## ESMOLOL SVT STUDIES

Numbers of Patients Experiencing an Adverse Reaction by Body System/Organ Class and Preferred Term

| | 8052-81-04 | | 8052-81-05 | | 8052-82-06 | 8052-82-07 | 8052-83-23 | 8052-83-31 | All Studies Combined | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | Esmolol | Propranolol | Esmolol | Placebo | Esmolol | Esmolol | Esmolol | Esmolol | Esmolol | Placebo | Propranolol |
| Total Number of Patients | 64 | 63 | 68* | 44** | 2 | 12 | 160 | 77 | 383 | 44 | 63 |
| CENTRAL NERVOUS SYSTEM | | | | | | | | | | | |
| Agitation | 0 | 0 | 0 | 0 | 0 | 0 | 7 | 0 | 7 | 0 | 0 |
| Anorexia | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 1 | 0 | 0 |
| Anxiety | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 1 | 0 | 0 |
| Asthenia | 0 | 0 | 0 | 0 | 0 | 0 | 2 | 0 | 2 | 0 | 0 |
| Confusion | 0 | 0 | 0 | 0 | 0 | 0 | 5 | 3 | 8 | 0 | 0 |
| Depression | 0 | 0 | 0 | 0 | 0 | 0 | 2 | 0 | 2 | 0 | 0 |
| Dizziness | 1 | 0 | 1 | 1 | 0 | 1 | 6 | 4 | 13 | 1 | 0 |
| Drowsiness | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 1 | 0 | 0 |
| Fatigue | 0 | 0 | 0 | 0 | 0 | 1 | 3 | 1 | 5 | 0 | 0 |
| Generalized Convulsion | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 1 | 0 | 0 |
| Headache | 0 | 1 | 0 | 1 | 0 | 0 | 6 | 4 | 10 | 1 | 1 |
| Irritability | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 0 |
| Lightheadedness | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 0 |
| Paresthesia | 0 | 0 | 1 | 0 | 0 | 0 | 2 | 0 | 3 | 0 | 0 |
| Sleepiness | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 1 | 0 | 0 |
| Somnolence | 0 | 0 | 0 | 0 | 0 | 0 | 11 | 0 | 11 | 0 | 0 |
| Thinking Abnormal | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 1 | 0 | 0 |
| Weakness | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 0 |
| Number of Patients Experiencing a CNS Adverse Reaction | 2 | 1 | 4 | 2 | 0 | 2 | 39 | 12 | 59 | 2 | 1 |
| Percentage of Patients Experiencing a CNS Adverse Reaction | 3% | 2% | 6% | 5% | 0% | 17% | 24% | 16% | 15% | 5% | 2% |

* Includes 32 placebo patients who were crossed-over to esmolol
** Includes 8 esmolol patients who were crossed-over to placebo

## ESMOLOL SVT STUDIES

Numbers of Patients Experiencing an Adverse Reaction by Body System/Organ Class and Preferred Term

| | 8052-81-04 | | 8052-81-05 | | 8052-82-06 | 8052-82-07 | 8052-83-23 | 8052-83-31 | All Studies Combined | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | Esmolol | Propranolol | Esmolol | Placebo | Esmolol | Esmolol | Esmolol | Esmolol | Esmolol | Placebo | Propranolol |
| Total Number of Patients | 64 | 63 | 68* | 46** | 2 | 12 | 180 | 77 | 383 | 44 | 63 |
| **GASTROINTESTINAL** | | | | | | | | | | | |
| Abdominal Discomfort | 0 | 0 | 0 | 0 | 0 | 0 | 2 | 1 | 3 | 0 | 0 |
| Constipation | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 1 | 2 | 0 | 0 |
| Dyspepsia | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 1 | 0 | 0 |
| Mouth Dry | 0 | 0 | 0 | 0 | 0 | 0 | 3 | 0 | 3 | 0 | 0 |
| Nausea | 0 | 4 | 0 | 1 | 0 | 0 | 20 | 4 | 24 | 1 | 4 |
| Taste Perversion | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 |
| Vomiting | 0 | 1 | 0 | 0 | 0 | 0 | 3 | 1 | 4 | 0 | 1 |
| Number of Patients Experiencing a GI Adverse Reaction | 0 | 4 | 0 | 1 | 0 | 0 | 28 | 5 | 31 | 1 | 4 |
| Percentage of Patients Experiencing a GI Adverse Reaction | 0% | 6% | 0% | 2% | 0% | 0% | 16% | 6% | 8% | 2% | 6% |
| **GENITOURINARY** | | | | | | | | | | | |
| Dysuria | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 1 | 0 | 0 |
| Oliguria | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 1 | 0 | 0 |
| Urinary Retention | 0 | 0 | 0 | 0 | 0 | 0 | 3 | 0 | 3 | 0 | 0 |
| Number of Patients Experiencing a Genitourinary Adverse Reaction | 0 | 0 | 0 | 0 | 0 | 0 | 3 | 2 | 5 | 0 | 0 |
| Percentage of Patients Experiencing a Genitourinary Adverse Reaction | 0% | 0% | 0% | 0% | 0% | 0% | 2% | 3% | 1% | 0% | 0% |

* Includes 32 placebo patients who were crossed-over to esmolol
** Includes 9 esmolol patients who were crossed-over to placebo

## ESMOLOL SVT STUDIES

Numbers · Patients Experiencing an Adverse Reaction by Body System/Organ Class and Preferred Term

| | 8052-81-04 | | 8052-81-05 | | 8052-82-06 | 8052-82-07 | 8052-83-23 | 8052-83-31 | All Studies Combined | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | Esmolol | Propranolol | Esmolol | Placebo | Esmolol | Esmolol | Esmolol | Esmolol | Esmolol | Placebo | Propranolol |
| Total Number of Patients | 64 | 65 | 68* | 44** | 2 | 12 | 160 | 77 | 383 | 44 | 65 |
| **INJECTION SITE** | | | | | | | | | | | |
| Burning at IV Site | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 0 |
| Injection Site Inflammation | 2 | 0 | 1 | 0 | 0 | 0 | 18 | 4 | 25 | 0 | 0 |
| IV Infiltration | 2 | 0 | 0 | 1 | 0 | 0 | 7 | 0 | 9 | 1 | 0 |
| Number of Patients Experiencing an Injection Site Adverse Reaction | 5 | 0 | 1 | 1 | 0 | 0 | 22 | 4 | 32 | 1 | 0 |
| Percentage of Patients Experiencing an Injection Site Adverse Reaction | 8% | 0% | 1% | 2% | 0% | 0% | 14% | 5% | 8% | 2% | 0% |
| **RESPIRATORY** | | | | | | | | | | | |
| Atelectasis | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 1 | 0 | 0 |
| Bronchospasm | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 1 | 0 | 0 |
| Common Cold | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 1 | 0 | 0 |
| Cyanosis | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 |
| Dyspnea | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 1 | 0 | 0 |
| Nasal Congestion | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 1 | 0 | 0 |
| Pharyngitis | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 1 | 0 | 0 |
| Pulmonary Edema | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 1 | 0 | 0 |
| Rales | 1 | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 2 | 0 | 0 |
| Rhonchi | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 1 | 2 | 0 | 0 |
| Shortness of Breath | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 |
| Wheezing | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 1 | 2 | 0 | 0 |
| Number of Patients Experiencing a Respiratory Adverse Reaction | 1 | 1 | 0 | 0 | 0 | 0 | 8 | 2 | 11 | 0 | 1 |
| Percentage of Patients Experiencing a Respiratory Adverse Reaction | 2% | 2% | 0% | 0% | 0% | 0% | 4% | 3% | 3% | 0% | 2% |

