Ketorolac and Enoxaparin Affect Arterial Thrombosis and Bleeding in the Rabbit

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Background: Nonsteroidal anti-inflammatory drugs (NSAIDs) may interfere with hemostasis during the perioperative period, and the combination of NSAID and enoxaparin could increase this effect. The aim of this prospective, blinded experimental study was to assess these effects using a model of arterial thrombosis and bleeding in the rabbit.

Methods: After anesthesia was induced and monitors placed, the common carotid arteries were exposed, and 60% stenosis of the right common carotid artery was produced. Twenty minutes later, a compression injury of the artery was produced that triggered a series of cyclic episodes of thrombosis and clot lysis. This was manifested as cyclic flow reductions (CFR; measured with an electromagnetic flow meter). After the first flow reduction was noted, the rabbits were immediately and randomly assigned to one of four groups (n = 10 each) that received intravenous infusions: control, ketorolac (2 mg/kg), enoxaparin (0.5 mg/kg), and ketorolac plus enoxaparin (2 mg/kg and 0.5 mg/kg, respectively). The number of CFRs that occurred in the subsequent 20-min period was used as a measure of treatment effect. The contralateral common carotid artery was exposed, and both stenosis and injury were produced. The ability of the administered drug to prevent thrombosis was assessed as the number of CFRs that occurred during the first 20-min period after vessel injury. In addition, both before and after group assignment and drug injection, bleeding times were noted and a platelet aggregation test was performed. Laparotomy was followed by a spleen section, and the extent of the wound and the amount of splenic bleeding were measured.

Results: The treatment effect was indicated by the median number of CFRs, which was 5.5 in the control group, 1 in the ketorolac group, 2 in the enoxaparin group, and 0 in the ketorolac + enoxaparin group. The prevention effect was indicated by the median number of CFRs, which was 4 in the control group, 0 in the ketorolac group, 2 in the enoxaparin group, and 0.5 in the ketorolac + enoxaparin group. Bleeding time was significantly lengthened in the enoxaparin and in the ketorolac + enoxaparin groups. Splenic and wound bleeding was greater in the ketorolac group. Platelet aggregation was completely inhibited in the ketorolac and the ketorolac + enoxaparin groups.

Conclusions: Ketorolac had an important antithrombotic activity. The association of enoxaparin with ketorolac seemed to lengthen the bleeding time observed with ketorolac. (Key words: Artery; cyclic flow reduction; enoxaparin; ketorolac; low molecular weight heparin; nonsteroidal anti-inflammatory drugs.)

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NONSTEROIDAL anti-inflammatory drugs (NSAIDs) are widely prescribed during the perioperative period as analgesics.[1] They interfere with primary hemostasis by reversibly blocking platelet cyclo-oxygenase[1] and therefore act, like aspirin does, as antiplatelet agents. Data from *in vitro* and *ex vivo* comparisons of the antithrombotic activity and induced bleeding risk of different NSAID are still lacking.[2] One NSAID, ketorolac, because of its association with perioperative bleeding complications,[3] was withdrawn from the market in France in December 1993 by the National Health Authority.

Low molecular weight heparins (LMWH) are used widely to prevent venous thromboembolism during the perioperative period; the association of NSAIDs with LMWHs in particular could increase the bleeding risk because of the inhibition of platelet function by NSAIDs

Fig. 1. Arterial flow recordings. The vessel was injured and stenosed, before spontaneous cyclic flow reductions occurred and corresponded to thrombosis, followed by spontaneous embolization (release) and recurrence of all phenomena. No time scale is provided because the time is shorter on the right portion of the figure to facilitate the reader's understanding of the thrombosis process. However, the injury and the stenosis required <30 s, and every cyclic flow reduction required about 3 or 4 min in the control group.
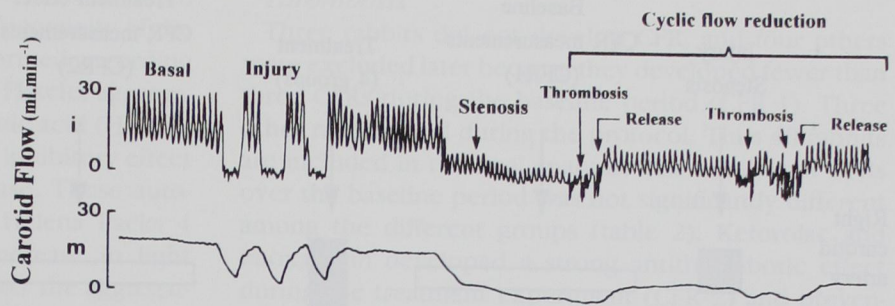
and the induction of an anticoagulant effect by LMWH.[4] Few data are available concerning this commonly observed association during the postoperative period.

