

Meloxicam in the management of post-operative pain: Narrative review

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Abstract

Oral formulations of meloxicam, a preferential cyclooxygenase-2 (COX-2) inhibitor, have long been used to treat osteoarthritis, rheumatoid arthritis, ankylosing spondylitis, as well as various pain syndromes of skeletomuscular origin (e.g., low back pain). However, these preparations are rarely indicated for the treatment of acute pain due to a poor dissolution rate and consequently a slow onset of action. The recent introduction of an intravenous (IV) NanoCrystal Colloidal Dispersion formulation opens up the possibility of using this drug during the perioperative period. The present review summarizes the pharmacologic properties of meloxicam, including its pharmacokinetics, adverse effects, and tolerability. In addition, we critically examined a number of recently completed clinical trials that evaluated the efficacy and safety of meloxicam IV in the treatment of post-operative pain. Literature retrieval was performed through PubMed and Medline (through March 2018) 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 In addition, bibliographical information, including contributory unpublished data, was requested from the company developing the drug. Clinical trials suggest that single IV doses of 30 mg meloxicam significantly reduce post-operative pain as well as opioid requirements. We conclude that meloxicam IV is an effective and well-tolerated analgesic agent for the management of moderate to severe post-operative pain.

Keywords: Acute pain, intravenous, meloxicam, pharmacology

Introduction

Post-operative pain is an expected consequence of surgery. Although opioid analgesics have been the primary therapy for treating acute pain, they are associated with a multitude of adverse effects, including respiratory depression, nausea and vomiting, ileus, urinary retention, pruritus, as well as concerns over potential addiction.^[1] Therefore, the “Practice Guidelines for Acute Pain Management in the Perioperative Setting” adopted by the American Society of Anesthesiology (as well as numerous other relevant organizations) recommend multimodal strategies for the management of post-operative pain. More specifically, the guidelines state

that “unless contraindicated, patients should receive an around-the-clock regimen of Non-steroidal Anti-inflammatory Drugs (NSAIDs), COX-2 inhibitors (COXIBs), or acetaminophen.”^[2]

Meloxicam, an enol-carboxamide non-steroidal anti-inflammatory drug (NSAID) related to piroxicam, has long been used to treat acute pain and inflammation. In contrast to other NSAIDs, it has a greater inhibitory activity against the inducible isoform of cyclooxygenase (COX-2) than against the constitutive isoform (COX-1).^[3] COX-1 induces the synthesis of prostacyclin, which is responsible for vascular homeostasis, platelet aggregation, renal function, and gastric cytoprotection. The expression of COX-2 isoform increases during inflammation. Consequently, although meloxicam’s

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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 (e.g., 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] Consequently, oral preparations of meloxicam are rarely indicated for treatment of acute (i.e., post-operative) pain.

A novel intravenous (IV) formulation of NanoCrystal Colloidal Dispersion Meloxicam has recently 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 the efficacy and safety of IV meloxicam for the treatment of post-operative pain in a number of clinical settings.^[7,8] This article provides an overview of the pharmacological properties of various meloxicam preparations (i.e., oral vs. parenteral vs. transdermal) as well as its clinical efficacy and tolerability in the treatment of post-operative pain in a variety of post-operative pain models. A systematic and comprehensive literature search was conducted through March 2018 using PubMed and Medline for preparation of this review.

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 30 mg dose.^[5] Maximum meloxicam plasma concentration (C_{max}) was achieved after 5–6 hours (t_{max}) when administered after breakfast.^[9] When administered in a fasting state, the C_{max} for meloxicam doubled. When used chronically, NSAIDs are typically administered after a meal; thus, C_{max} = 5–6 hours is the more clinically relevant figure. The absorption of meloxicam is independent of the dose over the range 7.5–30 mg, leading to dose-linear increases in meloxicam plasma concentrations.^[10] This consideration enables easy dose titration in those patients requiring higher or lower doses than normal.

