International Journal of Anesthesiology & Research (IJAR)
ISSN 2332-2780

Meloxicam: An Update On Its Use In The Perioperative Period

Research Article

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Abstract

Meloxicam, a preferential COX-2 inhibitor, has been used to treat osteoarthritis, rheumatoid arthritis, ankylosing spondylitis, as well as various chronic skeletomuscular pain syndromes. Where as oral meloxicam preparations are rarely indicated for treatment of acute pain due to a poor dissolution rate and slow on set of action, the introduction of an intravenous NanoCrystal Colloidal Dispersion formulation of meloxicam provides the possibility of using this drug for acute pain during the perioperative period. This review summarizes pharmacologic properties of meloxicam, including its pharmacokinetics, pharmacodynamics, adverse effects, and tolerability. We examine and discuss recently completed clinical trials that evaluated the efficacy and safety of intravenous meloxicam in the treatment of postoperative pain. Literature retrieval was performed through PubMed (through June 2020) using combinations of the terms meloxicam, acute pain, and pharmacology. In addition, bibliographical information, including contributory unpublished data, was requested from the company developing the drug. Based on the summary of the current literature, we conclude that intravenous meloxicam is an effective and well-tolerated analgesic agent for the management of moderate to severe acute postoperative pain.

Introduction

Postoperative pain is a natural and expected consequence of surgery, and opioids have been relied upon as the main stay of treatment for acute pain. However, significant side effects and risks can be associated with opioids, which include respiratory depression, nausea and vomiting, ileus, urinary retention, pruritus, as well as potential dependence and addiction. [1] The "Practice Guidelines for Acute Pain Management in the Perioperative Setting", adopted by the American Society of Anesthesiology, recommend multimodal strategies for the management of postoperative pain, stating that "unless contraindicated, patients should receive an around-the-clock regimen of NSAIDs, COXIBs, or acetaminophen."[2]

Meloxicam, an enol-carboxamide NSAID related to piroxicam, has long been used to treat pain and inflammation. Unlike other NSAIDs, it has a greater inhibitory activity against the inducible isoform of cyclo-oxygenase (COX-2) than against the constitutive isoform (COX-1). [3] COX-1 induces synthesis of prostacyclin, which is responsible for vascular homeostasis, platelet aggregation, renal function, and gastric cyto-protection. The expression of COX-2 isoform increases during inflammation. While meloxicam's anti-inflammatory and analgesic properties are similar to non-selective NSAIDs, it has both gastric mucosal and renal protective properties. [4]

Oral formulations of meloxicam are widely used to treat osteoarthritis, rheumatoid arthritis, ankylosing spondylitis, as well as various pain syndromes of skeletomuscular origin, such as low back pain. The half-life of meloxicam is approximately 20 hours. Maximum meloxicam plasma concentration following oral administration (patient in fasted state) was achieved after approximately 10 hours for the most part due to its poor dissolution rate. [5] Therefore, oral preparations of meloxicam are not frequently indicated for the treatment of acute or postoperative pain.

A novel intravenous formulation of NanoCrystal Colloidal Dispersion Meloxicam has been developed in the last decade for the management of acute pain. [6] A number of phase 2 and phase 3 studies have been recently completed to evaluate efficacy and safety of IV meloxicam for treatment of postoperative pain

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Received: January 15, 2021
Accepted: January 29, 2021
Published: February 27, 2021

Citation: Carolyn Kloepping, Stephen Van Beek, Alex Bekker. Meloxicam: An Update on its Use in the Perioperative Period. *Int J Anesth Res.* 2021;09(01):611-618.
doi: http://dx.doi.org/10.19070/2332-2780-21000122

in a number of clinical settings [7-14]. This article provides an overview of the pharmacological properties of various meloxicam preparations (i.e. oral, parenteral, and transdermal) as well as clinical efficacy and tolerability in the treatment of postoperative pain. [15]

Pharmacokinetic Properties

Absorption

The absorption of meloxicam has been studied following its administration via intramuscular, oral, and rectal routes. The absolute bioavailability (F) was 89% for oral capsules after a single 30mg dose. [5] Maximum meloxicam plasma concentration (Cmax) was achieved after 5-6 hours (tmax) when administered after breakfast [16]. When administered in a fasting state, the Cmax for meloxicam doubled. When used chronically, NSAIDs are typically administered after a meal: thus, Cmax=5-6 hours is more clinically relevant. The absorption of meloxicam is independent of dose over the range 7.5-30 mg, leading to dose-linear increases in meloxicam plasma concentrations. [17] This consideration enables easy dose titration in those patients requiring higher or lower doses than normal.

Distribution

Meloxicam, as most NSAIDS, is highly protein bound (>99%) to albumin. [18] The binding is consistent over the concentration range encountered in clinical practice. This high protein binding results in a restricted volume of distribution (Vd) of 10-15 L [17], similar to that reported for other NSAIDs. [19, 20] Animal experiments suggest that meloxicam is predominantly distributed to highly perfused (albumin rich) compartments such as the blood, liver, kidney, etc., with the volume of distribution approximating the extracellular space.[18] Meloxicam does penetrate local tissue as well, for example, 40-45% of the accompanying steady-state meloxicam plasma concentrations are found in synovial fluid, slightly lower concentrations being observed in the adjacent tissues. [21]

Metabolism

Meloxicam is primarily eliminated by metabolic degradation, about equal parts renal and fecal elimination, with <0.25% eliminated unchanged in the urine and 1.6% of the parent compound present in feces. [8] Meloxicam undergoes extensive phase 1 eliminations, and no conjugated derivatives have been identified. The metabolism of meloxicam is primarily mediated by CYP450 2C, on the isoenzyme CYP2C9. [22] The main metabolite is formed by the oxidation of the methyl group of the thyiozyl moiety; the metabolites do not change renal blood flow, and are not nephrotoxic. [23]

Elimination

The total clearance of oral meloxicam is 0.42-0.48 L/h. The elimination half-life (t 1/2) is approximately 20 hours, which is relatively short compared to other NSAID of the same class [16]. Unlike diclofenac, which has a short elimination half-life (1-2 hours) and require a slow-release formulation for a once-daily regimen, the longer elimination half-life of meloxicam allows for daily dosing without a slow release formulation. The efficacy of slow-release formulations can be influenced by food in take, as in with Diclofenac where there are variations in concentration-profiles based on food intake. [16] This effect is less likely in meloxicam due to its longer elimination half-life.