* Includes 32 placebo patients who were crossed-over to esmolol
** Includes 9 esmolol patients who were crossed-over to placebo

ESMOLOL SVT STUDIES

Numbers of Patients Experiencing an Adverse Reaction by Body System/Organ Class and Preferred Term

| | 8052-81-04 | | 8052-81-05 | | 8052-82-06 | 8052-82-07 | 8052-83-23 | 8052-83-31 | All Studies Combined | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | Esmolol | Propranolol | Esmolol | Placebo | Esmolol | Esmolol | Esmolol | Esmolol | Esmolol | Placebo | Propra-nolol |
| Total Number of Patients | 64 | 63 | 68* | 44** | 2 | 12 | 160 | 77 | 383 | 44 | 63 |
| MISCELLANEOUS | | | | | | | | | | | |
| Enlarged Macular Area | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 1 | 0 | 0 |
| Fever | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 1 | 0 | 0 |
| Pain | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 1 | 0 | 0 |
| Pleural Pain | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 1 | 0 | 0 |
| Rigors | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 1 | 0 | 0 |
| Skin Discoloration | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 1 | 0 | 0 |
| Speech Disorder | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 1 | 0 | 0 |
| Vision Abnormal | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 1 | 2 | 0 | 0 |
| Number of Patients Experiencing a Miscellaneous Adverse Reaction | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 1 | 0 | 0 |
| Percentage of Patients Experiencing a Miscellaneous Adverse Adverse Reaction | 0% | 0% | 0% | 0% | 0% | 0% | 1% | 1% | 0% | 0% | 0% |

* Includes 32 placebo patients who were crossed-over to esmolol
** Includes 9 esmolol patients who were crossed-over to placebo

## ESMOLOL ANESTHESIA STUDIES

Numbers of Patients Experiencing an Adverse Reaction by Body System/Organ Class and Preferred Term

| | Reves 8052-82-21 | | Kaplan 8052-83-25 | | Zsigmond 8052-83-44 | Gold 8052-83-45 | | Murthy/ McCammon 8052-83-48 | | Carotid 8052-83-49 | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | Esmolol | Control* | Esmolol | Placebo | Esmolol | Esmolol | Placebo | Esmolol | Placebo | Esmolol | Placebo |
| Total Number of Patients | 32 | 10 | 10 | 10 | 40 | 31 | 10 | 17 | 17 | 37 | 37 |
| CARDIOVASCULAR | | | | | | | | | | | |
| Bradycardia | 0 | 0 | 0 | 1 | 0 | 1 | 0 | 0 | 0 | 0 | 1 |
| Hypertension | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 5 |
| Hypotension | 1 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 5 | 5 |
| Junction Rhythm | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0 |
| Myocardial Ischemia | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0 |
| ST-segment Depression | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0 |
| Tachycardia | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 3 |
| Number of Patients Experiencing a Cardiovascular Adverse Reaction | 1 | 0 | 0 | 1 | 0 | 1 | 0 | 0 | 0 | 8 | 8 |
| Percentage of Patients Experiencing a Cardiovascular Adverse Reaction | 3% | 0% | 0% | 1% | 0% | 3% | 0% | 0% | 0% | 22% | 22% |
| INJECTION SITE | | | | | | | | | | | |
| Itching | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Number of Patients Experiencing an Injection Site Adverse Reaction | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Percentage of Patients Experiencing an Injection Site Adverse Reaction | 0% | 0% | 0% | 0% | 0% | 0% | 0% | 0% | 0% | 0% | 0% |

* Standard Therapy

## ESMOLOL ANESTHESIA STUDIES

Numbers of Patients Experiencing an Adverse Reaction by Body System/Organ Class and Preferred Term

| | ASA I & II 8052-84-51A | | ASA III & IV 8052-84-51B | | All Studies Combined | | |
|---|---|---|---|---|---|---|---|
| | Esmolol | Placebo | Esmolol | Placebo | Esmolol | Placebo | Control[a] |
| Total Number of Patients | 58 | 54 | 36 | 37 | 261 | 165 | 10 |
| **CARDIOVASCULAR** | | | | | | | |
| Bradycardia | 0 | 0 | 0 | 0 | 1 | 2 | 0 |
| Hypertension | 0 | 0 | 0 | 0 | 1 | 5 | 0 |
| Hypotension | 0 | 0 | 0 | 0 | 7 | 5 | 0 |
| Junction Rhythm | 0 | 0 | 0 | 0 | 1 | 0 | 0 |
| Myocardial Ischemia | 0 | 0 | 0 | 0 | 1 | 0 | 0 |
| ST-segment Depression | 0 | 0 | 0 | 0 | 1 | 0 | 0 |
| Tachycardia | 0 | 0 | 0 | 0 | 0 | 3 | 0 |
| Number of Patients Experiencing a Cardiovascular Adverse Reaction | 0 | 0 | 0 | 0 | 10 | 9 | 0 |
| Percentage of Patients Experiencing a Cardiovascular Adverse Reaction | 0% | 0% | 0% | 0% | 4% | 5% | 0% |
| **INJECTION SITE** | | | | | | | |
| Itching | 0 | 1 | 0 | 0 | 0 | 1 | 0 |
| Number of Patients Experiencing an Injection Site Adverse Reaction | 0 | 1 | 0 | 0 | 0 | 1 | 0 |
| Percentage of Patients Experiencing an Injection Site Adverse Reaction | 0% | 2% | 0% | 0% | 0% | 1% | 0% |

[a] Standard Therapy

## ESMOLOL ANESTHESIA STUDIES

Numbers of Patients Experiencing an Adverse Reaction by Body System/Organ Class and Preferred Term

| | Reves 8052-82-21 | | Kaplan 8052-83-25 | | Zsigmond 8052-83-44 | Gold 8052-83-45 | | Murthy/ McCammon 8052-83-48 | | Carotid 8052-83-49 | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | Esmolol | Control* | Esmolol | Placebo | Esmolol | Esmolol | Placebo | Esmolol | Placebo | Esmolol | Placebo |
| Total Number of Patients | 32 | 10 | 10 | 10 | 40 | 31 | 10 | 17 | 17 | 37 | 37 |
| CENTRAL NERVOUS SYSTEM | | | | | | | | | | | |
| Agitation | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0 |
| Number of Patients Experiencing a CNS Adverse Reaction | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0 |
| Percentage of Patients Experiencing a CNS Site Adverse Reaction | 0% | 0% | 0% | 0% | 0% | 0% | 0% | 0% | 0% | 3% | 0% |
| RESPIRATORY | | | | | | | | | | | |
| Bronchospasm | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0 |
| Wheezing | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 |
| Number of Patients Experiencing a Respiratory Adverse Reaction | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 1 |
| Percentage of Patients Experiencing a Respiratory Adverse Reaction | 0% | 0% | 0% | 0% | 0% | 0% | 0% | 0% | 0% | 3% | 3% |

