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### Permalink

<https://escholarship.org/uc/item/0k95x85g>

### Journal

Clinical Pharmacology in Drug Development, 9(7)

### ISSN

2160-763X

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### Publication Date

2020-10-01

### DOI

10.1002/cpdd.772

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Peer reviewed

# Platelet Function: Meloxicam Intravenous in Whole Blood Samples From Healthy Volunteers

Clinical Pharmacology  
in Drug Development  
2020, 9(7) 841–848  
© 2020 The Authors. *Clinical Pharmacology in Drug Development*  
published by Wiley Periodicals, Inc. on  
behalf of American College of Clinical  
Pharmacology  
DOI: 10.1002/cpdd.772

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## Abstract

Nonsteroidal anti-inflammatory drugs (NSAIDs) are effective treatments for pain but may induce bleeding events due to platelet dysfunction associated with inhibition of cyclooxygenase (COX)-1 impairing thromboxane production. An intravenous nanocrystal formulation of meloxicam, a COX-2 preferential nonsteroidal anti-inflammatory drug, is under development for the treatment of moderate to severe pain. This single-center ex vivo study evaluated the effect of meloxicam intravenous and ketorolac on platelet function in whole blood samples from healthy volunteers. Each whole blood sample was aliquoted to allow analysis using a platelet function analyzer under negative control (untreated), positive control (2 therapeutic ketorolac concentrations), and meloxicam intravenous (1 therapeutic, 3 supratherapeutic concentrations) using both collagen with epinephrine and collagen with adenosine diphosphate reagent cartridges. The platelet function analyzer determines closure time by simulating platelet adhesion and aggregation following vascular injury. The final analysis set included data from 8 subjects. The collagen with adenosine diphosphate analysis (sensitive to thrombocytopathies) showed no significant differences in closure time for meloxicam- or ketorolac-treated samples and untreated control. The collagen with epinephrine analysis (sensitive to aspirin-induced platelet abnormalities) produced no significant difference in closure time between any meloxicam concentration and untreated control. Ketorolac was associated with significantly longer closure times vs untreated control at both the 2.5- and 5- $\mu\text{g}/\text{mL}$  concentrations ( $P = .003$  and  $.0257$ , respectively) and vs meloxicam at several concentrations. Similar results were observed when all analyzed samples were included. Meloxicam intravenous had no significant effect on closure times at therapeutic or supratherapeutic concentrations in this ex vivo study.

## Keywords

anti-inflammatory agents, ketorolac tromethamine, meloxicam, nonsteroidal anti-inflammatory drug, platelet aggregation

Nonsteroidal anti-inflammatory drugs (NSAIDs) are effective and well-established agents for the treatment of acute and chronic pain. They are an integral part of the World Health Organization Pain Ladder, which has been applied across acute and chronic pain settings, where they are considered first-line agents for the prevention and treatment of pain.<sup>1</sup> Although NSAIDs are effective and generally well tolerated, a concern with these agents when used in the surgical setting is the risk of perioperative bleeding complications caused by inhibition of cyclooxygenase (COX) activity and prostaglandin biosynthesis resulting in the loss of platelet adhesion.<sup>2,3</sup> The NSAID-related risk of bleeding has been demonstrated to be primarily related to reductions in thromboxane associated with the inhibition of COX-1 by nonselective NSAIDs, and a lower risk of events is observed with the use of COX-2-selective NSAIDs.<sup>4</sup> However, highly COX-2-selective NSAIDs are associated with an increased risk of cardiovascular

events (eg, thrombosis, myocardial infarction) relative to COX-1-selective agents.<sup>5,6</sup>

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Submitted for publication 21 October 2019; accepted 10 December 2019.

