A Monoclonal Antibody Against the Platelet Glycoprotein IIb/IIIa Receptor Complex Prevents Platelet Aggregation and Thrombosis in a Canine Model of Coronary Angioplasty

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Background. The comparative effects of aspirin and F(ab')$_2$ fragments of monoclonal antibody 7E3 against the platelet glycoprotein IIb/IIIa receptor on ex vivo platelet aggregation and in vivo thrombosis were studied in a canine coronary balloon angioplasty model.

Methods and Results. Three groups were studied. Group 1 ($n=8$) was pretreated with saline placebo, group 2 ($n=8$) was pretreated with 325 mg aspirin, and group 3 ($n=8$) was pretreated with 0.8 mg/kg 7E3 F(ab')$_2$. Coronary angioplasty was performed in the left anterior descending coronary artery of open-chest dogs under fluoroscopic control; serial measurements of basal and hyperemic coronary blood flows were then made for 2 hours after application of an external stenosis that decreased hyperemic flow by 50%. There were no significant differences in platelet counts or hemodynamic measurements during the experiments. Platelet aggregation was decreased by treatment: group 1, 64±13% versus 50±13% ($p=NS$); group 2, 57±4% versus 25±4% ($p<0.001$); and group 3, 77±5% versus 10±6% ($p<0.0002$). Compared with initial measurements, the 7E3 antibody was superior to aspirin in maintaining hyperemic coronary blood flow after release of the external stenosis: group 1, 177±14 versus 21±14 ml/min ($p<0.0003$); group 2, 189±9 versus 110±28 ml/min ($p<0.008$); and group 3, 194±12 versus 181±15 ml/min ($p<0.02$). In group 1, arterial occlusion developed in five dogs, and nonocclusive thrombus was seen in three dogs. In group 2, arterial occlusion developed in one dog, and nonocclusive thrombus was seen in five dogs. No thrombotic material was visualized in group 3 dogs treated with 7E3 F(ab')$_2$.

Conclusions. In this animal model, the 7E3 antiplatelet antibody is superior to aspirin in inhibiting platelet aggregation, thrombosis, and acute closure after deep arterial injury caused by coronary balloon angioplasty. (Circulation 1991;84:2463–2469)

Acute closure during percutaneous transluminal coronary angioplasty is the most serious procedural complication limiting more widespread use of this nonsurgical alternative to revascularize atherosclerotic coronary arteries. The reported incidence of acute closure is 2–8%,1–9 but it may be higher in centers where more complex lesions are being approached. Topol$^{10}$ has estimated that persistent acute closure occurred in at least 10,000 patients in 1987, resulting in more than 6,000 emergency coronary bypass graft surgeries and more than 1,000 deaths. An unknown number of additional patients had impending or temporary acute closure that responded to nonsurgical interventions. The most common pathophysiological event precipitating acute closure is a complex intimal tear with subsequent thrombus formation.$^{2,4,11,12}$

Arterial injury initiates platelet activation and thrombin production, which can result in the formation of a platelet-rich occlusive thrombus.$^{13,14}$ Platelet activation is mediated by one of three pathways through the action of either collagen and thrombin or ADP and serotonin or arachidonic acid.$^{14}$ Aspirin reduces but does not prevent the acute thrombotic complications associated with coronary angioplasty.$^{15–20}$ by inhibiting
the arachidonic acid pathway and decreasing platelet aggregation. A more potent agent that completely prevented platelet aggregation could eliminate the risk of acute thrombosis in coronary angioplasty.13

The final common pathway resulting in platelet aggregation involves cross-linking platelets by binding fibrinogen and other adhesive glycoproteins (GPs) to the GP IIb/IIIa receptor complex on the platelet surface membrane.13,14 Coller and colleagues21-25 developed a murine monoclonal antibody (7E3) that blocks the binding of fibrinogen to the GP IIb/IIIa receptor complex. The purified F(ab')2 fragment is capable of blocking 85% of the available receptor sites,22,24-27 decreasing platelet aggregation by more than 90%.22-29 Although bleeding times are consistently prolonged to more than 30 minutes,26,27 significant bleeding complications have not been described.22,24-29 This may be because other platelet receptor sites continue to promote platelet adhesion by interacting with von Willebrand factor and collagen and because facilitation of fibrin formation by platelet release is not inhibited.22,24,25,27,28

