Received: 24 March 2022 | Accepted: 31 March 2022

DOI: 10.1111/jcpt.13669

REVIEW ARTICLE

Journal of Clinical Pharmacy and Therapeutics WILEY

Pharmacokinetics, safety and efficacy of intra-articular non-steroidal anti-inflammatory drug injections for the treatment of osteoarthritis: A narrative review

Daniel J. Selig MD[1] | Adrian T. Kress MD[1] | Isaiah M. Horton MD[2] | Jeffrey R. Livezey MD[3] | Eliot J. Sadik BS[4] | Jesse P. DeLuca DO[1]

[1]Walter Reed Army Institute of Research, Silver Spring, Maryland, USA

[2]Walter Reed National Military Medical Center, Bethesda, Maryland, USA

[3]Uniformed Services University of the Health Sciences, Bethesda, Maryland, USA

[4]Georgetown University School of Medicine, Washington, District of Columbia, USA

Correspondence
Daniel J. Selig, Clinical Pharmacology, Walter Reed Army Institute of Research, 503 Robert Grant Avenue, Silver Spring, MD 20910, USA.
Email: daniel.j.selig.mil@mail.mil

Abstract

What is known and Objective: Osteoarthritis (OA) is a common cause of joint disease and activity limitation in adults. Common therapies to treat OA-related pain are oral and topical non-steroidal anti-inflammatory drugs (NSAIDs) and intra-articular (IA) corticosteroids. However, prolonged courses of oral NSAIDs are associated with systemic adverse effects and repeat IA corticosteroid injections may cause cartilage degeneration. IA NSAIDs may be an alternative therapy possibly minimizing systemic side effects while maintaining efficacy. Therefore, we sought to summarize the pharmacokinetics, safety and efficacy of IA NSAIDs to help providers make a more informed decision on the use of IA NSAIDs.

Methods: We searched the National Library of Medicine Database with terms "intraarticular and nsaid", yielding 1032 results. Only traditional formulations of NSAIDs were considered for inclusion. Animal studies were included if animals were healthy or if the method of arthritis induction was a reasonable model of osteoarthritis. Human studies were included if humans were healthy or if the primary disease studied was osteoarthritis of a large joint. Of 1032 results, 31 research articles met the inclusion criteria and were summarized in this review.

Results and Discussion: We found that single doses of IA NSAIDs provided far less total systemic and synovial exposure compared to a one week course of oral NSAIDs, but maximum concentrations to the synovium with IA administration were much higher. IA NSAIDs had an excellent safety profile in small animals, large animals and humans, although these injections were associated with non-specific cartilage inflammation in healthy animals. In animal models, IA NSAIDs had similar efficacy to PO NSAIDs in treating OA-related pain. In humans, IA NSAIDs had similar efficacy to PO NSAIDS and IA corticosteroids in treating OA-related pain; however, many trials did not have a placebo control and outcome measures were heterogeneous.

What is new and Conclusion: Overall, single doses of IA NSAIDs appear safe and efficacious across animals and humans. The optimal use of IA NSAIDs is still to be

determined and further research is needed. However IA NSAIDs may be an additional beneficial therapy to treat OA-related pain. Potential uses may be to augment IA corticosteroids injections, to interrupt multiple IA corticosteroid injections or as an alternative in patients that are high risk for corticosteroid-related adverse events.

KEYWORDS
anti-inflammatory agents, non-steroidal, injections, intra-articular, osteoarthritis, sports medicine

1 | WHAT IS KNOWN AND OBJECTIVE

Osteoarthritis (OA) is the most common form of arthritis and among the most common conditions affecting a large proportion of the USA population with increased risk with age.[1] Given current trends, estimates suggest that up to one in four USA adults will have some form of arthritis and by the year 2040, the total could reach 78 million people.[2] OA also carries with it significant economic burden estimated to be as high as $81 billion annually.[3] Additionally, military populations and other young highly active populations are exposed to multiple potential risk factors for earlier development of OA which, further highlighting the need for safe and effective treatment.[4]

Non-steroidal anti-inflammatory (NSAIDs) is among the most commonly used medications and one of the mainstays of treatment for OA.[5] NSAIDs are a large class of compounds that can be categorized in different ways to include via chemical structure, target selectivity and pharmacokinetic characteristics. NSAIDs are weak acids, highly protein bound with small volumes of distribution and include salicylic acid derivatives (aspirin), aryl acetic acid derivatives (ibuprofen, naproxen), indole acetic acid derivatives (indomethacin), anthranilic acid derivatives (diclofenac) and enolic acid derivatives (meloxicam).[6] All NSAIDs prevent the conversion of arachidonic acid into prostanoids to include prostaglandin, prostacyclin and thromboxane via inhibition of the cyclooxygenase pathway. Although NSAIDs inhibit both isoforms of cyclooxygenase (COX-1, COX-2), the extent of inhibition varies based on the selectivity of the NSAID. The most commonly used NSAIDs including naproxen, diclofenac, aspirin and ibuprofen non-selectively inhibit both COX-1 and COX-2 while celecoxib and meloxicam are capable of inhibiting both COX enzymes but with a five to 50 time preferential selectivity for COX-2.[7] COX-1 is expressed in most tissues and is involved in a wide variety of functions to include protecting the gastric mucosa, regulating renal blood flow and regulating vascular homeostasis. The constitutive expression of COX-2 is limited to fewer tissues but its expression increases dramatically during the inflammatory process while at baseline, it plays an important role in vascular homeostasis.

While oral use of NSAIDs is by far the most common route of administration, both topical application and intra-articular (IA) injections of NSAIDs have become more common in a variety of settings both in order to presumptively increase NSAID concentration in the target tissue as well as potentially reduce more broad systemic exposure in order to lower the risks of known gastrointestinal, cardiovascular and renal adverse effects of the compounds.[8] One such common application is post-operative analgesia, in particular for arthroscopy. Despite these clinical applications, of note, to our knowledge, there is no NSAID currently Food and Drug Administration (FDA) approved for IA injection. Corticosteroids are FDA approved for IA injection to treat OA-related pain. However, IA joint corticosteroid injections are limited in their duration of use and carry the potential for additional adverse events.[9] Given their frequency of use, there are several reviews evaluating IA corticosteroid use. While there are comprehensive reviews of topical[10] and oral[11] NSAID use, reviews on IA use are scarce. In this paper, we aim to provide a comprehensive review of IA use of NSAIDs focusing on the pharmacokinetic, efficacy and safety profiles of IA NSAIDs in both animals and humans with OA.

2 | METHODS

The National Library of Medicine Database was searched on 27AUG2021 for original research articles that described the pharmacokinetics, safety or efficacy of intra-articular NSAID injections. Animal studies were included in this review if animals in the given study were healthy or the method of arthritis induction was generally accepted to be a reasonable model of osteoarthritis. Similarly, human studies were included if humans were healthy or if the primary disease being studied was osteoarthritis of a large joint. Studies focusing on novel formulations of NSAID delivery to the joint were generally excluded. However, such studies sometimes included a traditional formulation of NSAID delivered IA as a comparator. In such cases, the traditional IA NSAID arm may have been included. The search terms used were "intraarticular and nsaid," which yielded 1032 results. Of the 1032 results, 148 abstracts were extracted that possibly met the inclusion criteria. Of these 148 abstracts, 20 animal studies and 11 human studies met the inclusion criteria. One animal study was not found in the initial search, but was found incidentally reviewing references of included studies.[12] Patient populations, endpoints of studies and control groups were very heterogeneous. Therefore a qualitative description of study results supported by descriptive statistics when applicable was performed. Statistical calculations were performed in R (version 4.1.0) with R Studio (version 1.4.1717)