* Standard Therapy

## ESMOLOL ANESTHESIA STUDIES

Numbers of Patients Experiencing an Adverse Reaction by Body System/Organ Class and Preferred Term

| | ASA I & II 8052-84-51A | | ASA III & IV 8052-84-51B | | All Studies Combined | | |
|---|---|---|---|---|---|---|---|
| | Esmolol | Placebo | Esmolol | Placebo | Esmolol | Placebo | Control* |
| Total Number of Patients | 58 | 54 | 36 | 37 | 261 | 165 | 10 |
| CENTRAL NERVOUS SYSTEM | | | | | | | |
| Agitation | 0 | 0 | 0 | 0 | 1 | 0 | 0 |
| Number of Patients Experiencing a CNS Adverse Reaction | 0 | 0 | 0 | 0 | 1 | 0 | 0 |
| Percentage of Patients Experiencing a CNS Site Adverse Reaction | 0% | 0% | 0% | 0% | 0% | 0% | 0% |
| RESPIRATORY | | | | | | | |
| Bronchospasm | 0 | 0 | 0 | 0 | 1 | 0 | 0 |
| Wheezing | 0 | 1 | 0 | 0 | 0 | 2 | 0 |
| Number of Patients Experiencing a Respiratory Adverse Reaction | 0 | 1 | 0 | 0 | 1 | 2 | 0 |
| Percentage of Patients Experiencing a Respiratory adverse Reaction | 0% | 2% | 0% | 0% | 0% | 3% | 3% |

* Standard Therapy

## Appendix 2D - Case Report Summaries of Patients in Study 49 with Myocardial Ischemia or Significant ST-Segment Changes

# ESMOLOL TREATED PATIENTS EXHIBITING ST-SEGMENT CHANGES DURING THE STUDY

#229

- No major HR, BP or ECG changes during infusion
- ST-segment depression noted postinfusion minute 10 in association with decreased SBP
- Tx with Mephentermine and BP increased, ST-segment improved
- ST-segment depression recurred despite adequate BP
- Propranolol administered to slow HR (from 90s to 80s) and NTG was started
- ST-segment depression was slow to respond to NTG
- Surgery cancelled, no cardiac complications

#602

- Four minutes into infusion tachycardia was noted associated with panic response caused by inability to breath after atracurium was given (HR 110, BP 305/113)
- J-point depression secondary to tachycardia occurred two minutes later
- By minute seven of the infusion, 1 mm ST-segment depression was noted, further depressed to 2 mm then returned to 1 mm (HR 108, BP 215/110)
- By two minutes postinfusion the ST-segment had returned to normal (HR 74, BP 153/72)

## ESMOLOL TREATED PATIENTS EXHIBITING ST-SEGMENT CHANGES DURING THE STUDY

(CONTINUED)

#611

- ST-SEGMENT DEPRESSION OF > 2 MM NOTED THROUGHOUT BASELINE
- ST-SEGMENT DEPRESSION IMPROVED (TO 1-2 MM) FROM INDUCTION UNTIL END OF INFUSION ASSOCIATED WITH DECREASING HR AND SBP (FROM BASELINE)
- FURTHER IMPROVEMENT (TO 1 MM) DURING THE POST-INFUSION PERIOD

#613

- ST-SEGMENT DEPRESSION WORSENED (1 TO 1.5 MM) DURING THE BASELINE PERIOD (T-WAVES FLATTENED)
- AT MINUTE ONE OF THE INFUSION ST-SEGMENT DEPRESSION RETURNED TO 1 MM AND T-WAVES RETURNED TO UPRIGHT
- ISOFLURANE (2%) STARTED AND TWO MINUTES LATER
- A JUNCTIONAL RHYTHM (48 BPM) IN CONJUNCTION WITH HYPOTENSION (70/35 MM HG) WAS NOTED, ST-SEGMENT FURTHER DEPRESSED TO 1.5 MM
- ST-SEGMENT DEPRESSION PROGRESSED TO 1.8 MM BY END OF INFUSION AND FURTHER TO 2 MM AT POST-INFUSION MINUTE TWO
- BY 15 MINUTES POSTINFUSION ST-SEGMENT HAD RETURNED TO BASELINE (1 MM, HR=55 BPM, BP = 98/59 MM HG)
- SECOND EPISODE OF JUNCTIONAL RHYTHM WITH HYPOTENSION OCCURRED NEAR THE END OF SURGERY (APPROXIMATELY THREE HOURS AFTER INFUSION)

## ESMOLOL TREATED PATIENTS EXHIBITING ST-SEGMENT CHANGES DURING THE STUDY

(CONTINUED)

#617

- ST-SEGMENT CHANGES THROUGHOUT BASELINE PERIOD UNTIL INDUCTION
- ST-SEGMENT "PSEUDO" NORMALIZED POSTINDUCTION FOR THREE MINUTES, NO HR BP CHANGES ASSOCIATED
- ST-SEGMENT RETURNED TO BASELINE IN THE 15 MINUTE POSTINFUSION PERIOD

#619

- ST-SEGMENT DEPRESSION OF 1 MM WITH BIPHASIC T-WAVE THROUGHOUT BASELINE PERIOD
- BY MINUTE 3 OF INFUSION, T-WAVES BECAME UPRIGHT
- ST-SEGMENT UPSLOPED POSTINDUCTION
- ST-SEGMENT RETURNED TO 1 MM DEPRESSION BY TWO MINUTES POSTINFUSION
- NO SIGNIFICANT CHANGES

#624

- ST-SEGMENT DEPRESSION (2.5-3.2 MM) WAS OBSERVED DURING THE BASELINE PERIOD
- 2.9 MM DEPRESSION DURING FIRST SIX MINUTES OF INFUSION
- 2.5 MM DEPRESSION PRIOR TO INDUCTION
- 2.0 MM DEPRESSION POSTINDUCTION
- 2.9 MM DEPRESSION AT THE END OF INTUBATION (INFUSION MINUTE NINE)
- 1.9-2.0 MM DEPRESSION POSTINFUSION MINUTES 2-15

III. Patients with ST-segment depression of special interest #229, 602, 613, and 624 for Study #8052-83-49.

For each patient, provided are:

1) Case Report Summary from the NDA Medical Summary Appendix

2) Outcome Summary derived form the medical records

3) Table of Clinical Observations and Procedures with Reference Times

PATIENT NUMBER/INITIALS: 229/

AGE/SEX: 63/M

DRUG GROUP: Esmolol

HISTORY:
1. Hypertension (1974)
2. Chronic obstructive pulmonary disease
3. Cerebrovascular atherosclerotic disease
4. Transient ischemic attacks (1975)
5. Right carotid endarterectomy (May 1984)
6. Average baseline: heart rate 90 bpm
   blood pressure 197/110 mm Hg

PRIOR MEDICATIONS:

1. Hydrochlorothiazide 25 mg p.o. b.i.d.
2. Potassium chloride (K-lor®) 25 mEq p.o. b.i.d.
3. Theophylline (Slo-bid®) 300 mg p.o. b.i.d.
4. Albuterol (Ventolin®) inhaler 2 puffs INH q.i.d.
5. Triazolam (Halcion®) 0.25 mg p.o. x 1

