Effects of Rivaroxaban on Platelet Aggregation

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Abstract: Rivaroxaban is a direct oral anti-factor Xa anticoagulant. It has recently been suggested that rivaroxaban may affect platelet function in vitro; however, little is known about the clinical impact of this likely antiplatelet effect and whether this probable phenomenon is dose-dependent. Our aim was to determine whether rivaroxaban at 4 different doses inhibits direct platelet aggregation. We included adult patients of both sexes and who were allocated to one of the following groups depending on the prescribed daily dose of rivaroxaban: 5, 10, 15, and 20 mg. In 80 patients (20 patients/group), the percentage of platelet aggregation was determined by means of platelet aggregometry tests before and after rivaroxaban use. Basal samples were obtained before starting rivaroxaban and 1 month after treatment, both 2 and 24 hours after the last dose of the drug (12 hours after in the case of rivaroxaban 5 mg). We used 5 platelet agonists: adenosine diphosphate, epinephrine, arachidonic acid, collagen, and thrombin. There were no significant changes in the percentage of platelet aggregation before and after rivaroxaban use independently of the dose administered and the agonist used. Our results have clearly shown that rivaroxaban, even at a high dose, does not directly affect platelet aggregation.

Key Words: rivaroxaban, platelet function, antiplatelet effects, platelet aggregometry, platelets

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INTRODUCTION

Rivaroxaban (5-chloro-N-{[(5S)-2-oxo-3-[4-(3-oxomorpholin-4-yl)phenyl]-1,3-oxazolidin-5-yl]methyl}thiophene-2-carboxamide) is a direct factor Xa (FXa) inhibitor with potent anticoagulant effects. Its molecular weight is 436 g/mol, and its selectivity for FXa is 10,000-fold higher than other serin proteases.[1] It has a half-life of 7–11 hours and exhibits a peak effect 2–3 hours after oral intake.[2] Rivaroxaban was approved in 2008 in Europe for the prevention of venous thromboembolic disease (VTD) in patients who required major orthopedic surgery.[3,4] Currently, rivaroxaban has been approved in several clinical scenarios, namely, treatment of symptomatic acute VTD,[5] prevention of cardioembolic events in patients with nonvalvular atrial fibrillation,[6] treatment of pulmonary embolism,[7] and treatment of patients in the acute phase of acute coronary syndromes.[8,9] Depending on the clinical indication, accepted doses of rivaroxaban for these arterial or venous thrombotic scenarios are 5 or 15 mg twice a day (BID) or 10, 15, and 20 mg OD.

No laboratory monitoring of the anticoagulant effect of rivaroxaban is required, a fact that perhaps represents a major advantage as compared with vitamin K antagonists. Anticoagulant effect of rivaroxaban depends on a direct inhibitory effect on FXa in the common pathway of the fluid phase of hemostasis. As a result, thrombin generation as well as the activity of the prothrombinase complex may decrease.[10] These effects may be evident in some cases when the prothrombin time and activated partial thromboplastin test become prolonged, depending on both the dose administered and the reagents used in the tests.[11] Because thrombin plays a major role in platelet aggregation, it has been reported that rivaroxaban may also have some inhibitory effects on platelet function. Indeed, several authors have searched for these antiplatelet effects of rivaroxaban; however, published results have been contradictory.[12–15] Although this likely antiplatelet effect of rivaroxaban seems quite attractive in patients with acute coronary syndromes in which platelets have a main pathophysiological role,[8] there is no specific and convincing evidence demonstrating an inhibitory role of this drug on platelet function. Moreover, it is not known whether the likely antiplatelet effects of rivaroxaban are dose-dependent. Therefore, our aim was to determine the effect of rivaroxaban on platelet aggregation.

METHODS

The study protocol was approved by the ethics committee of our institution. Although platelet aggregation is a commonly used diagnostic test, this assay is not commonly performed in individuals receiving rivaroxaban. Because blood drawing was required before the first sample was taken from each patient, we obtained informed consent after subjects received information about the nature of the study. Confidentiality of the results was always warranted. Only the investigators had access to complete data of the participants. Blinding was broken in case of significant clinical or laboratory abnormalities. The study was approved by the ethics committee of our institution, and it was

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conducted according to the following national and international regulations for clinical research: Ley de General de Salud, Helsinki Declaration, and the Code of Nuremberg.