The interest in animal models of arterial thrombosis has increased tremendously in the past few decades.[5-8] Folt's model of arterial thrombosis is reproducible and mimics unstable angina.[9-12] A vascular wall injury associated with stenosis induces cyclic flow reduction (CFR), which can lead to a permanent cessation of flow (thrombosis). The endothelial damage induces platelet accretion and the formation of a platelet plug, which embolizes and is formed again in a periodic cycle (fig. 1). Antiplatelet agents inhibit CFR, whereas epinephrine increases them by enhancing platelet activation. This model was developed in the rabbit[12] using carotid arteries rather than coronary arteries (as in Folts' original model) because of the ease of access and the less severe cardiac risk. A bleeding model has been added.

Thus we conducted a prospective, blinded study to assess the effects of an NSAID (ketorolac) and an LMWH (enoxaparin) given separately or in combination with a double model of arterial thrombosis and bleeding in the rabbit.

Materials and Methods

Care of the animals conformed to the recommendations of the Helsinki Declaration, and the study was performed in accordance with the regulations of the official edict of the French Ministry of Agriculture. The study involved two parts: application of Folt's model of the carotid arteries of the rabbit, and a bleeding model involving wound and spleen section and ear immersion bleeding time.

Surgical Procedure

Fifty male New Zealand rabbits weighing 2.4 ± 0.2 kg were used (Elevage des Dombes, Romans, France).

Anesthesia was induced using intravenous sodium pentobarbital (30 mg/kg). Tracheotomy and mechanical ventilation (Harvard Apparatus; Harvard Instruments, Boston, MA) were performed. Anesthesia was maintained with sodium pentobarbital, as required. Ventilatory parameters were adjusted to maintain arterial carbon dioxide partial pressure (Pa_{CO_2}) between 28 and 38 mmHg. The electrocardiogram was recorded using five hypodermic electrodes. A femoral artery catheter was placed, and arterial blood invasive pressure was recorded continuously using a pressure transducer (P23XL 95497 Viggo-Spectramed; Gould-France, Ballainvilliers, France) connected to a multichannel electrostatic recorder (ES 2000, Gould-France). Body temperature was recorded using a rectal probe and maintained at a constant level with an electric blanket and a warming table (Scientific Research Instruments, Edenbridge, Kent, UK).

Arterial blood samples were collected in ethylenediaminetetraacetic acid tubes (Becton Dickinson-France, Le Pont de Claix, France) for platelet counts and hemoglobin (co-oxymeter model 482; Instrumentation Laboratory, Milan, Italy) and blood gas analysis (model BG3; Instrumentation Laboratory) and in 3.8% trisodium citrated tubes (9:1 vol/vol; Becton Dickinson) for platelet aggregation measurements.

Both common carotid arteries were isolated and exposed over approximately a 2-cm length. A precalibrated electromagnetic circular flow probe (Skalar Instruments, Delft, The Netherlands) that was 1.5 mm in diameter was placed around the right common carotid artery on the distal part of the exposed segment and connected to a flowmeter (model MDL 1401; Skalar Instruments). Zero calibration was obtained directly by occluding the artery with a cotton-tipped swab.

