

Eptifibatide/PERIGREE

McDONALD  
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DIVISION OF CARDIO RENAL DRUG PRODUCTS  
Review of Study Report (PERIGEE)

NDA# 20,718

Drug Identifier: Integrilin™ (eptifibatide) injection

Sponsor: COR Therapeutics, Inc.

Medical reviewer: Maryann Gordon, M.D.

Date: December 17, 1997

**Subject:** Review of report for protocol 94-016A entitled "A randomized, double blind evaluation of the effects of integrilin versus placebo on *ex vivo* platelet aggregation and GP IIb/IIIa receptor occupancy in patients with unstable angina or non-Q wave myocardial infarction (PERIGEE): a substudy within the main study 94-016 (PURSUIT)." Only pharmacokinetic and pharmacodynamic data were presented in the study report. All data, figures and tables are from vol 2.37.

**Protocol Issue date:** April 29, 1996

**Amendments:** none

**Introduction:** PERIGEE, a pharmacokinetic/pharmacodynamic substudy, was to determine the effects of 2 doses of integrilin and placebo on platelet aggregation (IC<sub>50</sub>) by

-comparing 2 anticoagulants: sodium citrate and D-Phenylalanyl-L-prolyl-L-arginine chloromethy ketone (PPACK). The currently accepted method, sodium citrate, is thought to underestimate the IC<sub>50</sub> because of its calcium chelator properties. PPACK, the new anticoagulant being tested, inhibits thrombin without altering free calcium concentrations;

-using Thrombin Receptor Agonist Peptide (TRAP, also known as SFLLRN-NH<sub>2</sub>) as well as ADP;

-using the Ligand-Induced Binding Site (LIBS) assay to obtain an estimation of GP IIb/IIIa receptor occupancy by Integrilin.

This review does not discuss the PURSUIT study results.

PERIGEE

The study objectives were

- 1) to determine the dose- and concentration-response curves of 2 doses of integrilin vs placebo for *ex vivo* platelet aggregation and platelet GP IIb/IIIa receptor occupancy in patients with unstable angina/non Q wave myocardial infarction (NQMI);
- 2) to determine the fraction of patients achieving  $\geq 80\%$  inhibition of *ex vivo* platelet aggregation and  $\geq 80\%$  GP IIb/IIIa receptor occupancy in the setting of unstable angina/NQMI;
- 3) to compare the effects of 2 different anticoagulants (sodium citrate and PPACK), on the *ex vivo* pharmacodynamics of Integrilin;
- 4) to compare the effects of integrilin on *ex vivo* platelet aggregation induced by ADP or TRAP;
- 5) to determine the pharmacokinetics of Integrilin in patients with unstable angina/NQMI;

6) to determine the IC50 and IC80 for Integrilin in the setting of unstable angina/NQMI in comparison with historical controls obtained in patients with coronary heart disease undergoing coronary angioplasty.

The patient population was derived from those enrolled in the PURSUIT study (patients presenting with acute coronary syndrome of unstable angina/probable NQMI). All patients who were eligible for PURSUIT were also eligible for PERIGEE. For complete inclusion/exclusion criteria, see PURSUIT protocol.

The substudy design was multicenter (14 centers were used although 20 were planned), randomized, and placebo controlled. The total sample size was originally set at 150 but only 99 subjects were actually studied.

The 3 dosing arms were

- initial bolus and infusion placebo,
- initial bolus 180 ug/kg and infusion 1.3 ug/kg•min
- initial bolus 180 ug/kg and infusion 2.0 ug/kg•min

The duration of infusion was 72 hours. The lower dose of integrilin was discontinued after 2397 patients were enrolled into PURSUIT.

The pharmacokinetic profile of integrilin was to be determined by a total of 9 blood samples collected per patient. Samples were to be drawn prior to start of bolus of study drug and then at 5 minutes, and 1, 4, 24, 48, and 72 hours after drug administration. Specimens were assayed for

- Integrilin concentrations,
- ex vivo platelet aggregation and
- GP IIb/IIIa receptor occupancy.

Blood samples for the pharmacodynamic parameters, ADP- and TRAP-induced *ex vivo* platelet aggregation and *ex vivo* GP IIb/IIIa receptor occupancy, were drawn prior to start of bolus of study drug and then at 5 minutes, and 1, 4, 24, 48, and 72 hours after drug administration as well as at hours 4 and 8 after discontinuation of the infusion.

