What’s New in NSAID Pharmacotherapy: Oral Agents to Injectables

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Abstract

Objective. Nonsteroidal anti-inflammatory drugs (NSAIDs) represent a critically important class of medications useful in numerous musculoskeletal and inflammatory diseases. The focus of NSAID use has recently centered on gastrointestinal (GI) side effects and potential cardiovascular toxicity. Innovative new oral and intra-articular pharmacetically engineered dosage forms are examined. We review recently developed intravenous NSAIDs and their potential advantages over oral products in the perioperative setting.

Design. Databases searched included PubMed, Google Scholar, Ovid, and Athens. We contacted key U.S. and Japanese manufactures who are developing new and innovative NSAID technologies for inclusion in this overview. Early attempts at mitigating GI toxicity with oral agents combined with gastroprotective additives are outlined.

Results. Contemporary technologies coupled with uniquely advanced pharmaceutical manipulations to improve safety and efficacy are discussed including combined vasodilating agent naproxcinod as the prototypical cyclooxygenase-inhibiting nitric oxide (NO) donor; hydrogen sulfide-releasing compounds to protect GI mucosa; glycoscience technologies combining the intra-articular hyaluronic acid SI-613 combined with NSAIDs; and nano-formulated SoluMatrix submicron technologies that include diclofenac, indomethacin, naproxen, and meloxicam.

Conclusions. New NSAIDs under development are intended to address GI and cardiovascular pitfalls inherent to current therapy options across the entire NSAID drug class. NO or hydrogen sulfide donating drugs, new reliable injectables for perioperative and inpatient use, novel intra-articular extended-release NSAIDs combined with IAHA, and nano-formulations of submicron NSAIDs featuring delivery of decreased doses without diminished efficacy promise to afford innovative technologies that likely will be the future of NSAID therapy.

Key Words. NSAID; Cyclooxygenase-Inhibiting Nitric Oxide Donor; Glycoscience; Nano-Formulated; SI-613

Introduction

Nonsteroidal anti-inflammatory drugs (NSAIDs) represent a critically important class of medications useful in numerous musculoskeletal and inflammatory diseases [1]. The focus of NSAID use has most recently centered on their gastrointestinal (GI) side effects and potential cardiovascular toxicity [1–3]. The first successful attempt to reduce GI side effects combined NSAIDs with gastroprotective agents (proton pump inhibitor, H2 receptor antagonist, or misoprostol), and despite lack of validated benefit, some combination products were approved (see Table 1) [4]. From intravenous (IV) to oral (PO) products in development, the priority is reducing side effects while maintaining or improving efficacy.
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Table 1  Comparison of available combination nonsteroidal anti-inflammatory drugs (NSAIDs) with gastroprotective agents

<table>
<thead>
<tr>
<th>NSAID + Gastroprotection</th>
<th>U.S. Approval</th>
<th>Formulations</th>
<th>↓ Gastric Ulcers</th>
<th>↑ CV Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arthrotec® (diclofenac/misoprostol)</td>
<td>1997</td>
<td>50 mg or 75 mg/200 μg</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Vimovo® (naproxen/esomeprazole)</td>
<td>2010</td>
<td>375 mg or 500 mg/20 mg</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Duexis® (ibuprofen/famotidine)</td>
<td>2011</td>
<td>800 mg/26.6 mg</td>
<td>Yes</td>
<td>Yes</td>
</tr>
</tbody>
</table>

Sources: Gastric Ulcer Data Cochrane Review 2011 update [4]; CV Risk Data CNT 2013 [3].
CV = cardiovascular.

NSAIDs with Vasodilators

Naproxinod

Naproxinod was the first of a novel class referred to as cyclooxygenase (COX)-inhibiting nitric oxide (NO) donors, which is a unique approach to improving the safety profile of NSAIDs. Naproxinod is a Prodrug metabolized by jejunal esterases to the nonselective COX NSAID naproxen and butanediol mono-nitrate, metabolized to NO and subsequently to the vasodilator nitrate [5]. The rationale for this approach was to help restore the protective effects of prostaglandins via NO which stimulates many protective factors adversely affected by COX inhibition including bicarbonate secretion, mucus production, and gastric mucosal blood flow [6,7]. An NO donor, especially a prodrug, presumably has the potential to improve the GI safety profile and counterbalance suppressed prostacyclin by providing symptomatic relief (vasodilatation) to the vasoconstrictive and prothrombotic effects of increased thromboxane otherwise believed to result in increased cardiovascular risk [8].

