FK633: A Potent and Selective Platelet GPIIb/IIIa Antagonist

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INTRODUCTION

Platelet activation and aggregation have been shown to play a central role in thromboembolic disorders (20,35,37). Platelets are activated by a variety of agonists. They adhere to the injured blood vessel walls and, subsequently, aggregate. These processes lead to the formation of occlusive thrombi in the lumen of the injured vessel (16,23,53).

The efficacy of such common antiplatelet agents as aspirin and ticlopidine is limited because they inhibit only some of the many pathways in platelet activation (2,33,39). Antagonism of the platelet glycoprotein (GP) IIb/IIIa receptor represents an attractive antiplatelet strategy, because it inhibits the final common step in platelet aggregation irrespective of the inducing agonist (3,12,13). The inhibition of platelet function with some GPIIb/IIIa antagonists has led to significant clinical benefits in reducing acute coronary ischemic syndrome (47–49).

FK633 is a potent and selective GPIIb/IIIa antagonist that inhibits human platelet aggregation induced by a wide variety of agonists (3). In vivo experiments suggest that it is effective in the prevention of arterial thrombus formation and in the suppression of reocclusion and restenosis in the injured vessel after thrombolysis (3,4,28). In this review, we present the pharmacological profile, pharmacokinetics, toxicology, and some clinical data on FK633, and discuss the future direction for GPIIb/IIIa antagonists.

CHEMISTRY

FK633, 4-(4-amidinophenoxy)butanoylaspartylvaline monohydrate (Fig. 1), was designed from the putative active structure of the Arg-Gly-Asp (RGD)-containing peptide generated using computer simulation and was synthesized at Fujisawa Pharmaceutical Co., Ltd. (45,46). The compound is available in the form of white crystals or crystalline

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powder, with a melting point of 184°C and a molecular weight of 454.48. It is soluble in water, ethanol, and dimethyl sulfoxide. Crystals of FK633 are stable for 30 months, and solution is stable for 7 days at room temperature.

PHARMACOLOGY

\textit{\textsuperscript{\textit{125}}I-labeled Fibrinogen Binding and RGD-mediated Cell Adhesion Studies}

The platelet GPIIb/IIIa antagonism of FK633 was examined by \textit{\textsuperscript{\textit{125}}I-labeled fibrinogen binding assay (3). FK633 effectively inhibited \textit{\textsuperscript{\textit{125}}I-labeled fibrinogen binding to ADP-activated platelets with an IC\textsubscript{50} of 88 nmol (Fig. 2). FK633 is more potent in inhibiting binding than is the linear RGD-containing peptide inhibitor, RGDS (Arg-Gly-Asp-Ser), which is the interacting sequence of fibrinogen with GPIIb/IIIa (42). This RGD sequence is also present in adhesive proteins, such as fibronectin and vitronectin, which bind to several other integrins in an RGD-dependent manner. Since FK633 was originally derived from an RGD peptide, the effects of FK633 on these integrins were evaluated using adhesions of human umbilical vein endothelial cells (HUVECs) to vitronectin or fibronectin (3). The results of these studies demonstrated that FK633 was \textit{\textsuperscript{>1000-fold less potent in inhibiting these HUVECs’ adhesions than in inhibiting fibrinogen binding to platelets}}, whereas RGDS was equally effective in both systems. Thus, FK633 is likely to inhibit fibrinogen binding to GPIIb/IIIa selectively.

\textbf{FIG. 1.} Chemical structure of FK633, 4-(4-amidinophenoxy)butanoylaspartylvaline monohydrate. From ref. 3.

\textbf{FIG. 2.} Inhibition of \textit{\textsuperscript{\textit{125}}I-fibrinogen binding to washed human platelets by FK633 (■) and Arg-Gly-Asp-Ser (RGDS) (○). Points, means of five experiments; bars, S.E.M. From ref. 3.
Generally, GPIIb/IIIa antagonists are divided into two groups for their integrin selectivity: GPIIb/IIIa selective antagonists and broad inhibitors of RGD-dependent integrins (3,14,25). Which of the two groups is superior in the therapy of thrombosis is a matter of controversy. For instance, the first GPIIb/IIIa antagonist, abciximab (c7E3), shows long-term benefits in reducing cardiovascular events after percutaneous coronary intervention (51). The mechanism of this long-term effect is thought to involve blockade of vitronectin receptor (αvβ3), as well as of GPIIb/IIIa (αIIbβ3), because this integrin has been shown to play an important role in the migration and proliferation of vascular smooth muscle cells (10). Although αvβ3 coblockade has many beneficial effects, broad inhibitors also have unwanted side effects, since αvβ3 is involved in many other physiological systems, such as bone resorption, osteoporosis, and angiogenesis (17,18,25). Chronic use of the non-selective antagonist may, therefore, lead to unwanted side effects.