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Meloxicam is an NSAID with a preferential, but not exclusive, inhibition of COX-2 and a more favorable gastrointestinal adverse event profile compared with nonselective NSAIDs.<sup>7</sup> Oral meloxicam has demonstrated efficacy in the treatment of chronic pain (eg, rheumatoid arthritis, osteoarthritis).<sup>8,9</sup> However, oral meloxicam is not indicated for the treatment of acute pain, primarily because it has poor solubility and slow absorption. Peak concentrations occur 2.5 to 7 hours after oral administration of a 15-mg dose and 9 to 11 hours after a 30-mg dose, resulting in a delayed onset of action.<sup>7</sup> Intravenous meloxicam uses a novel nanocrystal formulation of meloxicam and is being developed for the management of moderate to severe pain alone or in combination with other analgesics. Meloxicam intravenous was evaluated in 4 phase 2 and 3 phase 3 postoperative studies in subjects with moderate to severe pain following hard-tissue<sup>10–13</sup> or soft-tissue surgeries.<sup>13–15</sup> Due to its preferential COX-2 inhibition, meloxicam intravenous is expected to have a lower risk for platelet dysfunction–related events relative to other nonselective NSAIDs.<sup>16,17</sup> The objective of this study was to describe the potential effect of meloxicam intravenous on platelet function vs both negative (untreated) and positive (ketorolac-treated) controls when assessed by an ex vivo analysis.

## Methods

### Study Design

This was an ex vivo study conducted at Pharmaceutical Research Associates, Inc, Salt Lake City, Utah. The study was conducted according to US Food and Drug Administration regulations governing clinical trials, Title 21 Code of Federal Regulations Parts 50, 54, 56, and 312; International Conference on Harmonisation–Good Clinical Practice Guidelines; and other regulations as applicable. The study was reviewed and approved by the study site's institutional review board (Midlands Independent Review Board, Overland Park, Kansas), and all subjects provided written informed consent.

### Key Eligibility Criteria

Healthy men or women (aged 18–40 years) who were non-tobacco users (ie, never used or stopped using at least 6 months prior to screening visit) were eligible for enrollment. Subjects were excluded if they had taken any medications (prescription or over-the-counter) or supplements (eg, vitamins) within 14 days prior to blood collection at screening; if they were women of childbearing potential using hormonal contraception; or if they had a history of anemia or thrombocytopenia, alcohol abuse (ie, regularly drinks >4 units of alcohol per day), or prescription/illicit drug abuse within

**Table 1.** Timing and Sequence of Sample Analysis

Testing Sequence	End Concentration	Platelet Function Analyzer Reagent Cartridge
1 <sup>a</sup>	NA (untreated control)	CEPI
2 <sup>a</sup>	NA (untreated control)	CADP
3	Meloxicam 5 µg/mL	CEPI
4	Meloxicam 5 µg/mL	CADP
5	Meloxicam 10 µg/mL	CEPI
6	Meloxicam 10 µg/mL	CADP
7	Meloxicam 15 µg/mL	CEPI
8	Meloxicam 15 µg/mL	CADP
9	Meloxicam 20 µg/mL	CEPI
10	Meloxicam 20 µg/mL	CADP
11	Ketorolac 2.5 µg/mL	CEPI
12	Ketorolac 2.5 µg/mL	CADP
13	Ketorolac 5 µg/mL	CEPI
14	Ketorolac 5 µg/mL	CADP

CEPI, collagen with epinephrine; CADP, collagen with adenosine diphosphate; NA, not applicable.

<sup>a</sup>If platelet function analyzer closure time for control samples with CEPI reagent (Test 1) was  $\geq 150$  seconds OR control samples with CADP reagent (Test 2) was  $\geq 110$  seconds, sample analysis was discontinued, and no further samples were processed from the subject's blood sample.

5 years. Subjects were also not allowed to have received any investigational product within 30 days prior to screening or to have received meloxicam intravenous in previous clinical trials.

### Study Material Preparation, Blood Collection, and Sample Processing

Meloxicam intravenous 30-mg/mL drug product (Baudax Bio [formerly Recro Pharma, Inc], Malvern, Pennsylvania; Batch No. 30004) and ketorolac injection 15 mg/mL (Red Rock Pharmacy, Salt Lake City, Utah; Batch No. 67-031-DK) were diluted with 5% dextrose in water within 2 hours prior to study use. The final solution concentrations were 0.33 µg/µL for meloxicam intravenous and 0.1667 µg/µL for ketorolac (Table 1). One preparation of diluted meloxicam and ketorolac solution was used for all treated samples for each individual subject.

