Acetaminophen and meloxicam inhibit platelet aggregation and coagulation in blood samples from humans

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Acetaminophen (Ace) and meloxicam (Mel) are the two types of analgesic and antipyretic medications. This study investigated the dose responses of acetaminophen and meloxicam on platelet aggregation and coagulation function in human blood samples. Blood samples were collected from six healthy humans and processed to make platelet-adjusted (100×10^3 cells/μl) blood samples. Acetaminophen (Tylenol, Q-PAP, 100 mg/ml) was added at the doses of 0 μg/ml (control), 214 μg/ml (the standard dose, 1×), 4×, 8×, 10×, 12×, 16×, and 20×. Similarly, meloxicam (Metacam, 5 mg/ml) was added at doses of 0 μg/ml (control), 2.85 μg/ml (the standard dose, 1×), 4×, 8×, 10×, 12×, 16×, and 20×. Fifteen minutes after the addition of acetaminophen and/or meloxicam, platelet aggregation was stimulated with collagen (2 μg/ml) or arachidonic acid (0.5 mmol/l) and assessed using a Chrono-Log 700 aggregometer. Coagulation function was assessed by prothrombin time (PT), activated partial thromboplastin time (aPTT), and using Rotem thrombelastogram. A robust inhibition by acetaminophen and/or meloxicam was observed in arachidonic acid-stimulated platelet aggregation starting at 1× dose. Collagen-stimulated platelet aggregation was inhibited by ACE starting at 1× (78 ± 10% of control), and by meloxicam starting at 4× (72 ± 5% of control, both $P < 0.05$). The inhibitions by acetaminophen and meloxicam combined were similar to those by acetaminophen or meloxicam. aPTT was prolonged by meloxicam starting at 4×. No changes were observed in PT or any of Rotem measurements by acetaminophen and/or meloxicam. Acetaminophen and meloxicam compromised platelet aggregation and aPTT. Further effort is warranted to characterize the effects of acetaminophen and meloxicam on bleeding *in vivo*. *Blood Coagul Fibrinolysis* 25:831–837 © 2014 Wolters Kluwer Health | Lippincott Williams & Wilkins.

Blood Coagulation and Fibrinolysis 2014, **25**:831–837

Keywords: and human blood, nonsteroidal anti-inflammatory drug (NSAID), platelet aggregation, thrombelastogram

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Received 18 February 2014 **Revised** 7 April 2014
Accepted 2 May 2014

Introduction

Acetaminophen is an over-the-counter analgesic and antipyretic drug. It has been widely used for over 50 years to relieve pains associated with arthritis, headache, muscular aches, and to reduce fever in adults and children. As in most drugs, the benefit of acetaminophen comes with its risks, such as liver toxicity [1,2] and potential adverse effects on coagulation. Limited reports have shown that acetaminophen at prescription dose of 650 mg did not affect coagulation function in normal volunteers, but its overdose caused increases of international normalized ratio (INR) and prothrombin time (PT) in hospitalized patients [3]. The dose response of acetaminophen on hemostasis is unclear.

Meloxicam is a nonsteroidal anti-inflammatory drug (NSAID) and was approved for use in 2000. It has been clinically proven effective to relieve from acute, surgical, and chronic pain with a favorable gastrointestinal tolerability profile at recommended doses [4,5]. Although meloxicam at recommended doses did not affect bleeding time in normal subjects [6,7], it is unclear whether there is potential risk at higher doses.

Acetaminophen and meloxicam are included in the pill-pack for medics in far forward environments. Recent reports have revealed previously unrecognized overuse of NSAIDs and acetaminophen in the military because of self-treatment of injuries sustained in combat environments [8,9]. A survey of soldiers at a forward operating base showed the following pattern of NSAID use: 52% with daily use, 40% with once or twice weekly use, and only 8% with no use [8]. A report from the Military Health System showed that acetaminophen overdose increased 40% annually from 2004 to 2008 in active duty service members, with juniors enlisted six times more likely to overdose than officers [9]. Thus, it is imperative to investigate whether overuse of these drugs will predispose soldiers put in harm's way to increased bleeding risk on the battlefield. This study was designed to