Pharmacodynamic Properties

Anti-inflammatory and Antioxidant

The anti-inflammatory effects of meloxicam is well demonstrated in rat models, inhibiting effects such as carrageenan or kaolin-induced rat paw edema, granuloma formation following cotton implantation in rats, kaolin-induced rat pleurisy, and rat adjuvant-induced arthritis. [16, 17] In these models, a single dose of meloxicam curbed inflammation for a prolonged period of time.

Additionally, the antioxidant effects of meloxicam have been a topic of interest and research. Meloxicam protects from hepatotoxicity by strengthening the antioxidant barrier, and has been cited as being neuroprotective in mice by augmenting antioxidant enzymes. [24, 25, 26] Pawlukianiec et al, found that meloxicam inhibits protein glycation, reduces protein oxidation products when exposed to glycating and pro-oxidant factors, and increases antioxidant properties of albumin. [24] This lends to further investigative work on utilization of meloxicam as an antioxidant and antiglycating agent in management of processes such as rheumatic diseases. [24]

Analgesic

Meloxicam has been demonstrated to exert a prolonged effect against inflammatory pain in the rat, and has also been studied in other animal models. [27] Following a single oral administration, the analgesic effect of meloxicam is not reduced by 50% until 18 hours after administration. [3] Additionally, meloxicam has a markedly longer duration of action than piroxicam, diclofenac, and indomethacin.

Anti-pyretic

Meloxicam, like other NSAIDs, has no effect on body temperature in normothermic mammals; however, NSAIDs are influential on pyrogen-induced fever. Meloxicam shows lower potency against yeast-induced pyrexia than diclofenac and piroxicam. At a dose of 0.1mg/kg, meloxicam was found to reduce endotoxin-induced fever in a cat. [28, 29]

Perioperative Use Of Meloxicam

Meloxicam is used for the management of acute and chronic pain, and a number of studies on use of meloxicam for the treatment of osteo- and rheumatoid arthritis have been published. [30-35] In the following discussion, we will focus on the studies which compare pharmacokinetic and efficacy of various meloxicam preparations in the perioperative setting as well as for treatment of neuropathic pain.

Although oral administration of meloxicam as 7.5 mg and 15 mg tablet are most common, other doses and methods of meloxicam delivery are available, such as transdermal and intravenous forms.

Table 1. Summary of Oral Perioperative Meloxicam Use.

Author	Study	Study Design	Intervention	Patients
Furst et al.[30]	Treatment of rheumatoid arthritis	Randomized, double blind, double dummy, parallel group	Meloxicam 7.5 mg daily PO Meloxicam 22.5 mg daily PO Diclofenac 150 mg BID PO Placebo	n=894
Altman et al.[32]	Patients with hip or knee OA on chronic NSAIDs or acetaminophen randomized to receive meloxicam for 12 weeks	Randomized, double blind	Meloxicam 5 mg PO Meloxicam 10 mg PO Placebo	n=403
Hosie et al.[33]	Patients with OA of the hip or knee were treated with either meloxicam or diclofenac daily for 6 months	Randomized, double blind	Meloxicam 7.5 mg PO Diclofenac 100 mg PO	n=335
Kurukahveciogluet al.[36]	Patients for inguinal hernia repair under local anesthesia randomized to pre operative meloxicam (30 minutes prior to surgery)	Prospective, randomized	No pre operative meloxicam Meloxicam 15 mg PO	n=50
Thompson et al.[37]	Pre operative meloxicam on post operative pain after abdominal hysterectomy	Randomized, double blind, placebo controlled	Meloxicam 15 mg rectal Placebo	n=36
Aghadavoudi et al.[38]	Pre operative meloxicam or celecoxib on post operative analgesia for lower extremity surgery	Randomized, double blind	Meloxicam 15 mg PO Celecoxib 400 mg PO	n=68
Orozco-Solís et al.[40]	Analgesic, anti inflammatory, and anti trismus effect of diclofenac or meloxicam 1 hour prior to mandibular third molar extraction	Randomized, double blind, parallel group	Diclofenac 100 mg PO Meloxicam 15 mg PO	n=36
Calvo et al.[41]	Meloxicam 7.5 or 15 mg was administered once daily after lower third molar removal for 4 days. On subsequent contralateral lower third molar removal, crossover dose was given	Randomized, double blind crossover	Group A: Requiring osteotomy Group B: Not requiring osteotomy	n=49
Nekoofar et al.[42]	Patients received meloxicam, piroxicam, or placebo after root canal	Randomized, double blind, placebo controlled, parallel group	Meloxicam 15 mg PO Piroxicam 20 mg PO Placebo	n=51
Zarif Najafi et al.[43]	Pre procedural acetaminophen, ibuprofen, and meloxicam in reducing pain after separator placement	Randomized, double blind, parallel group	Acetaminophen 650 mg PO Ibuprofen 400 mg PO Meloxicam 7.5 mg PO	n=241
Ren et al. [44]	Preoperative meloxicam versus postoperative meloxicam in patients receiving total hip arthroplasty	Randomized, double-blind, placebo-controlled trial	Meloxicam 15 mg PO at 24 h pre-op Meloxicam 7.5 mg PO at 4 h, 24 h, 48 h and 72 h post-op	n=132
Shao et al. [45]	Preoperative meloxicam versus postoperative meloxicam in patients receiving total knee arthroplasty	Randomized, controlled study	Meloxicam 15 mg PO at 24 h pre-op Meloxicam 7.5 mg PO at 4 h, 24 h, 48 h and 72 h post-op	n=98
Yuan et al. [46]	Very early preemptive meloxicam, early preemptive meloxicam, and postoperative meloxicam for patients undergoing arthroscopic knee surgery	Randomized, controlled study	Meloxicam 15 mg PO 24 h pre-op Meloxicam 7.5 mg PO 1 h pre-op Meloxicam 7.5 mg PO 24 h post-op Meloxicam 15mg PO 1h pre-op Meloxicam 7.5mg PO 4h post-op Meloxicam 15mg PO 4h post-op Meloxicam 7.5mg PO 24h post-op	n=306

NSAID=Non steroidal anti inflammatory drugs; OA=Osteoarthritis; PO = By mouth; BID = Two times a day

Product formulation may have a significant impact, not only on absorption rates but also on penetration depth and length of effect.