3 | RESULTS AND DISCUSSION

3.1 | General overview of NSAID pharmacokinetics

The clinical pharmacokinetics of NSAIDs commonly used in clinical practice are extensively described.[13–16] The terminal elimination half-life of NSAIDs varies dramatically ranging from 1–2 h (ibuprofen) to 60–70 h (tenoxicam). NSAIDS's are typically administered orally (PO) or topically for long-term therapy, and intramuscularly (IM) for control of more severe acute pain. Administration via PO or IM routes provide similar systemic exposure for most NSAIDs which is comparable to the systemic exposure after intravenous NSAID administration (bioavailability 90%–100%).[16–18] However, due to first pass metabolism, the oral bioavailability of diclofenac is only on average 55%.[19] Penetration of NSAID to synovial joints after systemic administration is adequate, with synovial fluid achieving approximately 0.25–0.5 of steady-state plasma concentrations.[15,16,20,21]

Topical diclofenac is an effective NSAID for the treatment of osteoarthritis.[22] Systemic exposure to NSAID is greatly reduced with use of topical diclofenac gel at FDA-labeled doses.[23] Diclofenac 24-h area under the curve (AUC) after topical administration (total daily dose 16–48 g/day) has been estimated to be approximately 5%–20% of diclofenac AUC after oral administration (50 mg PO three times daily).[24,25] Synovial fluid concentrations after diclofenac gel administration have been estimated to be approximately 50%–80% of those observed in plasma.[26,27] However, although the relative proportion of synovial:plasma concentrations is slightly higher with topical versus oral diclofenac administration, the absolute exposure is likely far lower given the lower comparative systemic exposure.

3.2 | Pharmacokinetics of intra-articular NSAID injections

Intra-articular (IA) delivery of NSAIDs offers the possibility of achieving very high drug concentrations locally to a synovial joint while minimizing systemic exposure. However, surprisingly, when traditional formulations of NSAIDs are injected into synovial joints, the systemic exposure is very similar to that after IM or IV doses (Table 1). Although the majority of these PK studies were performed in rats, the relative bioavailability of IA NSAIDs compared to IM or IV doses was similar in all animal species regardless of NSAID tested (range 0.65–1.36).[12,28–31] In humans, the bioavailability of indomethacin IA compared to IV was 0.78, demonstrating significant systemic exposure which is consistent with the rat PK experiments.[32] Based on these studies, the plasma time to maximum concentration (T_{max}) after IA NSAID delivery occurs approximately 0.3–1 h after the injection and after several half-lives, there is a little detectable drug in the synovial fluid (0.04–0.075 snyovial:plasma ratio). The maximum concentration in the synovial joint may be estimated by considering the dose to be analogous to an IV bolus in the joint space using the following equation:

TABLE 1 Summary of pharmacokinetics of intra-articular knee NSAID injections in animals and humans

Study type	Drug	Dose	Route	T_{last} (h)	Plasma AUC_{last} (μg h/ml)	Plasma C_{max} (μg/ml)	Plasma HL (h)	Plasma T_{max} (h)	Relative bioavailibility	Synovial: Plasma concentration ratio	Reference
Rat	Naproxen	0.66 mg/kg	IV	9	66.6	8.4	6				Thing et al. (2013)[31]
	Naproxen	0.66 mg/kg	IA	9	43.3	5.7	6	0.6	0.65		
Rat	Piroxicam	0.6 mg/kg	IM	24	69.5	5.3	7.3	0.8			Park et al. (2014)[12]
	Piroxicam	0.6 mg/kg	IA	24	59	5.1	8.1	0.9	0.85		
	Piroxicam and HA	0.6 mg/kg	IA	24	62.5	5.1	9	1.1	0.9		
Rat	Piroxicam	0.2 mg/kg	IA	24	39.3	2.9	15.2	1		0.075[a]	Kim et al. (2016)[29]
Rat	Piroxicam	0.2 mg/kg	IA	24	51.8	3.7	16.8	0.8		0.04[a]	Kim et al. (2016)[28]
Rat	Ketorolac	4 mg/kg	IM	24	30.5	12.9	1.9	0.3			Kim et al. (2019)[30]
	Ketorolac	4 mg/kg	IA	24	35	12.5	2.1	0.3	1.15		
	Ketorolac and HA	4 mg/kg	IA	24	41.4	12.5	2	0.3	1.36		
Human	Indomethacin	10 mg	IV	24	2.5		2.4				Neander et al. (1992)[32]
Human	Indomethacin	10 mg	IA	24	1.9	0.6	2.8	0.68	0.78		

Abbreviation: NSAID, non-steroidal anti-inflammatory drug.
[a]Only compared at 12 and 24 h post-dose.

$$C_0 = \frac{\text{Dose}}{V_{\text{joint}}}, \quad (1)$$

where C_0 is the concentration in the joint space instantaneously after delivery, Dose = the amount of drug delivered to the joint space and V_{joint} is the total volume of the joint space. In the case of Neander et al.'s PK study,[32] where 10 mg indomethacin was injected into the knee, assuming a human knee has volume of 10 ml = 0.01 L,[33] then the maximum concentration in the knee synovial fluid would be estimated as $C_0 = \frac{10}{0.01} = 1000$ mg/L. In contrast, the plasma C_{max} after IV administration in Neander et al. was approximately 10 mg/L, roughly translating to a theoretical C_{max} of 2.5–5 mg/L in the synovial fluid if applying the steady-state synovial:plasma ratios found after systemic administration of NSAIDs cited above.

The total systemic exposure as measured by AUC is similar between IM, IV, IA and PO administration of typical formulations of NSAIDs. Therefore, these findings suggest a single dose of IA NSAIDs may achieve a two to three fold increase in maximum synovial concentration (at the targeted joint) compared to a PO dose. However, total systemic and synovial exposure measured by AUC for a single IA injection would be approximately 10-fold less than a one-week course of PO NSAIDs and would be similar to a one-week course of topical NSAIDs (Table 2).

3.3 | Summary of animal safety studies

Safety of IA NSAID injections has been extensively studied in a variety of animal models (Table 3). The majority of testing has been performed in rats; however, IA NSAIDs have also been tested in rabbit and equine models.[34,35] Generally, safety of IA NSAIDs has been tested in healthy animals using sham injection as a negative control. The sham injection was either delivered in the contralateral knee of the same animal, or to different animals designated as a control group.

Doses of IA NSAIDS tested in these animal models varied significantly when considering difference in size of animal species and range of human doses for specific NSAIDs. For example, Irwin et al. and Riggins et al. tested IA injections of 2.5 and 3 mg, respectively, in rats.[36,37] Typical human doses of ketorolac are 30–60 mg IM, which correspond approximately to 1–2 mg doses in a 0.3 kg rat.[38] In contrast, lornoxicam, which may be given as a single 8 mg dose, corresponds approximately to a rat equivalent dose of 0.2 mg and a rabbit equivalent dose of 0.75 mg (assuming a 1.8 kg rabbit). However, Saricaoglu et al. tested 1 mg IA lornoxicam in rats (five-times human equivalent dose) and Schroeder et al. tested up to 4 mg in rabbits (five-times human equivalent dose).[34,39] Kütahya tested 25 mg ibuprofen IA in rats, which is comparable to the commonly prescribed 800 mg dose in humans.[40]

Similarly, the amount of solution injected into the animal joints varied greatly when scaled to the size of the animal model. A typical human knee injection varies by local clinical practice but is approximately 3 ml in total volume.[41] With simple allometric scaling to a rat (assuming a 70 kg human and a 0.3 kg rat), this would correspond approximately to a 10 μl IA injection for rats. However, the most commonly tested injection volumes in rats were 100–250 μl (0.1–0.25 ml).[34–37,39,40,42,43] Of note, IA injections greater than 30 μl are not recommended for rats and IA injection volumes of 100 μl have been associated with rat knee joint capsular tears and fluid overflow into the subdermal space.[44]