0957-5235 © 2014 Wolters Kluwer Health | Lippincott Williams & Wilkins DOI:10.1097/MBC.0000000000000162

Report Documentation Page

Form Approved
OMB No. 0704-0188

1. REPORT DATE	2. REPORT TYPE	3. DATES COVERED
01 DEC 2014	**N/A**	**-**

4. TITLE AND SUBTITLE	5a. CONTRACT NUMBER
Acetaminophen and meloxicam inhibit platelet aggregation and coagulation in blood samples from humans	5b. GRANT NUMBER
	5c. PROGRAM ELEMENT NUMBER
6. AUTHOR(S)	5d. PROJECT NUMBER
Martini A. K., Rodriguez C. M., Cap A. P., Martini W. Z., Dubick M. A.,	5e. TASK NUMBER
	5f. WORK UNIT NUMBER
7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES)	8. PERFORMING ORGANIZATION REPORT NUMBER
US Army Institute of Surgical Research, JBSA Fort Sam Houston, Texas	
9. SPONSORING/MONITORING AGENCY NAME(S) AND ADDRESS(ES)	10. SPONSOR/MONITOR'S ACRONYM(S)
	11. SPONSOR/MONITOR'S REPORT NUMBER(S)

12. DISTRIBUTION/AVAILABILITY STATEMENT
Approved for public release, distribution unlimited

13. SUPPLEMENTARY NOTES

14. ABSTRACT

15. SUBJECT TERMS

16. SECURITY CLASSIFICATION OF:			17. LIMITATION OF ABSTRACT	18. NUMBER OF PAGES	19a. NAME OF RESPONSIBLE PERSON
a. REPORT	b. ABSTRACT	c. THIS PAGE			
unclassified	**unclassified**	**unclassified**	**UU**	**7**	

Standard Form 298 (Rev. 8-98)
Prescribed by ANSI Std Z39-18

comprehensively assess the dose responses of acetaminophen and meloxicam on coagulation in blood samples from normal healthy volunteers.

Materials and methods

Human blood collection

This study was conducted under a protocol reviewed and approved by the US Army Medical Research and Materiel Command Institutional Review Board and in accordance with the approved protocol. Native whole blood (NWB) samples were withdrawn via venous puncture from six normal volunteers with signed informed consent. Each participant was sampled once with a total of 100-ml blood volume. Exclusion criteria included pregnancy, ongoing therapeutic anticoagulation, and use of over-the-counter drugs such as aspirin, ibuprofen, herbal products, or nonsteroidal anti-inflammatory drugs within 7 days.

Preparation of platelet-adjusted whole blood samples

Blood samples were collected into 22 citrate tubes (4.5 ml blue top containing 3.2% Na Citrate; Becton-Dickenson, Franklin Lakes, New Jersey, USA) and were allowed to incubate for 15 min at room temperature. An aliquot of the collected NWB was used for measurements of blood gas (the Omni-9 Blood Gas Analyzer; AVL, Montpellier, France) and blood cell counts (ABX Pentra 120 Hematology Analyzer; ABX Diagnostics, Inc., Irvine, California, USA), including platelet counts and hematocrit. The remaining blood samples were divided into two portions: one was reserved as NWB samples, and the other was used to make platelet-adjusted whole blood samples (PAWB samples), following procedures developed at our Institute [10]. Briefly, NWB samples were centrifuged at 2000*g* for 15 min to separate platelet-poor plasma (top layer), the buffy coat (middle layer, containing platelets), and red cells (bottom layer). Platelet-poor plasma was first collected via aspiration from the top clear layer. Upon removal of the buffy coat layer under platelet-poor plasma, red blood cells were collected. By adding platelet-poor plasma to collected red blood cells to obtain the hematocrit level identical to that of NWB samples, a stock of platelet-poor whole blood was made. Afterwards, NWB samples and platelet-poor whole blood samples were mixed in appropriate amounts to obtain a platelet count of 100×10^9 cells/l blood sample, referred to as PAWB samples. As a platelet level of 100×10^9 cells/l was considered the critical level for platelet transfusion in trauma patients, this level was selected to assess the dose–response effects of acetaminophen and meloxicam in this study. The engineered PAWB was then divided into three sets (eight tubes each) to test the dose responses of acetaminophen, meloxicam, and combined acetaminophen and meloxicam.