Naproxinod 750 mg twice daily is equimolar to naproxen 500 mg twice daily, but results in a 23% decrease in peak effect (Cmax) compared with naproxen, perhaps due to reduced exposure [7,9]. Three phase III trials in patients with osteoarthritis compared naproxinod, naproxen, and placebo over 13 weeks, and demonstrated naproxinod superiority and efficacy over placebo [10–12]. Pooled analysis of adverse effects from all phase III trials demonstrated that naproxinod had a similar adverse effect profile to naproxen, but even with a reduced noninferiority margin of 70%, naproxinod failed to demonstrate noninferiority to naproxen [9].

Naproxinod is a perfect example of rational drug design not translating into tangible benefits for real patients. The effect of nitrate on blood pressure (BP) between naproxen and naproxinod was an average difference of 4.3 mmHg but was not sustained throughout the dosing interval [9,13]. At Cmax, naproxinod exhibited significant orthostatic hypotension (5.6%), which was nearly double naproxen (2.6%) and placebo (2.9%) and may have been problematic for elderly patients [9,13]. U.S. The Food and Drug Administration (FDA) denied the new drug application (NDA) for naproxinod in 2010 and concluded that a longer trial to further evaluate effect on BP and GI safety would be required for drug approval [9]. With the denial of naproxinod, the FDA sent a clear signal that NDAs for NSAIDs, even if not new molecular entities, will be heavily scrutinized for safety and improved efficacy demonstrated in trials of longer duration. In 2011, naproxinod failed to gain approval in Europe, but promising preclinical data was recently released for the treatment of muscular dystrophy reenergizing speculation about the drug’s future [14].

Hydrogen Sulfide (H₂S) Therapies

The importance of hydrogen sulfide (H₂S)-releasing compounds has just recently been elucidated, and results in animal models for inflammation and cardiovascular shock are promising [15–17]. Interest in development of H₂S-releasing NSAIDs intensified after H₂S-producing and H₂S-releasing cells in the gastric mucosa were identified [15]. H₂S production is decreased in rats receiving NSAIDs impairing gastric blood flow and predisposing them to gastric damage [18,19]. H₂S-releasing diclofenac (H₂S-diclofenac) was the first NSAID tested in rats, suppressing prostaglandin synthesis while sparing gastric mucosa. In fact, HS-diclofenac caused 90% less gastric damage compared with traditional diclofenac [18].

Several H₂S-releasing NSAIDs are currently being developed in preclinical studies including diclofenac, naproxen, indomethacin, ketorolac, and aspirin [17]. Antibe Therapeutics Inc. is currently focused on ATB-346, an H₂S-naproxen combination in preclinical studies [20]. CTG-Pharma is also reportedly developing ACS-15, an H₂S-diclofenac combination, which has shown some promise [21]. The identification of H₂S and its biochemical roles makes it an attractive target for drug research, but it may be some time before a comprehensive understanding of its effects and potential toxicities are understood.

IV Products

IV Ibuprofen

Since 1989, the only IV NSAID approved within the United States for pain was ketorolac tromethamine (Toradol®) which is indicated for moderate to severe pain requiring opioids; however, ketorolac is contraindicated in the
perioperative setting and can only be used short term (≤5 days) because of serious toxicity potential [22]. IV ibuprofen (Caldolor®) was approved in 2009 for reduction of fever, management of mild to moderate pain, and management of moderate to severe pain as an adjunct to opioid analgesics [23]. IV ibuprofen is the only IV NSAID approved for reduction of fever or peripartum pain management (prior to surgery or during surgery).

The recommended IV ibuprofen dose is 800 mg, available as 100 mg/mL (8-mL vials) but must be diluted to 4 mg/mL (800 mg in 200 mL) [23]. The pharmacokinetic comparison of IV with PO ibuprofen correlates very closely for half-life (2 hours) and total exposure (area under curve [AUC] 196 h*μg/mL). When IV ibuprofen is infused over 5–7 minutes, the peak plasma concentration (Cmax) is approximately double the oral dose (120 μg/mL vs 63 μg/mL) and is achieved much more rapidly (tmax 0.11 hour vs 1.50 hours) [24]. There is data suggesting that higher plasma levels of ibuprofen are associated with increased analgesia, which would make IV ibuprofen's increased Cmax especially useful in the perioperative setting [25].

The IV ibuprofen trials for pain can be difficult to interpret because endpoints largely rely on subjective reporting from patients utilizing a visual analog scale (VAS). As a result, reduction in daily morphine usage were the primary and secondary endpoints, VAS scores with movement (VASM) and at rest (VASR) measured at regular intervals [26–28]. All three studies reported statistically significant results for reduction in morphine use and reductions in patient-reported VAS scores (see Table 2) [26–28]. Singla et al. showed the largest consistent decrease in VASM, VASR, and reduction in morphine (31%) use throughout the first 24 hours [27]. They studied orthopedic surgery patients with first dose at anesthesia induction where the other two studies included mainly abdominal and hysterectomy surgical patients with first dose at site closure (end of surgery) [26–28]. These factors have led to speculation that type of surgery and time of administration may impact the efficacy of perioperative IV ibuprofen. Few therapeutic options have displayed decreased perioperative opioid use potentially translating to fewer opioid-related side effects, the result of which may decrease hospital length of stay and reduce expenditures [29].