Significant thrombocytopenia has been avoided by excluding the Fc portion of the immunoglobulin molecule, which could lead to premature clearance of antibody-coated platelets by splenic macrophages containing Fc receptors.22,24-28

Previous experimental studies in animal models have demonstrated that the 7E3 F(ab')2 antibody prevents thrombosis24,28 facilitates thrombolysis,26 and prevents reocclusion after successful thrombolysis.27,29 The present study was designed to test the relative efficacies of aspirin and the 7E3 F(ab')2 antibody on ex vivo platelet aggregation and in vivo thrombosis in a canine model of coronary angioplasty.

Methods

Surgical Preparation and Instrumentation

Mongrel dogs of either sex weighing 15-25 kg were anesthetized with intravenous sodium pentobarbital (35 mg/kg) and ventilated with room air via a Harvard respirator. ECG limb leads were attached to monitor heart rate and rhythm. The left carotid artery and jugular vein were dissected free for 2-3 cm. An intravenous catheter was placed into the vein for fluid and drug administration. A 9F angiographic introducer sheath was placed into the artery for introduction of angiographic catheters. A left thoracotomy was performed, and the heart was suspended in a pericardial cradle. Then, the proximal left anterior descending coronary artery (LAD) was dissected free for 2 cm. An appropriate size and calibrated electromagnetic flow probe (model EP 200, Carolina Medical Electronics, King, N.C.) was placed proximally on the artery, and an elastic band was placed distal to the flow probe so that blood flow could be intermittently interrupted. A high-fidelity micromanometer catheter (Millar Instruments, Houston, Tex.) was passed through the apex of the heart into the left ventricular cavity to measure systolic blood pressure, left ventricular end-diastolic pressure, and the first derivative of left ventricular pressure (dP/dt).

Protocol

Twenty-four dogs were randomized to one of three intravenous treatment groups: group 1, saline placebo; group 2, 325 mg aspirin; and group 3, 0.8 mg/kg antibody 7E3 F(ab')2.3,5 The production of antibody 7E3 F(ab')2 (Centocor, Inc., Malvern, Pa.) has been described.21,22,27 Blood for platelet count and platelet aggregation studies was withdrawn from the internal jugular sheath as described below. Continuous recordings of heart rate, systolic arterial pressure, left ventricular end-diastolic pressure, dP/dt, and LAD blood flow were obtained with an eight-channel physiological recorder (model 2800S, Gould Electronics, Cleveland, Ohio). Three to five measurements of basal coronary blood flow and hyperemic coronary blood flow after a 20-second occlusion were made in the LAD. Treatment was then administered by intravenous injection. Thirty minutes after treatment, an 8F Amplatz angioplasty guiding catheter (USCI, Billerica, Mass.) was inserted through the arterial sheath and positioned in the left main coronary artery. A 4.0x20 mm balloon angioplasty catheter (USCI) was then advanced into the LAD under fluoroscopic control until the balloon was just distal to the flow probe. Arterial injury was accomplished by inflating the oversized balloon twice for 60 seconds at 10 atm with 60 seconds between the inflations. After the catheters were withdrawn, a rigid C clamp was applied to the artery and adjusted to create a stenosis that decreased hyperemic blood flow by 50%. Repeat hemodynamic and blood flow measurements were made every 15 minutes for 2 hours. Arterial occlusion was determined by the absence of blood flow as measured by the electromagnetic flow probe. The C clamp was released after 2 hours, and repeat measurements were made. Blood for platelet count and aggregation studies was again withdrawn. Finally, 400 mg of Evans blue dye dissolved in 20 mg of isotonic saline was injected intravenously. Five minutes later, the dog was killed by injecting 20 mg potassium chloride i.v., and the heart was excised. The LAD was then longitudinally opened and inspected for macroscopic intravascular thrombus formation. The arterial lumen was flushed clean and inspected for blue staining to confirm arterial injury.30,31