Dosing of acetaminophen and meloxicam

The Food and Drug Administration (FDA)-approved standard dose for acetaminophen is 15 mg/kg every 6 h. Assuming an average person has blood volume of 70 ml/kg with 100% absorption, the estimated plasma concentration from the standard dose is 214 μg/ml. In the acetaminophen dose set of eight tubes containing PAWB samples, acetaminophen (Q-PAP Infants' drops, 100 mg/ml; Huntsville, AL) was added at the doses of 0 μg/ml (control), 214 μg/ml (the recommended oral dose, referred to as 1×), 4×, 8×, 10×, 12×, 16×, and 20×, respectively. Buffered blood bank saline (isotonic solution 0.85% w/v; Thermo Scientific, Waltham, Massachusetts, USA) was used for volume matching among the eight tubes of the acetaminophen dose set.

The FDA-approved standard dose for meloxicam is 0.2 mg/kg. Assuming an average person has blood volume of 70 ml/kg and with 100% absorption, the estimated plasma concentration from the standard dose is 2.85 μg/ml. In the meloxicam dose set of eight tubes containing PAWB samples, the veterinary form of meloxicam, Metacam (5 mg/ml, Boehringer Ingelheim, St. Joseph, Missouri, USA), was added at the doses of 0 μg/ml (control), 2.85 μg/ml (the standard dose, referred to as 1×), 4×, 8×, 10×, 12×, 16×, and 20×, respectively. Similarly, buffered blood bank saline was used for volume matching among the eight tubes in the meloxicam dose set.

In the combination set of acetaminophen and meloxicam, acetaminophen of 0 μg/ml, 214 μg/ml (1×), 4×, 8×, 10×, 12×, 16×, and 20×, and meloxicam of 0 μg/ml, 2.85 μg/ml (1×), 4×, 8×, 10×, 12×, 16×, and 20× were added to the combination set of the eight tubes containing PAWB samples, respectively, with total volume matched among the eight tubes using buffered blood bank saline.

Fifteen minutes upon the completion of dosing and volume matching, the dosed blood sample in each tube was aliquoted for three measurements: platelet aggregation by Chrono-Log; PT and activated partial thromboplastin time (aPTT) by STart (Diagnostica Stago, Rue des Freres Chausson, France); and thrombelastogram by Rotem (TEM, Munich, Germany). All measurements were made at 37°C.

Platelet aggregation

Platelet impedance aggregometry was assessed in PAWB samples using a Chrono-Log 700 aggregometer. At 15 min after the addition of acetaminophen and/or meloxicam, the aggregation was stimulated with either collagen (2 μg/ml) or arachidonic acid (0.5 mmol/l). The area under the curve was used to compare platelet aggregation.

Prothrombin time and activated partial thromboplastin time

Changes in PT and aPTT were measured from PAWB samples using STart, according to instruction stated in manufacture operation manual.

Thrombelastrogram Rotem

Changes of coagulation profile from platelet-adjusted whole blood were measured using Rotem. About 0.3 ml of dosed blood samples was added to the measurement cup followed by addition of Extem reagent. From the tracing of clotting curve, the following parameters were generated to represent coagulation profiles, coagulation time (the time from test start to an amplitude of 2 mm); clot formation time (CFT, the time between 2-mm amplitude and 20-mm amplitude); α-angle (angle between the baseline and a tangent to the clotting curve through the 2-mm point to represent the rate of clot formation); maximum clot firmness (MCF, the maximum amplitude reached during the test); and A_{10} (clot firmness at 10 min after coagulation time).

Statistical analysis

Data were expressed as means ± standard error of the mean (SEM) and analyzed using SAS statistical software (Cary, North Carolina, USA). A one-way analysis of variance (ANOVA) with repeated measures using a Dunnett adjustment was used to compare the changes to the baseline within each group. A two-way ANOVA with repeated measures using a Tukey adjustment was used to compare the changes over time between the groups. The statistically significant level was set at $P < 0.05$.