Considering in context that doses and injection volumes may have been significantly higher than corresponding human equivalents, overall, there were minimal safety signals in the animal studies presented in Table 3. In fact, six of 10 animal studies reported in Table 3 found no significant difference in safety endpoints when comparing IA NSAIDs to control. The remaining four studies generally found greater rates of non-specific inflammation in NSAID-injected joints compared to controls. Irwin et al. found severe inflammation (defined as presence of neutrophils and macrophages, synoviocyte hyperplasia and fibrin exudation) on pathologic examination of the knee joint in nine of 10 rat knees injected with NSAID compared to 0 of 10 rat knees with severe inflammation in the control group day 5 after injection.[36] Kütahya et al. reported 10 of 40 rat knees injected with ibuprofen to have hematoma compared to 0 of 40 rat knees injected with saline. Inflammation scores were generally higher in ibuprofen-injected knees compared to control knees; however, inflammation scores gradual decreased and were similar in ibuprofen or saline-

TABLE 2 Estimated human total diclofenac plasma and knee synovial exposure at 24 h and 7 days

Route	Dose	Plasma AUC0-24 (μg h/ml)	Plasma C_{max} (μg/ml)	Synovial AUC_{last} (μg h/ml)[f]	Synovial C_{max} (μg/ml)[f]	Plasma AUC day 7 (μg h/ml)	Synovial AUC day 7 (μg h/ml)
PO	150 mg/day	3890[a]	2270[a]	1945	1135	27,230	13,615
Topical	32 mg/day	389[b]	40[c]	194.5	20	2723	1361.5
IA	50 mg single injection	2593[d]	2270[e]	1296.5	5000[g]	2593[h]	1296.5[h]

[a]Mean AUC and C_{max} observed in Kienzler et al after 50 mg TID diclofenac.
[b]Applying an estimated 10% relative systemic exposure to PO based on Kienzler et al. and Moreira et al.
[c]Extrapolated based off of Kienzler et al (48 mg/day given).
[d]Assuming a 55% relative bioavailability PO to IA.
[e]Assuming similar plasma C_{max} IA and PO.
[f]Applying an assumed steady state synovial:plasma ratio of 0.5.
[g]Estimated via equation C_0 = Dose/V_{joint} and assuming a human knee joint 10 ml.
[h]IA injections are typically only given once, therefore the total plasma and synovial AUC at day 7 would be similar to the AUC0-24 given short half-life of 1–2 h.

TABLE 3 Summary of safety studies of intra-articular NSAID knee injections in healthy animals

Animal model	N	Drug	Dose	Route	Regimen	Summary of findings	Reference
Rat	35	ketorolac	2.5 mg	IA	Single injection	Significantly more inflammation in ketorolac-treated knees compared to controls (90% vs. 0 % grade 5 inflammation at day 5)	Irwin et al. (1998)[36]
	35	saline	0.25 ml	IA	Single injection		
Rat	52	tenoxicam	1 mg	IA	Single injection	Significantly more inflammation in tenoxicam-treated knees compared to controls up to 48 h after injection	Ozyuvaci et al. (2004)[42]
	52	saline	0.25 ml	IA	Single injection		
Rat	25	lornoxicam	1 mg	IA	Single injection	No significant difference in inflammation or degeneration of cartilage in NSAID versus vehicle-treated knees	Saricaoglu et al. (2008)[39]
	25	vehicle	0.25 ml	IA	Single injection		
Rat	35	dexketoprofen	9.23 mg	IA	Single injection	No significant difference in histopathologic inflammation	Sagir et al. (2013)[65]
	35	serum	0.25 ml	IA	Single injection		
Rat	35	dexketoprofen	6.25 mg	IA	Single injection	No significant difference in synovial or cartilage pathology in NSAID vs saline treated knees	Ekici et al. (2014)[66]
	35	saline	0.25 ml	IA	Single injection		
Rat	64	ketorolac	3 mg	IA	Single injection	No significant changes in knee kinematics, ACL mechanics, or cartilage histopathology and optical density in ketorolac-treated knees compared to controls	Riggin et al. (2014)[37]
	64	saline	0.1 ml	IA	Single injection		
Rat	25	tenoxicam	1 mg	IA	q Week × 10	Significant synovial hyperplasia, increased cartilage fibrosis and GI inflammation in NSAID groups compared to controls	Orak et al. (2015)[43]
	25	diclofenac	0.75 mg	IA	q Week × 10		
	25	methylprednisolone	1 mg	IA	q Week × 10		
	25	serum	0.1 ml	IA	q Week × 10		
Rat	40	ibuprofen	25 mg	IA	Single injection	Significant increase in knee hematoma in ibuprofen-injected knees (25% vs. 0 % in control). Significantly higher inflammation scores on days 1–14 in ibuprofen injected knees	Kütahya et al. (2019)[40]
	40	saline	0.25 ml	IA	Single injection		
Rabbit	5	lornoxicam	2 mg	IA	Up to 3 repeat injections weekly	No significant differences in histopathologic examination or inflammation between controls or active comparators throughout the duration of the study	Schroeder (2012)[34]
	5	lornoxicam	4 mg	IA	Up to 3 repeat injections weekly		
	5	hyaluronic Acid Derivative	4 mg	IA	3 injection once weekly		
	5	triamcinolone	20 mg	IA	Single injection		
	5	vehicle	0.5 ml	IA	Up to 3 repeat injections weekly		
Horse	5	bufexamac	20 mg	IA	q Week × 6	No significant differences in gross pathology, histopathology or optical density of cartilage in any group	Suominen et al. (2001)[35]
	5	bufexamac	60 mg	IA	q Week × 6		
	5	bufexamac	100 mg	IA	q Week × 6		
	5	saline	1 ml	IA	q Week × 6		

Abbreviations: IA, intra-articular; NSAID, non-steroidal anti-inflammatory drug.

injected knees by day 21 post-injection.[40] Orak et al. demonstrated longer lasting inflammatory changes after 10 weeks of repeat IA tenoxicam or diclofenac injections compared to saline and steroid controls. There were significantly higher rates of mild or prominent cartilage fibroblast infiltration in NSAID groups (100%, $N = 10$ rats) compared to the saline group (0%, $N = 5$ rats) and the methylprednisolone group (20%, $N = 5$ rats).[43]

TABLE 4 Summary of efficacy studies of intra-articular NSAID knee injections in animals models of osteoarthritis

Animal model	*N*	Drug	Dose	Route	regimen	Drug initiation	Summary of findings	Reference
Rat MIA-induced arthritis	24	Dexketoprofen	10, 30 or 100 μg/25 μl	IA	Single dose	Day 7 after arthritis-induction	Dose dependent nocioception inhibition observed and similar for both IA and PO administration of tramadol or dexketoprofen. All active drug treament arms better than saline treated with statistical significance compared to placebo in medium and high dose drug arms (IA or PO). Combination oral or IA tramadol-dexketoprofen was synergistic and produced the largest anti-nocioceptive effect	Cialdi et al. (2013)[45]
	48	Dexketoprofen	0.25–1 mg/kg	PO	Single dose	Day 7 after arthritis-induction		
	24	Tramadol	10, 30 or 100 μg/25 μl	IA	Single dose	Day 7 after arthritis-induction		
	48	Tramadol	0.5–5 mg/kg	PO	Single dose	Day 7 after arthritis-induction		
	6	Dexketoprofen-tramadol	10 μg/25 μl each drug	IA	Single dose	Day 7 after arthritis-induction		
	24	Dexketoprofen-tramadol	combination of above oral doses low to high	PO	Single dose	Day 7 after arthritis-induction		
	18	Saline	25 μl	IA	Single dose	Day 7 after arthritis-induction		
	42	Saline		PO	Single dose	Day 7 after arthritis-induction		
Rat ACL transection-induced arthritis	6	Meloxicam	1 mg	IA	q week × 5	5 weeks after surgery	Meloxicam-treated OA rats had sustained improvement in mechanical allodynia metrics, histopathology and inflammatory markers compared to saline treated OA rats 10 weeks after surgical OA induction. However, results were comparable between the 0.25 and 1 mg IA OA meloxicam-treated rats, with no clear dose response	Wen et al. (2013)[47]
	6	Meloxicam	0.25 mg	IA	q week × 5	5 weeks after surgery		
	6	Saline	0.1 ml	IA	q week × 5	5 weeks after surgery		
Rat MIA-induced arthritis	8	Piroxicam	0.6 mg/kg	IM	Single dose	Day 1 after arthritis-induction	No significant changes in knee swelling, PGEM, or weight distribution on day 1; however, day 3 demonstrated statistically significant improvements in all metrics (IM and IA compared to placebo). Synergistic effect and dose response observed in regards to improved swelling and pain with IA PX:HA compared to each drug	Park et al. (2014)[12]
	8	Piroxicam	0.6 mg/kg	IA	Single dose	Day 1 after arthritis-induction		
	8	Piroxicam and HA	(PX:HA, 4:1–1:4)	IA	Single dose	Day 1 after arthritis-induction		
	8	Vehicle	20 μl	IA	Single dose	Day 1 after arthritis-induction		
Rabbit Unilateral knee joint-induced arthritis	10	Celecoxib	1.2 mg	IA	q week × 5	6 weeks after surgery	Significant improvement in histopathological cartilage inflammation in HA and celecoxib groups compared to saline treated control. Significant reductions in synovial inflammatory markers IL1-beta, TNF-alpha and mRNA expression of MMP-3 in HA and celecoxib groups compared to saline treated control. No significant differences were found in any metrics between HA and celecoxib treatment groups	Jiang et al. (2010)[46]
	10	Hyaluronic acid	3 mg	IA	q week × 5	6 weeks after surgery		
	10	Saline	0.3 ml	IA	q week × 5	6 weeks after surgery		

