Comparative Antithrombotic Effects of Magnesium Sulfate and the Platelet Glycoprotein IIb/IIIa Inhibitors Tirofiban and Eptifibatide in a Canine Model of Stent Thrombosis

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Background—Antithrombotic effects of glycoprotein IIb/IIIa inhibitors and magnesium are known, but their comparative effects on stent thrombosis are not known. Our objective was to compare the antithrombotic effects of the glycoprotein IIb/IIIa inhibitors tirofiban and eptifibatide with magnesium in an ex vivo canine arteriovenous shunt model of stent thrombosis.

Methods and Results—Control nitinol stents were expanded to 2 mm in diameter in a tubular perfusion chamber interposed in the shunt and exposed to flowing arterial blood at a shear rate of 2100 s⁻¹ for 20 minutes (n=398 perfusion runs in 24 experiments in 8 dogs). The animals were treated intravenously with MgSO₄ (2 g bolus followed by 2 g/h infusion), eptifibatide (double bolus of 180 g/kg 10 minutes apart followed by 2 g/kg per minute), or tirofiban (0.3 μg/kg per minute), with or without heparin (50 U/kg). Effects of the test agents on thrombus weight, platelet aggregation (PA), platelet CD62 expression, bleeding time (BT), heart rate, and mean arterial blood pressure were assessed. Treatment with Mg+heparin reduced stent thrombus weight by 78±10% compared with baseline (19±4 mg, P<0.001). The antithrombotic effect of Mg+heparin was equivalent to that observed with tirofiban+heparin (78±13%) and eptifibatide+heparin (84±11%). Magnesium had no significant effect on PA and BT. Tirofiban and eptifibatide inhibited PA by >90% and prolonged BT up to 20 minutes. None of the test agents had effects on CD62 expression or activated clotting time. There were no significant bleeding or hemodynamic complications.

Conclusion—Magnesium produced a significant reduction in acute stent thrombus formation that was equivalent in magnitude to that produced by clinically relevant doses of tirofiban and eptifibatide. Its potential use in percutaneous coronary intervention requires further study. (Circulation. 2002;105:1970-1975.)

Key Words: platelets • thrombosis • stents

Platelet glycoprotein IIb/IIIa receptor inhibitors (GPIs) are potent antiplatelet agents that have been established to inhibit platelet-dependent thrombus formation in animal models as well as reduce the incidence of adverse thrombotic outcomes after percutaneous coronary intervention in humans. Experimental studies have demonstrated marked antithrombotic effects of intravenous magnesium. Significantly inhibitory effects of oral magnesium treatment on acute platelet-mediated thrombus formation in patients with coronary artery disease have also been established. We recently observed a significant antithrombotic effect of magnesium on acute platelet-dependent stent thrombosis in an ex vivo porcine arteriovenous shunt model of high-shear blood flow. The antithrombotic effects of magnesium were associated with no hemodynamic or bleeding complications, which raised the possibility of magnesium use as a potentially effective antithrombotic strategy in patients undergoing percutaneous coronary intervention.

The objective of this study was to compare the antithrombotic effects of magnesium sulfate (MgSO₄) with those of the small-molecule platelet GPIs tirofiban and eptifibatide in an ex vivo canine arteriovenous shunt model of stent thrombosis. The rationale of this study is based on the proven antithrombotic efficacy and safety of magnesium in this experimental model. Moreover, the potential low risk of bleeding complications together with a significant cost advantage as compared with GPIs makes magnesium an attractive antithrombotic agent for clinical use.

Method

Experimental Model
All procedures were approved by the Institutional Animal Care and Use Committee and conform to the American Heart Association.
Guidelines for Animal Research. Experiments were performed in 8 dogs (Antech, Inc, Barnhart, Mo) weighing 18 to 22 kg. Each dog underwent three experiments with a minimum interval of 2 weeks between studies.