**IV Parecoxib**

Parecoxib is an injectable NSAID first marketed in Europe in 2002 and used postoperatively for the short-term treatment of pain. It is a prodrug that undergoes hepatic metabolism to valdecoxib, which is ultimately metabolized by the hepatic cytochrome P450 system and excreted as inactive metabolites in the urine. Parecoxib selectively inhibits COX-2 and therefore presumably is associated with fewer GI adverse effects than other nonselective NSAIDs such as ketorolac and ibuprofen. Clinical trials completed in patients undergoing dental, orthopedic, gynecological, and coronary artery bypass graft procedures demonstrate the effectiveness of parecoxib in relieving postoperative pain and reducing opioid analgesic requirements [30]. Interestingly, in a small-scale study, Noveck and Hubbard demonstrated that concurrent heparin and parecoxib therapy does not confer an increased bleeding risk compared with heparin monotherapy [31].

**Tenoxicam** is a nonselective NSAID available in Europe as IV/intramuscular injections and oral tablets [32]. The injectable formulation is used for the treatment of pain and inflammation caused by osteoarthritis and rheumatoid arthritis, acute musculoskeletal disorders, and postoperative pain. Much like ketorolac, tenoxicam should only be administered for 1–2 days prior to transitioning patients to oral analgesic therapy [33]. Its use as a pain reliever and in reducing opioid requirements is similar to other injectable NSAID agents, and one study revealed potential antioxidant effects [32,34,35].

**Intra-Articular Hyaluronic Acid with NSAID**

According to the Osteoarthritis Research Society International 2010 guidelines for hip and knee osteoarthritis, two of the most effective treatments are intra-articular hyaluronic acid (IAHA) and topical NSAIDs [36]. Seikagaku Corporation, which means biochemistry in Japanese, is a research and development focused pharmaceutical company that specializes in the development of new treatments for osteoarthritis. The company has developed several products for the treatment of hip and knee osteoarthritis, including Caldolor® (IV ibuprofen) and OxyRex® (oral oxycodone). The company’s main focus is on developing new treatments for osteoarthritis, and they have several products in development, including a new NSAID and an IAHA for the treatment of osteoarthritis.

### Table 2  Comparison phase III intravenous (IV) ibuprofen: reduction in morphine use and pain measured on visual analog scale (VAS) at rest and movement

<table>
<thead>
<tr>
<th>Clinical Trial</th>
<th>N</th>
<th>Surgery Type</th>
<th>Admin Time</th>
<th>%↓Morphine</th>
<th>1–24 hours</th>
<th>6–24 hours</th>
<th>12–24 hours</th>
<th>1–24 hours</th>
<th>6–24 hours</th>
<th>12–24 hours</th>
</tr>
</thead>
<tbody>
<tr>
<td>Southworth et al. [26]</td>
<td>406</td>
<td>Abdominal</td>
<td>Site Closure</td>
<td>10.4%</td>
<td>13.7</td>
<td>16.7</td>
<td>19.1</td>
<td>18.7</td>
<td>23.4</td>
<td>26.6</td>
</tr>
<tr>
<td>Singla et al. [27]</td>
<td>185</td>
<td>Orthopedic</td>
<td>Induction</td>
<td>30.9%</td>
<td>13.9*</td>
<td>25.8†</td>
<td>NA</td>
<td>15.8*</td>
<td>31.8†</td>
<td>NA</td>
</tr>
<tr>
<td>Kroll et al. [28]</td>
<td>319</td>
<td>Hysterectomy</td>
<td>Site Closure</td>
<td>15.4%</td>
<td>14</td>
<td>20</td>
<td>24</td>
<td>21</td>
<td>27</td>
<td>37</td>
</tr>
</tbody>
</table>