Abbreviations: IA, intra-articular; NSAID, non-steroidal anti-inflammatory drug.

3.4 | Summary of animal efficacy studies

The efficacy of IA NSAIDs in animal models of arthritis has also been well described in the literature (Table 4). Rat models of arthritis were the most commonly utilized. However, unlike the animal safety studies described above, efficacy models tested NSAIDs on either chemically or surgically arthritic knees. Cialdai et al. and Park et al. tested IA NSAIDs in a Monoiodoacetate (MIA)-induced rat model of arthritis.[12,45] Jiang et al. and Wen et al. utilized surgical methods such as transecting knee ligaments to induce arthritis.[46,47] In the MIA-induced models, IA injections were implemented 1 or 7 days post-arthritis induction, in contrast to a delay of 5–6 weeks prior to IA drug therapy after surgical arthritis induction. Where the two studies utilizing MIA-induced arthritis tested only a single IA NSAID injection, repeat injections of IA NSAID were administered for 5 weeks, every week, to animals with surgical-induced arthritis.

In contrast to the safety studies, where IA NSAIDs were sometimes associated with development non-specific inflammation-IA NSAIDs significantly reduced inflammation in the animal arthritis models.[46,47] Intra-articular NSAIDs were also associated with improved reduction in nociception and clinical swelling and improved weight bearing on the arthritic knee. Whenever PO or IM NSAIDs were used as comparators, similar improvements were found with clinical and laboratory assessments as to the use of IA NSAIDs.

Wen et al. did not demonstrate a clear dose-response, where 0.25 mg and 1 mg IA meloxicam injections both showed similar and sustained improvement in mechanical allodynia metrics, histopathology and inflammatory markers compared to saline-treated OA rats 10 weeks after arthritis induction.[47] Park et al., however, demonstrated a dose-response where increasing doses of IA piroxicam to rat knees were associated with corresponding improvements in both clinical swelling and pain compared to IA saline-treated controls.[12] Further Park et al. was able to demonstrat this dose-response again when combining doses of piroxicam with hyaluronic acid, and found a ratio of 1:1 or 1:2 piroxicam:hyaluronic acid provided optimal pain control and reduced swelling.

3.5 | Summary of human studies

There were a total of 11 human studies (eight prospective, three retrospective) meeting the inclusion criteria with a total of 722 participants across all studies. Tenoxicam was tested in five studies, ketorolac in four studies and parecoxib[48] and indoprofen[49] were each tested in one study. Reported mean age (range 52–71.5 years) and body mass index (range 23–31.6 kg/m^2) are summarized in Table 5. All studies examined either the knee ($N = 9$ studies) or hip ($N = 3$ studies) with one examining both the knee and hip. Inclusion criteria was heterogeneous throughout the studies and OA was defined by either American College of Rheumatology Classification Criteria ($N = 5$), American Academy of Orthopedic Surgeons ($N = 1$) or unspecified/alternative criteria ($N = 5$). Regardless of criteria to define OA, most studies ($N = 9$) used the Kellgren–Lawrence score to classify the radiologic severity of OA. Of the two studies that did not use Kellgren–Lawrence scores one used an unspeficied, but similar radiologic severity criteria[50] and the other did not use a radiologic severity criteria.[49,50] Of the nine studies using Kellgren–Lawrence scoring, studies most commonly included patients with Kellgren–Lawrence scores of 2 or 3 ($N = 6$); however, some studies included patients with Kellgren–Lawrence scores of 0 or 1 ($N = 3$).[48,51,52]

Efficacy endpoints were also heterogeneous with the most common being the Visual Analog Score (VAS) ($N = 8$). Of these eight studies using the VAS, other metrics were also utilized to categorize range of motion and stiffness. Western Ontario and McMaster University Osteoarthritis Index (WOMAC) ($N = 3$ studies) was common. Many other metrics such as range of motion quantification, Knee Society Score, Hospital for Special Surgery (HSS) scores and Hip or Knee Injury Osteoarthritis and Outcome Scores (HOOS or KOOS) were also used. Most studies did not clearly define primary versus secondary outcomes. Only 3 studies used a statistical correction for multiple comparisons.[9,52,53] Of the three studies that did not use VAS, one study had their own scoring system based only on pain with various degrees of movement.[50] The other two studies used the WOMAC index[54] or the Harris hip score (HHS) and verbal numeric pain scale (VNS).[55] Of these three studies only, Park et al. used a statistical correction for multiple comparisons.

Comparator groups were also heterogeneous. Four studies compared efficacy endpoints IA to PO NSAIDs.[52,54,56] Two of these studies compared only IA to PO NSAIDs[52,56] where two had an additional negative control group (exercise or glucosamine).[48,54] Three studies periodically assessed outcome metrics weekly or monthly from 1 week to 6 months after treatment. However, Lu et al. only assessed clinical OA outcome metrics at 12 months after intervention. Findings were similar amongst the three studies with repeat outcome measures over shorter time intervals. Generally, IA NSAIDS led to more pronounced pain resolution and functionality before 1 month; however, by 2–6 months, IA and PO NSAIDs had similar efficacy. Lu et al. were an exception and showed that at 12 months after three IA parecoxib injections, every 2 weeks for a total of 6 weeks, VAS reduced from 4.1 to 0.8 on average. In comparison after 12 weeks of PO parecoxib at 12 months, VAS reduced from baseline 4 to 1.8. Both Unlu et al. and Lu et al. that had negative control groups showed that both IA and PO NSAIDs improved VAS or WOMAC scores compared to placebo at all times measured. Of note, Unlu et al. did not report VAS scores but rather rates of joint line and periarticular tenderness. Results were presented as raw data rather than difference from baseline. When converting the raw rates to change from baseline at 6 months, IA and PO NSAIDs performed comparably increasing rates of non-tender knees (both joint line and periarticular) by 20%–30% where placebo only increased rates of non-tender knees by 5%–10%.