Results

Blood characteristics

The characteristics of NWB and PAWB samples are listed in Table 1. As designed, platelet count in PAWB was reduced to 100×10^3 cells/μl. There were no differences in other measurements between NWB and PAWB samples (Table 1).

Platelet aggregation

Platelet aggregation was assessed in PAWB using arachidonic acid or collagen as the agonist. Compared with control (0 dose), acetaminophen inhibited collagen-induced platelet aggregation at all doses tested (Fig. 1). At 1× and 20× of acetaminophen, collagen-induced platelet aggregation was reduced to 78% ± 10% and 32% ± 5% of the control values, respectively (both $P < 0.05$). Meloxicam inhibited collagen-induced platelet aggregation starting at a dose of 4× (Fig. 1). At 4× and 20× meloxicam, collaged-induced platelet aggregation was reduced to 72 ± 5% and 50 ± 4% of the control value, respectively (both $P < 0.05$). When acetaminophen and meloxicam were combined, collagen-induced platelet aggregation was inhibited at doses of 4× and above (Fig. 1). At 4× and 20× of acetaminophen and meloxicam combined, collaged-induced platelet aggregation was reduced to 77 ± 1% and 38 ± 0% of the control values, respectively (both $P < 0.05$).

A significant inhibition of arachidonic acid-induced platelet aggregation was observed with acetaminophen, meloxicam, or combined acetaminophen and meloxicam (Fig. 2). At 1× and 4× doses of acetaminophen, arachidonic acid-induced platelet aggregation reduced to 19 ± 4% and 1 ± 6% of the control value, respectively (both $P < 0.05$). At 1× and 4× of meloxicam doses, arachidonic acid-induced platelet aggregation was reduced to 57 ± 11% and 1 ± 1% of the control value, respectively (both $P < 0.05$). At 1× and 4× of combined acetaminophen and meloxicam doses, arachidonic acid-induced platelet aggregation was reduced to 21 ± 5% and 0 ± 0% of the control value, respectively (both $P < 0.05$).

Prothrombin time and activated partial thromboplastin time

The effects of acetaminophen or meloxicam on PT and aPTT were assessed in PAWB samples. At all the doses tested, PT did not change by acetaminophen, meloxicam, or the combination of acetaminophen and meloxicam (Table 2). However, aPTT was prolonged by meloxicam starting at the dose of 4×, although no changes were observed at any dose of acetaminophen. When acetaminophen and meloxicam were combined, aPTT was prolonged starting at the dose of 10× and above (Table 2).

Thromboelastrogram measurements

At all the tested doses of acetaminophen, meloxicam, or the combinations of the two drugs, no significant changes were observed in coagulation time, CFT, alpha angle, MCF, or A_{10} (Table 3).

Discussion

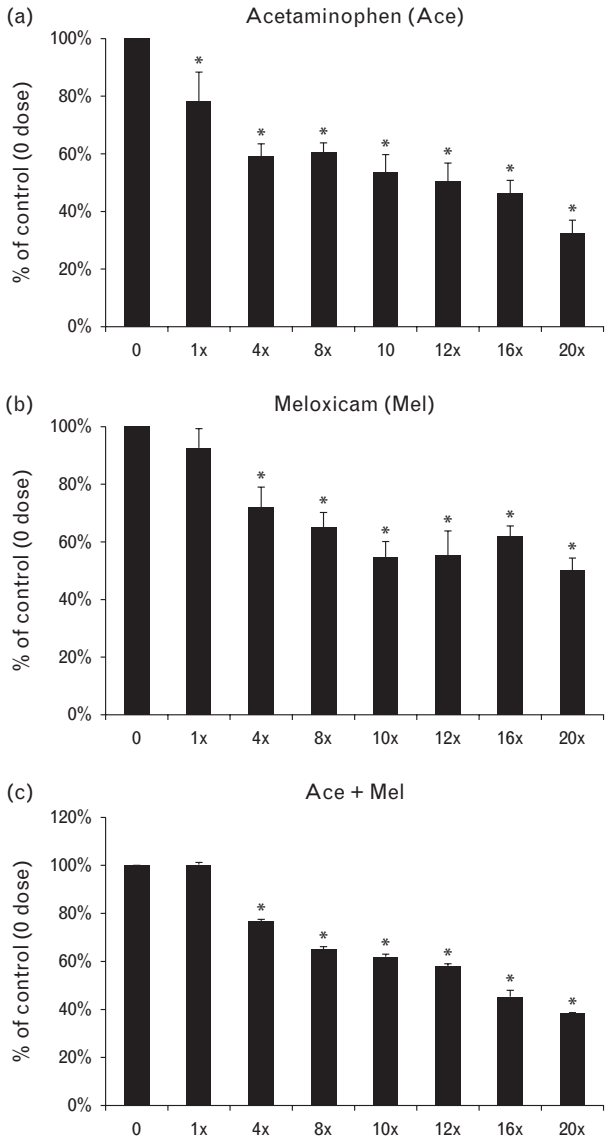
Hemorrhage is the leading cause of death from potentially survivable injury on the battlefield and a major cause of death in civilian trauma [11,12]. One of the most detrimental consequences of hemorrhage is the development of coagulopathy, increasing mortality four times of that without coagulopathy [13]. Damage control resuscitation (DCR) emphasizes the concept of preventing development or progression of coagulopathy by using blood component therapy and hypotensive resuscitation. Recent reports from military systems have revealed an