Distribution

Meloxicam, like most NSAIDs, is highly protein bound (>99%) to albumin.^[11] The binding is consistent over the concentration range encountered in clinical practice. This high protein binding results in a restricted volume

of distribution (V_d) of 10–15 l,^[10] which is similar to that reported for other NSAIDs.^[12,13] Animal experiments suggest that meloxicam is predominantly distributed to highly perfused (albumin rich) compartments such as the blood, liver, kidney, and so on.^[11] The volume of distribution equates approximately with the extracellular space, although meloxicam readily penetrates other tissues. 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.^[14]

Metabolism

Meloxicam is primarily eliminated by metabolic degradation. It undergoes roughly equal parts of 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, most probably on the isoenzyme 2C9.^[15] The main metabolite is formed by the oxidation of the methyl group of the thiazole moiety; it has no metabolic activity.

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 NSAIDs of the same class.^[9] The short $t_{1/2}$ allows daily dosing without the need for a slow release formulation. NSAIDs such as diclofenac have a short elimination half-life (1–2 hours) and require a slow release formulation for a once-daily regimen. The efficacy of slow release formulations may be influenced by food intake.^[9] Diclofenac is a well-known example of variations in concentration profiles based on food intake. Such food effects are rare with compounds like meloxicam due to its longer elimination half-life.

Pharmacodynamic Properties

Anti-inflammatory

The anti-inflammatory effects of meloxicam have been demonstrated in rat models 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.^[9,10] In all models, meloxicam suppressed inflammation at a single dose for a prolonged time. In human studies, meloxicam has been shown to decrease erythrocyte sedimentation rate (ESR) in patients with rheumatoid arthritis,^[16] and decrease ESR, C-reactive protein (CRP), and aquaporin-1 expression, serving as an analog to treatment efficacy in ankylosing spondylitis.^[17]

Analgesic

Meloxicam showed prolonged effect against inflammatory pain in the rat.^[18] Following a single oral administration, the analgesic effect of meloxicam is not reduced by 50% until 18 hours after administration. Meloxicam has a markedly longer duration of action than piroxicam, diclofenac, and indomethacin. Similarly, meloxicam has been used for the treatment of pain secondary to rheumatoid arthritis, osteoarthritis, and periprocedural pain in various human studies since its introduction.

Anti-pyretic

Meloxicam, like all other NSAIDs, has no effect on body temperature in normothermic mammals, because NSAIDs do not directly impact the calorific center. NSAIDs are only influential on pyrogen-induced fever. Meloxicam shows lower potency against yeast-induced pyrexia than diclofenac and piroxicam. At a dose of 0.1 mg/kg, meloxicam was found to reduce endotoxin-induced fever in a cat.^[19]

Perioperative Use of Meloxicam

Meloxicam is widely used for the treatment of acute and chronic pain. For example, a number of reviews on the use of this drug for the treatment of osteoarthritis and rheumatoid arthritis have been recently published.^[20-23] In the ensuing discussion, we will focus on the studies which compare pharmacokinetic and efficacy of various meloxicam preparations in the perioperative setting as well as for the treatment of neuropathic pain.

Although oral administration of meloxicam as 7.5 and 15 mg tablet is most common, other methods of meloxicam delivery are available, such as transdermal and IV forms. Product formulation may have a significant impact, not only on absorption rates but also on penetration depth.

Oral route

The use of oral meloxicam has been extensively studied for the treatment of post-operative surgical and dental pain [Table 1]. Single-dose pre-operative oral meloxicam was given to patients undergoing inguinal hernia repair under local anesthesia, with subsequent IV diclofenac administration in the post-operative period if visual analog scale (VAS) was >3 .^[24] Results showed a statistically significant lower reported value of VAS scores for the group pre-emptively treated with meloxicam and less use of rescue IV diclofenac (36% vs. 88%) in the meloxicam treated group.^[24]

Thompson *et al.*^[25] conducted a double-blind randomized control study to examine the analgesic effect of meloxicam suppository in patients undergoing a total abdominal hysterectomy. All patients received a morphine patient-

controlled analgesia (PCA) post-operatively, and pain scores and morphine usage were evaluated post-operatively. VAS scores were significantly lower in the meloxicam group. PCA morphine usage, however, was not decreased significantly in the treatment group.^[25]

Aghadavoudi *et al.*^[26] compared pre-operative 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. Pain severity was higher in the first 2 hours in the celecoxib group and 6 hours post-operatively in the meloxicam group, and there was no difference by 12 hours.^[26]

A Cochrane review recently attempted to evaluate the efficacy of oral meloxicam in acute post-operative pain, summarizing results from randomized double-blind placebo-controlled clinical trials involving meloxicam for acute post-operative pain relief.^[27] Unfortunately, none of the studies examined met inclusion criteria for analysis.