The remaining seven studies had no PO NSAID comparator to the IA NSAID group. One study had no comparator group,[50] one study compared to IA placebo,[49] one study compared to IA hyaluronic acid[53] and four studies compared to IA corticosteroids.[9,51,55,57] Papathanassiou et al. (tenoxicam IA, knee, no comparator) demonstrated a large majority of patients feeling great pain improvement

TABLE 5 Summary of efficacy and safety studies of intra-articular NSAID knee injections in humans

Joint	*N*	NSAID	Age (years)	BMI (kg/m^2)	Dosages and routes	Severity	Summary of findings	Reference
Knee	28	Tenoxicam	71.5		20 mg single IA knee with some repeat at 2 months	Mod-severe	Improvement in hydroarthrosis, and ROM, 40% of participants greatly improved while 12% worse for pain at 10 days. 2 allergic reactions	Papathanassiou (1994)[50]
Knee	69	Tenoxicam	54.8	30.8	1. 20 mg IA ×3 weekly 2. 20 mg oral daily ×3 weeks 3. 3) Exercise only	Grade 2/3 KL	Minor differences between groups for some outcomes. Ultimately, no total WOMAC difference and no difference overall at 6 months between all 3 groups	Unlu et al. (2005)[54]
Knee	30	Tenoxicam	52		1. 20 mgIA tenoxicam ×1 2. 20 mg PO daily ×10 days	Grade 2/3 KL and effusion	Earlier onset of improvement in VAS, and reduced number of effusions at 1 year in IA group	Oztuna et al. (2007)[56]
Knee	60	Tenoxicam	65.5	30.6	1. 20 mg IA teonixicam ×3 weekly 2. 20 mg PO daily ×3 weeks	Grade 1/2/3 KL	Outcomes improved in both groups; Gastrointestinal intolerabilty and treatment interuption higher in PO group	Erbas et al. (2015)[52]
Knee	90	Tenoxicam	67	30	1. 20 mg IA tenoxicam 2. 20 mg IA triamcinolone 3. Both	Grade 1/2 KL	Individual injections and combo better after 1 month but combination triamcinolone/ tenoxicam better than either individually at 6 months	Yilmaz (2019)[51]
Knee	43	Ketorolac plus HA	68		1. IA HA alone ×5 weekly 2. 30 mg IA HA plus ketorolac ×3 weekly, then HA alone ×2 weekly	Grade 2/3 KL	Benefit seen for combination compared to HA alone in early time points; 5 ketorolac participants developed about 8 h of post injection knee pain	Lee et al. (2011)[53]
Hip	98	Ketorolac	59	23	1. 40 mg triamcinolone 2. 30 mg ketorolac	Grade2/3 KL	No difference between ketorolac and triamcinolone. 4 localized adverse events in ketorolac group. No systemic adverse events	Park et al. (2015)[55]
Knee	35	Ketorolac	53	31.6	1. 30 mg ketorolac 2. 80 mg triamcinolone	Mean grade 3 KL	Significant difference in VAS and WOMAC for both injection groups. Cost difference better for ketorolac	Bellamy et al. (2016)[57]
Knee/Hip	120	Ketorolac	65	31	1. 80 mg triamcinolone 2. 30 mg ketorolac	Grade 2 and above KL	Similar benefit for hip and knee injections between traimcinolone vs. ketorolac Neither with significant adverse effect	Jurgensmeier et al. (2021)[9]
Hip	39	Indoprofen	52.7		1. 25 mg IA 2. Placebo	Mild to moderate	No difference between groups. Half of all participants had improvement	Egsmose et al. (1984)[49]
Knee	110	Parecoxib	52	25	1. basic care+PO glucosamine 2. basic care, PO celecoxib, PO glucosamine 3. 3) 40 mg IA parecoxib q2weeks × 3	Grade 0/1/2 KL	All treatments effective for outcome measures compared to baseline. Satisfaction, IL-6 and TNF-alpha reduction and IL-10 increase greatest for IA parecoxib	Lu et al. (2019)[48]

Abbreviations: IA, intra-articular; NSAID, non-steroidal anti-inflammatory drug.

10 days after injection (40%, $N = 10$) and improved range of motion (ROM) 1 month after injection (60%, $N = 15$). However, two patients had allergic reactions to the IA injections and 12% and 16 % of patients had worse pain and range of motion compared to baseline, respectively. Similarly Egsmose et al. (indoprofen IA, hip, placebo control) demonstrated approximately 50% of patients ($N = 11$) had

improvement in pain in the 12 week sub-study. The authors did not report which of these 11 patients received placebo or NSAID, but did note that there was no significant difference in VAS scores in NSAID or placebo groups. This highlights that the dramatic percent of pain reduction seen in Papathanassiou et al. may be attributed to a placebo effect rather than the IA tenoxicam.

Lee et al. compared repeat injections of IA ketorolac and hyaluronic acid (three weekly injections followed by two injections of hyaluronic acid alone) to IA hyaluronic acid alone (five weekly injections) without a placebo group. Patients receiving IA ketorolac had statistically significantly reduced VAS scores from weeks 1 to 3 after the initial injection compared to patients receiving hyaluronic acid alone. However, by 16 weeks, there was no longer a statistically significant difference in VAS scores between the groups. Of note, when comparing weekly change in VAS score from previous week's baseline, IA ketorolac only outperformed hyaluronic acid alone in the first week.

The remaining four studies[9,51,55,57] compared IA NSAID injections to IA corticosteroid injections. Three studies compared ketorolac to corticosteroid and one study compared tenoxicam to corticosteroid. No placebo group was included in any of these four studies. Generally, regardless of IA NSAID and metric, improvement in pain and functionality was similar between IA NSAID and IA corticosteroid groups. Interestingly, Yilmaz et al. found that a combination of IA tenoxicam and corticosteroid was superior in reducing VAS and sustaining reduced VAS compared to IA tenoxicam or corticosteroid alone. This was very pronounced at 6 months where the combination group had an average 5.6 point reduction in VAS compared to 0.27 and 0.33 point reductions for the IA NSAID alone and IA corticosteroid alone groups.

From a safety perspective, adverse events were rare but did range differently across studies. Besides the two allergic reactions in the Papathanassiou et al. study, three studies described specific side effects. Jurgensmeier et al. reported a bleeding episode 2 months after the injection of NSAID but was also associated with an increase dose of warfarin. Lee et al. and Park et al. reported local pain in the injected joint that was self-limited and mild.

4 | DISCUSSION

We provide a comprehensive review of the pharmacokinetic, efficacy and safety profiles of IA NSAIDs in both animals and humans. Providers have classically thought IA NSAIDs minimize systemic side effects by reducing systemic exposure to NSAIDs. Our review challenges this notion and provides significant insights on the relationship of NSAID PK to the desired pharmacodynamic effect of pain control. Although there are comprehensive reviews of PO and topical NSAID use, reviews on IA use are scarce. This review fills an essential gap in the literature and provides strong rationale for the clinical use of IA NSAIDs based on favorable safety and efficacy data.

From a pharmacokinetic perspective, the benefit of IA NSAIDs is unclear. The presumed advantage of IA administration is its minimal systemic exposure and maximal local efficacy. However, when compared to IV or IM doses, IA NSAIDs lead to similar systemic exposure, likely because the medication rapidly diffuses out of the joint space into the plasma. Neander et al. demonstrated that the bioavailability of indomethacin IA compared to IV was 0.78., and the studies of Park et al., Kim et al. and Thing et al. demonstrated that there was little detectable drug in the synovial fluid (0.04–0.075 snyovial:plasma ratio) after several half-lives. Further, repeat oral doses likely lead to much higher sustained synovial NSAID concentrations compared to the single IA (Table 3). However, a single IA dose likely leads to a 2–3 log-fold increase in synovial C_{max} compared to oral or topical doses. Cialdi et al. (rat induce MIA-arthritis) demonstrated similar pain control after single doses of IA or PO NSAIDs. This would suggest overall exposure and not C_{max} would be the driver of efficacy. However, four human studies demonstrated similar response in pain control after 2 months in patients receiving IA or PO NSAIDs. This would suggest that C_{max} plays a component in sustained efficacy and challenges overall sustained exposure as the main driver of efficacy. This may be partially explained by the use of tenoxicam which has a very long half-life and accumulation due to repeat injections. However, Unlu et al. randomized patients to either three weekly doses of tenoxicam 20 mg or 20 mg daily PO tenoxicam for 3 weeks. Therefore, the PO group had approximately seven-times the systemic exposure compared to the IA group, yet both groups had similar pain control and stiffness WOMAC scores through 6 months.