Oral route

The use of oral meloxicam has been extensively studied for the treatment of postoperative pain from elective surgery and dental procedures. In a study involving patients undergoing inguinal hernia repair under local anesthesia, patients were randomized to receive or not receive preoperative oral meloxicam dosing. In the postoperative period, IV diclofenac was administered for pain control. Results showed significantly lower VAS scores for the group preoperatively treated with meloxicam, and less use of rescue IV diclofenac (36% vs. 88%). [36]

For patients undergoing a total abdominal hysterectomy (n=36), Thompson et al. conducted a double blind randomized control study to examine the analgesic effect of a meloxicam suppository versus placebo suppository, administered preoperatively. [37] Postoperatively, patients received a morphine PCA, and pain scores and morphine usage were evaluated. VAS scores were sig-

Table2. Summary of Transdermal Meloxicam.

Author	Study	Study Design	Intervention	Patients
Rajeswari et al.[47]	Patients requiring periodontal flap surgery with applied transmucosal meloxicam films for pain control	Randomized, double-blind, parallel group	45 mg film 30 mg film 20 mg film 10 mg film	n=60
Yuan et al. [49]	Meloxicam synovial and plasma concentrations in beagle dogs	Randomized, crossover animal study	Meloxicam tablets 0.31 mg/kg Meloxicam gel 1.25 mg/kg	n=6

Table 3. Summary of Intravenous Meloxicam.

Author	Study	Study Design	Intervention	Patients
Christensen et al.[8]	Single IV meloxicam dose, ibuprofen, or placebo after dental impaction surgery	Randomized, double blind, placebo controlled	Meloxicam 15 mg IV Meloxicam 30 mg IV Meloxicam 60 mg IV Ibuprofen 400 mg PO Placebo	n=230
Gottlieb et al.[22]	Daily dose of IV meloxicam or placebo for post-bunionectomy pain control	Randomized, double-blind, placebo-controlled	Meloxicam 30 mg IV Meloxicam 60 mg IV Placebo	n=59
Rømsing et al.[51]	Post-operative analgesic requirements in patients receiving local or IV meloxicam for inguinal hernia repair	Randomized, double-blind	Meloxicam 7.5 mg IV Meloxicam 7.5 mg local infiltration	n=56
Bindewald and Singla[9]	Patients undergoing abdominoplasty randomized to IV meloxicam or placebo every 24 h for up to three doses	Randomized, double-blind, placebo-controlled	Meloxicam 30 mg IV Placebo	n=219
Berkowitz and Sharpe[10]	Patients undergoing orthopedic surgeries randomized to IV meloxicam 30 mg or placebo every 24 hours up to 7 doses	Randomized, double-blind, placebo-controlled	Meloxicam 30 mg IV Placebo	n=379
Melson and Boyer[11]	Patients with advanced age and impaired renal function undergoing major elective surgery	Randomized, double-blind, placebo-controlled	Meloxicam 30 mg IV Placebo	n=119
Rechberger et al. [12]	Postoperative IV meloxicam after open abdominal hysterectomy	Randomized, double-blind, placebo- and active-controlled trial	Meloxicam 5mg IV Meloxicam 7.5mg IV Meloxicam 15mg IV Meloxicam 30mg IV Meloxicam 60mg IV Placebo	n=486
Bergese et al. [13]	Patients undergoing major elective surgeries randomized to IV meloxicam 30 mg or placebo postoperatively, once daily	Randomized, double-blind, placebo-controlled trial	Meloxicam 30mg IV Placebo	n=702
Silinsky et al. [14]	Patients undergoing primary open or laparoscopic colorectal surgery with bowel resection and/or anastomosis received meloxicam IV 30 mg or placebo once daily, beginning 30 min before surgery.	Randomized, double-blind, placebo-controlled trial	Meloxicam 30mg IV Placebo	n=57

IV=Intravenous; PO = By mouth

nificantly lower in the meloxicam suppository group, but PCA morphine usage was not decreased significantly in the treatment group. [37]

Aghadavoudi et al. compared preoperative dosing of meloxicam (15 mg) and celecoxib (400 mg) for the treatment of pain in a double-blind randomized control study for lower extremity surgery. [38] Although pain severity was higher in the first two hours in the celecoxib group and six hours postoperatively in the meloxicam group, by 12 hours there was no significant difference in pain scores. [38]

An updated Cochrane review recently evaluated the analgesic efficacy of a single dose oral analgesics in acute postoperative pain, summarizing results from randomized double-blind placebo controlled clinical trials involving NSAIDs (including meloxicam), paracetamol, and opioids for acute postoperative pain relief, through 2011. [39] In regards to the studies involving meloxicam,

none met inclusion criteria for analysis, thus no final determination could be made. [39]

In addition to postoperative surgical pain, oral meloxicam has also been assessed in the management of pain following dental cases. [40, 41] Orozco-Solis et al. administered single-dose preprocedural meloxicam (15mg) or diclofenac (100mg) for patients undergoing mandibular third molar removal. Statistically significant decreased postoperative pain and increased mouth opening 24 hours post-surgery was evident in the meloxicam group, as well as an observed, but non-significant, decrease in facial swelling in both groups. [40] Calvo et al. compared the effects of 7.5mg meloxicam vs. 15mg meloxicam, administered in the postoperative period for up to four days, for pain also following third molar removal. [41] Patients receiving 7.5mg meloxicam who required osteotomy reported higher pain scores than those who did not require osteotomies, and used more rescue analgesics than those without osteotomy.[41] However, in the group which received 15mg of meloxicam, there was no significant difference in rescue analgesic dosing between osteotomy and non-osteotomy groups. [41]