Table 1 Measurements from venous NWB collected from healthy volunteers and processed PAWB

	pH	Glucose (mmol/l)	HCO_3^- (mmol/l)	BE (mmol/l)	Hct (%)	Hgb (g/dl)	Platelet (10^3 cells/μl)
NWB	7.20 ± 0.01	5.4 ± 0.2	18.7 ± 0.2	−6.7 ± 0.3	39 ± 1	12.9 ± 0.2	221 ± 9
PAWB	7.25 ± 0.03	5.1 ± 0.2	19.8 ± 1.8	−7.7 ± 0.6	40 ± 1	13.0 ± 0.4	106 ± 5*

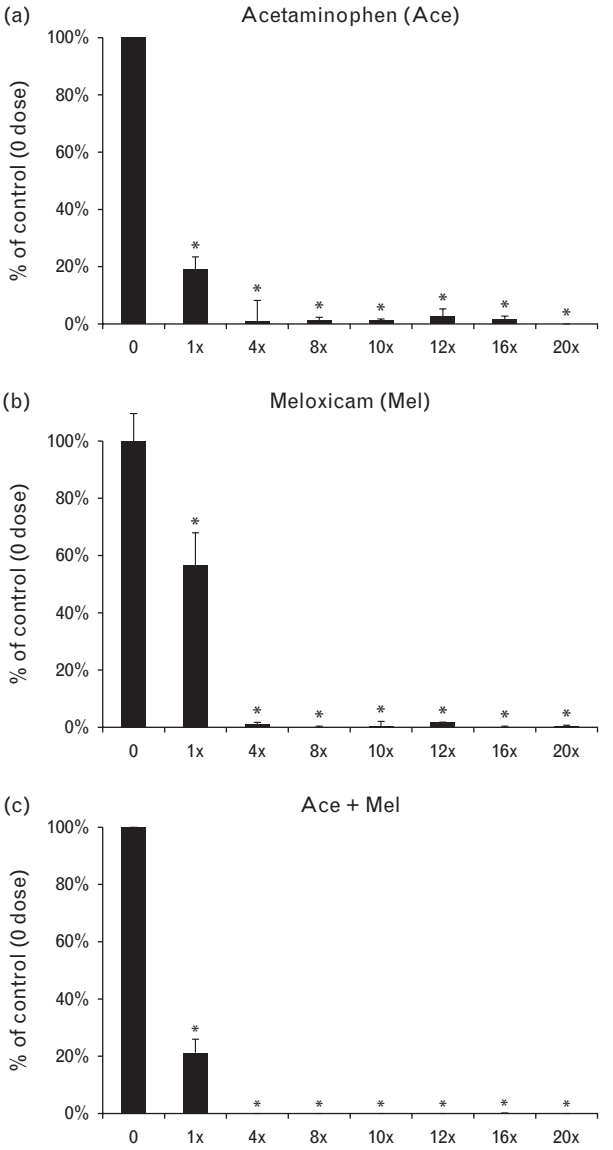
Human blood samples were collected in citrate blue top tubes. Data are expressed as means ± standard error. NWB, native whole blood; PAWB, platelet-adjusted whole blood. *$P < 0.05$ PAWB vs. NWB.