Sample Selection

In this prospective, controlled, longitudinal study, we analyzed blood samples of adult patients of both sexes who received treatment with rivaroxaban. Patients were recruited from the Clinica de Anticoagulacion of the Hospital General Regional "Carlos McGregor Sanchez Navarro," Instituto Mexicano del Seguro Social. Rivaroxaban (Xarelto; Bayer Healthcare, Berlin, Germany) was always indicated following the recommendations of the pharmaceutical company and according to the suggested therapeutic doses. Patients were allocated to one of the following groups according to the required therapeutic dose of rivaroxaban: group 1: 10 mg Once a day (OD); group 2: 15 mg OD; group 3: 20 mg OD. Group 4 included healthy volunteers who received rivaroxaban 2.5 mg twice daily. Patients and volunteers were encouraged to avoid any medication with known antiplatelet effects for at least 15 days before basal blood drawing and during the study period. Inclusion criteria were that patients were required to have a normal platelet count and a basal platelet aggregometry >50% for all platelet agonists used in the assays. Samples were obtained before and 30 days after treatment with rivaroxaban. For groups 1, 2, and 3, after 1 month of treatment with rivaroxaban, blood samples were obtained 2 and 24 hours after the last dose of the anticoagulant. For group 4, post-treatment samples were obtained 2 and 12 hours after the last dose of rivaroxaban.

Sample Collection

The study was performed during a 6-month period. We obtained 10.8 mL of blood from patients and healthy volunteers taking rivaroxaban (5 mg) as well as from controls (healthy blood donors). Blood was collected in 4 vacuum tubes with 3.2% sodium citrate (vol:vol = 1:9) (Vacutainer; Beckton Dickinson, Rutherford, NJ). Basal and post-treatment blood samples were obtained before breakfast except samples required for the tests performed 2 hours after rivaroxaban intake (due to the fact that rivaroxaban is better absorbed after meals). After blood drawing, samples were allowed to stand at room temperature for 30 minutes before centrifugation. Platelet-rich plasma (PRP) and platelet-poor plasma were obtained after centrifugation at 800*g* for 10 minutes and 1500*g* for 10 minutes, respectively. In addition, we use washed platelets to evaluate platelet aggregation with thrombin. Briefly, platelets were washed in buffer CGS-EDTA pH = 6.5 (sodium citrate 1.29 mM, citric acid 3.12 mM, ethylenediaminetetraacetic acid 4.99 mM) in a 1: 1 vol/vol and centrifuged for 15 minutes at 900 rpm. The supernatant was discharged, and the platelet package obtained was resuspended in 3 mL of buffer CGS pH = 6.5 (3.87 mM sodium citrate, 36.96 mM sodium chloride, and anhydrous dextrose 9.99 mM) and centrifuged for 12 minutes at 1000 rpm. Plasma was removed using plastic Pasteur pipettes. For internal quality control tests, plasma samples were obtained as previously mentioned from healthy blood donors. Selection of blood donors and platelet aggregation studies were similar as mentioned for the patients.

Sample Size

To obtain the sample size, we used the percentage of platelet aggregation (PPA) obtained from results of adenosine diphosphate (ADP)–induced platelet aggregation from controls. We calculated sample size using a 75 ± 15 value of the PPA (mean ± 1 SD) with $\alpha = 0.05$ and $1\text{-}\beta = 0.9$. On these bases and considering that a PPA value is clinically relevant when <55%, the sample size obtained was 12 patients/group. A sample size = 20 was finally used to have a more representative sample.

Platelet Aggregometry Studies

All lipemic, hemolyzed, or icteric samples were discarded. We used a commercial platelet aggregometer (810-CA; Chrono-log Corp, Havertown, PA). Platelet concentration in the PRP was adjusted to 250×10^3 platelets/μL. Platelet-poor plasma was used as a blank and as a dilutor of the PRP. The aggregometer requires 450 μL of the PRP. Samples were in the cuvette for 1 minute at 37°C, and a 1-minute period was also required to evaluate the presence of autoaggregation of the sample (as an indicator of previous platelet activation) before adding the platelet agonists. Five platelet agonists were used at standardized final concentrations: ADP (10 μM), epinephrine (10 μM), arachidonic acid (0.5 mM), collagen (2 μg/mL), and thrombin (1 U/mL). Maximum PPA was obtained between 5 and 7 minutes. The same procedure was used for the control samples.