Nekoofar et al examined use of meloxicam for endodontic pain requiring root canal. Patients were administered 15 mg meloxicam, 20 mg piroxicam, or a placebo preoperatively, and evaluated for postoperative pain rating. [42] The mean change of VAS between pre-dental procedure and eight hours post procedure was highest in the meloxicam group; however, the overall reduction of pain between meloxicam, piroxicam, and placebo was not significant. [42] In a similar, but large prospective double-blind randomized clinical trial, preoperative meloxicam (7.5 mg), acetaminophen (650 mg), and ibuprofen (400mg) were compared for efficacy in reducing pain after separator placement for orthodontic surgery; results did not reveal a statistical statistically significant difference in pain perception scores between the three groups. [43]

Utilization of preoperative versus postoperative oral meloxicam dosing in patients for orthopedic procedures has also been an area of focus. [44, 45, 46] Ren et al randomized scheduled total hip replacement patients to receive meloxicam 15 mg at 24 hours preoperation, 7.5 mg at 4 h, 24 h, 48 h and 72 h post-operation; or meloxicam 15 mg at 4 hours post-operation, then 7.5 mg at 24 h, 48 h and 72 h post-operation. [44] Between the two groups, PCA consumption, VAS scores at rest 6h, 12h, 24 hrs after surgery, and VAS with activity, 6 and 12 hrs after surgery, were decreased in patients administered preoperative meloxicam. Satisfaction scores were also higher in the preoperative meloxicam group versus postoperative. [44] In patients receiving total knee replacement with the above protocol, a similar decrease in PCA consumption and VAS scores was noted in those patients who received meloxicam preoperatively. [45] Likewise, for patients undergoing knee arthroscopies, preoperative meloxicam (24 hours or 1 hour) prior to surgery resulted in decreased patient global assessment (PGA) score, and less consumption of rescue pethidine. [46]

Transdermal/Transmucosal formulations

Alternative delivery options of meloxicam, such as transmucosal and transdermal, have been implemented for post-procedure periodontal and dental impaction surgeries. Transmucosal mucoadhesive meloxicam films at doses of either 45 mg, 30 mg, 20 mg, or 10 mg meloxicam per film were applied to post-periodontal flap surgery over surgical sites for a duration of four days, in a study by Rajeswari et al.[47] There were no reported adverse effects, and all patients noted immediate pain relief with application of the film, with pain control best captured in the 45mg and 30 mg groups; this subset had adequate pain control for the first 24 hours.[47]

Transdermal formulations of meloxicam, resulting in less systemic side effects as first pass metabolism would be avoided, have also been examined. Chen et al. focused on features needed in the transdermal delivery of meloxicam that would enhance permeation of meloxicam through the stratum corneum and the skin. [48] Formulation types including gels, liposomes, patches, micro emulsions, and physical approaches including electroporation, iontophoresis, and sonophoresis were reviewed, and although the author concluded that patches would be a better choice given more accurate dosing and compliance, further research is needed to ensure safety and desired effect. [48]

Pharmacokinetic studies comparing drug levels of meloxicam in plasma and synovial fluid following oral meloxicam, as well as meloxicam gel administration to hind legs in beagles, revealed higher concentrations in synovial fluid underlying the applied target site (gel administration) compared to oral delivery. [49] Furthermore, in the untreated leg, synovial fluid concentrations of meloxicam were similar to plasma concentrations following oral administration of meloxicam. [49]

Zhang et al compared conventional liposome, deformable liposome (transfersome) and microemulsion formulations as potential carriers for the dermal delivery of meloxicam. [50] Both liposomes and microemulsions were subjected to structural studies and applied to human cadaver skin. Transfer somes revealed a greater ability to penetrate the skin compared to the classical non-deformable liposomes, likely due to presence of surfactants acting as edge activators and destabilizing lipid bilayers, suggesting better potential as a transdermal drug carrier for meloxicam. [50]

Continued research and development of transdermal formulations of meloxicam may yield an alternate therapy option for patients with the potential to cause fewer systemic side effects.

Intravenous Administration

The use of intravenous meloxicam was evaluated in the 2001 by Romsing et al., where in postoperative patients were randomized to receive 7.5 mg meloxicam intravenously or via local wound infiltration following inguinal hernia repair. [51] Subsequently, a fixed postoperative pain regimen (acetaminophen plus codeine every six hours prn) was administered, and if necessary, supplemented with intravenous fentanyl for break through pain. Results reflected significantly lower plasma concentrations of meloxicam in the local infiltration group compared to the IV group, but no significant difference in pain scores or use of supplemental analgesics between groups. [51]

More recently, there has been renewed interest in the use of intravenous meloxicam, with several published studies and on going clinical research trials for postoperative pain control for abdominoplasty, orthopedic surgery, podiatric surgery, dental procedures, and other major surgical procedures. These studies utilized a formulation of intravenous meloxicam designed with a NanoCrys-

tal colloidal dispersion that would enhance the bioavailability of meloxicam. [8-22]

Treatment of post-procedure dental pain with the intravenous NanoCrystal meloxicam formulation for removal of impacted third molars was assessed by Christensen et al in 2018. [8] The randomized, double-blind controlled trial evaluated the post-operative pain intensity, safety, and tolerability of intravenous meloxicam compared to ibuprofen and placebo. [8] Patients in the study needed greater than 2, third-molar removals, one of which required bony extraction. Those with significant pain within five hours post procedure were randomized to receive either IV meloxicam (15, 30, or 60mg), IV placebo, or PO ibuprofen tablets. [8] Meloxicam IV 60 mg produced the greatest reduction in pain, followed by 30mg and 15mg dosing. Additionally, a more rapid on set of pain relief was seen with IV meloxicam than for ibuprofen, with duration of effect lasting 24 hours. Although there was less rescue analgesia needed in the IV meloxicam groups, this was not statistically significant when compared to placebo. [8]

