An Ex-vivo Assessment of the Effects of Meloxicam IV on Platelet Function

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INTRODUCTION

Non-steroidal anti-inflammatory drugs (NSAIDs) are an integral part of the World Health Organization (WHO) Pain Ladder, which has been applied across acute and chronic pain settings, as a first line defense to prevent or treat pain[1]. Intravenous (IV) meloxicam (Meloxicam IV) is a novel formulation of NanoCrystal Colloidal Dispersion® meloxicam being developed for the management of moderate to severe pain. A concern of NSAID use in the peri- or postoperative setting is the potential for platelet dysfunction and risk of bleeding related events[2,3]. However, research has demonstrated that the association of NSAID use with increased bleeding risk is primarily related to reductions in thromboxane associated with inhibition of cyclooxygenase-1 (COX-1) by nonselective NSAIDs, and that a lower risk of events has been observed with the use of cyclooxygenase-2 (COX-2) selective NSAIDs[4]. Meloxicam IV, with its higher affinity for COX-2 inhibition is anticipated to have a lower risk for platelet dysfunction related events while maintaining a prolonged duration of analgesic action[5,6].

Table 1: COX Selectivity of Common NSAIDS (COX-2/COX-1 IC_{80} Ratio)

	Drug	COX-2/COX-1 IC_{80} Ratio[7]
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

One method of evaluating the effects of drugs or other conditions on platelet function is in analyzing blood samples using the platelet function analyzer (PFA-100; Siemens Healthcare Diagnostics, Deerfield, IL, USA), a device that determines a closure time (CT) by simulating the platelet adhesion and aggregation that would occur following a vascular injury. Analysis can be performed using two different testing reagent cartridges, collagen with epinephrine (CEPI) and collagen with adenosine diphosphate (CADP). The CEPI cartridges are known to be sensitive to aspirin-induced platelet abnormalities, while the CADP cartridges are primarily sensitive to various thrombocytopathies with lower sensitivity to aspirin effects[8].

OBJECTIVE

The objective of the study was to assess the effect of meloxicam on platelet function as demonstrated through the PFA-100® Platelet Function Analyzer.

METHODS

- This study underwent institutional review board (IRB) review and approval, and all subjects (blood donors) provided informed consent prior to participation.
- Healthy volunteers provided a single whole blood sample (~20 mL) for analysis.
- Each whole blood sample was aliquoted to allow analysis under negative control (1 condition), positive control (2 conditions), and meloxicam IV (4 conditions) test conditions, using both the CEPI and CADP cartridges.
- Whole blood aliquots were treated according to the test condition and incubated for approximately 10 minutes prior to analysis in the PFA-100.
- All blood samples were to be analyzed within 2.5 hours of collection.

Subject/Donor Eligibility Criteria:

- 18-40 year-old male and female non-tobacco users
- No recent medication use; prescription, OTC, or vitamin/nutritional supplement
- No known medical history affecting coagulation or platelet function (i.e. anemia, thrombocytopenia).
- Negative control (untreated sample) CT within normal range; CEPI < 150 seconds and CADP < 110 seconds.

Testing Conditions:

- Negative Control: untreated whole blood
- Positive Control: Ketorolac IV 2.5 and 5 µg/mL; reflecting approximate C_{max} following a 15 and 30 mg ketorolac IV bolus respectively[9].
- Meloxicam IV: 5, 10, 15 and 20 µg/mL; reflecting approximate C_{max} following a 30 mg meloxicam IV dose (5 µg/mL), along with additional concentrations exceeding the exposure at the planned therapeutic dose.

Statistical Analysis:

- Test results were evaluated for quality control (QC) based on a repeat sample analysis from a single meloxicam IV test condition, with an acceptance criteria of ≤ 20% variance from the original result.
- Treatment effect on CT was analyzed using an analysis of variance (ANOVA) to assess treatment effect with and without controlling for covariates.

RESULTS

- Whole blood samples were analyzed from 13 eligible subjects (7 male, 6 female).
- The statistical analyses included data from 8 subject samples (2 male, 6 female); 5 subject samples excluded, 1 due to instrument malfunction and 4 due to out of range QC sample result.
- Data are reported for the statistical analysis set unless otherwise noted.

CADP Analysis:

- Sample analysis using the CADP reagent cartridge did not demonstrate a significant overall treatment effect on CT (p=0.5715).
- No individual treatment demonstrated a significant change in CT versus untreated control (p≥0.0907; Table 2).

Table 2: LS Mean Closure Times and Comparison By Treatment - CADP Reagent

	Untreated Control	Ketorolac IV		Meloxicam IV			
		2.5 µg/mL	5 µg/mL	5 µg/mL	10 µg/mL	15 µg/mL	20 µg/mL
LS Mean (SE) Closure Time	74.54 (5.311)	79.41 (5.311)	87.95 (5.658)	75.41 (5.311)	74.91 (5.311)	76.66 (5.311)	74.91 (5.311)
P-value vs. Untreated control		0.5179	0.0907	0.9074	0.9602	0.7776	0.9602

CEPI Analysis:

- In the CEPI reagent analysis, a significant treatment effect was observed for changes in CT (p=0.0441).
- No significant difference was observed in CT for the meloxicam IV treated samples vs. untreated control at any of the evaluated concentrations (p≥0.5400).
- When compared to untreated control, the ketorolac treated sample CT values were significantly prolonged in both the 2.5 and 5 µg/mL concentrations (p≤0.0257).
- All meloxicam IV concentration levels had a significantly shorter CT compared to the 2.5 µg/mL ketorolac concentration (p<0.005).
- All meloxicam IV concentration levels had numerically shorter CTs compared to the 5 µg/mL ketorolac concentration, though only the 10 µg/mL meloxicam IV concentration reached statistical significance.
- Data trends were maintained when analyses were performed including results from all eligible subjects (N=13) and all subjects without instrument errors (N=12).

Table 3: LS Mean Closure Times and Comparison By Treatment - CEPI Reagent

	Untreated Control	Ketorolac IV		Meloxicam IV			
		2.5 µg/mL	5 µg/mL	5 µg/mL	10 µg/mL	15 µg/mL	20 µg/mL
LS Mean (SE) Closure Time	90.50 (16.544)	180.87 (16.544)	143.38 (16.544)	101.75 (16.544)	95.13 (16.544)	104.00 (16.544)	104.63 (16.544)
P-value vs. Untreated control		0.0003	0.0257	0.6252	0.8406	0.5580	0.5400
P-value vs. 2.5 µg/mL Ketorolac			0.1084	0.0012	0.0005	0.0017	0.0018
P-value vs. 5 µg/mL Ketorolac				0.0757	0.0408	0.0923	0.0974

CONCLUSIONS

- No significant prolongation in CT was observed in meloxicam IV treated whole blood samples at concentrations reflecting therapeutic and supratherapeutic exposure levels compared with untreated control.
- In contrast, significant prolongations in CT were observed in samples reflecting therapeutic ketorolac concentrations compared with untreated control.
- When compared with ketorolac, meloxicam IV therapeutic exposure levels were observed to have numerically shorter CTs.
- These results suggest a potential clinical benefit of meloxicam IV over ketorolac with regard to a decreased risk of platelet dysfunction.

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