Thrombosis

After 20 min of stabilization, a 60% stenosis of the right common carotid artery was produced using a vas-
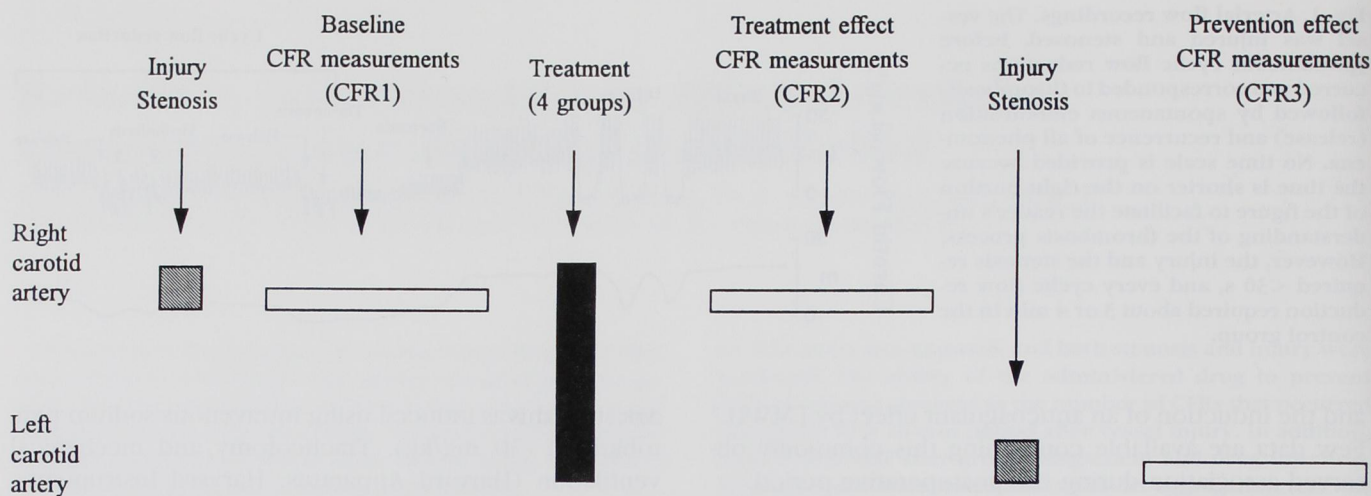
Fig. 2. The thrombosis experiment. The treatment effect was assessed by comparing the rate of cyclic flow reductions before and after the administration of the drug in the right common carotid artery, whereas the prevention effect was assessed by comparing the rate of cyclic flow reductions in the left common carotid artery with that of the right common carotid artery at baseline.

cular clamp placed around the artery in the proximal part of the 2-cm exposed segment. This stenosis was released after 20 min. An arterial injury was induced by three consecutive cross-clampings of the middle of the exposed segment of the artery during <10 s with a Mayo-Hegar needle holder forceps (Harvard Instruments) with three ratchet clicks closed, and a 60% stenosis was applied below the injury. This resulted in a series of CFRs characterized by repetitive decreases in blood flow followed by an abrupt spontaneous return of flow to original levels (fig. 1). These occur as a result of cyclic thrombosis and platelet plug lysis. Beginning with the first CFR, the thrombosis process was observed for 20 min (baseline, CFR 1). The number of CFRs during this 20-min observation period were counted, assuming that a decrease in the number of CFR was related to the antithrombotic activity of the studied drug. If no CFR was observed during this period, arterial injury was repeated at the same place, and a new 20-min period of observation was allowed. If no CFR occurred during this period, the experiment was stopped.

After the first 20-min period of observation with CFR (CFR 1), the drug to be tested, 2 mg/kg ketorolac (Toradol; Roche, Basel, Switzerland), 0.5 mg/kg enoxaparin (Lovenox; Rhône Poulenc Rorer, Antony, France), or the two drugs together (2 mg/kg ketorolac + 0.5 mg/kg enoxaparin) were injected intravenously, and a new 20-min observation period (CFR 2) was begun to assess the treatment effect (fig. 2). A stenosis (60%) and an

injury were thereafter applied on the contralateral carotid, and CFRs were recorded for 20 min (CFR 3) to assess the prevention effect. This last part of the study allowed us to reevaluate the effects of the drugs injected before the artery was damaged.