The blind was maintained by assigning a special code to each patient used for the purposes of this substudy.

## RESULTS

**Study patients:** Of the 99 patients enrolled into PERIGREE, 50 received placebo, 1 received low dose (dose was prematurely terminated, see above), and 48 received high dose integrilin.

### Pharmacokinetics

Discarded data points: data showing integrilin concentrations 3 times higher than the theoretical concentration at steady state (C<sub>ss</sub>) –2 data points– and post infusion timepoints for patients who did not received the complete 72 hour infusion –6 data points–were not utilized in the modeling of the pooled data. In addition, only 42 of the 48 patients who received the high dose had concentrations of integrilin above the lower limit of quantification (43.5 ng/ml). Data from the 1 patient who received the lower dose was not used in the PK analysis.

Not all patients had PK values at all time points. Therefore, concentration-time data from all subjects were analyzed using a population PK approach. The table below shows the estimated PK parameters for integrilin. Metabolites were not assayed.

PK parameters

Parameter (units)	Integrilin high dose
	Estimate (standard error)
C <sub>ss</sub> (ng/ml)	2201 (^)
AUC <sub>0-∞</sub> (ng•hr/ml)	161768 (^)
t <sub>1/2</sub> alpha (hr)	0.267 (0.166)
CL (ml/min•kg)	0.909 (^)
V <sub>dss</sub> (l/kg)	0.185 (^)

^Not calculated

Figure 1 shows the concentration-time profile for integrilin.

The report states that C<sub>ss</sub> of integrilin for this study was higher than that obtained in normal volunteer studies.

Pharmacodynamics

The percent of study patients achieving ≥ 80% inhibition of platelet aggregation was measured at various time points using both ADP- and TRAP-induced *ex vivo* platelet aggregation methods and PPACK as the anticoagulant. The results are shown in the table below for the high dose integrilin group only; the results for the placebo group were 0 at all time points.

Number and (percent) of patients+

Time relative to start of infusion/no. of patients	ADP agonist	TRAP agonist
5 min/29	24 (83)	2 (7)
1 hr/25	12 (48)	1 (4)
4 hr/13	7 (54)	0
24 hr/32	27 (84)	4 (13)
48 hr/16	16 (100)	3 (18)
72 hr/5	5 (100)	0

+A total of 48 patients received the high dose.

Table 4

The results from the ADP-induced aggregation showed that while 83% of patients achieved ≥ 80% inhibition of platelet aggregation during the bolus, this percent was not maintained at hours 1 and 4 of the constant infusion. By 24 hours of the infusion, all patients with data had achieved the target inhibition of platelet aggregation and this was maintained through 48 and 72 hours (only 5 patients had data at 72 hours). Figure 2 displays these findings.

The concentration-response relationship (measured as *ex vivo* platelet aggregation) using ADP as the agonist and PPACK as the anticoagulant is shown in Figure 3. Similarly shaped curves are obtained when TRAP is used. However, the IC<sub>50</sub> and IC<sub>80</sub> are different. These are shown

below.

Derived IC (95% limits)

parameter	ADP induced platelet aggregation		TRAP induced platelet aggregation	
	PPACK	Na citrate	PPACK	Na citrate
Total observations/n	143/35	43/31	144/35	42/30
IC50 ng/ml	557 (450, 659)	431 (323, 546)	1038 (852, 1234)	635 (426, 824)
IC80 ng/ml	1107 (946, 1264)	785 (587, 1060)	3848 (3014, >5000)	2147 (1579, 3174)

The TRAP-induced aggregation showed a much lower percent of patients who achieved  $\geq 80\%$  inhibition of platelet aggregation at all time points. This is shown in Figure 4.

The percent of patients achieving  $\geq 80\%$  inhibition of platelet aggregation (ADP as the agonist) at 24 hours of infusion was 84% with the use of PPACK as the anticoagulant and 100% with sodium citrate as the anticoagulant. This is shown in Figure 5.

The fraction of patients showing  $\geq 80\%$  GP IIb/IIIa receptor occupancy with PPACK as the anticoagulant is shown in Figure 6. Using different anticoagulants affected the results: at 24 hours of infusion the percent occupancy was 67% with PPACK compared to 91% with sodium citrate.