Statistical Analysis

We used the Sigma-Stat statistical program v.3.5 (Systat Software Inc, San Jose, CA). For description of demographics, central tendency and dispersion measures were used; 2.5 and 97.5 percentiles were used to establish the reference values for PPA in the control group. Results of PPA before and after treatment with rivaroxaban are expressed as mean ± SD. Results of basal versus post-treatment PPA were compared using the paired *t* test. The paired *t* test was also used to compare the results of PPA obtained at 2 hours versus 12 and 24 hours after the last dose of rivaroxaban. Comparison of the results obtained from the different study groups was performed with a 1-way analysis of variance. The Student–Newman–Keuls test was used to perform multiple comparisons. The Student *t*-test was used to compare the results of PPA obtained 2 hours versus 12 and 24 hours after the last dose of rivaroxaban. The Kolmogorov–Smirnov test was used to establish whether data distribution was consistent with a normal distribution curve: A P value < 0.05 was considered significant.

RESULTS

Demographics

One hundred twenty-eight patients were originally enrolled in the study, but post-treatment samples were obtained in only 80 subjects (40 women and 40 men). All groups had 20 patients (10 men and 10 women). The median age for men was 40 years (range 18–65 years), 55 years (range 30–77 years), 71 years (range 55–75 years), and 60

years (range 39–77 years) for groups 1, 2, 3, and 4, respectively. For women, the median age was 45 years (range 26–65 years), 55 years (range 18–90 years), 70 years (range 56–78 years), and 69 years (range 43–90 years) for groups 1, 2, 3, and 4, respectively. There were no significant differences in terms of age between men and women and among the study groups ($P > 0.05$).

Basal Platelet Aggregometry Studies

Because no significant differences were observed in the PPA between men and women ($P > 0.05$), results for the 4 study groups are shown as a whole in Tables 1–3. Table 1 shows basal results of the PPA according to the 4 study groups. Results of the control group were used to establish the reference values for the PPA for the 5 agonists used. Basal PPA was similar among the 4 treatment groups and for the 5 platelet agonists (Table 1). We did not find significant differences between basal PPA from the control group as compared with the PPA from groups 1, 2, and 3 ($P > 0.05$) (data not shown). In group 4, basal PPAfrom healthy volunteers undergoing rivaroxaban treatment was significantly higher than basal PPA from groups 1, 2, and 3 ($P \leq 0.05$) (data not shown). However, these differences found in group 4 did not influence the results because mean PPA was between reference values.

Direct Effect of Rivaroxaban on Platelet Aggregometry Studies

After 30 days of treatment with rivaroxaban, we observed some random, nonsignificant changes in PPA in the 4 study groups (Table 2). In groups 1 and 2, PPA with ADP decreased from 77% to 75% and from 81% to 78%, respectively. On the other hand, nonsignificant increments after rivaroxaban treatment were observed with the 5 agonists in the 4 study groups. Because there were no significant differences in the PPA between basal and post-treatment phases, we did not perform a statistical analysis to determine differences in the PPA after treatment with rivaroxaban among the study groups.

TABLE 1. Basal Results of PPA in the Study Groups

Agonist	Group 1	Group 2	Group 3	Group 4	RV
Arachidonic acid	79 ± 11	81 ± 14	76 ± 14	92 ± 8*	50–100
ADP	77 ± 10	81 ± 15	74 ± 13	87 ± 10*	55–100
Epinephrine	79 ± 12	79 ± 15	79 ± 14	88 ± 9*	52–95
Collagen	80 ± 13	83 ± 14	78 ± 12	77 ± 14	54–98
Thrombin	85 ± 12	82 ± 11	83 ± 15	83 ± 10	64–100

ANOVA, analysis of variance; RV, reference values.

Results are expressed as mean ± SD. A 1-way ANOVA and a Student–Newman–Keuls test were used for the analysis of results. The Kolmogorov–Smirnov test showed that basal results of PPA in the 4 study groups were normal ($P \geq 0.05$). n = 20 patients/group.

*$P \leq 0.05$ rivaroxaban 5 mg versus rivaroxaban 10, 15, and 20 mg.

PPA 2 Hours versus 12 and 24 Hours After the Last Rivaroxaban Dose

When we compared the results of PPA2 hours versus 12 or 24 hours after the last dose of rivaroxaban, we did not find significant differences among the 4 groups and among the 5 platelet agonists used (Table 3). Noteworthy, in some patients, PPA after 2 hours of rivaroxaban intake was higher than basal values although mean values were always between reference values.