Bleeding

Bleeding time was measured before injection and 30 min later.[13] The ear was cleaned and shaved on the external side. A small incision (5 mm long) was made with a surgical blade (Surgicutt ITC; Ortho-Diagnostics-France, Roissy, France), and the ear was placed in a beaker containing 20 ml saline solution maintained at 37°C. Bleeding time was measured until the trickle caused by the incision stopped.

At the end of the experiment, a xyphopubic laparotomy was performed. The spleen was isolated and cut in half transversly at mid-level. Bleeding was recorded until it stopped spontaneously. The total amount of blood loss (splenic and wound bleeding) was measured by weighing the swabs inserted just after the laparotomy close to the spleen, 15 min later.

Platelet Aggregation

After arterial blood sampling, tubes were centrifuged, and platelet aggregation analysis was done rapidly. Platelet-rich plasma was obtained by centrifuging whole blood at 200g for 10 min at 37°C. Platelet-poor plasma was prepared from the same blood sample by centrifug-

ing blood at 1,500g for 20 min. Platelets were counted in platelet-rich plasma to check the homogeneity of the samples. An aggregation test was performed according to the turbidimetric method of Born.[14] Platelet aggregation was induced by 5 mg/ml arachidonic acid (Helena-France, St. Leu, France) to examine the inhibitory effect of ketorolac on platelet cyclo-oxygenase. These automated tests were performed using a Helena Packs 4 aggregometer (Helena-France). The increase in light transmission was recorded for 4 min after the aggregating agent (agonist) was added. Aggregation induced by the agonist in platelet-rich plasma was evaluated by measuring light transmission in stimulated platelet-rich plasma, assuming that light transmission was 100% in platelet-poor plasma and 0% in nonstimulated platelet-rich plasma.

The *maximal intensity of platelet aggregation* was defined as the maximal increase in light transmission, and *velocity of platelet aggregation* (slope of the curve) was defined as the speed of the increase in light transmission, after addition of the aggregating agent, as computed by the software.

Statistical Analysis

Data are expressed as mean ± SD, except for discrete variables (such as CFR) that are expressed as medians with ranges. Several means were compared using analysis of variance and the Newman-Keuls test. Medians were compared using the Kruskall-Wallis test for independent measures and completed when significant by a Mann-Whitney U test, and by a Friedman test for repeated measure, which was completed when significant by a Wilcoxon's test. All comparisons were two-sided. Probability values <0.05 were required to reject the null hypothesis. Statistical analysis was performed on a computer using PCSM software (Deltasoft, Meylan, France).

Results

No significant difference was observed among the four groups for body weight and the blood gas parameters (pH, Pa_{CO_2}, and Pa_{O_2}) before and after injection of the drug tested. No significant difference was observed among the groups for hemoglobin values and platelet counts before and after the injection. Temperatures were recorded continuously during the study, and there were no significant differences among the groups (table 1).

Thrombosis

Three rabbits did not develop CFR, and four others were excluded later because they developed fewer than three CFRs during the baseline period (CFR 1). Three other rabbits died during the protocol. Thus 40 rabbits are included in the final analysis. The number of CFRs over the baseline period was not significantly different among the different groups (table 2). Ketorolac and enoxaparin developed a strong antithrombotic effect during the treatment experiment (CFR 2) and prevention experiment (CFR 3). The additive effect of the association of ketorolac and enoxaparin cannot be ruled out, but this study did not have sufficient power to detect this effect.

Bleeding

Bleeding time was highly reproducible (n = 40; mean, 79 s; 95% CI, [75–87]). Bleeding time increased in the enoxaparin and ketorolac + enoxaparin groups compared with the control group (table 3). The most important increase in bleeding time was noted in the ketorolac + enoxaparin group (+56% *vs.* control group) and in the enoxaparin group (+43% *vs.* control group). No significant difference was noted in the ketorolac group. Splenic and wound bleeding were significantly greater with ketorolac (+41% *vs.* control group; table 3) compared with the control group.