Use of intravenous meloxicam for ERAS protocols in colorectal surgeries was evaluated in a clinical trial by Silinsky et al. [14] Patients were administered 30mg IV meloxicam or placebo approximately 30 minutes prior to the procedure, and every 24 hours until discharge or administration no longer clinically appropriate. [14] Statistically significant findings included a decreased length and cost of hospital stay, reduction in opioid use, reduced postoperative pain intensity, reduced time to first bowel sound, and first flatus and first bowel movement, when compared to placebo. [14]

In a trial involving patients with moderate to severe pain following bunionectomy, the use of postoperative intravenous meloxicam (30 mg or 60 mg) administered every 24 hours for up to three days resulted in rapid on set of analgesia and significant decrease in pain intensity compared to placebo; there was no measurable difference between the two doses. [22] Similarly, daily dosing of intravenous meloxicam for patients following abdominoplasty (n=219), led to a significant reduction in pain intensity, pain global assessment scores, and decrease rescue dosing of oxycodone when compared to the placebo group. [9]

Two recent phase three studies evaluated the effect of postoperative daily intravenous meloxicam (30mg) vs. placebo for postoperative pain control for orthopedic and major elective surgeries. [10, 11] A statistically significant reduction in total opioid use was seen through out the treatment period in the IV meloxicam group compared to the placebo group. [10] A subsequent phase 3 randomized placebo-controlled study evaluated the safety of intravenous meloxicam (30 mg, once daily) following major elective surgery led to similar findings-reduced opioid consumption (23.6%) in subjects with moderate to severe postoperative pain following major elective surgery. [13]

Lastly, a phase two randomized clinical trial examined the effect of daily intravenous meloxicam (5-60 mg) on providing analgesia to subjects with moderate to severe pain after open abdominal hysterectomy. [12] There was a statistically significant improvement in the summed pain intensity difference and total pain relief over the first 24 hours after dosing compared with placebo, with quick on set of pain relief (within 6-8 minutes after IV meloxicam administration), and reduced total rescue opioid consumption (42%–71%) with meloxicam IV compared to placebo. [12]

Meloxicam For Treatment Of Neuropathic Pain

There has been some literature and research completed in examining the effect of meloxicam on neuropathic pain. Takeda et al. evaluated the role of spinal COX-2 on the pathophysiology of neuropathic pain by using an intrathecal infusion of meloxicam vs. saline following L5/L6 spinal nerve ligation in rats. [52] Intrathecal infusions were either introduced immediately after nerve ligation, or 7 days after ligation. A third subset introduced systemic meloxicam 7 days after ligation. [52] Intrathecal meloxicam was shown to prevent development of neuropathic pain and spinal glial activation, but it did not reverse mechanical allodynia or thermal hyperalgesia. Systemic meloxicam partially reversed existing allodynia and hyperalgesia. This suggests that spinal COX-2 plays a role in development of neuropathic pain, while peripheral COX-2 may improve the maintenance of neuropathic pain. [52]

In a subset of chemotherapy-induced neuropathic pain, Yamamoto et al. evaluated the administration of meloxicam for symptomatic neuropathy in patients receiving doxorubicin and paclitaxel for breast cancer. [53] Of the 43 patients in the clinical trial, 15 patients developed neuropathy during paclitaxel and received 10mg meloxicam daily. [53] There was a statically significant reduction in sensory neuropathy in 5 of the 15 patients, but motor neuropathy did not improve after 2 months of meloxicam therapy. [53]

Tolerability

Gastric

Gastric ulcers are a concern with all NSAIDs, and can be dose-limiting side effect to their usage. The pathology behind gastric ulcers with NSAIDs is related to the inhibition of the biosynthesis of cytoprotective prostaglandins in the gastric mucosa [28]; specifically, PGE2 and PGI1 protect the mucosa and inhibit acid secretion in the stomach. As meloxicam is a weak inhibitor of PGE2 in the rat stomach, it is less of a stimulator of gastric acid secretion.

Tolerability of meloxicam compared to other NSAIDs has been extensively evaluated by Zeidler et al. [34] In an observational cohort of more than 13,000 patients, patients received meloxicam at doses of 7.5mg or 15mg meloxicam daily to treat osteoarthritis, rheumatoid arthritis, ankylosing spondylitis, or other painful inflammatory disorders of the musculoskeletal system-for 4-12 weeks. General tolerability was rated as "very good" or "good" for 94% of the patients, but of note, two serious adverse events: surgery for perforated gastric ulceration in a patient using meloxicam in conjunction with aspirin and diclofenac, and ileus in a patient using 45 mg meloxicam daily and prednisolone. [34] The most common gastrointestinal adverse events were dyspepsia (0.3%), nausea (0.2%), abdominal pain (0.1%), and diarrhea (0.1%); however, there was no dose effect seen between the 7.5mg and 15mg doses. [34]

In the Meloxicam Large-scale International Study Safety Assessment (MELISSA) trial, a double blind, randomized, controlled, prospective trial, assessed thetolerability of meloxicam versus diclofenac in 9323 patients with osteoarthritis. [35] Patients who

met inclusion criteria received meloxicam (7.5mg) or diclofenac (100mg) for 28 days. Overall, patients who received meloxicam had less GI adverse events (13%) compared to diclofenac (19%), including dyspepsia, nausea, vomiting, abdominal pain, and diarrhea. [35] Furthermore, the GI events were not found to be as severe in patients who were given meloxicam, compared to diclofenac. [35] Of the patients examined, three patients who received meloxicam spent a total of 5 days hospitalized due to GI events, and ten patients who received diclofenac spent a total of 121 days hospitalized for adverse GI events. [35]

Renal

In patients with normal, mild, and moderate renal impairment, daily dosing of 15mg meloxicam resulted in similar free meloxicam concentrations in all three groups, suggesting that meloxicam dose may not need to be adjusted in patients with mild to moderate renal impairment. [54] A phase 3 multicenter trial involving intravenous meloxicam administration in patients with renal impairment for postoperative pain control showed a low incidence of renal adverse events, and no significant difference in pharmacokinetics between patients with renal impairment and those without renal dysfunction. [11] Likewise, in a systemic review conducted by Asghar et al., evaluating 19 studies for renal and cardiovascular risk in meloxicam use, meloxicam did not result in an increase in the odds ratio of renal adverse events, as was seen with most NSAIDs (excluding ibuprofen). [55] Zeidler et al.'s research, noted above, described renal adverse reactions in four patients but did not detail the extent of reactions. [34]