There was a decline in the mean ADP induced platelet aggregation and receptor occupancy within 4 to 8 hours after the infusion was discontinued but the numbers of patients with data are small.

In summary,

- the  $C_{ss}$  is reported to be higher in patients than in normal volunteers
- the results of platelet aggregation and occupancy rates are dependent upon the agonist and anticoagulant used. All results, however, were in approximately the same range;
- there is a concentration-effect relationship for both platelet aggregation and receptor occupancy,
- there is a decline in the fraction of patients with  $\geq 80\%$  platelet GP IIb/IIIa receptor occupancy and in the fraction of patients with  $\geq 80\%$  inhibition of platelet aggregation at 1 and 4 hours post bolus and the start of the infusion. This may have implications regarding efficacy.

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**Figure 1.** Eptifibatide Plasma Concentration-Time Profile in Patients with Unstable Angina or NQMI After Administration of INTEGRILIN™ 180 µg/kg IV Bolus Immediately Followed by a Continuous 2.0 µg/kg·min IV Infusion for 72 Hours (Protocol 94-016A).

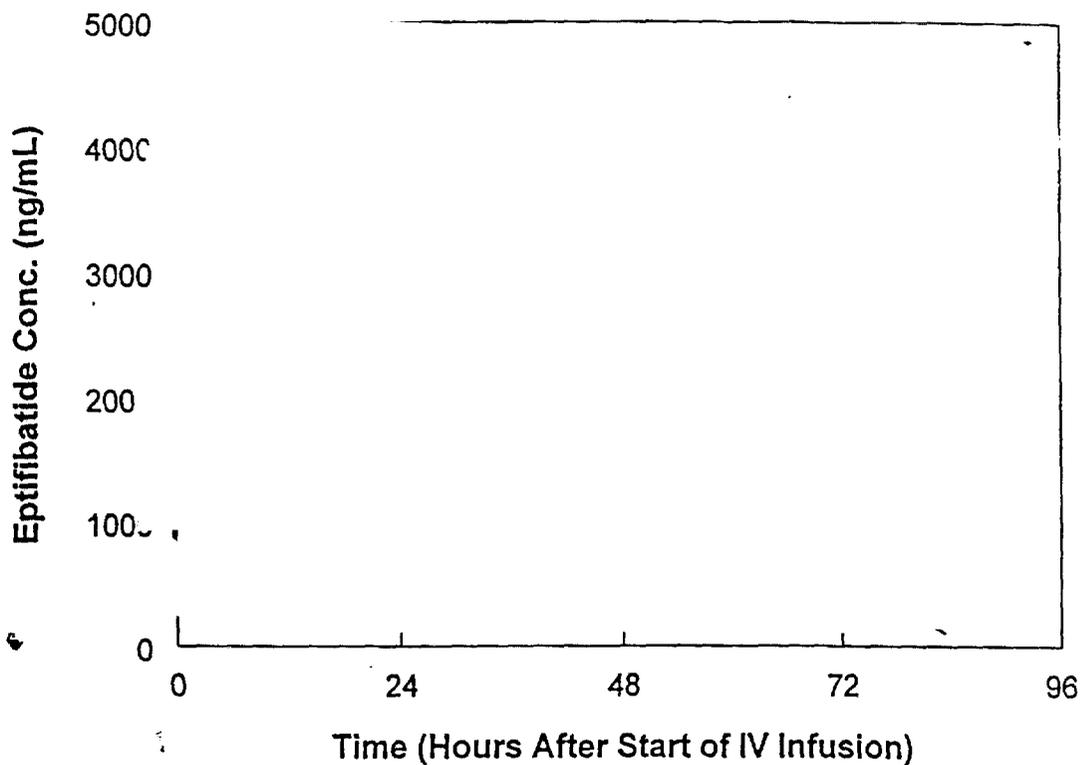
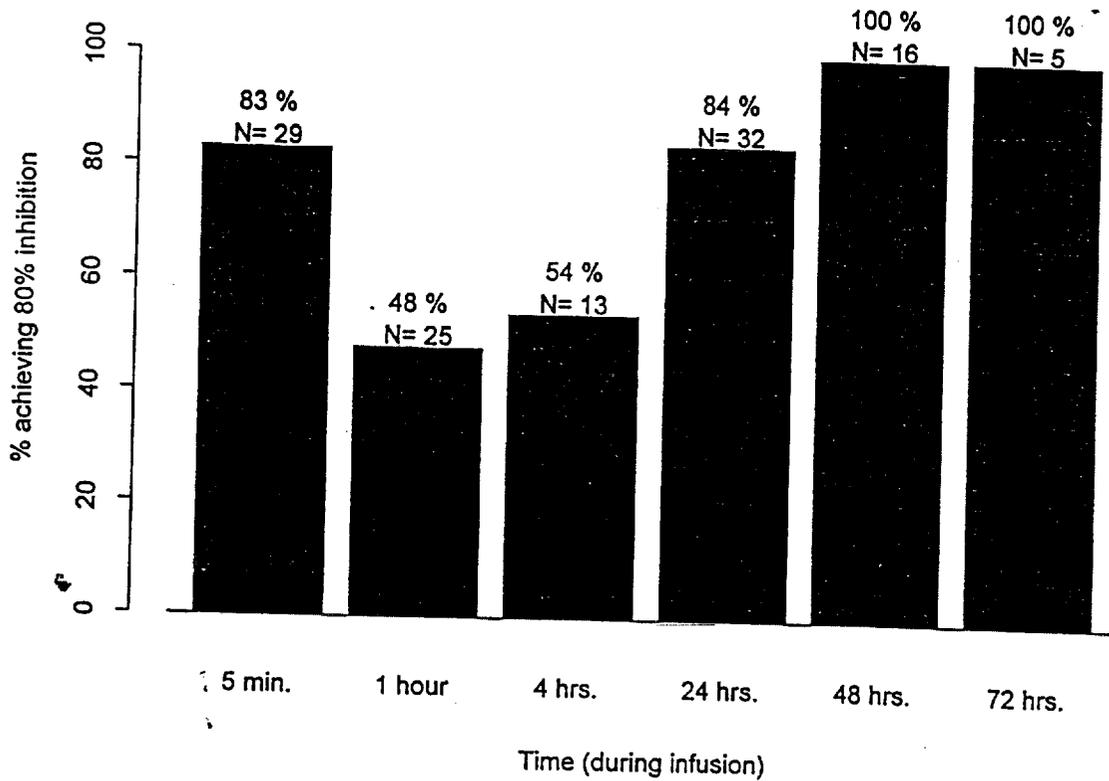