* Measured 2.8 hours postsurgery.
† 6–28 hours instead of 6–24.
NA = not available; VASM = VAS scores with movement; VASR = VAS scores at rest.
A company developing innovative products involving hyaluronic acid and specializing in glycoscience. Glycopolymers, complex sugar chains, occur naturally on the surface of nearly all cells as glycoproteins or glycolipids, and glycoscience is the study and development of binding technologies and delivery vehicles to specific cellular targets based upon their unique glycofingerprint [37]. Seikagaku already markets IAHA products but is currently developing SI-613, which is an injectable intraarticular hyaluronic acid bound chemically to an NSAID using their own unique binding technology. The NSAID has been designed for sustained release to provide pain relief and an anti-inflammatory effect directly at the site of action similar to topical NSAIDs [37]. SI-613 is currently in phase II clinical trials in Japan, and the NSAID being used has not been disclosed. Because the NSAID is bound to HA and slowly released for topical analgesic relief, the amount of NSAID utilized in the formulation would likely be a much smaller quantity than therapeutic concentrations required by systemic oral and injectable formulations. Such a small amount released slowly should result in insignificant concentrations available for transfer into systemic circulation, which would quickly be bound to plasma proteins (NSAID class >90% protein binding) where it exerts no biological effect [38]. Similar to topical NSAIDs, limited systemic exposure should result in a favorable side effect profile [36]. IAHA and topical NSAIDs have both shown considerable utility in knee osteoarthritis [38].

Nano-Formulated NSAIDs

Optimization is the goal of nanotechnology, improving drug dissolution and absorption by increasing surface area leading to quicker onset of analgesia at lower than conventional doses [39]. Drug particles are reduced to finer particles approximately 10 times smaller than conventional formulations (see Figure 1), achieving comparable peak plasma concentrations (Cmax) with lower overall extent of systemic exposure (AUC) [40]. Utilizing SoluMatrix technology (licensed from iCeutica Inc.), Iroko Pharmaceuticals is the industry leader in submicron NSAIDs including diclofenac, indomethacin, naproxen, and meloxicam products, with promising results at various stages of clinical development [41].

Iroko’s submicron diclofenac (Zorvolex) and indomethacin (Tiforbex) products have completed phase III trials, and preliminary data have been presented at national conferences but full results are not yet published [42–46]. In phase III trials for elective surgery (bunionectomy), both lower dose submicron indomethacin 40 mg PO tid and submicron diclofenac 35 mg PO tid demonstrated similar efficacy to celecoxib 200 mg PO bid and were superior to placebo [32,42,46]. Lower dose submicron diclofenac also demonstrated superiority to placebo in a phase III hip/knee osteoarthritis trial [44]. Phase III clinical trials for submicron meloxicam commenced in March 2013, and naproxen Phase III studies are planned to begin in 2014 [41]. In addition, two submicron NSAIDs celecoxib and ibuprofen are currently in preclinical development [41].

There is significant evidence demonstrating that NSAID-related adverse effects are dose dependent [3,47]. Preliminary results demonstrate that lower dose submicron NSAIDs preserve Cmax, believed to correlate closely with efficacy, while reducing AUC that may potentially reduce the incidence of side effects [25]. Recommended dose equivalencies for submicron and traditional NSAIDs are summarized in Table 3. Submicron NSAIDs mechanistically appear advantageous with enormous therapeutic potential; however, approval will likely hinge on safety data from the phase III clinical trials not yet published. Given the importance of the NSAID class and recent history of serious adverse effects, we expect that the FDA will require long-term postmarketing surveillance studies.
Discussion and Conclusions

When COX-2 inhibitors were first marketed in 1999, there was a 50% overall increase in NSAID prescriptions from the previous year (1998), indicating that physicians and patients were waiting for NSAIDs with improved safety and efficacy [48]. While gastroprotective agents have been successful in decreasing the incidence of GI adverse events allowing some patients to continue therapy, for many physicians and patients the risks of NSAID therapy remain too high [1–4]. New NSAIDs currently under development reflect these concerns and include: NO or hydrogen sulfide donating drugs, new reliable injectables for perioperative and inpatient use, novel intra-articular extended-release NSAIDs combined with IAHA, and nano-formulations of submicron NSAIDs featuring delivery of decreased doses without diminished efficacy. The therapeutic importance of NSAIDs cannot be overstated, and therefore the research and development of innovative NSAID products and delivery vehicles capable of significantly improving their safety profile are immensely important. These new and innovative technologies will likely be the future of NSAID therapy.

Table 3  Recommended dose equivalencies for submicron and traditional nonsteroidal anti-inflammatory drugs (NSAIDs)

<table>
<thead>
<tr>
<th>NSAID</th>
<th>Nano</th>
<th>Traditional</th>
<th>Nano</th>
<th>Traditional</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diclofenac (mg)</td>
<td>35</td>
<td>50</td>
<td>18</td>
<td>25</td>
</tr>
<tr>
<td>Indomethacin (mg)</td>
<td>40</td>
<td>50</td>
<td>20</td>
<td>25</td>
</tr>
<tr>
<td>Naproxen (mg)</td>
<td>400</td>
<td>500</td>
<td>200</td>
<td>250</td>
</tr>
</tbody>
</table>

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