Fig. 1



Dose effects of acetaminophen (Ace), meloxicam (Mel), and combined acetaminophen and meloxicam (Ace + Mel) on collagen-induced platelet aggregation in platelet-adjusted human blood samples. Data are expressed as means ± standard error. $^*P < 0.05$ compared with corresponding control (0 dose).

Fig. 2



Dose effects of acetaminophen (Ace), meloxicam (Mel), and combined acetaminophen and meloxicam (Ace + Mel) on arachidonic acid-induced platelet aggregation in platelet-adjusted human blood samples. Data are expressed as means ± standard error. $^*P < 0.05$ compared with corresponding control (0 dose).

unrecognized risk factor for coagulopathy: overuse of nonsteroidal anti-inflammatory drugs (NSAIDs) and acetaminophen [8,9]. The impact of this overuse on DCR is unclear and has not been included in DCR studies. This study was undertaken to assess whether high doses of acetaminophen and meloxicam can adversely affect hemostasis. Our data showed that acetaminophen and meloxicam, individually or combined, inhibited platelet aggregation and prolonged aPTT, suggesting that the acute overuse of these drugs may predispose soldiers to the risk of a self-induced bleeding diathesis.

Primary hemostasis involves a series of complex interactions between platelet and von-Willebrand's factor, leading to hemostatic plug formation. Platelet function in this process is dependent on the synthesis of thromboxane A_2 (TxA_2) from prostaglandin H_2, which is generated from arachidonic acid by cyclo-oxygenase (COX-1). The antiplatelet effects of various NSAIDs are manifested as impaired platelet aggregation through inhibition of COX-1 activity and reduction of TxA_2 synthesis [6,14]. In the current study, we observed significant inhibition on arachidonic acid-induced platelet aggregation by acetaminophen and/or meloxicam,

Table 2 The individual and combined effects of Ace and Mel on PT and aPTT from platelet-adjusted human blood samples

	0	1×	4×	8×	12×	16×	20×
Ace							
PT (s)	16.0 ± 0.2	15.7 ± 0.5	15.0 ± 0.3	15.4 ± 0.6	15.6 ± 0.6	15.0 ± 0.7	15.0 ± 0.6
aPTT (s)	41.8 ± 2.5	41.9 ± 2.6	40.4 ± 1.9	40.8 ± 3.2	41.9 ± 3.3	39.9 ± 2.8	42.1 ± 2.9
Mel							
PT (s)	15.7 ± 0.5	15.0 ± 0.4	14.7 ± 0.5	15.3 ± 0.6	15.1 ± 0.8	15.0 ± 0.7	15.2 ± 0.8
aPTT (s)	41.7 ± 0.4	46.5 ± 1.5	48.2 ± 0.7*	50.8 ± 1.1*	52.8 ± 1.1*	53.4 ± 1.1*	55.3 ± 3.1*
Ace + Mel							
PT (s)	15.8 ± 0.1	15.7 ± 0.2	15.9 ± 0.3	15.6 ± 0.2	15.9 ± 0.1	16.0 ± 0.3	15.8 ± 0.2
aPTT (s)	39.5 ± 1.8	41.2 ± 2.4	41.9 ± 2.4	42.6 ± 3.4	45.4 ± 2.4*	48.2 ± 2.6*	49.0 ± 1.9*

Data expressed as means ± standard error. Ace, acetaminophen; aPTT, activated partial thromboplastin time; Mel, meloxicam; PT, prothrombin time. * $P < 0.05$ compared with corresponding control (0 dose) values.

starting at their recommended therapeutic doses. Collagen-induced platelet aggregation was also inhibited by acetaminophen or meloxicam, starting at 1× or 4× of recommended doses, respectively. When acetaminophen and meloxicam were combined, inhibition patterns were similar to those of the individual drugs, suggesting that there were no synergistic responses to the drugs. Considering the long turnover time of platelets in humans (5–9 days) [15], the marked inhibition of platelet functions observed in this study supports the notion of using platelet transfusion or products that compensate for reduced platelet function (such as fibrinogen concentrate) in trauma patients with acute drug overuse and bleeding complications.