The extracorporeal shunt system utilized in this study has been extensively characterized and described.8–10 Arteriovenous shunts were created between the femoral artery and the femoral vein for the first two sets of experiments and between the carotid artery and the jugular vein for the third set of experiments in each animal. Thrombogenic nitinol stents were expanded on a tapered mandrel to an outer diameter of 2.0 mm, mounted in the Badimon chamber, and perfused with blood for 20 minutes. Blood was circulated through the system at a flow rate of 70 mL/min generating a shear rate of 2100 s⁻¹ at the stent surface. The shear rates were calculated according to the following formula: Shear rate = 4Q/R², where Q is volume flow and R is radius.11 At the end of the perfusion period, saline was circulated through the circuit for several minutes to clear any visible blood before another stent was mounted. At the completion of each perfusion period, the stents (weighed before perfusion) were removed from the chamber, dried, and weighed again. Thrombus weight (TW) was calculated as a difference between pre- and postperfusion stent weights.

Digital images of stents were obtained with a Nikon 950 digital camera, downloaded into a personal computer, and processed with image-analysis software (PhotoShop Adobe 5.0).

A total of 24 experiments were performed in 8 dogs with an average of 17 stent perfusion runs per experiment. Therefore, the total number of stent perfusion runs was 398. A total of 63 stents were used for these 398 perfusion runs. Each stent was cleaned meticulously at the end of each experiment with BTS-450 solution (Beckman Instruments, Inc) and reused ~6 to 7 times.

The experiment protocol is summarized in Figure 1. In each animal, 3 to 4 stents were perfused before administration of any drug to obtain control TW. The animals were treated randomly with intravenous magnesium sulfate, tirofiban, or eptifibatide with or without heparin. Heparin was administered as 50 U/kg IV bolus followed by 25 to 50 U/kg per hour IV to keep activated clotting time (ACT) between 150 and 200 seconds, and perfusion studies were performed 20 to 30 minutes after administration of heparin. Magnesium sulfate was administered as 2-g bolus for 20 minutes followed by 2-g/h infusion (Figure 1A). This was determined to be the optimal dose based on a previous study.10 To assess a potential time-dependent antithrombotic effect of magnesium, perfusion studies were performed within 20 minutes after MgSO₄ bolus (Mg-Early) and 20 minutes after MgSO₄ bolus (Mg-Late). Tirofiban was administered as an intravenous infusion of 0.3 µg/kg per minute, and perfusion studies were performed ~140 minutes after administration of the drug (Figure 1B). Eptifibatide was administered intravenously as a double bolus of 180 µg/kg 10 minutes apart followed by 2 µg/kg per minute infusion, and perfusion studies were performed ~90 minutes after starting infusion (Figure 1C). The time interval and the dose of the GPIs were chosen on the basis of >85% inhibition of platelet aggregation in our experiments.

TW was measured after each stent perfusion. Whole-blood platelet aggregation, platelet CD62 expression, ACT, and bleeding time were assessed before and after treatment. ACT was also measured hourly after heparin was started. Serum magnesium level was assessed before treatment, at the end of MgSO₄ bolus, and after completing MgSO₄ infusion. Complete blood count was quantified at the beginning and end of each experiment. Mean arterial blood pressure (MABP) and heart rate were monitored and recorded throughout the protocol.

Platelet Studies

Platelet Aggregation Assay

Thirty minutes after administration of the drug, 3 mL venous blood was collected in a siliconized test tube containing 0.3 mL of 0.129-mol/L sodium citrate (Becton Dickinson Vacutainer System). Whole-blood aggregometry (Chronolog Corp) was used to measure 5 µg/mL collagen-induced platelet aggregation.8–10 Aggregation was expressed as maximal increase in electrical impedance measured in ohms at 8 minutes after the addition of collagen.

Platelet CD62 Expression Flow Cytometry

Aliquots of control and treated venous blood were collected in 0.3 mL 0.129 mol/L sodium citrate solution and incubated with saturating concentrations of fluorescein isothiocyanate–conjugated CD61 and phycoerythrin-conjugated CD62 (Becton Dickinson) monoclonal antibodies for 20 minutes. Specimens were fixed with 1% formaldehyde and analyzed in a FACScan flow cytometer (Becton Dickinson Immunocytometry Systems) as per a previously described protocol.12 CD62 expression was measured at baseline and after activation with thrombin (0.5 µmol/L). Thrombin was chosen as the platelet agonist because ADP did not consistently activate canine platelets.