Platelet Aggregation

Arachidonic acid-induced platelet aggregation was completely inhibited in the ketorolac and ketorolac + enoxaparin groups (table 4). In contrast, there were no significant changes in platelet aggregation in the enoxaparin and control groups.

Discussion

We showed that ketorolac and enoxaparin induced significant antithrombotic activity on injured carotid arteries in the rabbit and that enoxaparin alone or combined with ketorolac also increased bleeding time. We did not find an additive antithrombotic effect of the combination of ketorolac and enoxaparin because of the already maximal action obtained with ketorolac or enoxaparin alone. Only ketorolac increased wound and splenic bleeding significantly.

We tried to control most of the parameters that could interfere with the potential occurrence of CFR. First, continuous recording of blood pressure provided hemo-

Table 1. Blood Gases, Hematologic Parameters, and Temperature before and 30 min after Injection of the Study Drug

		Control (n = 10)	Ketorolac (n = 10)	Enoxaparin (n = 10)	Ketorolac + Enoxaparin (n = 10)
Arterial pH	Before	7.5 ± 0.1	7.5 ± 0.1	7.5 ± 0.1	7.5 ± 0.1
	After	7.4 ± 0.1	7.5 ± 0.1	7.5 ± 0.1	7.5 ± 0.1
Pa_{O_2} (mmHg)	Before	115 ± 21	112 ± 19	99 ± 27	103 ± 23
	After	105 ± 26	105 ± 19	103 ± 21	108 ± 12
Pa_{CO_2} (mmHg)	Before	29 ± 6	33 ± 9	34 ± 10	35 ± 10
	After	32 ± 8	32 ± 7	34 ± 6	32 ± 8
Hemoglobin (g · 100 ml^{-1})	Before	12.2 ± 0.8	11.5 ± 1.8	12.3 ± 1.1	12.6 ± 0.6
	After	11.1 ± 1.4	11.0 ± 1.8	11.6 ± 0.7	11.6 ± 0.7
Platelets (G · l^{-1})	Before	248 ± 77	254 ± 66	269 ± 75	224 ± 38
	After	249 ± 62	237 ± 71	263 ± 70	234 ± 28
Temperature (°C)	Before	37.9 ± 0.8	38.2 ± 0.7	38.2 ± 0.5	38.3 ± 0.4
	After	37.6 ± 0.5	37.8 ± 0.5	38.2 ± 0.4	37.7 ± 04

Pa_{O_2} = arterial partial pressure of oxygen; Pa_{CO_2} = arterial partial pressure of carbon dioxide.

Values are mean ± SD. There were no significant differences between groups.

dynamic stability and protection against variations of flow independent of the intensity of the stenosis of the vessel. Blood gases were measured to maintain pH and acceptable oxygenation because hypercapnia and hypoxia have a deleterious effect on the formation and migration of the platelet plug *in vivo.*[15] Important modifications in platelet aggregation during acidosis and hypercapnia have been reported *ex vivo.*[16] Hematologic parameters were controlled to check the stability of hematocrit and platelet counts. Cadroy and Hanson[17] showed that variations in hematocrit of 20% influence the formation of the platelet plug and modify platelet aggregation even when the macroscopic hemostasis of the subject is not modified. Finally, temperature was monitored and maintained constant to avoid variations in platelet aggregation in relation to the perturbation of platelet reactivity during hypothermia.[18]

Platelets have an established role in the development of arterial thrombosis, leading to myocardial infarction, peripheral ischemia, or stroke. Therefore, to screen for therapeutic measures that could control this thrombotic process, many experimental models of arterial thrombosis have been devised. Folts *et al.*[9-11] designed a quantitative model of platelet thrombus formation that involved stenosis and intimal injury of the coronary artery in the dog and monkey. They showed that marked stenosis associated with an injury promoted platelet accretion into the injured vessel wall. If the vessel was fixed for ultrastructural examination during the nadir of flow reduction during CFR, the stenotic area of the vessel contained a platelet plug. This model has been used to investigate the interactions between platelets and fibrinogen and between platelets and the vascular wall and to compare the effects of antithrombotic drugs.[19-21] The high reproducibility of this model in the rabbit led us to use it as an experimental model of arterial thrombosis.[22] We chose to conduct this study on carotid arteries rather than on coronary arteries because of the ease of access and the possibility of studying therapeutic and preventive actions.

