prescription accessible NSAID