Oral meloxicam has also been widely used and studied for controlling post-procedural pain, swelling, and trismus following dental cases.^[28,29] Orozco-Solís *et al.*^[28] administered pre-procedural meloxicam (15 mg) or diclofenac (100 mg), with results reflecting statistically significant decreased post-operative pain and increased mouth opening in the meloxicam group, as well as an observed but non-significant decrease in swelling in both groups. Calvo *et al.*^[29] compared the effects of 7.5 mg meloxicam versus 15 mg meloxicam, administered in the post-operative period for up to 4 days, for pain following third molar removal. Patients receiving 7.5 mg meloxicam who required osteotomy reported higher pain scores than those who did not require osteotomies and used more rescue analgesics than those without osteotomy.^[29] However, in the group which received 15 mg of meloxicam, there was no significant difference in rescue analgesic dosing between osteotomy and non-osteotomy groups.^[29] Overall, like in the research findings of Orozco-Solís *et al.*, there was no significant difference in swelling.

Nekoofar *et al.*^[30] administered 15 mg meloxicam, 20 mg piroxicam, or a placebo via randomization pre-operatively to patients with endodontic pain requiring root canal for treatment. The mean change in VAS between pre-dental procedure and 8 hours post procedure was highest in the meloxicam group; however, the overall reduction in pain among meloxicam, piroxicam, and placebo was not significant.^[30] Similarly, in a large, prospective, double-blind randomized clinical trial, pre-operative meloxicam (7.5 mg), acetaminophen (650 mg), and ibuprofen (400 mg) were compared for efficacy in reducing pain after separator placement for orthodontic surgery.^[31] No statistically significant difference in pain

perception scores was found between the three groups, which the authors concluded as indicating equivalent effectiveness of all three drugs for post-separator pain.^[31]

Transdermal/transmucosal formulations

Newer preparations of meloxicam have also been examined for post-procedure periodontal and dental impaction surgeries. Transmucosal adhesive meloxicam films were developed and applied to post-periodontal flap surgery over surgical sites for a duration of 4 days at doses of 45, 30, 20, or 10 mg meloxicam per film.^[32] There were no reported adverse effects, and all patients noted immediate pain relief with application of the film; pain control was least effective in the 10 mg group and was poor in the 20 mg group. The 45 and 30 mg groups had adequate pain control for the first 24 hours.^[32]

A review article by Chen and Gao^[33] focused on transdermal delivery of meloxicam, with the premise that application of the drug overlying the area of pain would result in less systemic side effects and avoid first-pass hepatic metabolism. In order for meloxicam to be available via transdermal route, multiple formulations and chemical enhancement techniques have been studied to enhance permeation of meloxicam through the stratum corneum and across the skin. Formulation types include gels, liposomes, patches, microemulsions, and physical approaches including electroporation, iontophoresis, and sonophoresis. 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 compared to oral delivery.^[34] Furthermore, in the untreated leg, synovial fluid concentrations of meloxicam were similar to plasma concentrations following oral administration of meloxicam but were less compared to that of the treated leg.^[34] 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 [Table 2].

Intravenous administration

The use of IV meloxicam has been evaluated in the past by Rømsing *et al.*, wherein patients were administered 7.5 mg meloxicam intravenously or received wound infiltration of 7.5 mg meloxicam for post-operative pain control following inguinal hernia repair.^[35] Subsequently, a fixed combination of a post-operative pain regimen (acetaminophen plus codeine every 6 hours prn) was given, and if pain control was insufficient, the pain regimen was supplemented with IV fentanyl. Results showed no significant difference in pain scores or use of supplemental analgesics between groups but did show significantly lower plasma concentrations of meloxicam in the local infiltration group compared to the IV group.^[35]

More recently, there has been renewed interest in the use of IV meloxicam, with several published studies and ongoing clinical research trials for post-operative pain control for abdominoplasty, orthopedic surgery, podiatric surgery, dental procedures, and other major surgical procedures at doses that differ from the Rømsing study. These studies are described in further detail below [Table 3].