Study subjects (n = 13) had approximately 20 mL of whole blood collected in tubes containing 3.2% (0.105 M) buffered sodium citrate (1 part anticoagulant to 9 parts blood). Each blood sample was aliquoted for untreated analysis (negative control), as well as for analysis of samples treated with ketorolac (positive control) and meloxicam intravenous. Meloxicam intravenous 0.33 µg/µL was added to whole blood aliquots to yield end concentrations of 5, 10, 15, and 20 µg/mL. This was designed to yield 1 sample that reflected approximate maximum plasma concentrations following a

30-mg dose (ie, 5  $\mu\text{g}/\text{mL}$ ), the anticipated therapeutic dose, and 3 samples with concentrations exceeding the exposure of the anticipated therapeutic dose.<sup>7,17</sup> Similarly, ketorolac 0.1667  $\mu\text{g}/\mu\text{L}$  was added to whole blood aliquots to yield end concentrations of 2.5  $\mu\text{g}/\text{mL}$  and 5  $\mu\text{g}/\text{mL}$ , which were designed to mimic peak concentrations following 15-mg and 30-mg intravenous ketorolac doses, respectively.<sup>18</sup>

### Assessment of Platelet Function

Platelet function was evaluated using a platelet function analyzer (PFA-100 Platelet Function Analyzer; Siemens Healthcare Diagnostics, Deerfield, Illinois). The platelet function analyzer is US Food and Drug Administration approved to identify drug-induced platelet abnormalities under flow conditions that create a high shear, similar to flow through the blood vessel.<sup>19,20</sup> The platelet function analyzer supplanted the bleeding time test, which is no longer recommended.<sup>20,21</sup> Use of this device to measure the effect of drugs on platelet adhesion is well documented.<sup>22</sup> The platelet function analyzer determines a sample closure time by simulating the platelet adhesion and aggregation that occurs following vascular injury. Analysis was performed using both collagen with epinephrine (CEPI) and collagen with adenosine diphosphate (CADP) reagent cartridges. The CEPI cartridges are responsive to congenital thrombocytopenia, von Willebrand disease, and aspirin-induced platelet abnormalities, while the CADP cartridges are responsive to thrombocytopathies and von Willebrand disease but generally not to aspirin.<sup>23</sup> Thus, use of the 2 cartridges allows differentiation between congenital defects and aspirin-induced abnormalities.

Each whole blood sample was aliquoted to allow analysis under negative control (untreated), positive control (2 ketorolac concentrations), and meloxicam intravenous (4 concentrations) using both the CADP and CEPI cartridges. Whole blood aliquots were treated according to the test condition and incubated for approximately 10 minutes prior to analysis in the platelet function analyzer. All blood samples were analyzed within 2.5 hours of the time of collection. Closure time results were reported for each test condition and reagent cartridge. Test results were evaluated for quality control based on a single repeat sample analysis within each subject, with an acceptance criterion of within 20% variance of the original result. Samples outside this range were excluded from the primary analysis.

### Statistical Analysis

Using the platelet function analyzer, treatment effect on closure time was analyzed with a covariance model

that had the main effect of treatment and covariate of sex to assess treatment effect with (ie, the full model) and without (ie, the reduced model) controlling for covariates (treatment, sex, the interaction between treatment and sex). Treatment effect was analyzed twice: the first analysis (primary analysis) excluded samples that did not meet the quality-control criteria ( $n = 8$ ), whereas the second analysis (confirmatory analysis) included all samples ( $n = 12$ ; 1 subject excluded due to instrument malfunction). Pairwise comparisons were performed; nominal  $P$  values were reported without controlling for multiplicity. Subgroup analysis by gender was also performed. All analyses were performed separately for each reagent.