Table 2. Number of Cyclic Flow Reductions (CFR) over a 20-min Period

	Control (n = 10)	Ketorolac (n = 10)	Enoxaparin (n = 10)	Ketorolac + Enoxaparin (n = 10)
Baseline (CFR 1)	7 (4–9)	6 (4–10)	5.5 (4–9)	6.5 (4–11)
Treatment effect (CFR 2)	5.5 (3–9)	1 (0–3)*†	2 (0–4)*†	0 (0–3)*†
Prevention effect (CFR 3)	4 (4–7)	0 (0–2)*†	2 (0–4)*†	0.5 (0–2)*†

Values are median (extremes).

* $P < 0.05$ *versus* baseline.

† $P < 0.05$ *versus* control group.

Table 3. Bleeding Time (BT) before Treatment and 30 min after Injection of the Study Drug

	Control (n = 10)	Ketorolac (n = 10)	Enoxaparin (n = 10)	Ketorolac + Enoxaparin (n = 10)
BT before treatment (s)	77 ± 13	77 ± 11	79 ± 10	81 ± 19
BT after treatment (s)	89 ± 20	116 ± 28	128 ± 37†	139 ± 44†
Spleen and wound bleeding (g)	12 ± 4	17 ± 6†	15 ± 4	16 ± 7

Values are mean ± SD.

* Spleen and wound bleeding were measured at the end of the experiment.

† $P < 0.05$ *versus* control group.

Our study showed the antithrombotic activity of ketorolac and enoxaparin and the association of these drugs during the treatment and prevention experiments. Ketorolac is an NSAID with a short half-life (5 h). The duration of its action on platelet aggregation therefore is limited.[23] Pharmacologic studies have found an *ex vivo* inhibition of platelet aggregation beginning at a low dose of 0.5 mg/kg.** In our study, ketorolac (2 mg/kg) developed an important antithrombotic effect while inhibiting CFR during assessments of the therapeutic and preventive effects. A previous study comparing ketorolac (1 mg/kg) with aspirin (10 mg/kg) found an antithrombotic effect with aspirin and a more limited effect with ketorolac. Aspirin completely abolished CFR during the treatment period in all rabbits, except one.[22] No effect was observed during this phase with 1 mg/kg ketorolac or saline. During the prevention period, a partial inhibition of CFRs was induced by ketorolac and aspirin. Postinjection bleeding time did not differ among the three groups.[22]

In this study, we chose a dose of 2 mg/kg ketorolac, which is close to the daily pharmacologic dose given to humans, assuming that the NSAIDs antiplatelet effect

** Unpublished data. Roche Laboratories, Basel, Switzerland.

is dose-dependent. This antithrombotic effect of ketorolac may be a new means of using this product as an antiplatelet agent in situations that require short antiplatelet activity (such as angioplasty or vascular surgery). Several studies have shown that ketorolac could induce important bleeding effects.[24] In our study, we found no significant increase in bleeding time with regard to the control group, despite complete inhibition of platelet aggregation. Nevertheless, wound bleeding was significantly increased in the ketorolac group.

These different results may invoke several remarks. First, the bleeding risk induced by the association of ketorolac with enoxaparin is actual and can probably be assessed by the important increase in bleeding time observed with this association. Second, the problem of the relation between an increase in the bleeding time and the bleeding risk has not yet been resolved.