Platelet Studies

Blood (20 ml) was withdrawn from the internal jugular cannula into a plastic syringe containing 3.2% sodium citrate as the anticoagulant (1:10 citrate/blood, vol:vol) at baseline and 2 hours after treatment. The platelet count was determined with a Haema Count MK-4/HC system (J.T. Baker, Allen-town, Pa.). Platelet-rich plasma (PRP), the supernatant present after centrifuging anticoagulated whole blood at 1,000 rpm for 5 minutes (140g), was diluted with platelet-poor plasma (PPP) to achieve a platelet
count of 200,000/mm³. PPP was prepared after the PRP was removed by centrifuging the remaining blood at 12,000g for 10 minutes and discarding the bottom cellular layer. Ex vivo platelet aggregation was measured by established spectrophotometric methods using a four-channel aggregometer (BioData-PAP-4, BioData Corporation, Hatboro, Pa.) by recording the increase in light transmission through a stirred suspension of PRP maintained at 37°C. Aggregation was induced with arachidonic acid (0.65 mM). Epinephrine (550 nM) was used to prime the platelets before arachidonic acid stimulation. Values were expressed as percent aggregation, which represented the percentage of light transmission standardized to PRP and PPP samples yielding 0% and 100% light transmission, respectively.

Statistical Analysis

Effects of intervention on hemodynamic variables and coronary blood flow were assessed by two-factor repeated-measures analysis of variance. When significant interactions between drug and time were found, a Bonferroni multiple comparisons test was used to determine which factor level mean was significantly different from baseline and between treatment groups. Differences in platelet counts and platelet aggregation were determined using a paired t test. A probability value of <0.05 was considered significant. Data are expressed as mean ± SEM.

Results

Platelet Studies

Treatment with aspirin or antibody 7E3 did not significantly change the platelet count during the experiment (Figure 1). Platelet aggregation in the control group decreased insignificantly from 64±13% to 50±13% (Figure 2). Platelet aggregation decreased significantly from 57±4% to 25±4% (p=0.001) 2 hours after intravenous aspirin administration. After antibody 7E3 administration, platelet aggregation was further reduced from 77±5% to 10±6% (p=0.0002).

Hemodynamics

Treatment did not change heart rate, systolic arterial pressure, left ventricular end-diastolic pressure, or dP/dt before coronary thrombosis occurred. Measurements were not evaluated after thrombosis because the intent was to measure treatment effect, not the additive effect of coronary thrombosis.

Coronary Blood Flow

Basal coronary blood flow significantly decreased only in the control group (42.8±3.4 versus 9.0±6.5 ml/min, p=0.001) due to the high rate of arterial occlusion (Table 1). Basal flow in the control group was significantly different from that in the aspirin group at 30 minutes (p=0.001) and from that in the 7E3 group at 15 minutes (p=0.001). Hyperemic flow (Table 2 and Figure 3) in the control group was significantly different (p=0.001) from that in the aspirin and 7E3 groups at 15 minutes and remained low throughout the experiment (177.0±14.2 versus 20.6±14.3 ml/min, p=0.0003). After the C clamp was released, a 42% decrease in hyperemic flow was seen in the aspirin group (188.6±8.9 versus 110.1±27.7 ml/min, p=0.008) compared with a 12% decrease in the antibody 7E3 group (194.3±11.7 versus 181.3±14.9 ml/min, p=0.02).