Cardiovascular

In regards to the risk of cardiovascular events with use of NSAIDs, there is concern as to whether COX selectivity affects the occurrence of these adverse events. In the review by Asghar et al., five studies that reported >90 days of meloxicam usage and exposure did not show any increased risk of myocardial adverse events, but NSAIDs such as rofecoxib and diclofenac were found to show increased risk. [55] Meloxicam was found to have an elevated odds ratio in regards to vascular events compared to myocardial and renal events; however, of the NSAIDs evaluated, naproxen had the highest odds ratio of vascular events. [55] In composite risk of cardiovascular and renal outcomes, meloxicam was found to have an elevated composite odds ratio, but this was not related to meloxicam dose. [55] In the study by Zeidler et al., no cases of myocardial infarction, hypertension, or cerebrovascular events were reported. [34]

Hepatobiliary

There are few studies that have directly examined hepatobiliary adverse events specifically with meloxicam, with the focus rather on other NSAIDs. In the MELISSA trial noted earlier, serious adverse hepatobiliary events were seen in five patients in the diclofenac group, but no such events were observed in the meloxicam group. [35] Further, statistically significant abnormal ALT and AST, as well as increases in creatinine and urea levels, were only seen in the diclofenac group. [35]

Conclusion

Systemic administration of meloxicam is a safe and effective therapy to treat postoperative pain, and has been shown to improve postoperative VAS scores, and reduce opioid consumption and use of rescue analgesia in many of the studies referenced in this review. Various delivery formulations have been established, including transdermal, transmucosal, oral, and intravenous. The relative selectivity of meloxicam for COX-2 may contribute to an improved tolerability profile, and given its safety profile, can be considered in individuals with mild to moderate renal or hepatobiliary impairment. These findings, combined with the faster on set of analgesia and longer duration of action, make meloxicam a suitable alternative to traditional NSAIDs during the perioperative period.

References

[1]. Wunsch H, Wijeysundera DN, Passarella MA, Neuman MD. Opioids Prescribed After Low-Risk Surgical Procedures in the United States, 2004-2012. JAMA. 2016 Apr 19;315(15):1654-7.Pubmed PMID: 26978756.

[2]. Practice Guidelines for Acute Pain Management in the Perioperative Setting. An Updated Report by the American Society of Anesthesiologists Task Force on Acute Pain Management. Anesthesiology 2012, 116: 248-273.

[3]. Engelhardt G. Pharmacology of meloxicam, a new non-steroidal anti-inflammatory drug with an improved safety profile through preferential inhibition of COX-2. Br J Rheumatol. 1996 Apr;35 Suppl 1:4-12.Pubmed PMID: 8630636.

[4]. Van Hecken A, Schwartz JI, Depré M, De Lepeleire I, Dallob A, Tanaka W, et al. Comparative inhibitory activity of rofecoxib, meloxicam, diclofenac, ibuprofen, and naproxen on COX-2 versus COX-1 in healthy volunteers. J Clin Pharmacol. 2000 Oct;40(10):1109-20.Pubmed PMID: 11028250.

[5]. Türck D, Roth W, Busch U. A review of the clinical pharmacokinetics of meloxicam. Br J Rheumatol. 1996 Apr;35 Suppl 1:13-6.Pubmed PMID: 8630630.

[6]. Ochi M, Kawachi T, Toita E, Hashimoto I, Yuminoki K, Onoue S, et al. Development of nanocrystal formulation of meloxicam with improved dissolution and pharmacokinetic behaviors. Int J Pharm. 2014 Oct 20;474(1-2):151-6.Pubmed PMID: 25138254.

[7]. Mack R, Freyer A, Du W. (409) An evaluation of the efficacy and safety of N1539, a novel intravenous formulation of NanoCrystal Meloxicam, in subjects with moderate to severe pain following hysterectomy. J Pain. 2016 Apr 1;17(4):S77.

[8]. Christensen SE, Cooper SA, Mack RJ, McCallum SW, Du W, Freyer A. A Randomized Double-Blind Controlled Trial of Intravenous Meloxicam in the Treatment of Pain Following Dental Impaction Surgery. J Clin Pharmacol. 2018 May;58(5):593-605.Pubmed PMID: 29329493.

[9]. Bindewald M, Singla S, Leiman D, Baynton B, Minkowitz HS, McCallum S, et al. Efficacy and Safety of N1539, Intravenous Meloxicam, in a Phase 3 Study of Subjects with Moderate to Severe Pain Following Abdominoplasty. Plast Reconstr Surg Glob Open. 2017 Sep;5(9 Suppl).

[10]. Berkowitz, R., Sharpe, Kipling et al. "Safety and Opioid Use Following Major Orthopedic Surgery in a Phase 3, Placebo-Controlled Study of Intravenous Meloxicam ".2017.

[11]. Melson, T., Boyer, David et al. "Safety and Opioid Use in Subjects of Advanced Age with Impaired Renal Function in a Phase 3, Placebo-Controlled Study of Intravenous Meloxicam Following Major Surgery." 2017.

[12]. Rechberger T, Mack RJ, McCallum SW, Du W, Freyer A. Analgesic Efficacy and Safety of Intravenous Meloxicam in Subjects With Moderate-to-Severe Pain After Open Abdominal Hysterectomy: A Phase 2 Randomized Clinical Trial. Anesth Analg. 2019 Jun;128(6):1309-1318.Pubmed PMID: 31094806.

[13]. Bergese SD, Melson TI, Candiotti KA, Ayad SS, Mack RJ, McCallum SW, et al. A Phase 3, Randomized, Placebo-Controlled Evaluation of the Safety of Intravenous Meloxicam Following Major Surgery [published correction appears in Clin Pharmacol Drug Dev. 2020 Aug;9(6):774]. Clin Pharmacol Drug Dev. 2019;8(8):1062-1072.