**In Vitro Platelet Aggregation Studies**

The effects of FK633 on *in vitro* platelet aggregation were studied using human platelet-rich plasma (PRP) (3). FK633 effectively inhibited human platelet aggregation induced by a variety of agonists, and its potency was approximately 1000 times higher than that of RGDS. IC_{50} values are summarized in Table 1. In contrast to FK633, the most commonly used antiplatelet agent, aspirin, could only inhibit platelet aggregation mediated by the activation of the arachidonic acid-cyclooxygenase cascade; aspirin only weakly inhibited ADP-, platelet-activating factor (PAF)-, and thrombin-induced aggregation (Table 1). The results of these studies demonstrated that the antiaggregational action of FK633 is independent of the agonists used and is probably due to inhibition of fibrinogen binding to activated platelets, which is the final obligatory step in aggregation.

**Effects of FK633 on Platelet Aggregation in Various Species**

The antiplatelet effects of FK633 varied among different species (3). FK633 effectively inhibited ADP-induced aggregation in dog and guinea pig PRP with IC_{50} values of 280 and 642 nmol, respectively. FK633 showed little activity in mice, with its IC_{50} value of 5.2 μmol. It was ineffective in rabbits and rats at concentrations up to 10 μmol. Other GPIIb/IIIa antagonists also have species-selective antiplatelet effects. These results suggest that the ligand recognition site within GPIIb/IIIa is likely to be species dependent, and

<table>
<thead>
<tr>
<th>Inducers of aggregation</th>
<th>Drugs(^a)</th>
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<tbody>
<tr>
<td></td>
<td>FK633 (nmol)</td>
</tr>
<tr>
<td>ADP, 2.5 μmol</td>
<td>103 ± 11(^c)</td>
</tr>
<tr>
<td>Collagen, 1.0 μg/ml</td>
<td>87 ± 18</td>
</tr>
<tr>
<td>Thrombin, 0.1 unit/ml</td>
<td>98 ± 14</td>
</tr>
<tr>
<td>PAF, 0.2 μg/ml</td>
<td>239 ± 58</td>
</tr>
</tbody>
</table>

\(^a\) Number of experiments: FK633, \(n = 3\) to \(5\); RGDS, \(n = 3\); aspirin, \(n = 5\).

\(^b\) Abbreviations: RGDS, Arg-Gly-Asp-Ser; PAF, platelet-activating factor.

\(^c\) Mean ± S.E.M.
synthetic antagonists, including FK633, cannot interact with rat and rabbit GPIIb/IIIa. This idea is supported by the results of our studies showing that antagonists, such as RGDS or pentamidine, inhibit rabbit fibrinogen binding to human platelets but not human fibrinogen binding to rabbit platelets (15).

**Association between LIBS (AP-5 Epitope) Expression by FK633 and $[\text{Ca}^{2+}]_i$ Signalling Related to TXA$_2$ Synthesis in Human Platelets**

Recent studies demonstrate that the conformations of GPIIb/IIIa are dynamically regulated (38). Binding of fibrinogen or some antagonists to GPIIb/IIIa leads to the expression of neoepitope on GPIIb/IIIa, termed ligand-induced binding site (LIBS) (21,22,29). Using an anti-LIBS antibody, AP-5 (27), we investigated whether FK633 could induce LIBS expression and compared its nature with the currently known specific GPIIb/IIIa antagonists (26), SC54701 (32), MK383 (24), and Ro44-9883 (50) (Fig. 3). As shown in Fig. 4, antagonists were divided into two groups by their abilities to induce LIBS expression (Fig. 4): group I, FK633 and SC54701, could induce AP-5 expression; group II, MK383 and Ro44-9883, could not. Further studies showed that the antagonists in group I also induced other LIBS expressions in GPIIIa, such as LIBS-1 and LIBS-2 epitopes. Since LIBS expression may explain the capacity of GPIIb/IIIa to initiate outside-in signaling, the effects of FK633 on $[\text{Ca}^{2+}]_i$ in thrombin-stimulated platelets were also studied. In platelets stimulated by low thrombin, a two-peaked $[\text{Ca}^{2+}]_i$ increase was observed, and inhibition studies with a thromboxane A$_2$ (TXA$_2$) antagonist indicated that the second peak was induced by late release of TXA$_2$ (6). The GPIIb/IIIa antagonists, FK633 and MK383, also suppressed the second peak, suggesting that GPIIb/IIIa acts as a signal-transducing molecule for TXA$_2$ formation (Fig. 5). However, a dose escalation study showed that the second peak and TXA$_2$ formation were regenerated in the presence of high FK633 con-