Coronary Artery Thrombosis

Arterial occlusion, as determined by absence of coronary blood flow, occurred in five of eight control dogs and one of eight aspirin-treated dogs (Figure 4). No dog treated with antibody 7E3 sustained arterial occlusion. Arterial occlusion was confirmed by direct visualization of the occlusive thrombus within the arterial lumen at the conclusion of the experiment. Nonocclusive thrombotic material was seen in the three remaining control dogs and in five of seven aspirin-treated dogs without arterial occlusion. No dog treated with antibody 7E3 had thrombotic material visualized.

Discussion

Arterial injury resulting from percutaneous transluminal coronary angioplasty activates platelets and the coagulation system. Collagen, thrombin, epinephrine, serotonin, ADP, and thromboxane A2 can induce conformational changes on the platelet surface membrane that expose approximately 50,000 GP IIb/IIIa complexes per platelet. This allows adhe-
sive GPs, most notably fibrinogen, to bind to receptors associated with the GP IIb/IIIa complex, cross-linking one platelet to another. Exuberant platelet aggregation can result in thrombus formation and the acute closure syndrome.

Several clinical predictors of acute closure have been identified,2,6,12,32-37 although a consensus opinion regarding many of them has not been reached. Results probably have been influenced by operator experience, case load, case selection, sample size, and whether steerable dilation systems were used. The common pathophysiological stimuli for platelet aggregation appear to be the depth and surface area of arterial dissection,38 wall shear rate,39 and thrombus surface area.40 Platelet activation after experimental balloon injury has previously been evaluated in the pig carotid artery model,38,41 the atherosclerotic rabbit iliac artery model,42 and the dog LAD model.31,43,44 In the present study, we altered our previous technique in the dog model by oversizing the balloon (4 versus 3 mm), increasing the inflation pressure (10 versus 2–5 atm), and increasing shear forces by applying an external stenosis. Thrombus formation was successfully stimulated in all eight control dogs, with five developing acute closure. Aspirin alone decreased platelet aggregation, thrombus formation, and acute closure in this model. In contrast, the 7E3 F(ab’)2 antibody completely prevented ex vivo platelet aggregation and acute in vivo thrombus formation.

Animal models do not fully reproduce the pathophysiological circumstances associated with clinical angioplasty. Elastic, nonatherosclerotic arteries are dilated in the pig and dog models, whereas the soft atherosclerotic lesions in the rabbit iliac artery are composed of foam cells without fibrocytes, calcium deposits, or a lipid pool.45 Therefore, arterial injury in an animal model such as ours is probably not as great as that seen in clinical angioplasty in chronic atherosclerotic human arteries, and the thrombogenic stimulus is probably less.38 Also, morphological situations, including branch points, bend points, lesion eccentricity, and plaque ulceration, that can influence blood flow and platelet deposition cannot

Table 1. Basal Flow

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*Includes one occlusion.
†Includes two occlusions.
‡Includes three occlusions.
§Includes four occlusions.
‖Includes five occlusions.

Table 2. Hyperemic Flow

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</table>

*Includes one occlusion.
†Includes two occlusions.
‡Includes three occlusions.
§Includes four occlusions.
‖Includes five occlusions.
be fully reproduced. Nevertheless, platelet deposition can be readily stimulated in these models, and the application of an external stenosis to decrease hyperemic coronary flow by 50% in this study resulted in an effective model of acute closure. The deep arterial injury secondary to balloon trauma in which endothelial injury from external trauma or direct electrical current was used in association with an external stenosis to stimulate thrombosis. Also, this model is somewhat different from the model of LAD angioplasty used by Anderson and colleagues to evaluate the effect of thromboxane A_2 or serotonin receptor antagonists on cyclic flow variations. In their study, the Folts model was modified by using intravascular balloon trauma rather than external mechanical trauma to disrupt the vascular surface. A tight external stenosis that reduces basal flow is usually required to produce cyclic flow variations. In contrast, the external stenosis used in this model was less severe, reduced hyperemic flow by only 50%, did not result in cyclic flow variations, and may more closely reproduce the clinical situation where critical stenoses are partially relieved after balloon trauma.