In regards to safety, IA NSAIDs appeared to have a very favorable safety profile. IA NSAIDs were safe in animal models where six of 10 animal studies found no significant difference in safety endpoints between NSAID and control groups. There was an association in some animal studies with IA NSAID delivery to non-specific inflammation; however, these findings appeared only in healthy animals. In efficacy animal models, where osteoarthritis was induced surgically or chemically, IA NSAIDs significantly reduced inflammation and were associated with pain reduction, decreased clinical swelling and improved weight bearing on the arthritic knee. In addition, it is possible that the non-specific inflammation found in animal safety models was related to high joint injection volumes. Injection volumes of 100–250 μl were routinely used in the rat IA NSAID safety models, but injection volumes of greater than 100 μl to the rat knee joint have been associated with capsular tear.[44] Side effects in human studies were also rare, generally mild and in some cases may not have been related to the IA NSAID injection.

IA NSAIDS also generally had a favorable efficacy profile in both animal and human studies when compared to placebo, oral NSAIDs or IA corticosteroids. However, there are several limitations to the efficacy data. It is important to note that animal studies utilized surgery or chemicals to induce arthritis, which causes acute inflammation. Osteoarthritis in humans, however, is often chronic in nature and without active inflammation. Therefore, the high efficacy of IA NSAIDs and NSAIDs in general in the animal models is likely an overestimate of the efficacy in humans. Nevertheless, these animal efficacy studies provide support that IA NSAIDs are efficacious, and

also appear as effective as oral NSAIDs within those controlled experiments.

Human studies were often limited by small sample size, and lack of a negative control group. Efficacy of PO NSAIDs compared to placebo for the treatment of OA is mixed. Although diclofenac 150 mg is consistently reported to statistically significantly reduce pain several NSAIDs evaluated within the same systematic reviews were no better than placebo.[11,58] Similarly, IA corticosteroids may be no more efficacious than placebo for the treatment of OA.[59,60] IA corticosteroids or PO NSAIDs were the most commonly active comparators to IA NSAIDS in the human IA NSAID efficacy studies. Therefore, without an internal placebo control in these trials, despite demonstrating IA NSAIDs have similar efficacy to PO NSAIDs or IA corticosteroids, all therapies may have been no better than placebo. This is highlighted by Egsmose et al. who found that IA indoprofen was no better than placebo to reduce VAS. However, despite these limitations, IA NSAIDs appear to be a promising therapeutic option and may have several important clinical applications. One example would be avoiding IA corticosteroids in a diabetic patient with poorly controlled blood sugars. Further, alternating IA NSAIDs with IA corticosteroids may be a sound approach to spare the long-term degenerative effects of corticosteroids on cartilage and bone. There are also several other possible indications for IA NSAIDs such as acute sports injuries or as an adjunct to improve analgesia for arthroscopy.

Of note, no IA injection trialed a traditional formulation of diclofenac. This was surprising as diclofenac is likely the most efficacious PO and topical NSAID. There are, however, newer formulations of diclofenac conjugated to HA (DF-HA) that prolong residence time within the joint and significantly minimize systemic exposure after IA injection.[61,62] This IA DF-HA product has been tested in phase II and phase III trials and appears to have a promising safety and efficacy profile.[62,63] Nishida et al. found in a 440 patient 1:1 randomized placebo controlled trial that after six repeat DF-HA IA injections q4 weeks that WOMAC scores were reduced at all times measured out to 24 weeks. However, the largest reduction in WOMAC scores was after the initial DF-HA injection and slopes of lines of decrease in WOMAC scores over time were henceforth similar in the DF-HA and placebo groups. This suggests that there is a little benefit to repeat DF-HA injections within a 24 week time period. Nevertheless, Nishida et al. also performed a study where 166 participants received an IA DF-HA injection q4 weeks for an entire year.[64] Treatment-related adverse effects were rare and generally well tolerated demonstrating a highly favorable safety profile of this novel IA NSAID formulation.

5 | WHAT IS NEW AND CONCLUSION

We have performed a comprehensive literature review of the PK, safety and efficacy of IA NSAIDs in animals and humans. A single IA NSAID injection leads to higher synovial maximum NSAID concentrations and far less total systemic and synovial exposure compared to a one-week course of PO NSAIDs. Traditional formulations of IA NSAIDS had favorable safety and efficacy profiles in small animals, large animals and humans and appear to at least as efficacious as PO NSAIDs or IA corticosteroids for pain control in the setting of hip or knee OA. IA NSAIDS, therefore, may be an important additional therapeutic modality to treat OA-related pain. In addition, newer formulations of diclofenac for IA injection allow for significantly longer joint residence time and sparing of systemic exposure. These formulations represent an exciting novel tool to treat OA-related pain. Further studies are needed to address long-term safety of IA NSAID injections as well as larger longitudinal randomized trials with positive and negative control groups to better understand long-term efficacy.

ACKNOWLEDGMENTS

We would like to thank Ms. Zanete Wright for her support of the WRAIR/USUHS Clinical Pharmacology Fellowship.

CONFLICT OF INTEREST

The authors have no conflicts of interest to report. Material has been reviewed by the Walter Reed Army Institute of Research, Walter Reed National Military Medical Center and the Uniformed Services University of the Health Sciences. There is no objection to its presentation and/or publication. The opinions and assertions expressed in this article are those of the authors and do not reflect the official policy or position of the U.S. Army Medical Department, Department of the Army, DoD, or the U.S. Government.

DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

ORCID

Daniel J. Selig https://orcid.org/0000-0002-6107-5984

REFERENCES

1. Dillon CF, Rasch EK, Gu Q, Hirsch R. Prevalence of knee osteoarthritis in the United States: arthritis data from the Third National Health and Nutrition Examination Survey 1991-94. *J Rheumatol*. 2006;33(11):2271-2279.
2. Hootman JM, Helmick CG, Barbour KE, Theis KA, Boring MA. Updated projected prevalence of self-reported doctor-diagnosed arthritis and arthritis-attributable activity limitation among US adults, 2015-2040. *Arthritis Rheumatol*. 2016;68(7):1582-1587. doi:10.1002/art.39692
3. Centers for Disease Control and Prevention. The cost statistics of arthritis in US adults. https://www.cdc.gov/arthritis/data_statistics/cost.htm
4. Showery JE, Kusnezov NA, Dunn JC, Bader JO, Belmont PJ Jr, Waterman BR. The rising incidence of degenerative and posttraumatic osteoarthritis of the knee in the United States military. *J Arthroplasty*. 2016;31(10):2108-2114. doi:10.1016/j.arth.2016.03.026
5. Singh G. Gastrointestinal complications of prescription and over-the-counter nonsteroidal anti-inflammatory drugs: a view from the ARAMIS database. Arthritis, Rheumatism, and Aging Medical Information System. *Am J Ther*. 2000;7(2):115-121. doi:10.1097/00045391-200007020-00008
6. Bindu S, Mazumder S, Bandyopadhyay U. Non-steroidal anti-inflammatory drugs (NSAIDs) and organ damage: a current