![Chemical structure of current GPIIb/IIIa antagonists.](Image)
centrations but not with MK383 (26). Furthermore, this partial agonistic effect was commonly observed with antagonists in group I but not group II (Fig. 6). Hence, the association between GPIIIa LIBS expression and GPIIb/IIIa-mediated TXA2 synthesis in platelets suggests that a conformational change in GPIIb/IIIa after receptor occupancy is responsible for the late release of TXA2. FK633 has a partial agonistic effect for late

**FIG. 4.** Effects of GPIIb/IIIa antagonists on AP-5 epitope expression. Washed platelets were incubated with serial concentrations of antagonists, and then biotinylated AP-5 was added to the mixtures. Fluorescein isothiocyanate (FITC)-conjugated streptavidin was added, and bound antibody was analyzed by flow cytometry. These results are representative of six experiments. From ref. 26.

**FIG. 5.** Effects of GPIIb/IIIa antagonists, FK633 and MK383, on changes in [Ca2+]i and aggregation induced by thrombin, 0.03 units/ml. Platelets were preincubated with these antagonists at 0.1 μmol before addition of thrombin (arrow). Ca2+ and AG indicate intracellular Ca2+ movement and aggregation curves, respectively. From ref. 6.
TXA₂ formation in thrombin-stimulated platelets, because of its ability to induce GPIIIa LIBS expression.

**Effects of FK633 on *ex vivo* Platelet Aggregation and Bleeding Time**

Fig. 7 shows the time course of the inhibitory effect on ADP-induced *ex vivo* platelet aggregation and the cutaneous bleeding time in dogs (3). Intravenous administration of FK633, 0.32 mg/kg, inhibited aggregation almost completely for 1 h. At the dose causing >50% inhibition of aggregation, bleeding time was prolonged 2-fold. At 2 h after treatment, the bleeding time returned to basal levels and the antiaggregational effect was reduced.

Similarly, reversible antiplatelet effects were observed in guinea pigs given a bolus
injection of FK633 (Fig. 8) (4). In these animals, not only ADP-but also collagen-induced aggregation was suppressed in a dose-dependent manner. In contrast to FK633, aspirin was a weak inhibitor of ADP-induced aggregation, while collagen-induced aggregation was effectively inhibited. The results of these studies indicate that FK633 is a reversible GPIIb/IIIa antagonist with antiaggregational effects against various agonists.

**In Vivo Antithrombotic Effects of FK633**

The antithrombotic effect of FK633 was studied in a canine coronary thrombosis model (3). Platelet-dependent cyclic flow reduction (CFR) was induced by mechanical injury and stenosis of the left circumflex coronary artery. Table 2 shows the dose-dependent prevention of CFR by FK633. By intravenous administration FK633, 0.1 mg/kg, inhibited by >40% ex vivo ADP-induced aggregation and significantly suppressed CFR, while coronary blood flow was maintained for 88 min. At this dose FK633 did not prolong bleeding time (Fig. 7). However, at 0.32 mg/kg i.v. (a dose that could elicit persistent patency of the coronary artery), FK633 caused a significant prolongation of bleeding time. These results suggest that FK633 is an effective inhibitor of thrombus formation at the stenosed site of the injured vessel. They also suggest that, at carefully selected doses, FK633 might provide efficient antithrombotic activity without prolongation of bleeding time and that the reversibility might eliminate serious bleeding.