Bleeding Time, ACT, and Serum Magnesium Assay

Bleeding time was measured from an incision on the ventral surface of the thigh with a No. 11 surgical knife. The time between incision and cessation of bleeding was recorded as bleeding time. ACT measurements were performed with a Hemocheck 400 (International Technidyne Corp) machine in standard fashion.9,10 Serum magnesium was measured spectrophotometrically using the magon dye method.13

Statistical Analysis

Data are presented as mean±SD. The statistical difference between means was determined by one-way ANOVA. If means were shown to be significantly different, multiple comparisons by pairs were performed by the Bonferroni test (GraphPad Prism version 3.0). A value of P<0.05 was considered significant.

Results

Stent Thrombosis

Effect of Magnesium

In the first set of experiments, effects of magnesium on stent thrombosis were examined with and without heparin administration, and the results are shown in Figure 2A. Pretreatment stent TW (20±4 mg) was reduced by 30±10% (14±4 mg), 56±16% (9±3 mg), and 44±22% (11±5 mg) in the Mg-Early–alone, Mg-Late–alone, and heparin-alone groups, respectively (all P<0.001 versus before treatment). The anti-thrombotic effects of combined treatment with heparin+Mg-Early (62±19%, 7±3 mg) and heparin+Mg-Late (78±9%,...
4±2 mg) were significantly more pronounced compared with Mg alone. Thrombus reduction in the heparin+Mg-Late group was significantly greater than in the heparin+Mg-Early group (P<0.001, ANOVA). Thus, for comparison studies with GPs, only the heparin+Mg-Late treatment group was used.

To exclude the possibility that prolonged anesthesia and repetitive instrumentation may have effects on stent thrombosis, new stents were placed in the extravascular circuit and perfused 3 hours after stopping infusion of MgSO4 to ensure return of stent TWs toward baseline pretreatment values. The stent TW averaged 19±3 mg at the beginning of the experiment and 18±2 mg at the end of the experiment (n=12 stents in 4 experiments). One typical example is shown in Figure 2B.

**Comparative Effects of Magnesium, Tirofiban, and Eptifibatide**

Representative photographs of the antithrombotic effects of combined treatment with heparin+Mg-Late, tirofiban, or eptifibatide are shown in Figure 3 and data quantified in Figure 4.

Control TWs obtained before any drug treatment did not differ significantly among the different treatment groups. Stent TW was reduced by 78±10% in the heparin+Mg-Late group (from 20±3 to 4±2 mg), 78±13% in the tirofiban-treated group (from 19±3 to 4±2 mg), and 84±11% in the eptifibatide-treated group (from 19±3 to 2±3 mg) (all P<0.001 versus before treatment). A significantly greater reduction in TW was observed in the Mg+heparin group compared with Mg alone (78±10 versus 56±16%, P<0.001). Tirofiban+heparin treatment also produced a slightly greater, but statistically significant, reduction in stent TW compared with tirofiban alone (78±13 versus 69±11%, P<0.05). However, combined treatment of heparin with eptifibatide had no incremental effects on stent thrombosis compared with eptifibatide alone (84±11 versus 81±9, P=NS).

**Platelet and Hematologic Studies**

The effects of study drugs on ACT, bleeding time, collagen-induced platelet aggregation, and thrombin-stimulated platelet CD62 expression are shown in Table 1. Heparin significantly prolonged ACT and also produced a slight, but statistically significant, increase in bleeding time. None of the agents had any effect on ACT over and beyond heparin. Bleeding time was not significantly affected by magnesium, but was prolonged by both tirofiban (from 4.7±0.9 at baseline to 19.7±1.8 minutes) and eptifibatide (from 4.3±0.7 to 20±1.2 minutes) (both P<0.001).

Magnesium had no significant effects on platelet aggregation. Both tirofiban and eptifibatide produced >90% inhibition in platelet aggregation responses. None of the agents had any effect on platelet CD62 expression. Furthermore, no
significant effects on either platelet or white blood cell counts or hematocrit were observed with any of the treatment agents (Table 2). There were no serious bleeding complications encountered in any of the dogs.