perspective. *Biochem Pharmacol*. 2020;180:114147. doi:10.1016/j.bcp.2020.114147
7. Bacchi S, Palumbo P, Sponta A, Coppolino MF. Clinical pharmacology of non-steroidal anti-inflammatory drugs: a review. *Antiinflamm Antiallergy Agents Med Chem*. 2012;11(1):52-64. doi:10.2174/187152312803476255
8. Coxib, traditional NTC, Bhala N, et al. Vascular and upper gastrointestinal effects of non-steroidal anti-inflammatory drugs: meta-analyses of individual participant data from randomised trials. *Lancet*. 2013;382(9894):769-779. doi:10.1016/S0140-6736(13)60900-9
9. Jurgensmeier K, Jurgensmeier D, Kunz DE, Fuerst PG, Warth LC, Daines SB. Intra-articular injections of the hip and knee with triamcinolone vs ketorolac: a randomized controlled trial. *J Arthroplasty*. 2021;36(2):416-422. doi:10.1016/j.arth.2020.08.036
10. Derry S, Conaghan P, Da Silva JA, Wiffen PJ, Moore RA. Topical NSAIDs for chronic musculoskeletal pain in adults. *Cochrane Database Syst Rev*. 2016;4:CD007400. doi:10.1002/14651858.CD007400.pub3
11. da Costa BR, Reichenbach S, Keller N, et al. Effectiveness of non-steroidal anti-inflammatory drugs for the treatment of pain in knee and hip osteoarthritis: a network meta-analysis. *Lancet*. 2017;390(10090):e21-e33. doi:10.1016/S0140-6736(17)31744-0
12. Park CW, Ma KW, Jang SW, Son M, Kang MJ. Comparison of piroxicam pharmacokinetics and anti-inflammatory effect in rats after intra-articular and intramuscular administration. *Biomol Ther (Seoul)*. 2014;22(3):260-266. doi:10.4062/biomolther.2014.037
13. Davies NM, Anderson KE. Clinical pharmacokinetics of diclofenac. Therapeutic insights and pitfalls. *Clin Pharmacokinet*. 1997;33(3):184-213. doi:10.2165/00003088-199733030-00003
14. Rainsford KD. Ibuprofen: pharmacology, efficacy and safety. *Inflammopharmacology*. 2009;17(6):275-342. doi:10.1007/s10787-009-0016-x
15. Skjodt NM, Davies NM. Clinical pharmacokinetics of lornoxicam. A short half-life oxicam. *Clin Pharmacokinet*. 1998;34(6):421-428. doi:10.2165/00003088-199834060-00001
16. Nilsen OG. Clinical pharmacokinetics of tenoxicam. *Clin Pharmacokinet*. 1994;26(1):16-43. doi:10.2165/00003088-199426010-00003
17. Roche. Naproxen Package Insert. https://www.accessdata.fda.gov/drugsatfda_docs/label/2007/017581s108,18164s58,18965s16,20067s14lbl.pdf
18. Radhofer-Welte S, Dittrich P, Simin M, Branebjerg PE. Comparative bioavailability of lornoxicam as single doses of quick-release tablet, standard tablet and intramuscular injection: a randomized, open-label, crossover phase I study in healthy volunteers. *Clin Drug Investig*. 2008;28(6):345-351. doi:10.2165/00044011-200828060-00002
19. Novartis. Diclofenac Package Insert. https://www.accessdata.fda.gov/drugsatfda_docs/label/2009/019201s038lbl.pdf
20. Cox SR, Gall EP, Forbes KK, Gresham M, Goris G. Pharmacokinetics of the R(-) and S(+) enantiomers of ibuprofen in the serum and synovial fluid of arthritis patients. *J Clin Pharmacol*. 1991;31(1):88-94. doi:10.1002/j.1552-4604.1991.tb01892.x
21. Makela AL, Lempiainen M, Ylijoki H. Ibuprofen levels in serum and synovial fluid. *Scand J Rheumatol Suppl*. 1981;39:15-17. doi:10.3109/03009748109095329
22. Bariguian Revel F, Fayet M, Hagen M. Topical diclofenac, an efficacious treatment for osteoarthritis: A narrative review. *Rheumatol Ther*. 2020;7(2):217-236. doi:10.1007/s40744-020-00196-6
23. Novartis. Topical Diclofenac Package Insert. https://www.accessdata.fda.gov/drugsatfda_docs/label/2009/022122s006lbl.pdf
24. Kienzler JL, Gold M, Nollevaux F. Systemic bioavailability of topical diclofenac sodium gel 1% versus oral diclofenac sodium in healthy volunteers. *J Clin Pharmacol*. 2010;50(1):50-61. doi:10.1177/0091270009336234
25. Moreira SA, Liu DJ. Diclofenac systemic bioavailability of a topical 1% diclofenac + 3% menthol combination gel vs. an oral diclofenac tablet in healthy volunteers: a randomized, open-label, crossover study. *Int J Clin Pharmacol Ther*. 2017;55(4):368-372. doi:10.5414/CP202753
26. Radermacher J, Jentsch D, Scholl MA, Lustinetz T, Frolich JC. Diclofenac concentrations in synovial fluid and plasma after cutaneous application in inflammatory and degenerative joint disease. *Br J Clin Pharmacol*. 1991;31(5):537-541. doi:10.1111/j.1365-2125.1991.tb05576.x
27. Seefried L, Blyth M, Maheshwari R, et al. Penetration of topical diclofenac into synovial tissue and fluid of osteoarthritic knees: a multicenter, randomized, placebo-controlled, pharmacokinetic study. *Ther Adv Musculoskelet Dis*. 2020;12:1759720X20943088. doi:10.1177/1759720X20943088
28. Kim HS, Cho HR, Ho MJ, Kang MJ, Choi YS. Determination of piroxicam from rat articular tissue and plasma based on LC-MS/MS. *Arch Pharm Res*. 2016;39(12):1653-1662. doi:10.1007/s12272-016-0845-2
29. Kim SR, Ho MJ, Kim SH, et al. Increased localized delivery of piroxicam by cationic nanoparticles after intra-articular injection. *Drug Des Devel Ther*. 2016;10:3779-3787. doi:10.2147/DDDT.S118145
30. Kim SH, Park KW, Kim JM, et al. Pharmacokinetics and four-week repeated-dose toxicity of hyaluronic acid and ketorolac combination following intra-articular administration in normal rats. *Regul Toxicol Pharmacol*. 2019;102:79-89. doi:10.1016/j.yrtph.2019.01.011
31. Thing M, Lu Y, Agardh L, et al. Prolonged naproxen joint residence time after intra-articular injection of lipophilic solutions comprising a naproxen glycolamide ester prodrug in the rat. *Int J Pharm*. 2013;451(1-2):34-40. doi:10.1016/j.ijpharm.2013.04.056
32. Neander G, Eriksson LO, Wallin-Boll E, Ersmark H, Grahnen A. Pharmacokinetics of intraarticular indomethacin in patients with osteoarthritis. *Eur J Clin Pharmacol*. 1992;42(3):301-305. doi:10.1007/BF00266352
33. Heilmann HH, Lindenhayn K, Walther HU. Synovial volume of healthy and arthrotic human knee joints. *Z Orthop Ihre Grenzgeb*. 1996, 8;134(2):144. doi:10.1055/s-2008-1039786
34. Schroeder S, Heuser A, Tellmann A, Goebel KJ, Woehrmann T. Local tolerance of intraarticular administration of lornoxicam into the rabbit knee joint. *Rheumatol Int*. 2012;32(9):2661-2667. doi:10.1007/s00296-011-2012-x
35. Suominen MM, Tulamo RM, Anttila MO, et al. Effects of intra-articular injections of bufexamac suspension in healthy horses. *Am J Vet Res*. 2001;62(10):1629-1635. doi:10.2460/ajvr.2001.62.1629
36. Irwin MG, Cheung KM, Nicholls JM, Thompson N. Intra-articular injection of ketorolac in the rat knee joint: effect on articular cartilage and synovium. *Br J Anaesth*. 1998;80(6):837-839. doi:10.1093/bja/80.6.837
37. Riggin CN, Tucker JJ, Soslowsky LJ, Kuntz AF. Intra-articular tibiofemoral injection of a nonsteroidal anti-inflammatory drug has no detrimental effects on joint mechanics in a rat model. *J Orthop Res*. 2014;32(11):1512-1519. doi:10.1002/jor.22674
38. Nair AB, Jacob S. A simple practice guide for dose conversion between animals and human. *J Basic Clin Pharm*. 2016;7(2):27-31. doi:10.4103/0976-0105.177703
39. Saricaoglu F, Dal D, Atilla P, et al. Effect of intraarticular injection of lornoxicam on the articular cartilage & synovium in rat. *Indian J Med Res*. 2008;127(4):362-365.
40. Cepni Kutahya E, Oc B, Ugurluoglu C, Duman I, Arun O. The effects of intra-articular injection of ibuprofen on knee joint cartilage and synovium in rats. *Acta Orthop Traumatol Turc*. 2019;53(4):292-296. doi:10.1016/j.aott.2019.03.013
41. Lockman LE. Practice tips. Knee joint injections and aspirations: the triangle technique. *Can Fam Physician*. 2006;52(11):1403-1404.
42. Ozyuvaci H, Bilgic B, Ozyuvaci E, Altan A, Altug T, Karaca C. Intra-articular injection of tenoxicam in rats: assessment of the local effects on the articular cartilage and synovium. *J Int Med Res*. 2004;32(3):312-316. doi:10.1177/147323000403200311