The PT test reflects the enzymatic activation of the extrinsic system, including the activation of factors II, VII, and X, whereas the aPTT test represents enzymatic reactions of the intrinsic system, including the activation of factors II, IX, X, XI, and XII. Routine clinical PT and aPTT tests are performed in plasma samples. In this study, PT and aPTT were measured in whole blood samples, which included contributions of cellular components, such as red cells and platelets. Our data showed that neither acetaminophen nor meloxican caused any change in PT at all of doses tested. In contrast, aPTT was prolonged by meloxicam at the dose of 4× and higher, although aPTT did not change by acetaminophen at any of the tested doses. Consistent to our results, prolonged aPTT from meloxicam has been reported in dogs undergoing orthopedic surgery [16] as well as in healthy dogs [17]. The significant changes in aPTT and lack of changes in PT by meloxicam suggest that meloxicam has differential effects on the intrinsic and extrinsic pathways of coagulation. As there are more enzymatic reactions involved in the intrinsic pathway as compared with the extrinsic pathway, the fact that aPTT, not PT, was prolonged by meloxicam may be because of the accumulative effects of the enzymatic steps. Further effort is needed to provide confirmative and mechanistic explanations.

It is worth emphasizing that coagulation changes from acetaminophen and meloxicam in this study did not include systemic effects, which, therefore, might underestimate the adverse effects of the drugs. This point is

Table 3 Individual and combined effects of Ace and Mel on Rotem measurements from platelet-adjusted human blood samples

	0	1×	4×	8×	12×	16×	20×
Ace							
CT (s)	61 ± 3	63 ± 4	60 ± 1	61 ± 2	63 ± 3	61 ± 5	50 ± 2
CFT (s)	176 ± 20	197 ± 26	213 ± 29	193 ± 34	174 ± 24	176 ± 15	197 ± 28
Alpha (a)	59 ± 3	59 ± 3	57 ± 5	60 ± 5	59 ± 4	61 ± 2	58 ± 4
MCF (mm)	48 ± 1	49 ± 2	49 ± 2	50 ± 2	51 ± 2	50 ± 1	48 ± 1
A_{10} (mm)	39 ± 2	38 ± 3	36 ± 3	38 ± 3	41 ± 3	41 ± 2	40 ± 2
Mel							
CT (s)	59 ± 3	61 ± 4	61 ± 3	57 ± 1	63 ± 4	68 ± 3	65 ± 4
CFT (s)	162 ± 11	167 ± 16	166 ± 14	166 ± 17	161 ± 15	174 ± 16	172 ± 15
Alpha (a)	63 ± 2	60 ± 2	62 ± 3	61 ± 3	60 ± 2	58 ± 2	59 ± 3
MCF (mm)	49 ± 1	49 ± 1	49 ± 1	50 ± 1	50 ± 1	49 ± 1	50 ± 1
A_{10} (mm)	41 ± 1	40 ± 2	40 ± 1	41 ± 1	42 ± 2	40 ± 1	41 ± 1
Ace + Mel							
CT (s)	60 ± 3	67 ± 7	60 ± 4	56 ± 3	58 ± 3	55 ± 4	62 ± 4
CFT (s)	194 ± 25	199 ± 20	192 ± 24	186 ± 22	204 ± 29	186 ± 18	219 ± 21
Alpha (a)	61 ± 7	59 ± 5	60 ± 5	60 ± 5	58 ± 3	58 ± 3	56 ± 3
MCF (mm)	47 ± 2	47 ± 2	49 ± 2	51 ± 2	49 ± 3	49 ± 3	47 ± 1
A_{10} (mm)	39 ± 2	38 ± 2	39 ± 3	40 ± 3	39 ± 4	41 ± 3	39 ± 2

Data expressed as means ± SE. α-angle, angle between the baseline and a tangent to the clotting curve through the 2 mm point to represent the rate of clot formation; A_{10}, clot firmness at 10 min after CT; Ace, acetaminophen; CFT, clot formation time, the time between 2 mm amplitude and 20 mm amplitude; CT, the time from test start to an amplitude of 2 mm is reached; MCF, maximum clot firmness, the maximum amplitude reached during the test); Mel, meloxicam. * $P < 0.05$ compared to corresponding control (0 dose) values.