Nonsteroidal anti-inflammatory drugs reversibly block cyclo-oxygenase and therefore inhibit platelet aggregation.[25] Many studies have tried to assess the bleeding effects of these drugs during operation.[26-29] When no additional hemostasis defect (such as hypothermia, decreased coagulation factor activity, or von Willebrand disease) is associated with NSAID treatment, a 30% increase in perioperative bleeding has been observed.[26]

Table 4. Platelet Aggregation Parameters before and after Treatment

		Control (n = 10)	Ketorolac (n = 10)	Enoxaparin (n = 10)	Ketorolac + Enoxaparin (n = 10)
Maximal intensity (%)	Before	36 ± 19	59 ± 12	38 ± 13	40 ± 17
	After	34 ± 16	5 ± 6*†	40 ± 12	10 ± 7*
Slope of the curve (% min⁻¹)	Before	51 ± 19	59 ± 15	52 ± 15	56 ± 11
	After	48 ± 16	3 ± 5*†	55 ± 12	6 ± 5*

Values are mean ± SD.

* $P < 0.05$ *versus* control group.

† $P < 0.05$ *versus* baseline (before) in the same group.

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The magnitude of primary hemostasis impairment differs according to the type of NSAID. Researchers tried to compare untreated patients and patients treated with NSAIDs[29] with regard to perioperative complications in a retrospective study including 165 patients having orthopedic surgery. In the treated group, 11 different NSAID molecules were used that differed one from another in their pharmacologic and pharmacodynamic properties. Perioperative bleeding was increased, and hemorrhagic complications during the postoperative period occurred more frequently in the NSAID group. These complications occurred more often with molecules that had long elimination half-lives. The authors stated that NSAIDs with short-elimination half-lives should be preferred during the perioperative period to minimize the bleeding risk.[29] Antithrombotic agents can be characterized by their prohemorrhagic or antithrombotic effects. The deliberate use of NSAIDs as antithrombotic drugs has not been reported frequently. Only flurbiprofene has been studied extensively in humans in this setting, and it has been tested in the prevention of arterial thrombosis.[25]

In dogs, a study comparing unfractionated heparin and LWMHs to prevent coronary thrombosis after an electrical injury[30] showed a higher effectiveness of LWMH. Others studies performed in animals have tried to quantify the induced bleeding risk by LWMH during the perioperative period. Holland *et al.*†† concluded that LWMH and unfractionated heparin increased the hemorrhagic risk when the bleeding rate was compared after resection of the rabbit leg. Low molecular weight heparins are widely used to prevent and manage venous thromboembolism.[31] Many studies and meta-analyses have shown the superiority of LWMHs compared with unfractionated heparin in the prophylaxis and management of deep vein thrombosis,[32,33] but only a few studies have tried to evaluate their effectiveness in the arterial field.[34] Clinical studies performed in arterial surgery have shown a higher antithrombotic activity of enoxaparin compared with unfractionated heparin to prevent thrombosis after femoropopliteal bypass,[34-36] but others studies have shown no difference between the groups treated with unfractionated heparin and with LWMH before aortic cross-clamping.[34,37] This problem is still being debated, and opinions remain divided

about the induced bleeding risk of LWMH during the perioperative period. The problem remains complex: Studies are too rare and different from one another to allow comparison and establish a precise mode of behavior. In addition, for the first time, a study has demonstrated the efficacy of LMWHs for the management of acute ischemic stroke compared with a placebo.[38]

The combination of NSAIDs and enoxaparin is used frequently in orthopedic surgery. Only a few studies performed in animals have tried to evaluate the antithrombotic or hemorrhagic effects of this association. A study on the rat mesenteric artery showed that LWMHs (nadroparin) associated with NSAIDs (piroxicam, indomethacin, or ketoprofen) impaired laser-induced thrombus formation and decreased the number of distal embolisms.[39-41] In humans, ketorolac was shown to lengthen bleeding time in volunteers. No significant modification was observed when heparin was added.[42] In a retrospective study of 86 patients undergoing total hip replacement, a significant increase in intraoperative bleeding was related to LWMH treatment associated or not with NSAID.[26]

In conclusion, our findings suggest that NSAIDs or LMWHs alone or in combination result in a comparable arterial antithrombotic effect in the rabbit. The lengthening of bleeding time observed with enoxaparin alone or combined with ketorolac suggests that the potential induced hemorrhagic risk must not be underestimated when these drugs are given together.

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