Heart Rate and Blood Pressure
Magnesium produced negligible effects on heart rate (101±16 bpm at baseline versus 93±15 bpm during MgSO₄ infusion, P=NS) and MABP (93±9 mm Hg at baseline versus 89±9 mm Hg during MgSO₄ infusion, P=NS). Neither of the GPIs had any effects on heart rate or MABP (data not shown).

Table 1. Effects on ACT, Bleeding Time, Platelet Aggregation, and Platelet Activation (CD62 Positivity)

<table>
<thead>
<tr>
<th></th>
<th>Before Treatment</th>
<th>After Treatment</th>
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</thead>
<tbody>
<tr>
<td>ACT, s</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heparin alone</td>
<td>113±6</td>
<td>164±28*</td>
</tr>
<tr>
<td>Heparin + Mg-Late</td>
<td>111±8</td>
<td>161±12*</td>
</tr>
<tr>
<td>Heparin + tirofiban</td>
<td>112±12</td>
<td>168±17*</td>
</tr>
<tr>
<td>Heparin + eptifibatide</td>
<td>114±4</td>
<td>168±19*</td>
</tr>
<tr>
<td>Bleeding time, min</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heparin alone</td>
<td>4.6±0.7</td>
<td>6.4±1.7*</td>
</tr>
<tr>
<td>Heparin + Mg-Late</td>
<td>4.3±0.6</td>
<td>6.0±0.3*</td>
</tr>
<tr>
<td>Heparin + tirofiban</td>
<td>4.7±0.9</td>
<td>19.7±1.8*†</td>
</tr>
<tr>
<td>Heparin + eptifibatide</td>
<td>4.3±0.7</td>
<td>20.1±2.4*†</td>
</tr>
<tr>
<td>Platelet aggregation, ohmmax</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heparin alone</td>
<td>23±5</td>
<td>20±7</td>
</tr>
<tr>
<td>Heparin + Mg-Late</td>
<td>21±7</td>
<td>16±6</td>
</tr>
<tr>
<td>Heparin + tirofiban</td>
<td>22±3</td>
<td>2±2*†</td>
</tr>
<tr>
<td>Heparin + eptifibatide</td>
<td>22±3</td>
<td>2±2*†</td>
</tr>
<tr>
<td>CD62 positive platelet, %</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heparin alone</td>
<td>28±12</td>
<td>34±15</td>
</tr>
<tr>
<td>Heparin + Mg-Late</td>
<td>32±12</td>
<td>35±14</td>
</tr>
<tr>
<td>Heparin + tirofiban</td>
<td>27±9</td>
<td>31±16</td>
</tr>
<tr>
<td>Heparin + eptifibatide</td>
<td>32±13</td>
<td>32±6</td>
</tr>
</tbody>
</table>

Values are mean±SD; n=5 to 8 observations in each group. ohmmax indicates maximum increase in impedance at 8 minutes after the addition of collagen (5 mg/mL).

Discussion
Utilizing a canine arteriovenous shunt model of high-shear blood flow, we have successfully demonstrated that MgSO₄ produces a significant inhibition of acute platelet-dependent stent thrombosis. The inhibitory effect of magnesium was equivalent in magnitude to that produced by clinically relevant doses of potent antithrombotic agents such as tirofiban and eptifibatide. However, unlike tirofiban and eptifibatide, the effect of magnesium on platelet-thrombus formation was evident without any significant effect on platelet aggregation or bleeding time. No significant hemodynamic complications were observed with magnesium. The antithrombotic effects of magnesium have been described previously by us and by several other investigators. However, this is the first study that has compared the effects of MgSO₄ with the GPIs tirofiban and eptifibatide on acute platelet-dependent stent thrombosis. Thus, magnesium may be an effective agent for preventing stent thrombosis.