Figure 2  
A.

Fraction of Patients with Unstable Angina or NQMI Which Achieved at Least 80% Inhibition of *Ex Vivo* Platelet Aggregation (Using PPACK-Collected Blood/ADP Agonist) After Administration of INTEGRILIN™ 180 µg/kg IV Bolus Immediately Followed by a Continuous 2.0 µg/kg·min IV Infusion for 72 Hours (Protocol 94-016A).



<sup>3</sup>  
**Figure 10.** Eptifibatide Plasma Concentration-Platelet Aggregation Response Relationship (Using PPACK-Collected Blood/ADP Agonist) in Patients with Unstable Angina or NQMI After Administration of INTEGRILIN™ 180 µg/kg IV Bolus Immediately Followed by a Continuous 2.0 µg/kg•min IV Infusion for 72 Hours (Protocol 94-016A).

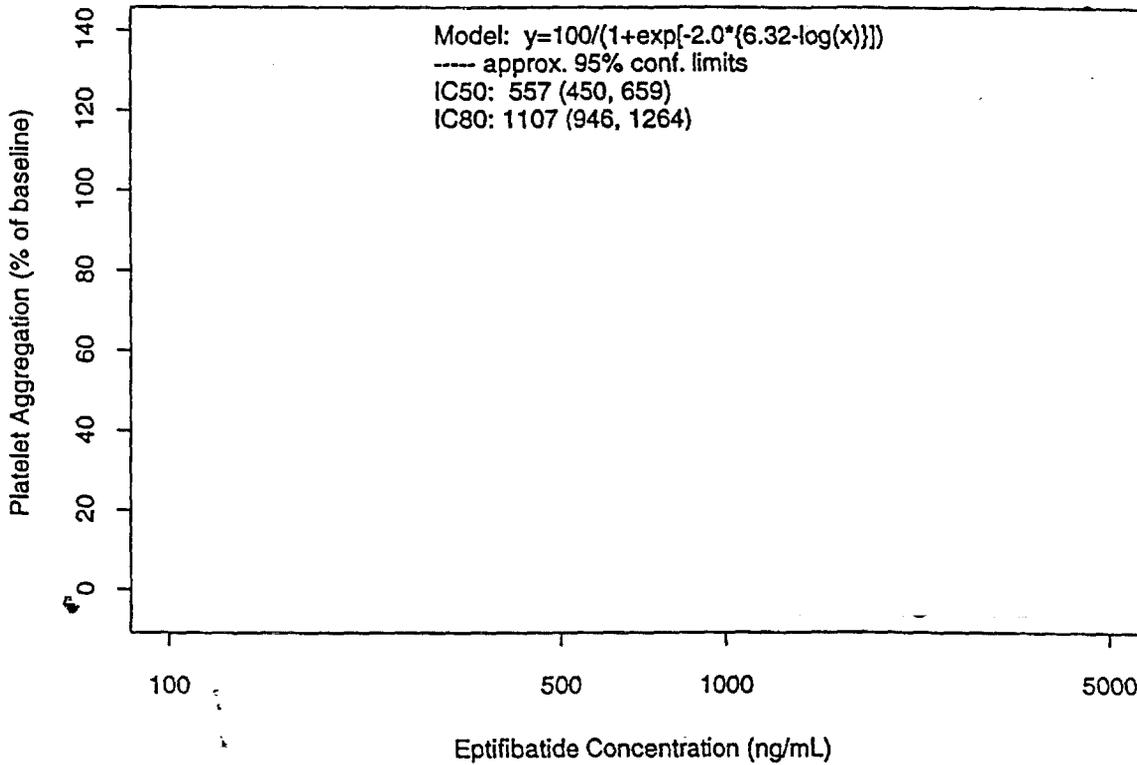


Figure 5. Fraction of Patients with Unstable Angina or NQMI Which Achieved at Least 80% Inhibition of *Ex Vivo* Platelet Aggregation (Using PPACK-Collected Blood/TRAP Agonist) After Administration of INTEGRILIN™ 180 µg/kg IV Bolus Immediately Followed by a Continuous 2.0 µg/kg·min IV Infusion for 72 Hours (Protocol 94-016A).