Aspirin has previously been shown to decrease but not prevent the acute ischemic complications associated with clinical coronary angioplasty, including acute closure, myocardial infarction, and the need for emergency bypass graft surgery. This experimental model successfully demonstrated the same phenomenon. The importance of adequate heparin dosage to decrease fibrin accumulation and platelet deposition after arterial injury has been recently reemphasized. Heparin was not used in this study, but it was not effective in preventing platelet activation and hyperemic coronary blood flow changes in a similar model.

Pharmacological interventions available to treat acute thrombus formation in the clinical setting include augmenting heparin and administering thrombolytic therapy, but they frequently are inadequate in quickly restoring blood flow. A number of mechanical alternatives to emergency surgery have been developed that can stabilize the artery. Preventing acute closure rather than developing new treatment strategies for it would be more clinically desirable. Although new thrombin antagonists may have use in this situation, platelet-directed therapy seems more reasonable since platelet-rich thrombi have been implicated in causing acute closure. The 7E3 monoclonal antibody appears to be superior to aspirin as an antiplatelet agent. Yasuda et al demonstrated that 7E3 F(ab')_2 prevents thrombosis in a sub–total occlusion model, whereas aspirin does not. Coller et al showed that the ability of 7E3 F(ab')_2 to prevent cyclic flow reductions in the Folts model of acute platelet thrombus formation is not reversed by epinephrine infusion, as occurs after aspirin inhibition. The present study shows that 7E3 F(ab')_2 is superior to aspirin in decreasing ex vivo platelet aggregation and in vivo thrombus formation after balloon arterial injury. Unfortunately, electron microscopy was not performed to confirm that vascular injury was similar in the three groups and to verify that platelet deposition was reduced in animals treated with the antibody.

The 7E3 F(ab')_2 antibody is easy to administer, inhibits platelet aggregation for more than 24 hours, and has not caused serious bleeding in this or previous studies. However, bleeding risk will need to be carefully evaluated in clinical trials in which administration of heparin will probably be used. Results from the present study confirm previous research demonstrating that hemodynamic values and platelet counts are not perturbed by 7E3 F(ab')_2. Immunogenicity is minimal and has been further reduced in subsequent research by using the Fab fragment instead of the F(ab')_2 fragment of the 7E3 immunoglobulin, potentially allowing repeat future administration of murine antibodies in many patients. The ability of 7E3 to prevent acute platelet-mediated thrombosis suggests several possible clinical applications. First, 7E3 could be more successful than aspirin in preventing the acute complications associated with unstable angina pectoris and non-Q wave myocardial infarction. Second, preliminary evidence suggests that 7E3 F(ab')_2 can facilitate thrombolysis and prevent reocclusion, so it could...
prove to be a powerful adjunct to thrombolytic therapy in acute myocardial infarction. Third, the ability to prevent acute thrombotic occlusion might make direct angioplasty or rescue angioplasty more clinically attractive strategies in patients with acute myocardial infarction. Finally, use of 7E3 could decrease the acute ischemic complications associated with high-risk angioplasty, allowing patients currently referred for surgical revascularization to be treated with percutaneous technology and possibly reducing or even obviating the need for surgical standby.

Summary

We developed an animal model that can be used to test new pharmacological strategies to prevent acute closure after coronary angioplasty. The present study suggests that the 7E3 F(ab')2 monoclonal antibody is superior to aspirin in inhibiting ex vivo platelet aggregation and in vivo thrombus formation in this model. Based on encouraging preliminary safety and efficacy trials in animals and humans, multicenter clinical trials have recently been initiated with this agent in treating acute closure after coronary angioplasty (Abrupt Closure Trial) and in preventing reocclusion after thrombolytic therapy with tissue-type plasminogen activator in acute myocardial infarction (Thrombosis in Acute Myocardial Infarction, Phase 8).

Acknowledgments

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Key Words: aspirin • 7E3 monoclonal antibody • acute closure
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