Comparative Effects of Magnesium, Tirofiban, and Eptifibatide
The exact mechanism by which magnesium influences stent thrombus formation in this model is not clear. Potential mechanisms include effects on platelets, coagulation, and fibrinolysis. Consistent with the dominant role of platelets in this in vivo model of high-shear-mediated acute thrombogenesis, antiplatelet effects of magnesium are likely to contribute significantly to its antithrombotic properties. Previous studies have demonstrated that magnesium may suppress platelet function by affecting platelet activation, adhesion, or aggregation. In a similar experimental model in swine, we have recently shown that treatment with intravenous MgSO₄ produced marked inhibition of acute stent thrombosis without significant effect on platelet aggregation or bleeding time. In the present study, we observed the same finding and also...
TABLE 2. Effects on Hematologic Parameters

<table>
<thead>
<tr>
<th></th>
<th>WBC Count, ×10^3/mL</th>
<th>Hematocrit, %</th>
<th>Platelet Count, ×10^3/mL</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Before Treatment</td>
<td>After Treatment</td>
<td>Before Treatment</td>
</tr>
<tr>
<td>MgSO&lt;sub&gt;4&lt;/sub&gt;</td>
<td>6.1 ± 1.9</td>
<td>7.9 ± 2.5</td>
<td>36 ± 3</td>
</tr>
<tr>
<td>Tirofiban</td>
<td>7.7 ± 2.7</td>
<td>8.6 ± 1.7</td>
<td>34 ± 4</td>
</tr>
<tr>
<td>Eptifibatide</td>
<td>6.2 ± 1.9</td>
<td>7.7 ± 3.0</td>
<td>34 ± 5</td>
</tr>
</tbody>
</table>

Values are mean ± SD; n=7 to 9 for each variable. WBC indicates white blood cell.

P<sub>0.05</sub> not significant (ANOVA).

demonstrated that magnesium had no effect on thrombin-stimulated platelet activation.

This observation of a discrepancy between the profound effect of magnesium on platelet-thrombus formation and lack of a significant effect on platelet aggregation, activation, or bleeding time is not inconsistent with previous findings reported in different experimental models. The discrepant effect on platelet aggregation and platelet adhesion/thrombus formation may be likely related to the fact that the antiaggregatory effect of magnesium occurs at higher concentration (>5 mEq/L) compared with the antiadhesive effect. The serum magnesium levels achieved in this study were in the range where the antiaggregatory effects are less likely to be evident compared with the antiadhesive effects. Therefore, suppression of platelet adhesion is most likely to contribute to the inhibitory effects of magnesium on platelet-dependent stent thrombosis.

Consistent with their mechanism of action, the inhibitory effects of tirofiban and eptifibatide on stent thrombosis were associated with >90% suppression of platelet aggregation and significant prolongation of bleeding time. As expected, GPIs had no effect on platelet activation (CD62P expression). We have previously demonstrated in the same experimental model of stent thrombosis as used in this study that m7E3, a murine antibody that blocks the platelet glycoprotein IIb/IIIa receptor, produces profound antiplatelet effects when given before thrombus formation. The magnitude of the TW reduction produced by tirofiban, eptifibatide, and magnesium in the present study is comparable with that produced by murine 7E3 in the previous study. The known reduced affinity of chimeric 7E3 (clinically used abciximab) for canine platelets precluded its comparison with magnesium in our study. The murine 7E3, which is effective in canine and other animals, was not available to us for evaluation in the current experiments.

Time Dependency of Antithrombotic Effect of Magnesium

The antithrombotic effects of magnesium were significantly more pronounced when it was given 40 minutes before initiation of stent perfusion. This time dependency of the effect of magnesium has also been previously observed in a porcine arteriovenous shunt model of stent thrombosis and in experimental models of ischemia/reperfusion myocardial injury in a canine model and thrombosis in rats. Thus, platelet-thrombus formation is more easily inhibited when platelets are treated before exposure to thrombogenic stimuli. The importance of the timing of magnesium administration may also explain, in part, the negative results in ISIS-4, in which magnesium infusion was delayed, as compared with the positive results in LIMIT-2, in which treatment was initiated earlier. Knowledge of this time dependency may be important and should be implemented in the study design of future trials.