## Results

### Subjects

Whole blood samples were analyzed from 13 subjects (7 men, 6 women). The final analysis set included data from 8 subject samples for the CADP and CEPI reagent analyses. One subject was excluded due to instrument malfunction, and 4 subjects were excluded from the CADP and CEPI analyses due to out-of-range quality-control sample results (ie, repeat sample analysis for each subject had a  $>20\%$  variance from their original result).

### Collagen With Adenosine Diphosphate Reagent Analysis

Primary analysis using the CADP reagent cartridge found no overall treatment effect on closure time ( $P = .5715$ ). There were no statistically significant differences in closure time values between either the meloxicam intravenous- or ketorolac-treated samples and the untreated control samples (Table 2). There were no statistically significant differences in closure time between any of the meloxicam intravenous-treated samples (ie, 5, 10, 15, or 20  $\mu\text{g}/\text{mL}$ ) and either ketorolac-treated samples or between the 2 ketorolac-treated samples. A dose-response analysis showed no trend toward changes in closure time with increasing doses of meloxicam intravenous (Figure 1A). There were also no significant differences between men and women for closure time in the CADP reagent analysis for any of the ketorolac or meloxicam intravenous concentrations (Figure S1A).

Results were generally similar in the confirmatory analysis when samples from all 12 subjects (excluding 1 sample with instrument malfunction) were included, with the exception that the ketorolac 5- $\mu\text{g}/\text{mL}$  sample had a significantly longer closure time compared to the untreated control sample ( $P = .0162$ ) and to the meloxicam intravenous 10- $\mu\text{g}/\text{mL}$  sample ( $P = .0253$ ) (Table S1).

**Table 2.** Least Squares (LS) Mean Closure Times and Comparison by Treatment Using CADP Reagent (Final Analysis Set [8 Subjects])

	Untreated Control	Ketorolac		Meloxicam Intravenous			
		2.5 µg/mL	5 µg/mL	5 µg/mL	10 µg/mL	15 µg/mL	20 µg/mL
CADP Reagent							
LS mean (SE) closure time, sec	74.54 (5.31)	79.41 (5.31)	87.95 (5.66)	75.41 (5.31)	74.91 (5.31)	76.66 (5.31)	74.91 (5.31)
CEPI Reagent							
LS mean (SE) closure time, sec	90.50 (16.54)	180.87 (16.54)*	143.38 (16.54)*	101.75 (16.54)**	95.13 (16.54)**	104.00 (16.54)**	104.63 (16.54)**

CADP, collagen with adenosine diphosphate; CEPI, collagen with epinephrine; SE, standard error.

\* $P < .05$  vs untreated control.

\*\* $P \leq .005$  versus 2.5 µg/mL ketorolac.

\*\*\* $P < .05$  versus 5 µg/mL ketorolac.

### Collagen With Epinephrine Reagent Cartridge Analysis

In the CEPI reagent primary analysis, there was a significant overall treatment effect for changes in closure time ( $P = .0441$ ). Ketorolac, at both the 2.5- and the 5-µg/mL concentrations, was associated with significantly longer closure times compared to untreated control ( $P = .0003$  and  $.0257$ , respectively) (Table 3). In the meloxicam intravenous-treated samples, there were no significant differences in closure times vs untreated control at any of the evaluated concentrations ( $P > .05$  for all). Compared with ketorolac, all meloxicam concentration levels were associated with significantly shorter closure times vs the 2.5-µg/mL ketorolac concentration ( $P < .005$  for all). Meloxicam intravenous was also associated with numerically shorter closure times compared with the ketorolac 5-µg/mL concentration, although statistical significance was only reached at the meloxicam 10-µg/mL concentration ( $P = .0408$ ). The dose-response analysis observed a small trend of increased closure time with increasing doses of meloxicam intravenous (Figure 1B). However, there were no statistically significant differences between any of the meloxicam intravenous-treated closure time values. There were also no significant differences between men and women for closure time for either ketorolac or meloxicam in the CEPI reagent analysis (Figure S1), with the exception that mean closure time was significantly greater in men than in women in the meloxicam 15-µg/mL concentration (89.9 vs 69.8 seconds;  $P = .0180$ ).