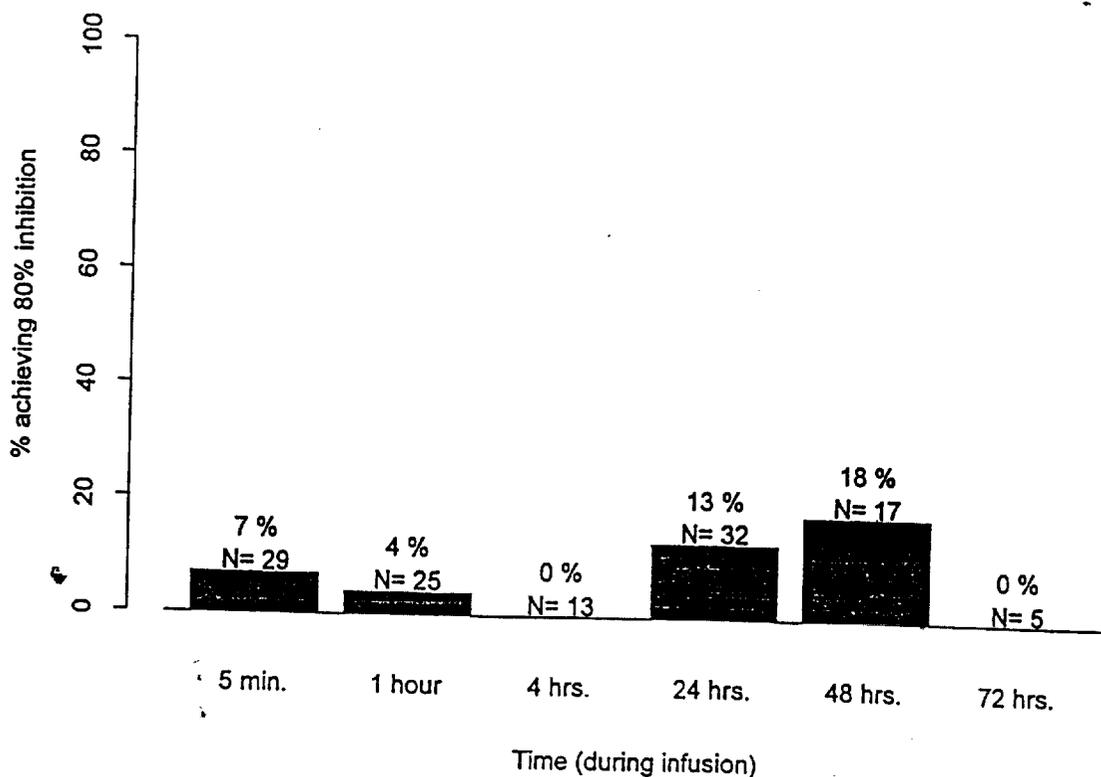


Figure 7. Fraction of Patients with Unstable Angina or NQMI Which Achieved at Least 80% Inhibition of *Ex Vivo* Platelet Aggregation at 24 Hours After Administration of INTEGRILIN™ 180 µg/kg IV Bolus Immediately Followed by a Continuous 2.0 µg/kg·min IV Infusion (Protocol 94-016A).

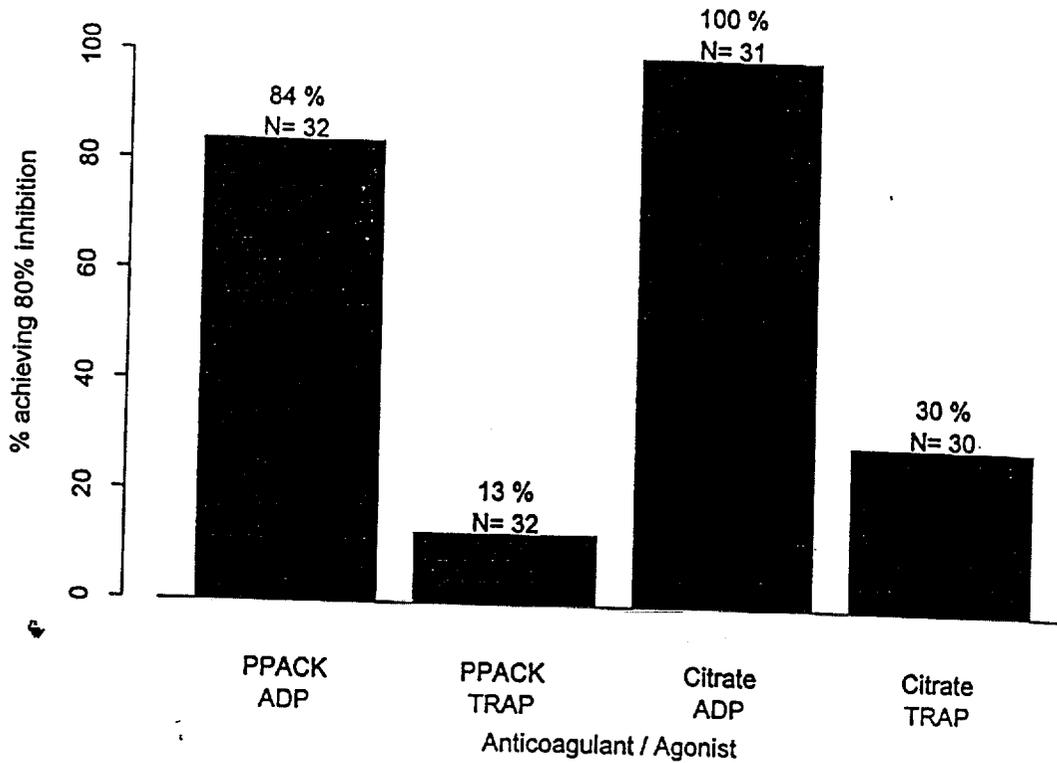


Figure 8.

Fraction of Patients with Unstable Angina or NQMI Which Achieved at Least 80% Platelet GP IIb/IIIa Receptor Occupancy (Using PPACK-Collected Blood) After Administration of INTEGRILIN™ 180 µg/kg IV Bolus Immediately Followed by a Continuous 2.0 µg/kg·min IV Infusion (Protocol 94-016A).