Incremental Effects of Heparin

Treatment with magnesium alone produced only modest inhibition of stent thrombus formation. The antithrombotic effects of combined treatment with heparin and magnesium were significantly more pronounced compared with magnesium alone (78±9% versus 56±16%). The mechanism of this interactive effect of combined treatment with heparin and magnesium on thrombus formation is not clear. It is possible that at high shear rates, comparable with those in the ex vivo model, plasma von Willebrand factor (vWF) is required for adhesion of platelets to the roughened surface of the stents as well as to subendothelium, perhaps as a bridge between platelets and thrombogenic surface. Heparin may supplement a moderate antiadhesive effect of magnesium by inhibiting vWF-dependent platelet function and vWF-platelet binding.

The addition of heparin to tirofiban produced a modest, but statistically significant, increase in antithrombotic effects compared with tirofiban alone. In contrast, heparin did not appear to produce an incremental effect on TW reduction when combined with eptifibatide. Given the near-complete blockade of platelet aggregation with tirofiban and eptifibatide, the lack of any significant incremental effects of the combined use with heparin (which likely has only a modest antiadhesive effect) is not completely unexpected. These observations are consistent with the lack of a consistent benefit of combination therapy with heparin and GPI over GPI monotherapy alone as demonstrated in previous clinical trials with lamifiban in PARAGON, with tirofiban in PRISM-Plus (in which combined treatment with tirofiban plus heparin produced greater clinical benefits compared with tirofiban alone at 7 days but not at 6-month follow-up), and with eptifibatide in the PURSUIT trial. The findings of reduced stent thrombosis by heparin in the present study are in contrast to our previous observations of the thrombotic process being resistant to heparin. This discrepancy may be likely related to a tendency for platelet inhibition associated with heparin in the current study as reflected by a nonsignificant inhibition of platelet aggregation and a slight but significant prolongation of bleeding time. Unlike the findings in the present study, platelet aggregation...
and bleeding time were not affected by heparin in the previous study. In addition, the small sample size (5 perfusion studies in the previous study versus 12 perfusion studies in the current study) might also contribute to the discrepancy. These findings of a modest antithrombotic effect of heparin in canine are also consistent with our recently published observations in a swine model.

The total amount of blood flow per stent perfusion run was 1400 mL (70 mL/min×20 minutes) thereby implying recycling of blood through the stent surface during each experiment. However, neither blood cell counts (white blood cells, red blood cells, and platelets) nor hemoglobin/hematocrit levels were significantly affected at the end of one or several perfusion runs, indicating similar hemorrhoiological conditions throughout each experiment. Furthermore, the return of end-of-experiment TW toward pretreatment baseline weight at the beginning of the experiment (as shown in Figure 2B) suggests no significant impact of recycling on thrombogenesis in this model.

Limitations
The ex vivo model used in our study, which primarily examines shear-mediated, platelet-dependent thrombus formation, does not allow us to explore the effect of magnesium, tirofiban, and eptifibatide on coagulation and pro- and anti-fibrinolytic factors that may modulate thrombogenesis in vivo conditions. Nonetheless, this validated model is useful to study interaction of blood elements with stents and thrombogenic surfaces under controlled and well-defined conditions. The reproducibility and simplicity of this ex vivo system makes it a sensitive tool to assess preclinical efficacy of antithrombotic therapeutic interventions. We have used the shunt model to demonstrate superior efficacy of potent antiplatelet agents such as abciximab and clopidogrel for the prevention of stent thrombosis well before there was any clinical evidence for this indication. Utilizing this arteriovenous shunt model, we have successfully demonstrated the antithrombotic effect of magnesium in swine. Despite our assessment of several parameters of platelet function (aggregation, CD62 flow cytometry, and bleeding time), the exact mechanism of action remains elusive. We speculate that the most likely mechanism may reflect an antiadhesive effect as described previously by other investigators using an appropriate adhesion assay.

Conclusions and Implications
In summary, intravenous treatment with magnesium produced a time-dependent inhibition of acute stent thrombosis under high-shear flow conditions, which was equivalent in magnitude to that produced by clinically relevant doses of tirofiban or eptifibatide. The antithrombotic effects of magnesium were evident without any hemostatic or significant hemodynamic complications. The potent antithrombotic effects of magnesium together with its safety, ease of administration, and low cost make it a potentially promising adjuvant treatment during percutaneous coronary intervention.

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References
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