particularly relevant for acetaminophen because acetaminophen causes liver toxicity even at standard doses and liver failure at higher doses [1]. Liver disease-related clotting complications are considered the most commonly occurred coagulation disturbances [18,19]. When liver function is impaired from drug overuse, synthesis of coagulation factors is inhibited and coagulation factors are more rapidly depleted. Consistently, clinical records have shown that factor VII levels were reduced and INR was increased in hospitalized patients with acute acetaminophen poisoning without prior liver disease [3]. Thus, the in-vivo effects on coagulation from these drugs may likely be more deleterious than what observed in the present in-vitro study. Consequently, the overuse of these drugs may significantly predispose soldiers to bleeding risk at far forward combat situations.

Despite significant inhibitions in platelet aggregation and prolonged aPTT from acetaminophen and meloxicam, no changes were observed in any of the Rotem measurements. It is possible that the in-vitro changes observed in the current study are too subtle to be reflected in Rotem measurements. Future effort with in-vivo bleeding tests will help to clarify the effects of acetaminophen and meloxicam on coagulation.

Ibuprofen is another commonly used NSAID. Ibuprofen was introduced to reduce the incidences of gastrointestinal bleeding and hemostatic disturbances, as compared with aspirin. However, some adverse effects of ibuprofen on coagulation have been recognized in normal subjects, such as prolonged bleeding times and inhibited platelet aggregation [20]. To replace ibuprofen, meloxicam is recently included of the pill pack in the US military. Data from this study indicate that meloxicam may be safer than Ibuprofen, but not without risk.

In this study, we tested the dose responses of acetaminophen on coagulation in an in-vitro system. As oral acetaminophen is rapidly and almost completely absorbed from the gastrointestinal tract (85–98% absorption) [21] and completely from IV, we estimated that a standard dose of 15 mg/kg would result in a maximum plasma concentration of 214 μg/ml [= (15 mg/kg)/(70 ml/kg)] in an in-vitro system. However, as acetaminophen is quickly and primarily metabolized in liver with the biologic half-life of 2–3 h, the peak plasma level of acetaminophen in fasted normal subjects is found to be about 20 μg/ml or twice that after intravenous infusion [22], which is 1/10–1/5 of our in-vitro estimate. Thus, it is important to note that the effects of acetaminophen on coagulation from this study are likely an exaggeration of the in-vivo effects of acetaminophen in humans. Taken together, the data suggest little to no effect of acetaminophen on coagulation at normal doses of intake.

In conclusion, we investigated dose responses of acetaminophen and meloxicam on hemostasis in human blood samples *in vitro*. Acetaminophen and meloxicam, individually or combined, inhibited platelet aggregation, starting at standard doses. Meloxicam, with or without acetaminophen, prolonged aPTT, starting at four times the standard dose. Recognizing the hepatic toxicity of acetaminophen, we consider that data from the current in-vitro setting might underestimate the deleterious effects of these drugs on hemostasis and the risk of a self-induced bleeding diathesis in soldiers at combat environment. Continuing research effort is warranted to investigate the in-vivo effects of acetaminophen and meloxicam on bleeding and to facilitate the search for optimum analgesic drugs for deployed soldiers.

Acknowledgements

We appreciate the support received from the Laboratory Support Division at the U.S. Army Institute of Surgical Research in coagulation measurements. We thank Mr. John Jones for his assistance with statistical analysis. A.K.M. designed and performed the study, analyzed the data, and wrote the manuscript; C.M. performed the aggregation assay and analyzed the data; A.P.C. edited manuscript; W.Z.M. designed and performed the study, analyzed data, and reviewed manuscript; and M.A.D. reviewed the manuscript.

This study was supported by the U.S. Army Medical Research and Materiel Command. The opinions or assertions contained herein are the private views of the authors and are not to be construed as official or as reflecting the views of the U.S. Department of the Army or the U.S. Department of Defense.

Conflicts of interest

Disclosure: The authors declare no conflict of interest.

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