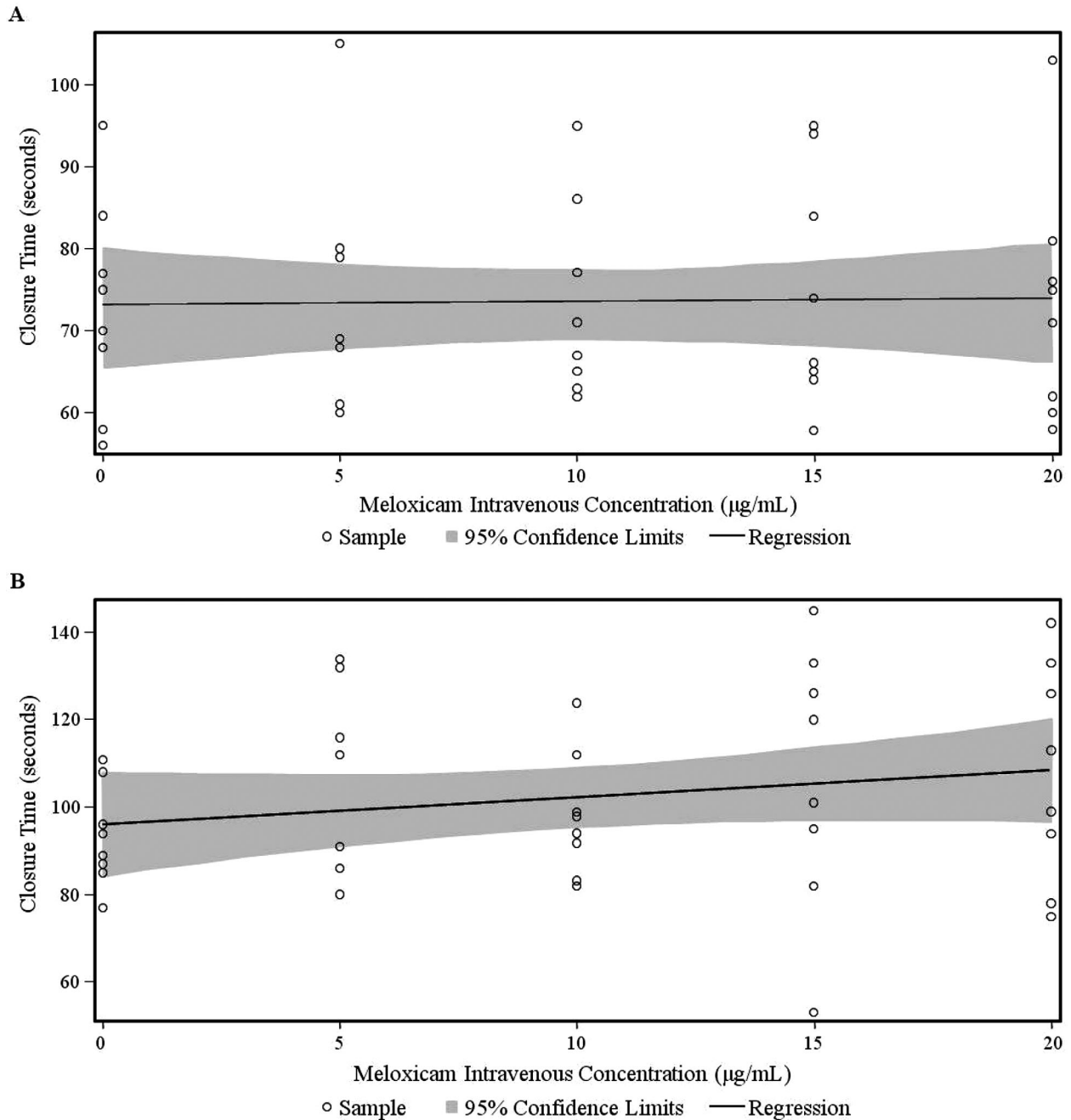
The overall results were generally similar in the confirmatory analysis when samples from all 12 subjects (excluding 1 sample with instrument malfunction) were included. Both ketorolac samples (2.5- and 5-µg/mL concentrations) demonstrated statistically significant longer closure times compared with the untreated control. Across the meloxicam intravenous