DETAILS: Prestudy 12-lead electrocardiogram showed ST-segment depression (the degree of ST-segment depression was not recorded) of in leads $V_{3-6}$. Esmolol was infused according to protocol with good tolerance through induction, intubation and infusion periods. No ST-segment depression was noted during these times. Ten minutes into the postinfusion period, ST-segment depression (the degree of ST-segment depression was not recorded) occurred. Approximately 1.5 minutes later, systolic blood pressure had decreased from 140 mm Hg to 116 mm Hg, and treated with mephentermine (Wyamine®) 15 mg IV. The systolic blood pressure decreased to 108 mm Hg before responding to Wyamine®. The ST-segment depression returned to baseline and the systolic blood pressure increasing to 150-160 mm Hg. Fifteen minutes postinfusion, in spite of adequate blood pressure, the ST-segments again depressed. Propranolol (Inderal®) 1.5 mg IV was administered at this time to decrease the heart rate (from mid 90's bpm to mid 80's bpm). A nitroglycerin infusion was also begun. The ST-segment depression slowly responded to the nitroglycerin.

The patient was awakened and surgery was cancelled to allow for further evaluation of his cardiac status. Post anesthesia recovery electrocardiogram showed a 1 to 1.5 mm ST-segment depression in the lateral chest leads. Cardiac enzymes were normal.

N 19386 (5 of 10)

PATIENT NUMBER/INITIALS: 429/

OUTCOME: Surgery cancelled;
MUGA, showed severe CAD;
Cardiac enzyme normal;
Cardial consultant suggested no MI;
Never had chest pain
Discharged

CAROTID

CLINICAL OBSERVATIONS WITH REFERENCE TIMES INCLUDED, BY PATIENT
(HEART RATE, SYSTOLIC, DIASTOLIC, AND MEAN ARTERIAL BLOOD PRESSURE, AND RATE-PRESSURE PRODUCT)

PATIENT=229 TREATMENT=ESMOLOL

| PHASE | INHALATION DOSE(%) | INFUSION TIME (MIN) | TIME | HEART RATE | SYSTOLIC BLOOD PRESSURE | DIASTOLIC BLOOD PRESSURE | MEAN ARTERIAL PRESSURE | RATE PRESSURE PRODUCT | TIME OF MAXIMUM HR | TIME OF MAXIMUM SBP | TIME OF MAXIMUM DBP |
|---|---|---|---|---|---|---|---|---|---|---|---|
| ISOFLURANE | 0.25 | | 9:02:08 | | | | | | | | |
| ISOFLURANE | 0.50 | | 9:03:27 | | | | | | | | |
| POST INF 5 MIN | | 5.0 | 9:04:00 | 80.0 | 173.0 | 110.0 | 131.0 | 13.8 | | | |
| POST INF 10 MIN | | 10.0 | 9:09:00 | 77.0 | 140.0 | 86.0 | 104.0 | 10.8 | | | |
| ST-SEGMENT DEPRESSION | | | 9:09:00 | | | | | | | | |
| ISOFLURANE | 0.25 | | 9:09:35 | | | | | | | | |
| ISOFLURANE | 0.00 | | 9:10:20 | | | | | | | | |
| WYAMINE 15 MG | | | 9:12:00 | | | | | | | | |
| NITROGLYCERIN | | | 9:13:00 | | 108.0 | | | | | | |
| POST INF 15 MIN | | 15.0 | 9:14:00 | 88.0 | 162.0 | 107.0 | 125.3 | 14.3 | | | |
| MAXIMUM (ALL) | | | 9:14:00 | 88.0 | 197.0 | 122.0 | 147.0 | 14.3 | 9:14:00 | 8:56:00 | 8:56:00 |
| ST-SEGMENT DEPRESSION | | | 9:14:00 | | | | | | | | |
| PROPRANOLOL 1.5 MG | | | 9:14:00 | 95.0 | | | | | | | |

CAROTID

CLINICAL OBSERVATIONS WITH REFERENCE TIMES INCLUDED, BY PATIENT
(HEART RATE, SYSTOLIC, DIASTOLIC, AND MEAN ARTERIAL BLOOD PRESSURE, AND RATE-PRESSURE PRODUCT)