DISCUSSION

Rivaroxaban is one of 4 oral anticoagulants recently released for thromboprophylaxis and treatment of thrombotic episodes in several clinical scenarios. Although designed to directly inhibit the procoagulant effect of FXa, we decided to perform this investigation because of the lack of consensus about the effect of rivaroxaban on platelets. It has been widely described that inhibition of FXa may interfere with the generation of thrombin and that, hypothetically, this inhibition may translate into an antiplatelet effect because thrombin is, perhaps, the main platelet activator.[16] It would be desirable

TABLE 2. Effects of Rivaroxaban on Platelet Aggregation

Agonist	Basal PPA	24 Hours Post-treatment PPA	*P*
Group 1			
Arachidonic acid	79 ± 11	86 ± 9	0.056
ADP	77 ± 10	75 ± 10	0.207
Epinephrine	79 ± 12	83 ± 15	0.602
Collagen	80 ± 13	77 ± 14	0.325
Thrombin	85 ± 12	83 ± 11	0.548
Group 2			
Arachidonic acid	81 ± 14	85 ± 14	0.487
ADP	81 ± 15	78 ± 13	0.876
Epinephrine	79 ± 15	80 ± 14	0.960
Collagen	83 ± 14	81 ± 12	0.283
Thrombin	82 ± 11	79 ± 14	0.627
Group 3			
Arachidonic acid	76 ± 14	78 ± 11	0.573
ADP	74 ± 13	75 ± 10	0.802
Epinephrine	79 ± 14	80 ± 14	0.777
Collagen	78 ± 12	75 ± 16	0.421
Thrombin	83 ± 15	83 ± 13	0.830
Group 4			
Arachidonic acid	92 ± 8	96 ± 8	0.789
ADP	87 ± 10	91 ± 9	0.867
Epinephrine	88 ± 9	92 ± 11	0.627
Collagen	77 ± 14	79 ± 11	0.756
Thrombin	83 ± 10	80 ± 13	0.714

Results are expressed as mean ± SD. A paired *t* test was used for the analysis of the results. The post-treatment results of PPA showed a normal distribution (Kolmogorov–Smirnov test; $P \geq 0.05$). n = 20 patients/group.

TABLE 3. PPA 12 or 24 Hours Versus 2 Hours After Rivaroxaban Intake

	Group 1		Group 2		Group 3		Group 4	
Agonist	**24 h**	**2 h**	**24 h**	**2 h**	**24 h**	**2 h**	**12 h**	**2 h**
Arachidonic acid	86 ± 9	90 ± 13	85 ± 14	91 ± 10	78 ± 11	80 ± 12	96 ± 8	90 ± 13
ADP	75 ± 10	81 ± 10	78 ± 13	83 ± 5	75 ± 10	80 ± 7	91 ± 9	87 ± 11
Epinephrine	83 ± 15	83 ± 11	80 ± 14	77 ± 16	80 ± 14	74 ± 17	92 ± 11	86 ± 14
Collagen	77 ± 14	78 ± 9	81 ± 12	84 ± 14	75 ± 16	76 ± 13	79 ± 11	74 ± 10
Thrombin	83 ± 11	82 ± 13	79 ± 14	80 ± 12	83 ± 13	86 ± 12	80 ± 13	81 ± 11

Results are expressed as mean ± SD. A paired *t* test was used for the analysis of the results. There were no significant differences among all the results evaluated in all groups between 2 and 24 hours and between 12 and 24 hours. Results obtained of PPA in the 4 study groups showed a normal distribution ($P \geq 0.05$).

to have an anticoagulant drug with antiplatelet effects, especially with the scenario of acute coronary syndromes; however, such beneficial effect may not be so desirable in case of patients treated for VTD in which an anticoagulant effect is primarily needed. Of course, addition of an antiplatelet effect to the anticoagulant effect may significantly increase the number of hemorrhagic episodes. As a result, such antiplatelet effect may not be as desirable as initially considered.