43. Orak MM, Ak D, Midi A, Lacin B, Purisa S, Bulut G. Comparison of the effects of chronic intra-articular administration of tenoxicam, diclofenac, and methylprednisolone in healthy rats. *Acta Orthop Traumatol Turc*. 2015;49(4):438-446. doi:10.3944/AOTT.2015.14.0312
44. Aytekin K, Uysal M, Sahiner GG, et al. Evaluation of different intraarticular injection volumes to assess optimum efficient amount; an experimental study in rat knee joints. *J Pharmacol Toxicol Methods*. 2020;101:106658. doi:10.1016/j.vascn.2019.106658
45. Cialdai C, Giuliani S, Valenti C, Tramontana M, Maggi CA. Comparison between oral and intra-articular antinociceptive effect of dexketoprofen and tramadol combination in monosodium iodoacetate-induced osteoarthritis in rats. *Eur J Pharmacol*. 2013;714(1-3):346-351. doi:10.1016/j.ejphar.2013.07.026
46. Jiang D, Zou J, Huang L, et al. Efficacy of intra-articular injection of celecoxib in a rabbit model of osteoarthritis. *Int J Mol Sci*. 2010;11(10):4106-4113. doi:10.3390/ijms11104106
47. Wen ZH, Tang CC, Chang YC, et al. Intra-articular injection of the selective cyclooxygenase-2 inhibitor meloxicam (Mobic) reduces experimental osteoarthritis and nociception in rats. *Osteoarthr Cartil*. 2013;21(12):1976-1986. doi:10.1016/j.joca.2013.09.005
48. Lu L, Xie Y, Gan K, Huang XW. Comparison of intra-articular injection of parecoxib vs oral administration of celecoxib for the clinical efficacy in the treatment of early knee osteoarthritis. *World J Clin Cases*. 2019;7(23):3971-3979. doi:10.12998/wjcc.v7.i23.3971
49. Egsmose C, Lund B, Bach AR. Hip joint distension in osteoarthrosis. A triple-blind controlled study comparing the effect of intra-articular indoprofen with placebo. *Scand J Rheumatol*. 1984;13(3):238-242. doi:10.3109/03009748409100392
50. Papathanassiou NP. Intra-articular use of tenoxicam in degenerative osteoarthritis of the knee joint. *J Int Med Res*. 1994;22(6):332-337. doi:10.1177/030006059402200604
51. Yilmaz E. The evaluation of the effectiveness of intra-articular steroid, tenoxicam, and combined steroid-tenoxicam injections in the treatment of patients with knee osteoarthritis. *Clin Rheumatol*. 2019;38(11):3243-3252. doi:10.1007/s10067-019-04641-y
52. Erbas M, Simsek T, Kiraz HA, Sahin H, Toman H. Comparison of the effectivity of oral and intra-articular administration of tenoxicam in patients with knee osteoarthritis. *Braz J Anesthesiol*. 2015;65(5):333-337. doi:10.1016/j.bjane.2013.12.003
53. Lee SC, Rha DW, Chang WH. Rapid analgesic onset of intra-articular hyaluronic acid with ketorolac in osteoarthritis of the knee. *J Back Musculoskelet Rehabil*. 2011;24(1):31-38. doi:10.3233/BMR-2011-0272
54. Unlu Z, Ay K, Tuzun C. Comparison of intra-articular tenoxicam and oral tenoxicam for pain and physical functioning in osteoarthritis of the knee. *Clin Rheumatol*. 2006;25(1):54-61. doi:10.1007/s10067-005-1136-3
55. Park KD, Kim TK, Bae BW, Ahn J, Lee WY, Park Y. Ultrasound guided intra-articular ketorolac versus corticosteroid injection in osteoarthritis of the hip: a retrospective comparative study. *Skeletal Radiol*. 2015;44(9):1333-1340. doi:10.1007/s00256-015-2174-9
56. Oztuna V, Eskandari M, Bugdayci R, Kuyurtar F. Intra-articular injection of tenoxicam in osteoarthritic knee joints with effusion. *Orthopedics*. 2007;30(12):1039-1042. doi:10.3928/01477447-20071201-07
57. Bellamy JL, Goff BJ, Sayeed SA. Economic impact of ketorolac vs corticosteroid intra-articular knee injections for osteoarthritis: a randomized, double-blind prospective study. *J Arthroplasty*. 2016;31(9 Suppl):293-297. doi:10.1016/j.arth.2016.05.015
58. da Costa BR, Pereira TV, Saadat P, et al. Effectiveness and safety of non-steroidal anti-inflammatory drugs and opioid treatment for knee and hip osteoarthritis: network meta-analysis. *BMJ*. 2021;375:n2321. doi:10.1136/bmj.n2321
59. Najm A, Alunno A, Gwinnutt JM, Weill C, Berenbaum F. Efficacy of intra-articular corticosteroid injections in knee osteoarthritis: a systematic review and meta-analysis of randomized controlled trials. *Joint Bone Spine*. 2021;88(4):105198. doi:10.1016/j.jbspin.2021.105198
60. Wheeler SG. Steroid knee injections for arthritis are no better than placebo in a randomized controlled trial. *J Gen Intern Med*. 2020;35(10):3137-3139. doi:10.1007/s11606-020-05647-y
61. Yoshioka K, Kisukeda T, Zuinen R, Yasuda Y, Miyamoto K. Pharmacological effects of N-[2-[[2-[2-[(2,6-dichlorophenyl)amino]phenyl]acetyl]oxy]ethyl]hyaluronamide (diclofenac Etalhyaluronate, SI-613), a novel sodium hyaluronate derivative chemically linked with diclofenac. *BMC Musculoskelet Disord*. 2018;19(1):157. doi:10.1186/s12891-018-2077-8
62. Nishida Y, Kano K, Nobuoka Y, Seo T. Sustained-release diclofenac conjugated to hyaluronate (diclofenac etalhyaluronate) for knee osteoarthritis: a randomized phase 2 study. *Rheumatology (Oxford)*. 2021;60(3):1435-1444. doi:10.1093/rheumatology/keaa605
63. Nishida Y, Kano K, Nobuoka Y, Seo T. Efficacy and safety of diclofenac-hyaluronate conjugate (diclofenac etalhyaluronate) for knee osteoarthritis: a randomized phase III trial in Japan. *Arthritis Rheumatol*. 2021;73(9):1646-1655. doi:10.1002/art.41725
64. Nishida Y, Kano K, Osato T, Seo T. Open-label phase 3 study of diclofenac conjugated to hyaluronate (diclofenac etalhyaluronate: ONO-5704/SI-613) for treatment of osteoarthritis: 1-year follow-up. *BMC Musculoskelet Disord*. 2021;22(1):233. doi:10.1186/s12891-021-04108-9
65. Sagir O, Sunay FB, Yildirim H, et al. Evaluation of the effects of dexketoprofen trometamol on knee joint: an in vivo & in vitro study. *Indian J Med Res*. 2013;138(6):912-918.
66. Ekici AG, Akyol O, Ekici M, Sitilci T, Topacoglu H, Ozyuvaci E. Intra-articular injection of dexketoprofen in rat knee joint: histopathologic assessment of cartilage & synovium. *Indian J Med Res*. 2014;140(2):227-230.

How to cite this article: Selig DJ, Kress AT, Horton IM, Livezey JR, Sadik EJ, DeLuca JP. Pharmacokinetics, safety and efficacy of intra-articular non-steroidal anti-inflammatory drug injections for the treatment of osteoarthritis: A narrative review. *J Clin Pharm Ther*. 2022;47(8):1122-1133. doi:10.1111/jcpt.13669