PATIENT=229 TREATMENT=ESMOLOL

| PHASE | INHALATION DOSE(%) | INFUSION TIME (MIN) | TIME | HEART RATE | SYSTOLIC BLOOD PRESSURE | DIASTOLIC BLOOD PRESSURE | MEAN ARTERIAL PRESSURE | RATE PRESSURE PRODUCT | TIME OF MAXIMUM HR | TIME OF MAXIMUM SBP | TIME OF MAXIMUM DBP |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 12L ECG, ST-SEGMENT DEPRESSION NOTED | | | | | | | | | | | |
| BASE -5 MIN | | -5.0 | 8:42:00 | 89.0 | 191.0 | 105.0 | 133.7 | 17.0 | | | |
| BASE -4 MIN | | -4.0 | 8:43:00 | 96.0 | 197.0 | 115.0 | 142.3 | 18.9 | | | |
| BASE -3 MIN | | -3.0 | 8:44:00 | 87.0 | 207.0 | 112.0 | 143.7 | 18.0 | | | |
| BASE -2 MIN | | -2.0 | 8:45:00 | 92.0 | 199.0 | 112.0 | 141.0 | 18.3 | | | |
| BASE -1 MIN | | -1.0 | 8:46:00 | 90.0 | 196.0 | 110.0 | 138.7 | 17.6 | | | |
| BASE 0 MIN | | 0.0 | 8:47:00 | 88.0 | 192.0 | 107.0 | 135.3 | 16.9 | | | |
| BASE AVERAGE | | | 8:47:00 | 90.3 | 197.0 | 110.2 | 139.1 | 17.8 | | | |
| LOAD DOSE START | | | 8:47:00 | | | | | | | | |
| ESMOLOL 1 MIN | | 1.0 | 8:48:00 | 82.0 | 193.0 | 104.0 | 133.7 | 15.8 | | | |
| ESMOLOL 2 MIN | | 2.0 | 8:49:00 | 75.0 | 189.0 | 101.0 | 130.3 | 14.2 | | | |
| ESMOLOL 3 MIN | | 3.0 | 8:50:00 | 74.0 | 186.0 | 101.0 | 129.3 | 13.8 | | | |
| ESMOLOL 4 MIN | | 4.0 | 8:51:00 | 76.0 | 190.0 | 106.0 | 134.0 | 14.4 | | | |
| INFUSION 300 START | | | 8:51:00 | | | | | | | | |
| ESMOLOL 5 MIN | | 5.0 | 8:52:00 | 73.0 | 181.0 | 98.0 | 125.7 | 13.2 | | | |
| ESMOLOL 5.5 MIN | | 5.5 | 8:52:30 | 73.0 | 182.0 | 100.0 | 127.3 | 13.3 | | | |
| INDUCTION | | | 8:52:30 | | | | | | | | |
| ESMOLOL 6 MIN | | 6.0 | 8:53:00 | 81.0 | 170.0 | 100.0 | 123.3 | 13.8 | | | |
| ESMOLOL 6.5 MIN | | 6.5 | 8:53:30 | 76.0 | 137.0 | 85.0 | 102.3 | 10.4 | | | |
| ESMOLOL 7 MIN | | 7.0 | 8:54:00 | 75.0 | 128.0 | 80.0 | 96.0 | 9.6 | | | |
| LARYNGOSCOPY START | | | 8:54:00 | | | | | | | | |
| END OF INTUBATION | | | 8:54:28 | | | | | | | | |
| ESMOLOL 7.5 MIN | | 7.5 | 8:54:30 | 73.0 | 132.0 | 89.0 | 103.3 | 9.6 | | | |
| ESMOLOL 8 MIN | | 8.0 | 8:55:00 | 77.0 | 178.0 | 118.0 | 138.0 | 13.7 | | | |
| MAXIMUM (EFFICACY) | | | 8:55:00 | 77.0 | 197.0 | 122.0 | 147.0 | 14.2 | 8:55:00 | 8:56:00 | 8:56:00 |
| ISOFLURANE | 0.50 | | 8:55:10 | | | | | | | | |
| ESMOLOL 8.5 MIN | | 8.5 | 8:55:30 | 74.0 | 183.0 | 113.0 | 136.3 | 13.5 | | | |
| ESMOLOL 9 MIN | | 9.0 | 8:56:00 | 72.0 | 197.0 | 122.0 | 147.0 | 14.2 | | | |
| ** EFFICACY TIME ** | | | 8:56:00 | | | | | | | | |
| ISOFLURANE | 1.00 | | 8:56:08 | | | | | | | | |
| ESMOLOL 9.5 MIN | | 9.5 | 8:56:30 | 70.0 | 187.0 | 111.0 | 136.3 | 13.1 | | | |
| ESMOLOL 10 MIN | | 10.0 | 8:57:00 | 69.0 | 183.0 | 106.0 | 131.7 | 12.6 | | | |
| ISOFLURANE | 0.50 | | 8:57:25 | | | | | | | | |
| ESMOLOL 10.5 MIN | | 10.5 | 8:57:30 | 69.0 | 172.0 | 101.0 | 124.7 | 11.9 | | | |
| ESMOLOL 11 MIN | | 11.0 | 8:58:00 | 68.0 | 170.0 | 97.0 | 121.3 | 11.6 | | | |
| ESMOLOL 11.5 MIN | | 11.5 | 8:58:30 | 71.0 | 163.0 | 97.0 | 119.0 | 11.6 | | | |
| ESMOLOL 12 MIN | | 12.0 | 8:59:00 | 73.0 | 156.0 | 94.0 | 114.7 | 11.4 | | | |
| INFUSION 300 STOP | | | 8:59:00 | | | | | | | | |
| ISOFLURANE | 0.25 | | 9:00:00 | | | | | | | | |
| POST INF 2 MIN | | 2.0 | 9:01:00 | 68.0 | 122.0 | 78.0 | 92.7 | 8.3 | | | |

PATIENT NUMBER/INITIALS: 602/

AGE/SEX: 59/F

DRUG GROUP: Esmolol

HISTORY:
1. Hypertension
2. Chronic obstructive pulmonary disease
3. Hemiparesis and expressive aphasia (April 1984)
4. Average baseline: heart rate 77 bpm
   blood pressure 151/69 mm Hg

PRIOR MEDICATION:

Heparin 1000 units q.1h continuous IV infusion

DETAILS: Esmolol was infused at 500 mcg/kg/min for 12 minutes due to an error in communication between the investigator and study nurse. Three minutes into the esmolol infusion atracurium (6 mg IV) was administered for "pre" muscle relaxation. One minute later the patient became panic stricken because of an inability to breathe. Her blood pressure increased to 226/126 mm Hg. One minute later the blood pressure read 305/113 mm Hg. Thiopental (75 mg IV) was administered at this time for induction of anesthesia and the panic reaction subsided. Sinus tachycardia (110 bpm) and J point depression began (minute five of the esmolol infusion) one minute after the administration of thiopental and lasted approximately two minutes.

At this time the patient then developed ST-segment depression of 1 mm two minutes after induction of anesthesia. The ST-segment depression became 2 mm but then improved to 1 mm just before intubation. The ST-segment changes then reverted to normal during the postinfusion period.

PATIENT NUMBER/INITIALS: 602/

OUTCOME: No further episodes during surgery;
Uneventful postoperative course;
ECG remained within normal limits

CAROTID

CLINICAL OBSERVATIONS WITH REFERENCE TIMES INCLUDED, BY PATIENT
(HEART RATE, SYSTOLIC, DIASTOLIC, AND MEAN ARTERIAL BLOOD PRESSURE, AND RATE-PRESSURE PRODUCT)