In patients undergoing more than two-third molar removals, patients with significant pain within 5 hours post procedure were randomized to receive IV meloxicam (15, 30, or 60 mg), IV placebo, or PO ibuprofen tablets.^[8] Meloxicam IV (60 mg) produced the greatest reduction in pain, followed by meloxicam IV (30 and 15 mg), with more rapid onset of pain relief with IV meloxicam than for ibuprofen and reduced usage of rescue medication; duration of effect lasted for 24 hours.^[8]

The use of post-operative IV meloxicam (30 or 60 mg) in 59 patients with moderate to severe pain from unilateral unionectomy, dosed every 24 hours for up to 3 days, resulted in rapid onset of analgesia and significant decrease in pain intensity compared to placebo; there was no measurable difference between the two doses.^[15] Likewise, in 219 patients with pain following abdominoplasty randomized to receive 30 mg IV meloxicam or a placebo dosed daily for 2 days, researchers noted statistically significant pain relief compared to placebo.^[36] Rescue dosing of oxycodone in the treatment phase was also significantly lower in the IV meloxicam group compared to the placebo group; there was no difference seen in the time to first rescue dose of oxycodone.^[36]

Two recent Phase 3 studies evaluated the effect of post-operative daily IV meloxicam (30 mg) versus placebo on opioid use following orthopedic procedures and major elective surgical procedures.^[37,38] A statistically significant reduction in total opioid use was seen throughout the treatment period in the IV meloxicam group compared to the placebo group.^[37]

Meloxicam for Treatment of Neuropathic Pain

A number of studies have been conducted on the role of meloxicam in the management of neuropathic pain. Takeda *et al.*^[39] evaluated the role of spinal COX-2 on the pathophysiology of neuropathic pain by using a continuous intrathecal infusion of meloxicam versus saline following L5/L6 spinal nerve ligation in rats. Intrathecal infusions were evaluated immediately after nerve ligation in the first group; in the second subset, intrathecal infusion was introduced 7 days after ligation; finally, a third subset introduced systemic meloxicam 7 days after ligation.^[39] Intrathecal meloxicam did prevent development of neuropathic

Table 1: Summary of oral peri-operative meloxicam use

Author	Study	Study design	Intervention	Patients
Furst <i>et al.</i> ^[20]	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 <i>et al.</i> ^[22]	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 <i>et al.</i> ^[23]	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
Kurukahvecioglu <i>et al.</i> ^[24]	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 <i>et al.</i> ^[25]	Pre-operative meloxicam on post-operative pain after abdominal hysterectomy	Randomized, double-blind, placebo-controlled	Meloxicam 15 mg rectal Placebo	n=36
Aghadavoudi <i>et al.</i> ^[26]	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 <i>et al.</i> ^[28]	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 <i>et al.</i> ^[29]	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 <i>et al.</i> ^[30]	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 <i>et al.</i> ^[31]	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

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

Table 2: Summary of transdermal preparations of meloxicam

Author	Study	Study design	Intervention	Patients
Rajeswari <i>et al.</i> ^[32]	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 <i>et al.</i> ^[34]	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

pain and spinal glial activation, but it did not reverse mechanical allodynia or thermal hyperalgesia. Systemic meloxicam partially reversed existing allodynia and hyperalgesia.^[39] The authors concluded that spinal COX-2 may mediate development of neuropathic pain and that peripheral COX-2 may improve the maintenance of neuropathic pain.^[39]

Yamamoto *et al.*^[40] evaluated the administration of meloxicam for symptomatic neuropathy (motor or sensory) in patients who were receiving doxorubicin and paclitaxel for breast cancer. Of the 43 patients in the clinical trial, 15 patients developed neuropathy during paclitaxel and received 10 mg meloxicam daily.^[40] 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.^[40]

Tolerability

Gastric

It is widely accepted that gastric ulcerogenicity is an adverse and dose-limiting side effect of all established NSAIDs. It has been shown that the complex pathogenesis of stomach ulcerations accompanying NSAIDs is related to the inhibition of the biosynthesis of cytoprotective prostaglandins (PEs) in the gastric mucosa^[19]; specifically, PGE2 and PGI1 protect the mucosa and inhibit acid secretion in the stomach. Meloxicam is a weak inhibitor of PGE2 in the rat stomach and is a much less potent stimulator of gastric acid secretion.