samples (5-, 10-, 15-, and 20-µg/mL concentrations), none was associated with a statistically significant increase in closure time compared with untreated control (Table S1).

### Discussion

NSAIDs have well-demonstrated activity in the treatment of postoperative pain, with additional benefits including decreased postoperative nausea and vomiting and potentially reduced opioid consumption.<sup>24</sup> However, a concern of NSAID use in the peri- or postoperative setting is the potential for platelet dysfunction and risk of bleeding-related events.<sup>3</sup> The mechanism for NSAID-induced platelet dysfunction for nonaspirin NSAIDs is inhibition of platelet COX, producing a reduction in the formation of thromboxane A<sub>2</sub> and a consequent inhibition of platelet aggregation and prolongation of bleeding time.<sup>3,4</sup> However, there are differences between the various NSAIDs in their effect on platelet function, primarily related to differences in the extent and duration of their effects on COX enzymes (ie, COX-1 and COX-2).<sup>3</sup> COX-1 is the only isozyme expressed in platelets, and research has demonstrated that the NSAID-related bleeding risk is primarily related to reductions in thromboxane via inhibition of COX-1.<sup>4,25</sup>

Table 3 summarizes the COX selectivity of common NSAIDs as expressed by the ratio of the NSAID concentration that inhibited 80% of the activity (IC<sub>80</sub>) of COX-2 to the IC<sub>80</sub> of COX-1.<sup>26</sup> Agents range from relatively selective for COX-1 (eg, ketorolac) to those that are more selective for COX-2 (eg, meloxicam, celecoxib). Data indicate that these differential effects on platelets have clinical significance, with nonselective NSAIDs being associated with a greater effect on platelet function and bleeding time compared with



**Figure 1.** Dose response analysis based on data with CADP (A) and CEPI (B) (final analysis set [8 subjects]). CADP, collagen with adenosine diphosphate; CEPI, collagen with epinephrine.

COX-2-selective NSAIDs, which do not inhibit thromboxane  $A_2$ .<sup>4</sup>

In the current study, there was no significant prolongation in closure time in meloxicam intravenously-treated whole blood samples, either at concentrations reflecting therapeutic levels or at supratherapeutic exposure levels, compared with untreated control when assessed by either the CADP or CEPI assay. In contrast, whole blood samples treated with therapeutic concentrations of ketorolac showed significant prolon-

gations in closure time compared with untreated controls in the CEPI analysis. There were significant differences between meloxicam and ketorolac in the CEPI analysis at several drug concentrations. The differential effects in the CADP and CEPI analyses are consistent with the rationales of the 2 assays. CADP cartridges are primarily affected by thrombocytopathies with a lower sensitivity to aspirin effects, while CEPI cartridges have a high sensitivity to aspirin-induced platelet abnormalities.<sup>23</sup> Overall, these data suggest that

**Table 3.** COX Selectivity of Common NSAIDs Based on the Ratio of Concentrations Needed to Inhibit 80% of the Activity (IC<sub>80</sub>) of COX-2 to the IC<sub>80</sub> of COX-1<sup>26</sup>

	Agent	COX-2/ COX-1 IC <sub>80</sub> Ratio
Greater COX-1 selectivity	Ketorolac	294
	Aspirin	3.8
	Naproxen	3
	Ibuprofen	2.6
	Diclofenac	0.23
	Celecoxib	0.11
	Meloxicam	0.091
Greater COX-2 selectivity	Rofecoxib	<0.05

COX, cyclooxygenase; IC, inhibitory concentration; NSAID, nonsteroidal anti-inflammatory drug.

meloxicam intravenous may have a lower risk than ketorolac for platelet dysfunction–related events.