----------PATIENT=602
TREATMENT=ESMOLOL----------

| PHASE | INHAL-ATION DOSE(%) | INFUSION TIME (MIN) | TIME | HEART RATE | SYSTOLIC BLOOD PRESSURE | DIASTOLIC BLOOD PRESSURE | MEAN ARTERIAL PRESSURE | RATE PRESSURE PRODUCT | TIME OF MAXIMUM HR | TIME OF MAXIMUM SBP | TIME OF MAXIMUM DBP |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 12L ECG, NORMAL | | | 7:31:00 | | | | | | | | |
| ** EFFICACY TIME ** | | | 7:32:00 | | | | | | | | |
| BASE -5 MIN | | -5.0 | 7:32:00 | 79.0 | 152.0 | 74.0 | 100.0 | 12.0 | | | |
| BASE -4 MIN | | -4.0 | 7:33:00 | 74.0 | 146.0 | 64.0 | 91.3 | 10.8 | | | |
| BASE -3 MIN | | -3.0 | 7:34:00 | 77.0 | 140.0 | 67.0 | 91.3 | 10.8 | | | |
| BASE -2 MIN | | -2.0 | 7:35:00 | 81.0 | 156.0 | 70.0 | 98.7 | 12.6 | | | |
| BASE -1 MIN | | -1.0 | 7:36:00 | 75.0 | 157.0 | 68.0 | 97.7 | 11.8 | | | |
| BASE 0 MIN | | 0.0 | 7:37:00 | 77.0 | 152.0 | 70.0 | 97.3 | 11.7 | | | |
| BASE AVERAGE | | | 7:37:00 | 77.2 | 150.5 | 68.8 | 96.1 | 11.6 | | | |
| LOAD DOSE START | | | 7:37:00 | | | | | | | | |
| ESMOLOL 1 MIN | | 1.0 | 7:38:00 | 78.0 | 154.0 | 69.0 | 97.3 | 12.0 | | | |
| ESMOLOL 2 MIN | | 2.0 | 7:39:00 | 72.0 | 143.0 | 66.0 | 91.7 | 10.3 | | | |
| ESMOLOL 3 MIN | | 3.0 | 7:40:00 | 71.0 | 167.0 | 78.0 | 107.7 | 11.9 | | | |
| ESMOLOL 4 MIN | | 4.0 | 7:41:00 | 78.0 | 226.0 | 126.0 | 159.3 | 17.6 | | | |
| ESMOLOL 5 MIN | | 5.0 | 7:42:00 | 60.0 | 305.0 | 113.0 | 177.0 | 18.3 | | | |
| INDUCTION | | | 7:42:00 | | | | | | | | |
| ESMOLOL 5.5 MIN | | 5.5 | 7:42:30 | 110.0 | 250.0 | 125.0 | 166.7 | 27.5 | | | |
| ESMOLOL 6 MIN | | 6.0 | 7:43:00 | 97.0 | 220.0 | 115.0 | 150.0 | 21.3 | | | |
| ST-SEGMENT DEPRESSION, 1MM | | | 7:43:00 | | | | | | | | |
| ESMOLOL 6.5 MIN | | 6.5 | 7:43:30 | 98.0 | 227.0 | 125.0 | 159.0 | 22.2 | | | |
| ESMOLOL 7 MIN | | 7.0 | 7:44:00 | 108.0 | 215.0 | 110.0 | 145.0 | 23.2 | | | |
| ESMOLOL 7.5 MIN | | 7.5 | 7:44:30 | 98.0 | 225.0 | 115.0 | 151.7 | 22.0 | | | |
| ESMOLOL 8 MIN | | 8.0 | 7:45:00 | 94.0 | 197.0 | 106.0 | 136.3 | 18.5 | | | |
| ST-SEGMENT DEPRESSION, 2MM | | | 7:45:00 | | | | | | | | |
| ESMOLOL 8.5 MIN | | 8.5 | 7:45:30 | 89.0 | 178.0 | 98.0 | 124.7 | 15.8 | | | |
| ESMOLOL 9 MIN | | 9.0 | 7:46:00 | 94.0 | 193.0 | 98.0 | 129.7 | 18.1 | | | |
| ST-SEGMENT DEPRESSION, 1MM | | | 7:46:00 | | | | | | | | |
| ESMOLOL 9.5 MIN | | 9.5 | 7:46:30 | 77.0 | 182.0 | 75.0 | 110.7 | 14.0 | | | |
| ESMOLOL 10 MIN | | 10.0 | 7:47:00 | 83.0 | 180.0 | 85.0 | 116.7 | 14.9 | | | |
| ESMOLOL 10.5 MIN | | 10.5 | 7:47:30 | 76.0 | 177.0 | 89.0 | 118.3 | 13.5 | | | |
| LARYNGOSCOPY START | | | 7:47:30 | | | | | | | | |
| ESMOLOL 11 MIN | | 11.0 | 7:48:00 | 77.0 | 177.0 | 90.0 | 119.0 | 13.6 | | | |
| END OF INTUBATION | | | 7:48:08 | | | | | | | | |
| ESMOLOL 11.5 MIN | | 11.5 | 7:48:30 | 76.0 | 155.0 | 80.0 | 105.0 | 11.8 | | | |
| ISOFLURANE | 2.00 | | 7:48:30 | | | | | | | | |
| ESMOLOL 12 MIN | | 12.0 | 7:49:00 | 74.0 | 156.0 | 80.0 | 105.3 | 11.5 | | | |
| INFUSION 300 STOP | | | 7:49:00 | | | | | | | | |
| ISOFLURANE | 0.25 | | 7:50:00 | | | | | | | | |

CAROTID

CLINICAL OBSERVATIONS WITH REFERENCE TIMES INCLUDED, BY PATIENT
(HEART RATE, SYSTOLIC, DIASTOLIC, AND MEAN ARTERIAL BLOOD PRESSURE, AND RATE-PRESSURE PRODUCT)

----------PATIENT=602
TREATMENT=ESMOLOL----------

| PHASE | INHAL-ATION DOSE(%) | INFUSION TIME (MIN) | TIME | HEART RATE | SYSTOLIC BLOOD PRESSURE | DIASTOLIC BLOOD PRESSURE | MEAN ARTERIAL PRESSURE | RATE PRESSURE PRODUCT | TIME OF MAXIMUM HR | TIME OF MAXIMUM SBP | TIME OF MAXIMUM DBP |
|---|---|---|---|---|---|---|---|---|---|---|---|
| POST INF 2 MIN | | 2.0 | 7:51:00 | 74.0 | 153.0 | 72.0 | 99.0 | 11.3 | | | |
| POST INF 5 MIN | | 5.0 | 7:54:00 | 75.0 | 113.0 | 46.0 | 68.3 | 8.5 | | | |
| ST-SEGMENT DEPRESSION RETURNS TO BASELINE | | | | | | | | | | | |
| POST INF 10 MIN | | 10.0 | 7:59:00 | 81.0 | 105.0 | 62.0 | 76.3 | 8.5 | | | |
| POST INF 15 MIN | | 15.0 | 8:04:00 | 85.0 | 119.0 | 70.0 | 86.3 | 10.1 | | | |
| MAXIMUM (ALL) | | | 8:04:00 | 85.0 | 177.0 | 90.0 | 119.0 | 13.6 | 8:04:00 | 7:48:00 | 7:48:00 |
| INCISION | | | 8:04:30 | | | | | | | | |

PATIENT NUMBER/INITIALS: 613/

AGE/SEX: 79/M

DRUG GROUP: Esmolol

HISTORY:
1. Hypertensive cardiovascular disease (1969)
2. Atherosclerotic cardiovascular disease
3. Inferior wall myocardial infarction (1977)
4. Average baseline: heart rate 53 bpm
blood pressure 178/69 mm Hg

PRIOR MEDICATIONS:

1. Prazosin (Minipress®) 2 mg p.o. b.i.d.
2. Methyldopa 250 mg p.o. t.i.d.
3. Potassium chloride (Slow-K®) 8 mEq p.o. b.i.d.
4. Hydrochlorothiazide 50 mg p.o. q.a.m.
5. Reserpine 0.125 mg p.o. q.a.m.

DETAILS: This patient was noted to have a 1 mm ST-segment depression at start of the five-minute baseline period, progressing to 1.5 mm depression by the end of the baseline period. T-waves went from upright to flattened at the same time. At minute one of the infusion, ST-segment depression returned to 1 mm and the T-waves were to upright. The T-wave again flattened and the ST-segment further depressed to 1.5 mm at nine minutes into the infusion period (*i.e.*, 1.5 minutes postintubation). A junctional rhythm (48 bpm) in conjunction with hypotension (70/35 mm Hg) was also noted at this time. ST-segment depression progressed to 1.8 mm by minute 12 of the infusion, then further to 2 mm by two minutes postinfusion. T-waves remained flattened throughout the study. Junctional rhythm also persisted. By 15 minutes postinfusion, the heart rate was 55 bpm, the blood pressure 98/59 mm Hg, and the ST-segment depression had returned to baseline (1 mm).