[14]. Silinsky JD, Marcet JE, Anupindi VR, Karkare SU, Shah DR, Mack RJ, et al. Preoperative intravenous meloxicam for moderate-to-severe pain in the immediate post-operative period: a Phase IIIb randomized clinical trial in 55 patients undergoing primary open or laparoscopic colorectal surgery with bowel resection and/or anastomosis. Pain Manag. 2020 Jan;11(1):9-21. Pubmed PMID: 33094682.

[15]. Bekker A, Kloepping C, Collingwood S. Meloxicam in the management of post-operative pain: Narrative review. J Anaesthesiol Clin Pharmacol. 2018 Oct-Dec;34(4):450-457.Pubmed PMID: 30774225.

[16]. Turck D, Busch U, Heinzel G, Narjes H. Clinical pharma-cokinetics of meloxicam. Eur J Rheumatol Inflamm 1995; 15:22-34.
[17]. Distel M, Bluhmki E. Global analysis of safety of meloxicam, a new enolic acid derived non-steroidal anti-inflammatory agent. Rheumatol Eur. 1995; 24(suppl. 3):39.
[18]. Verbeeck RK, Blackburn JL, Loewen GR. Clinical pharmacokinetics of non-steroidal anti-inflammatory drugs. Clin Pharmacokinet. 1983 Aug;8(4): fc297-331.
[19]. Busch U, Schmid J, Heinzel G, Schmaus H, Baierl J, Huber C, et al. Pharmacokinetics of meloxicam in animals and the relevance to humans. Drug Metab Dispos. 1998 Jun;26(6):576-84.Pubmed PMID: 9616195.
[20]. Guentert TW, Defoin R, Mosberg H. The influence of cholestyramine on the elimination of tenoxicam and piroxicam. Eur J Clin Pharmacol. 1988;34(3):283-9.Pubmed PMID: 3260866.
[21]. Degner F, Heinzel G, Busch U. Transsynovial kinetics of meloxicam. Scand J Rheumatol. 1994;23(Suppl 98):121.
[22]. Gottlieb IJ, Tunick DR, Mack RJ, McCallum SW, Howard CP, Freyer A, et al. Evaluation of the safety and efficacy of an intravenous nanocrystal formulation of meloxicam in the management of moderate-to-severe pain after bunionectomy. J Pain Res. 2018 Feb 16;11:383-393.Pubmed PMID: 29497329.
[23]. Engelhardt G, Trummlitz G. Biological activity of the main metabolites of meloxicam. Drugs Exp Clin Res. 1990;16(2):53-6.Pubmed PMID: 2401186.
[24]. Pawlukianiec C, Gryciuk ME, Mil KM, Żendzian-Piotrowska M, Zalewska A, Maciejczyk M. A New Insight into Meloxicam: Assessment of Antioxidant and Anti-Glycating Activity in In Vitro Studies. Pharmaceuticals (Basel). 2020 Sep 10;13(9):240.Pubmed PMID: 32927809.
[25]. Hassan MH, Ghobara M, Abd-Allah GM. Modulator effects of meloxicam against doxorubicin-induced nephrotoxicity in mice. J Biochem Mol Toxicol. 2014 Aug;28(8):337-46.Pubmed PMID: 24799355.
[26]. Park JH, Park YS, Lee JB, Park KH, Paik MK, Jeong M, et al. Meloxicam inhibits fipronil-induced apoptosis via modulation of the oxidative stress and inflammatory response in SH-SY5Y cells. J Appl Toxicol. 2016 Jan;36(1):10-23.Pubmed PMID: 25772694.
[27]. Randall LO. A method for measurement of analgesic activity on inflamed tissues. Arch Int Pharmacodyn.. 1957;111:409-19.
[28]. Engelhardt G, Homma D, Schlegel K, Utzmann R, Schnitzler C. Anti-inflammatory, analgesic, antipyretic and related properties of meloxicam, a new non-steroidal anti-inflammatory agent with favourable gastrointestinal tolerance. Inflamm Res. 1995 Oct;44(10):423-33.Pubmed PMID: 8564518.
[29]. Justus C, Quirke JF. Dose-response relationship for the antipyretic effect of meloxicam in an endotoxin model in cats. Vet Res Commun. 1995;19(4):321-30.Pubmed PMID: 8540243.
[30]. Furst DE, Kolba KS, Fleischmann R, Silverfield J, Greenwald M, Roth S, et al. Dose response and safety study of meloxicam up to 22.5 mg daily in rheumatoid arthritis: a 12 week multicenter, double blind, dose response study versus placebo and diclofenac. J Rheumatol. 2002 Mar 1;29(3):436-46.
[31]. Ahmed M, Khanna D, Furst DE. Meloxicam in rheumatoid arthritis. Expert Opin Drug Metab Toxicol. 2005 Dec 1;1(4):739-51.
[32]. Altman R, Hochberg M, Gibofsky A, Jaros M, Young C. Efficacy and safety of low-dose SoluMatrix meloxicam in the treatment of osteoarthritis pain: a 12-week, phase 3 study. Curr Med Res Opin. 2015 Dec;31(12):2331-43. Pubmed PMID: 26503347.
[33]. Hosie J, Distel M, Bluhmki E. Meloxicam in osteoarthritis: a 6-month, double-blind comparison with diclofenac sodium. Br J Rheumatol. 1996 Apr;35 Suppl 1:39-43.Pubmed PMID: 8630635.
[34]. Zeidler H, Kaltwasser JP, Leonard JP, Kohlmann T, Sigmund R, Degner F, et al. Prescription and tolerability of meloxicam in day-to-day practice: post-marketing observational cohort study of 13,307 patients in Germany. J Clin Rheumatol. 2002 Dec;8(6):305-15.Pubmed PMID: 17041399.
[35]. Hawkey C, Kahan A, Steinbrück K, Alegre C, Baumelou E, Bégaud B, et al. Gastrointestinal tolerability of meloxicam compared to diclofenac in osteoarthritis patients. International MELISSA Study Group. Meloxicam Large-scale International Study Safety Assessment. Br J Rheumatol. 1998 Sep;37(9):937-45.Pubmed PMID: 9783757.