The antithrombotic effects of FK633 were compared with those of the most common antiplatelet agent, aspirin, in a guinea pig model of FeCl₃-induced carotid arterial thrombosis (4). In this model, chemical injury to the artery causes formation of a platelet-rich occlusive thrombus. Drugs were administered 3 min before application of 20% FeCl₃ to the vessel. The time required for the complete occlusion of the artery was recorded and used for evaluation of the antithrombotic effects of the drugs. As shown in Fig. 9, pretreatment with FK633 prolonged the time required for the formation of the occlusive thrombus of the carotid artery in a dose-dependent manner. A significant effect was observed with FK633 at 0.32 mg/kg i.v. At the highest dose used, FK633 caused persistent perfusion of the carotid artery. In contrast, aspirin showed only a tendency to prolong the

![FIG. 8. Effects of FK633, 0.32 (●) and 1.0 (○) mg/kg i.v., and aspirin, 10 mg/kg i.v. (□), on ADP (A) and collagen (B)-induced ex vivo platelet aggregation in guinea pigs. Points, mean of five experiments; bars, S.E.M. From ref. 4.](Cardiovascular Drug Review Vol. 17, No. 2, 1999)
time to thrombosis; it did not significantly prevent the formation of thrombus, even at
doses at which it effectively inhibited collagen-induced platelet aggregation. These results
suggest that cyclooxygenase-independent pathways in platelet activation are likely to
contribute significantly to thrombus formation and that FK633, by inhibiting platelet
aggregation caused by many different agonists nonselectively, is likely to have better
antithrombotic effects than is aspirin.

Effects of FK633 on Thrombolysis and Reocclusion

The effects of FK633 on thrombolysis with recombinant tissue plasminogen activator (rt-PA) were determined to see if FK633 could accelerate thrombolysis and preserve vascular patency after reperfusion of the carotid artery (Fig. 10) (4). Thrombosis was induced in guinea pigs by FeCl₃-induced injury of the carotid artery. Drugs were administered 5 min after complete occlusion, and rt-PA was infused for 1 h. As shown in Table 3, high-dose rt-PA (group II) alone achieved reperfusion in four of five animals. Low-dose rt-PA, however, was less effective, whereas combination therapy with FK633, 0.32 mg/kg i.v., and rt-PA, at a low dose, achieved reperfusion in all animals and reduced the time to reperfusion without any incidence of reocclusion.

![FIG. 9. Effects of FK633 and aspirin on thrombus formation in a guinea pig model of FeCl₃-induced carotid arterial injury. The time at which the carotid arterial blood flow decreased to zero was recorded as the time to occlusion. Columns, mean of five experiments; bars, S.E.M. **, P < 0.01 vs. control. From ref. 9.](image_url)

<table>
<thead>
<tr>
<th>Dose of FK633 (mg/kg i.v.)</th>
<th>CFR duration* (min)</th>
<th>Time to rethrombosisb (min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.032</td>
<td>1.5 ± 0.10c</td>
<td>8.8 ± 4.2</td>
</tr>
<tr>
<td>0.10</td>
<td>2.5 ± 0.23</td>
<td>88 ± 32*</td>
</tr>
<tr>
<td>0.32</td>
<td>2.7 ± 0.66</td>
<td>&gt;90**</td>
</tr>
</tbody>
</table>

* P < 0.05, ** P < 0.01 vs. CFR duration.
* Mean duration of cyclical flow reduction (CFR) in each animal during the pretreatment periods.
* Time to the formation of occlusive thrombosis after treatment with FK633.
* Each value represents the mean ± S.E.M. of three experiments.

**TABLE 2. Effects of FK633 on cyclical flow reduction (CFR) in dog coronary artery**
Aspirin showed a trend to increase the incidence of reperfusion; however, reocclusion was observed in all animals. The results of this study demonstrated that FK633 can accelerate the thrombolytic effect of rt-PA, and that FK633 is more effective in preventing rethrombosis after reperfusion than is aspirin. Similarly, several reports indicate that platelet activation during thrombolysis is induced by a wide variety of agonists, such as TXA2 and thrombin (34–36). The more efficacious effect of FK633, as compared with aspirin, on thrombolysis can be explained by its agonist-independent mode of antiplatelet action.

**Effect of FK633 on Neointima Formation after Thrombolysis in the Injured Hamster Carotid Artery**

The antithrombotic and restenosis-preventing effects of FK633 were studied in the hamster carotid artery (28). Vascular injury with a 2GF catheter caused occlusive thrombus.