Rivaroxaban may hypothetically affect platelet function either directly (eg, via some unknown interactions with platelets or megakaryocytes) or indirectly in a thrombin-dependent way (because it clearly inhibits FXa and this means inhibition of thrombin generation). We demonstrated that there is no direct effect of rivaroxaban on platelet function because platelet aggregometry with several agonists remained unchanged after 1 month of use. We did not attempt to investigate the second alternative (that in all probability remains true). Therefore, we consider this lack of antiplatelet effect of rivaroxaban as a "direct effect." We decided to assay the likely direct antiplatelet effect of rivaroxaban after a reasonable period of treatment (1 month) to assure that a full effect of the drug was present at the time of testing. Moreover, we evaluated the effect on platelets 2 hours after the dose of rivaroxaban, at the peak time of the anti-FXa anticoagulant as demonstrated in pharmacokinetic studies.[17] Therefore, we assayed the likely effect of the drug on platelets at the highest expected point of anti-FXa activity during the acute effect of the medication. Owing to the possibility that the inhibitory effect of rivaroxaban on platelets may appear at a late point during its expected pharmacological curve, we also assayed the antiplatelet effect just before the next dose of the medication. As a consequence, we assayed the PPA either 24 hours (for 10, 15, and 20 mg doses) or 12 hours (for 5 mg dose) after the last dose of rivaroxaban. Our results clearly show that rivaroxaban has no acute or late antiplatelet effects during the entire period of activity of this anticoagulant.

We assayed several doses of rivaroxabán to evaluate whether the likely antiplatelet effect of rivaroxaban was dose-dependent. No evidence in this regard has been previously reported in the literature. Our results clearly show that neither the lowest nor the highest clinically used doses of this anticoagulant induce antiplatelet effects in the individuals studied.

Some facts about the design of our study should be addressed. First, we evaluated platelet function by means of platelet aggregometry, an assay that perhaps does not reflect the entire platelet activity. However, platelet aggregometry is still considered the gold standard for the clinical analysis of platelet function as shown when studies concerning resistance to aspirin or ADP antagonists are performed. As previously mentioned, we claim that there is no direct, clinically significant direct effect of rivaroxaban on platelet function. Regarding its likely indirect effect on thrombin-induced platelet aggregation, it is difficult to assess the impact of the drug because it may alter thrombin generation and not blocking its receptor sites. As such, it would be difficult to assess this likely indirect antiplatelet effect in clinical samples. Therefore, because the platelet aggregometry induced by 5 different agonists showed no changes before and after 1-month exposure to rivaroxaban, we believe that, at least from the clinical point of view, it is unlikely that rivaroxaban has significant antiplatelet effects. Second, we analyzed the PPAfrom either patients or healthy volunteers after a 1-month period of treatment with rivaroxaban. Although it may be possible that an antiplatelet effect could be achieved after exposure to this drug during shorter or longer periods of time, there is no direct or indirect evidence to sustain this assumption. Third, doses of rivaroxaban assayed in this study include those used in most clinical entities in which this drug has been approved; however, we did not test the 15-mg Twice a day (BID) dose, which may be considered the highest dose used for this drug in the setting of the acute treatment of VTD.[5] It is difficult to obtain blood samples for platelet aggregometry when a patient with an acute episode of VTD is diagnosed to have the basal aggregometry. Although we may use a group of healthy volunteers to evaluate this dose, the bleeding risks associated with such high anti-FXa activity were ethically unacceptable.

Because we did not find an antiplatelet effect associated with rivaroxaban, we may hypothesize that the other FXa inhibitors, namely, edoxaban and apixaban, do not have this effect because the mechanism of action for these 3 drugs is similar.[18,19] It may be possible that a specific configuration in the molecule of rivaroxaban would be responsible for the absence of antiplatelet effect and that such biochemical characteristic is not shared with the other anti-FXa drugs. This possibility is quite remote because of 2 facts: (1) Because of the low molecular weight of all these drugs, it is difficult for significant biochemical changes to be present[19,20]; (2) these drugs are all pharmacologically designed to directly inhibit

the active site of FXa with no known effects on other regions of this molecule.[19–22] On the other hand, because thrombin plays a major role in platelet activation, dabigatran, a potent thrombin inhibitor, may have a likely potent antiplatelet effect as recently suggested.[23] The search of a likely antiplatelet effect associated with dabigatran seems to be warranted.

CONCLUSION

Although it has been suggested that rivaroxaban may reduce platelet activation by inhibiting thrombin generation, in our study, platelet aggregation remained unaltered even at the highest dose at the expected highest plasma level of this anticoagulant. These results add information about the safety of rivaroxaban. The results also suggest that it must not be considered as an anticoagulant with antiplatelet effects in opposition to results of previous studies showing that this drug may have a synergistic effect with some antiplatelet drugs, reducing platelet activation and, in some cases, platelet aggregation. From this point of view, our results clearly show that this anticoagulant should not substitute for any antiplatelet agent. When indicated in combination with one of such drugs, no effect on inhibition of platelet function is present.

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