The results demonstrating that ketorolac has a significant effect on platelet function are consistent with previous studies. In several studies in healthy volunteers, therapeutic doses of ketorolac (0.4 mg/kg) caused a significant inhibition of epinephrine-, adenosine-, and collagen-induced platelet aggregation and also prolonged bleeding times.<sup>27–30</sup> Further, in studies evaluating the effect of ketorolac on platelet function in patients undergoing surgical procedures, some<sup>31</sup> but not all<sup>32</sup> studies found that intravenous ketorolac was associated with inhibition of platelet aggregation and prolonged bleeding time.

The current study is in agreement with previous studies evaluating the effect of oral meloxicam on platelet aggregation. Studies in healthy volunteers<sup>33–35</sup> and in patients with rheumatoid arthritis<sup>36</sup> have found that oral meloxicam was associated with minimal or no inhibitory effect on platelet aggregation. In contrast, the nonselective COX inhibitors (ie, indomethacin, naproxen) included for comparison in these studies significantly inhibited platelet aggregation.<sup>33–36</sup>

In this study, a single repeat sample analysis from each subject was performed to assess quality control, with an acceptance criterion of within 20% variance of the original result. Four subjects were excluded from the CADP and CEPI analyses because repeat sample analysis for each subject had a greater than 20% variance from their original result. When samples from all 12 subjects were included, the overall results were generally similar in the confirmatory analyses for both the CADP and CEPI cartridges.

Limitations of the study include the small sample size and the conduction in healthy volunteers and using ex vivo samples. Thus, the effects of meloxicam intravenous in patients with platelet disorders or in

patients with a history of bleeding or who have risk factors for bleeding remain to be established. Further, because the study only measured platelet aggregation rather than clinical bleeding events, results of the current study do not establish whether the differences identified will translate into fewer clinical bleeding events. In addition, although closure time as measured by the platelet function analyzer has been used in research studies, its use in therapeutic monitoring of platelet function in the clinical setting is less well established.<sup>37</sup> Additional studies of platelet aggregation with light-transmission aggregometry could augment identification of NSAID-induced platelet abnormalities and predict surgical bleeding risk. Future studies are needed to evaluate the effect of meloxicam intravenous on platelet function, bleeding parameters, and clinically significant bleeding events in clinical settings (eg, postsurgery).

## Conclusions

In summary, this study in healthy volunteers found that meloxicam intravenous, in contrast to ketorolac, had no significant effect on sample closure time at either therapeutic or suprathreshold exposure levels compared with untreated controls. Because sample closure time simulates platelet adhesion and aggregation following vascular injury, these results suggest that meloxicam intravenous may have a relatively lower risk for platelet dysfunction–related events, although additional data are needed to fully characterize bleeding risk.

## Acknowledgments

Assistance with manuscript preparation was provided by Bret Fulton, RPh, and Susan Martin, PhD, of The Medicine Group.

## Conflicts of Interest

J.S.J. receives honorarium and grant support from Baudax Bio (formerly Recro Pharma, Inc). R.J.M., S.W.M., S.H., K.M., and A.F. are/were employees of Baudax Bio. W.D. receives consultancies from Baudax Bio. S.S. declares no conflicts of interest.

## Funding

Funding for this study was provided by Baudax Bio (formerly Recro Pharma, Inc.), Malvern, Pennsylvania.

## Author Contributions

All authors contributed to the design of the study and its implementation. S.S. managed the subjects and contributed to acquisition of the data. W.D. provided statistical guidance for

data analysis and interpretation. All authors contributed to drafting the manuscript and/or critically reviewing it for important intellectual content. All have read and approved the final version for journal submission and agree to be accountable for all aspects of the work.

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### Supplemental Information

Additional supplemental information can be found by clicking the Supplements link in the PDF toolbar or the Supplemental Information section at the end of web-based version of this article.