PATIENT NUMBER/INITIALS: 613/

OUTCOME: Occasional PVCs/PACs postop,
Treated with potassium supplements;
ECG unchanged;
CPK within normal limits;
No perioperative MI

CAROTID

CLINICAL OBSERVATIONS WITH REFERENCE TIMES INCLUDED, BY PATIENT
(HEART RATE, SYSTOLIC, DIASTOLIC, AND MEAN ARTERIAL BLOOD PRESSURE, AND RATE-PRESSURE PRODUCT)

PATIENT=613

TREATMENT=ESMOLOL

| PHASE | INHALATION DOSE(%) | INFUSION TIME (MIN) | TIME | HEART RATE | SYSTOLIC BLOOD PRESSURE | DIASTOLIC BLOOD PRESSURE | MEAN ARTERIAL PRESSURE | RATE PRESSURE PRODUCT | TIME OF MAXIMUM HR | TIME OF MAXIMUM SBP | TIME OF MAXIMUM DBP |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 12L ECG, ST-SEGMENT DEPRESSION NOTED | | | | | | | | | | | |
| ** EFFICACY TIME ** | | | 7:34:00 | | | | | | | | |
| BASE -5 MIN | | -5.0 | 7:35:00 | 56.0 | 185.0 | 87.0 | 119.7 | 10.4 | | | |
| ST-SEGMENT DEPRESSION, 1MM | | | 7:35:00 | | | | | | | | |
| BASE -4 MIN | | -4.0 | 7:36:00 | 55.0 | 187.0 | 67.0 | 107.0 | 10.3 | | | |
| BASE -3 MIN | | -3.0 | 7:37:00 | 51.0 | 185.0 | 70.0 | 108.3 | 9.4 | | | |
| BASE -2 MIN | | -2.0 | 7:38:00 | 54.0 | 182.0 | 68.0 | 106.0 | 9.8 | | | |
| ST-SEGMENT DEPRESSION WORSENS, 1.5MM | | | 7:38:00 | | | | | | | | |
| BASE -1 MIN | | -1.0 | 7:39:00 | 51.0 | 163.0 | 60.0 | 94.3 | 8.3 | | | |
| BASE 0 MIN | | 0.0 | 7:40:00 | 51.0 | 168.0 | 63.0 | 98.0 | 8.6 | | | |
| BASE AVERAGE | | | 7:40:00 | 53.0 | 178.3 | 69.2 | 105.6 | 9.5 | | | |
| LOAD DOSE START | | | 7:40:00 | | | | | | | | |
| ESMOLOL 1 MIN | | 1.0 | 7:41:00 | 54.0 | 185.0 | 73.0 | 110.3 | 10.0 | | | |
| ST-SEGMENT DEPRESSION IMPROVES, 1MM | | | 7:41:00 | | | | | | | | |
| ESMOLOL 2 MIN | | 2.0 | 7:42:00 | 51.0 | 175.0 | 67.0 | 103.0 | 8.9 | | | |
| ESMOLOL 3 MIN | | 3.0 | 7:43:00 | 48.0 | 169.0 | 63.0 | 98.3 | 8.1 | | | |
| ESMOLOL 4 MIN | | 4.0 | 7:44:00 | 43.0 | 158.0 | 59.0 | 92.0 | 6.8 | | | |
| INFUSION 300 START | | | 7:44:00 | | | | | | | | |
| ESMOLOL 5 MIN | | 5.0 | 7:45:00 | 45.0 | 158.0 | 61.0 | 93.3 | 7.1 | | | |
| ST-SEGMENT IMPROVES, <1MM | | | | | | | | | | | |
| INDUCTION | | | 7:45:20 | | | | | | | | |
| ESMOLOL 5.5 MIN | | 5.5 | 7:45:30 | 48.0 | 155.0 | 63.0 | 93.7 | 5.9 | | | |
| ESMOLOL 6 MIN | | 6.0 | 7:46:00 | 43.0 | 173.0 | 59.0 | 97.0 | 7.4 | | | |
| ESMOLOL 6.5 MIN | | 6.5 | 7:46:30 | 48.0 | 152.0 | 62.0 | 92.0 | 7.3 | | | |
| ESMOLOL 7 MIN | | 7.0 | 7:47:00 | 46.0 | 132.0 | 55.0 | 80.7 | 6.3 | | | |
| LARYNGOSCOPY START | | | 7:47:10 | | | | | | | | |
| ESMOLOL 7.5 MIN | | 7.5 | 7:47:30 | 50.0 | 140.0 | 60.0 | 86.7 | 7.0 | | | |
| END OF INTUBATION | | | 7:47:33 | | | | | | | | |
| ISOFLURANE | 2.00 | | 7:47:35 | | | | | | | | |
| ESMOLOL 8 MIN | | 8.0 | 7:48:00 | 50.0 | 97.0 | 39.0 | 58.3 | 4.9 | | | |
| ESMOLOL 8.5 MIN | | 8.5 | 7:48:30 | 46.0 | 85.0 | 40.0 | 55.0 | 3.9 | | | |
| ESMOLOL 9 MIN | | 9.0 | 7:49:00 | 48.0 | 70.0 | 35.0 | 46.7 | 3.4 | | | |
| ST-SEGMENT WORSENS, 1.5MM | | | 7:49:00 | | | | | | | | |
| *DEVELOPS JUNCTIONAL RHYTHM | | | 7:49:00 | | | | | | | | |
| ESMOLOL 9.5 MIN | | 9.5 | 7:49:30 | 48.0 | 91.0 | 45.0 | 60.3 | 4.4 | | | |

* JUNCTIONAL RHYTHM CONTINUED THROUGHOUT OBSERVATION PERIOD
NOTE BY INVESTIGATOR: NEAR THE END OF SURGERY THE PATIENT AGAIN DEVELOPED NODAL (JUNCTIONAL RHYTHM) MAKING THE INITIAL REACTION PROBABLY NOT RELATED TO ESMOLOL.

CAROTID

CLINICAL OBSERVATIONS WITH REFERENCE TIMES INCLUDED, BY PATIENT
(HEART RATE, SYSTOLIC, DIASTOLIC, AND MEAN ARTERIAL BLOOD PRESSURE, AND RATE-PRESSURE PRODUCT)

PATIENT=613

TREATMENT=ESMOLOL

| PHASE | INHALATION DOSE(%) | INFUSION TIME (MIN) | TIME | HEART RATE | SYSTOLIC BLOOD PRESSURE | DIASTOLIC BLOOD PRESSURE | MEAN ARTERIAL PRESSURE | RATE PRESSURE PRODUCT | TIME OF MAXIMUM HR | TIME OF MAXIMUM SBP | TIME OF MAXIMUM DBP |
|---|---|---|---|---|---|---|---|---|---|---|---|
| ISOFLURANE | 0.25 | | 7:49:35 | | | | | | | | |
| ESMOLOL 10 MIN | | 10.0 | 7:50:00 | 50.0 | 70.0 | 35.0 | 46.7 | 3.5 | | | |
| ESMOLOL 10.5 MIN | | 10.5 | 7:50:30 | 51.0 | 100.0 | 55.0 | 70.0 | 5.1 | | | |
| ESMOLOL 11 MIN | | 11.0 | 7:51:00 | 51.0 | 95.0 | 55.0 | 68.3 | 4.8 | | | |
| ESMOLOL 11.5 MIN | | 11.5 | 7:51:30 | 51.0 | 99.0 | 50.0 | 66.3 | 5.0 | | | |
| ESMOLOL 12 MIN | | 12.0 | 7:52:00 | 53.0 | 105.0 | 56.0 | 72.3 | 5.6 | | | |
| INFUSION 300 STOP | | | 7:52:00 | | | | | | | | |
| ST-SEGMENT WORSENS, 1.8MM | | | 7:53:00 | | | | | | | | |
| ST-SEGMENT WORSENS, 2MM | | | 7:54:00 | | | | | | | | |
| POST INF 2 MIN | | 2.0 | 7:54:00 | 51.0 | 81.0 | 53.0 | 62.3 | 4.1 | | | |
| POST INF 5 MIN | | 5.0 | 7:57:00 | 51.0 | 103.0 | 66.0 | 78.3 | 5.3 | | | |
| POST INF 10 MIN | | 10.0 | 8:02:00 | 47.0 | 101.0 | 62.0 | 75.0 | 4.7 | | | |
| ST-SEGMENT IMPROVES, 1.5MM | | | 8:02:00 | | | | | | | | |
| POST INF 15 MIN | | 15.0 | 8:07:00 | 55.0 | 98.0 | 59.0 | 72.0 | 5.4 | | | |
| ST-SEGMENT IMPROVES, 1MM | | | 8:07:00 | | | | | | | | |
| MAXIMUM (ALL) | | | 8:07:00 | 55.0 | 140.0 | 66.0 | 86.7 | 7.0 | 8:07:00 | 7:47:30 | 7:57:00 |
| INCISION | | | 8:10:00 | | | | | | | | |