Tolerability of meloxicam compared to other NSAIDs has been extensively evaluated by Zeidler *et al.*,^[41] a study wherein

Table 3: Summary of intravenous use of meloxicam

Author	Study	Study design	Intervention	Patients
Christensen et al. ^[18]	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. ^[15]	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. ^[35]	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 ^[36]	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 ^[37]	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 ^[38]	Patients with advanced age and impaired renal function undergoing major elective surgery	Randomized, double-blind, placebo-controlled	Meloxicam 30 mg IV Placebo	n=119

IV=Intravenous; PO = By mouth

more than 13,000 patients involved in an observational cohort study were followed for 4–12 weeks at doses of 7.5 or 15 mg meloxicam daily to treat osteoarthritis, rheumatoid arthritis, ankylosing spondylitis, or other painful inflammatory disorders of the musculoskeletal system. General tolerability was rated as “very good” or “good” for 94% of the patients. There were 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.^[41] The most common gastrointestinal (GI) 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 7.5 mg and 15 mg doses.^[41]

In the Meloxicam Large-scale International Study Safety Assessment (MELISSA) trial, tolerability of meloxicam versus diclofenac was examined in the treatment of 9323 patients with osteoarthritis.^[42] In a double-blind randomized controlled prospective trial, patients who met inclusion criteria received meloxicam (7.5 mg) or diclofenac (100 mg) 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.^[42] Furthermore, the GI events were not found to be as severe in patients who were given meloxicam compared to those given diclofenac.^[42] 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.^[42]

Renal

There is concern that the prolonged use of NSAIDs can lead to adverse renal events, and researchers have posed questions

regarding the safety of meloxicam use in those with compromised renal function. In patients with normal, mild, and moderate renal impairment who were administered meloxicam (15 mg) daily, free meloxicam concentrations were measured, and were found to be similar in all groups, thus suggesting it may not be necessary for a meloxicam dosage adjustment in patients with mild to moderate renal impairment.^[43] Similarly, in a recent Phase 3 multi-center trial involving IV meloxicam use in patients with renal impairment for post-operative pain control, there was a low incidence of renal adverse events, and no significant difference in pharmacokinetics between patients with renal impairment and those without.^[38]

A systemic review conducted by Asghar and Jamali,^[44] evaluating 19 studies for renal and cardiovascular risk in meloxicam use, determined that meloxicam use did not result in an increase in the odds ratio of renal adverse events, as was seen with most NSAIDs (excluding ibuprofen). Zeidler et al.’s^[41] research, noted above, described renal adverse reactions in four patients but did not detail the extent of reactions.

Cardiovascular

There have also been concerns about the risk of cardiovascular events with the use of NSAIDs and whether COX selectivity affects the occurrence of these adverse events. In the review by Asghar and Jamali,^[44] five studies that reported >90 days of meloxicam usage and exposure did not show any increased risk of myocardial adverse events, but other NSAIDs such as rofecoxib and diclofenac were found to show increased risk. In regard to vascular events, meloxicam was found to have an elevated odds ratio compared to myocardial and renal events; however, of the NSAIDs evaluated, naproxen had the highest odds ratio of vascular events.^[44] In terms of composite risk of cardiovascular and renal outcomes, meloxicam was found to have an elevated

composite odds ratio, but this finding was not related to meloxicam dose.^[44]

In the comprehensive study by Zeidler *et al.*,^[41] no cases of myocardial infarction, hypertension, or cerebrovascular events were reported.

Hepatobiliary

There is a paucity of studies that have directly examined hepatobiliary adverse events with the use of meloxicam specifically, rather with 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.^[42] Furthermore, statistically significant abnormal alanine aminotransferase (ALT) and aspartate aminotransferase (AST), as well as increases in creatinine and urea levels, were only seen in the diclofenac group.^[42]

Conclusions

Systemic administration of meloxicam is a safe and effective therapy to treat post-operative pain. Its relative selectivity for COX-2 may contribute to an improved tolerability profile. Meloxicam consistently reduces patients' opioid requirement by approximately 40%. These improvements, combined with the faster onset of analgesia and long duration of action, make meloxicam an attractive alternative to traditional NSAIDs during the perioperative period.

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Conflicts of interest

There are no conflicts of interest.

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