<table>
<thead>
<tr>
<th>Group</th>
<th>Incidence</th>
<th>Time to reperfusion (min)</th>
<th>Flow recovery (%)</th>
<th>Reocclusion incidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>1/5</td>
<td>59 ± 0.0</td>
<td>93 ± 0.0</td>
<td>1/1</td>
</tr>
<tr>
<td>II</td>
<td>4/5</td>
<td>34 ± 8.4</td>
<td>70 ± 14</td>
<td>1/4</td>
</tr>
<tr>
<td>III</td>
<td>3/5</td>
<td>50 ± 9.0</td>
<td>109 ± 29</td>
<td>3/3</td>
</tr>
<tr>
<td>IV</td>
<td>5/5*</td>
<td>24 ± 13</td>
<td>120 ± 11</td>
<td>0/5***</td>
</tr>
</tbody>
</table>

*P < 0.05 vs. group I; **P < 0.05 vs. group III.
*Group I was given rt-PA at 0.3 mg/kg + 1.0 mg/kg/h i.v. (low dose); group II was given rt-PA at 0.6 mg/kg + 2.0 mg/kg/h i.v. (high dose); group III was given aspirin (ASA) at 10 mg/kg i.v., and a low dose of rt-PA; group IV was given FK633, 0.32 mg/kg i.v., and a low dose of rt-PA, respectively. Open bars represent patency, and hatched bars represent occlusion of the carotid artery. From ref. 4.

Aspirin showed a trend to increase the incidence of reperfusion; however, reocclusion was observed in all animals. The results of this study demonstrated that FK633 can accelerate the thrombolytic effect of rt-PA, and that FK633 is more effective in preventing rethrombosis after reperfusion than is aspirin. Similarly, several reports indicate that platelet activation during thrombolysis is induced by a wide variety of agonists, such as TXA2 and thrombin (34–36). The more efficacious effect of FK633, as compared with aspirin, on thrombolysis can be explained by its agonist-independent mode of antiplatelet action.

**TABLE 3. Carotid artery reperfusion and reocclusion by recombinant tissue plasminogen activator (rt-PA) combined with FK633 and aspirin**

* FIG. 10. Representation of the carotid artery patency status in individual guinea pigs receiving the following: group I given recombinant tissue plasminogen activator (rt-PA), 0.3 mg/kg + 1.0 mg/kg/h i.v. (low dose); group II given rt-PA, 0.6 mg/kg + 2.0 mg/kg/h i.v. (high dose); group III given aspirin (ASA), 10 mg/kg i.v., and a low dose of rt-PA; group IV given FK633, 0.32 mg/kg i.v., and a low dose of rt-PA, respectively. Open bars represent patency, and hatched bars represent occlusion of the carotid artery. From ref. 4.
bus formation in the lumen of the carotid artery. After thrombolysis with rt-PA, alone or with FK633, vascular patency and neointima formation were evaluated 14 days after the induction of injury. Infusion of FK633 was continued during the experimental period. The results of these studies demonstrated that FK633, 0.3 mg/kg/h i.v., for 14 days after vascular injury significantly improved vascular patency after thrombolysis with rt-PA and reduced neointima formation. A smooth muscle cell (SMC) proliferation assay suggested that after thrombolysis the acute phase of platelet recruitment into the exposed subendothelial layers might be responsible for the activation of SMCs and their migration and proliferation. It appears that FK633 could facilitate the resolution of the established thrombus by thrombolytic agents and reduce chronic vascular stenosis. It should be noted that FK633 alone cannot suppress restenosis. These findings imply that, in addition to platelets, other factors are important for the formation of neointima. These factors are likely to include the coagulation system (7,40), angiotensin II (30), and \( \alpha_v \beta_3 \) (31). Hence, the combined use of FK633 with these inhibitors may provide greater efficacy in reducing chronic restenosis after percutaneous transluminal coronary angioplasty (PTCA) or stenting therapy.

**TOXICOLOGY**

**Acute Toxicity Studies**

Single-dose toxicity studies with FK633 were conducted in rats and dogs. The acute LD\(_{50}\) values were higher than 100 mg/kg i.v. There were no sex-related differences. In dogs, a transient subcutaneous hemorrhage was observed at doses of >32 mg/kg.