[36]. Kurukahvecioglu O, Karamercan A, Ege B, Koksal H, Anadol Z, Tezel E, et al. Effect of meloxicam on postoperative pain relief after inguinal hernia repair with local anaesthesia. West Indian Med J. 2007 Dec;56(6):530-3. Pubmed PMID: 18646498.
[37]. Thompson JP, Sharpe P, Kiani S, Owen-Smith O. Effect of meloxicam on postoperative pain after abdominal hysterectomy. Br J Anaesth. 2000 Feb 1;84(2):151-4.
[38]. Aghadavoudi O, Saryazdi HH, Shafa A, Ramezani A. COMPARISON OF PRE-EMPTIVE EFFECT OF MELOXICAM AND CELECOXCIB ON POST-OPERATIVE ANALGESIA: A DOUBLE-BLIND, RANDOMIZED CLINICAL TRIAL. Middle East J Anaesthesiol. 2015 Oct;23(3):289-94.Pubmed PMID: 26860018.
[39]. Moore RA, Derry S, McQuay HJ. Single dose oral meloxicam for acute postoperative pain in adults. Cochrane Database Syst Rev. 2009;4:Cd007552.
[40]. Orozco-Solís M, García-Ávalos Y, Pichardo-Ramírez C, Tobías-Azúa F, Zapata-Morales JR, Aragon-Martínez OH, et al. Single dose of diclofenac or meloxicam for control of pain, facial swelling, and trismus in oral surgery. Med Oral Patol Oral Cir Bucal. 2016 Jan;21(1):e127-134.
[41]. Calvo AM, Sakai VT, Giglio FP, Modena KC, Colombini BL, Benetello V, et al. Analgesic and anti-inflammatory dose-response relationship of 7.5 and 15 mg meloxicam after lower third molar removal: a double-blind, randomized, crossover study. Int J Oral Maxillofac Surg. 2007 Jan;36(1):26-31. Pubmed PMID: 17112703.
[42]. Nekoofar MH, Sadeghipanah M, Dehpour AR. Evaluation of meloxicam (A cox-2 inhibitor) for management of postoperative endodontic pain: a double-blind placebo-controlled study. J Endod. 2003 Oct;29(10):634-7. Pubmed PMID: 14606784.
[43]. Zarif Najafi H, Oshagh M, Salehi P, Babanouri N, Torkan S. Comparison of the effects of preemptive acetaminophen, ibuprofen, and meloxicam on pain after separator placement: a randomized clinical trial. Prog Orthod. 2015;16:34.Pubmed PMID: 26467790.
[44]. Ren L, Meng L, Yan H, Sun W, Yao D. Preoperative meloxicam versus postoperative meloxicam for pain control, patients' satisfaction and function recovery in hip osteoarthritis patients who receive total hip arthroplasty: a randomized, controlled study. Inflammopharmacology. 2020 Aug;28(4):831-838.Pubmed PMID: 32506275.
[45]. Shao Y, Zhao X, Zhai Y, Yang J, Wang S, Liu L, et al. Comparison of analgesic effect, knee joint function recovery, and safety profiles between preoperative and post-operative administrations of meloxicam in knee osteoarthritis patients who underwent total knee arthroplasty. Ir J Med Sci. 2020 May;189(2):535-542.Pubmed PMID: 31732867.
[46]. Yuan Y, Cui D, Zhang Y. Preemptive meloxicam achieves a better effect on postoperative pain control and similar tolerance compared with postoperative meloxicam in patients receiving arthroscopic knee surgery. Inflammopharmacology. 2019 Dec;27(6):1091-1100.Pubmed PMID: 31254137.
[47]. Rajeswari SR, Gowda TM, Kumar TA, Thimmasetty J, Mehta DS. An appraisal of innovative meloxicam mucoadhesive films for periodontal postsurgical pain control: A double-blinded, randomized clinical trial of effectiveness. Contemp Clin Dent. 2015 Jul-Sep;6(3):299-304.Pubmed PMID: 26321824.
[48]. Chen J, Gao Y. Strategies for meloxicam delivery to and across the skin: a review. Drug Deliv. 2016 Oct;23(8):3146-3156.Pubmed PMID: 26956920.
[49]. Yuan Y, Chen XY, Li SM, Wei XY, Yao HM, Zhong DF. Pharmacokinetic studies of meloxicam following oral and transdermal administration in Beagle dogs. Acta Pharmacol Sin. 2009 Jul;30(7):1060-4.Pubmed PMID: 19543299.
[50]. Zhang J, Froelich A, Michniak-Kohn B. Topical Delivery of Meloxicam using Liposome and Microemulsion Formulation Approaches. Pharmaceutics. 2020 Mar 21;12(3):282.Pubmed PMID: 32245190.
[51]. Rømsing J, Mysager S, Vilmann P, Sonne J, Larsen NE, Østergaard D. Postoperative analgesia is not different after local vs systemic administration of meloxicam in patients undergoing inguinal hernia repair. Can J Anaesth. 2001 Nov 1;48(10):978-984.
[52]. Takeda K, Sawamura S, Tamai H, Sekiyama H, Hanaoka K. Role for cyclooxygenase 2 in the development and maintenance of neuropathic pain and spinal glial activation. Anesthesiology. 2005 Oct;103(4):837-44.Pubmed PMID: 16192777.
[53]. Yamamoto D, Iwase S, Yoshida H, Kuroda Y, Yamamoto C, Kitamura K, et al. Efficacy of meloxicam in combination with preoperative chemotherapy for breast cancer - Japan Breast Cancer Research Network (JBCRN) 02-1 trial. Anticancer Res. 2011 Oct;31(10):3567-71.Pubmed PMID: 21965779.
[54]. Boulton-Jones JM, Geddes CG, Heinzel G, Türck D, Nehmiz G, Bevis PJ. Meloxicam pharmacokinetics in renal impairment. Br J Clin Pharmacol. 1997 Jan;43(1):35-40.Pubmed PMID: 9056050.
[55]. Asghar W, Jamali F. The effect of COX-2-selective meloxicam on the myocardial, vascular and renal risks: a systematic review. Inflammopharmacology. 2015 Feb;23(1):1-16.Pubmed PMID: 25515365.