**Subacute Toxicity Studies**

In a 13-wk study in rats, repeated i.v. doses of FK633, 100 mg/kg, caused a slight suppression of body weight gain and food intake. The noneffective dose in this study was 32 mg/kg. In a 13-wk study in dogs, FK633 produced no adverse effects at doses up to 3.2 mg/kg i.v. At 10 mg/kg i.v., however, a slight decrease in platelet count and a hemorrhage of the gastric mucous membrane and gullet were observed.

**Fertility Studies**

Fertility studies were performed in rats and rabbits. The noneffective dose in both species was 32 mg/kg i.v. for adult animals and 100 mg/kg i.v. for fetuses and newborns.

**PHARMACOKINETICS AND METABOLISM**

Pharmacokinetic studies were performed in rats, guinea pigs, and dogs using cold FK633 and \(^{14}\)C FK633. The plasma half-lives of FK633 after i.v. administration to rats, guinea pigs, and dogs were 1.59, 7.91, and 7.52 h, respectively. When FK633 was administered at 10 mg/kg p.o. to either rats or dogs, no drug was detected in plasma at either 1 or 2 h after treatment.

After i.v. administration of \(^{14}\)C FK633 to rats, radioactivity was widely distributed throughout the body except for the brain. After 24 h, no radioactivity was detectable in any organ, with 85.2\% of the drug having been excreted: 77\% of FK633 and 23\% of its...
metabolite were excreted in the urine; 5% of FK633 and 95% of its metabolite were excreted in the feces during the 72 h after drug administration.

FK633 was stable in the plasma and homogenate of rat intestinal cells. However, it was unstable in rat intestinal juice; when incubated with the juice for 5 h, 74% of the drug was degraded (46).

**CLINICAL STUDIES**

FK633 (1- to 5-mg total dose) was infused i.v. to healthy male volunteers over a 2-h period. The drug inhibited *ex vivo* platelet aggregation in a dose-dependent manner. It inhibited ADP- and collagen-induced aggregation by 89% and 66%, respectively. In the same dose range, a dose-dependent prolongation of bleeding time was observed, and four of six volunteers who received 5 mg of FK633 experienced a 2.5-fold increase in bleeding time as compared with baseline values. These two clinical parameters returned to normal values within 4 h after discontinuation of the infusion.

In healthy volunteers, repeated doses of FK633 (4 mg/2 h b.i.d. for 4 days) inhibited ADP- and collagen-induced aggregation by 86% and 79%, respectively. At the same dose, a >2.5-fold prolongation of bleeding time was not observed, even after the last dose of FK633.

In either single- or repeated-dose studies, FK633 at 4 mg was safe and well tolerated; there were no hemorrhagic incidents or other adverse effects.

**SUMMARY AND FURTHER DIRECTION**

FK633, a reversible and selective GPIIb/IIIa antagonist, inhibits platelet aggregation induced by a wide variety of agonists. Since FK633 has no effect on GPIIb/IIIa-independent platelet activation, such as thrombin receptor-mediated intracellular calcium movement (6), its broad inhibitory profile for platelet aggregation is likely to be due to the blockade of fibrinogen binding to GPIIb/IIIa, the final step in platelet aggregation. FK633 prevents formation of platelet-rich arterial thrombi. When used as an adjunct to rt-PA, FK633 can be highly effective in preventing rethrombosis and restenosis after thrombolysis. As an antithrombotic, FK633 is more efficacious than is aspirin. In healthy human volunteers FK633, at therapeutic doses, produced no serious toxicological or other adverse effects. However, clinical development was discontinued, because it can be used only intravenously, and overdosing may lead to concern about hemorrhage and thrombocytopenia. In clinical studies, several GPIIb/IIIa antagonists have also been reported to increase the incidence of bleeding complications (1,41,50) and to be associated with thrombocytopenia (9,19). The desired GPIIb/IIIa antagonist should have high oral activity and less tendency to produce hemorrhagic or thrombocytopenic effects. Recent metabolic studies have led to the discovery of oral active antagonists (44), and the elimination of their ability to express LIBS (ligand-induced binding sites) in GPIIb/IIIa will improve the thrombocytopenic effect of these antagonists (8,11). According to recent reports, platelet aggregation-inhibitory effects of antagonists can be separated from their adverse effects on bleeding time, and some antagonists have a greater safety margin for these two effects (5,43,52). It is expected that, in the near future, a promising GPIIb/IIIa antagonist will offer safety and long-term advantages in therapeutic situations.
REFERENCES