PATIENT NUMBER/INITIALS: 617/

AGE/SEX: 66/M

DRUG GROUP: Esmolol

HISTORY:
1. Thoracic aneurysm (1980)
2. Coronary artery bypass graft surgery (1980)
3. Arteriosclerotic cardiovascular disease
4. Hypertensive cardiovascular disease
5. Transient ischemic attacks
6. Left carotid endarterectomy
7. Chronic obstructive pulmonary disease
8. Average baseline: heart rate 72 bpm
   blood pressure 183/85 mm Hg

PRIOR MEDICATIONS:

1. Hydralazine 50 mg p.o. t.i.d.
2. Chlorthalidone (Hygroton®) 25 mg p.o. 3X/week
3. Nifedipine 10 mg p.o. t.i.d.
4. Potassium chloride 10 mEq p.o. t.i.d.

DETAILS: Esmolol was infused according to protocol. One and one-half minutes after induction of anesthesia (seven minutes into the infusion), "pseudo" normalization of the ST-segment was noted. This normalization in a patient with prestudy depression of the ST-segment was a subtle indication of cardiac ischemia. The normalization of the ST-segment continued until ten minutes into the postinfusion observation period, when the ST-segment returned to prestudy depression.

PATIENT NUMBER/INITIALS: 617/

OUTCOME: Covered pre- and postop with calcium channel blocker therapy;
ECG unchanged;
CPK within normal limits;
No evidence of MI

CAROTID

CLINICAL OBSERVATIONS WITH REFERENCE TIMES INCLUDED, BY PATIENT
(HEART RATE, SYSTOLIC, DIASTOLIC, AND MEAN ARTERIAL BLOOD PRESSURE, AND RATE-PRESSURE PRODUCT)

----------PATIENT=617
TREATMENT=ESMOLOL----------

| PHASE | INHAL-ATION DOSE(%) | INFUSION TIME (MIN) | TIME | HEART RATE | SYSTOLIC BLOOD PRESSURE | DIASTOLIC BLOOD PRESSURE | MEAN ARTERIAL PRESSURE | RATE PRESSURE PRODUCT | TIME OF MAXIMUM HR | TIME OF MAXIMUM SBP | TIME OF MAXIMUM DBP |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 12L ECG, ST-SEGMENT DEPRESSION NOTED | | | 11:40:00 | | | | | | | | |
| ST-SEGMENT DEPRESSION | | | | | | | | | | | |
| BASE -5 MIN | | -5.0 | 11:40:00 | 71.0 | 183.0 | 83.0 | 116.3 | 13.0 | | | |
| BASE -4 MIN | | -4.0 | 11:41:00 | 71.0 | 189.0 | 83.0 | 118.3 | 13.4 | | | |
| BASE -3 MIN | | -3.0 | 11:42:00 | 73.0 | 186.0 | 85.0 | 118.7 | 13.6 | | | |
| BASE -2 MIN | | -2.0 | 11:43:00 | 72.0 | 182.0 | 80.0 | 114.0 | 13.1 | | | |
| BASE -1 MIN | | -1.0 | 11:44:00 | 75.0 | 176.0 | 88.0 | 117.3 | 13.2 | | | |
| BASE 0 MIN | | 0.0 | 11:45:00 | 71.0 | 184.0 | 90.0 | 121.3 | 13.1 | | | |
| BASE AVERAGE | | | 11:45:00 | 72.2 | 183.3 | 84.8 | 117.7 | 13.2 | | | |
| LOAD DOSE START | | | 11:45:00 | | | | | | | | |
| ESMOLOL 1 MIN | | 1.0 | 11:46:00 | 75.0 | 187.0 | 85.0 | 119.0 | 14.0 | | | |
| ESMOLOL 2 MIN | | 2.0 | 11:47:00 | 73.0 | 178.0 | 84.0 | 115.3 | 13.0 | | | |
| ESMOLOL 3 MIN | | 3.0 | 11:48:00 | 68.0 | 170.0 | 92.0 | 118.0 | 11.6 | | | |
| ESMOLOL 4 MIN | | 4.0 | 11:49:00 | 67.0 | 185.0 | 80.0 | 115.0 | 12.4 | | | |
| INFUSION 300 START | | | 11:49:00 | | | | | | | | |
| ESMOLOL 5 MIN | | 5.0 | 11:50:00 | 67.0 | 178.0 | 83.0 | 114.7 | 11.9 | | | |
| INDUCTION | | | 11:50:00 | | | | | | | | |
| ESMOLOL 5.5 MIN | | 5.5 | 11:50:30 | 67.0 | 176.0 | 80.0 | 112.0 | 11.8 | | | |
| ESMOLOL 6 MIN | | 6.0 | 11:51:00 | 67.0 | 178.0 | 83.0 | 114.7 | 11.9 | | | |
| ESMOLOL 6.5 MIN | | 6.5 | 11:51:30 | 64.0 | 169.0 | 85.0 | 113.0 | 10.8 | | | |
| ESMOLOL 7 MIN | | 7.0 | 11:52:00 | 68.0 | 175.0 | 97.0 | 123.0 | 11.9 | | | |
| ESMOLOL 7.5 MIN | | 7.5 | 11:52:30 | 74.0 | 181.0 | 110.0 | 133.7 | 13.4 | | | |
| ESMOLOL 8 MIN | | 8.0 | 11:53:00 | 76.0 | 169.0 | 107.0 | 127.7 | 12.8 | | | |
| LARYNGOSCOPY START | | | 11:53:00 | | | | | | | | |
| END OF INTUBATION | | | 11:53:20 | | | | | | | | |
| •ST-SEGMENT WORSENS | | | 11:53:20 | | | | | | | | |
| ESMOLOL 8.5 MIN | | 8.5 | 11:53:30 | 70.0 | 146.0 | 94.0 | 111.3 | 10.2 | | | |
| ISOFLURANE | 2.00 | | 11:53:30 | | | | | | | | |
| ESMOLOL 9 MIN | | 9.0 | 11:54:00 | 79.0 | 117.0 | 69.0 | 85.0 | 9.2 | | | |
| ESMOLOL 9.5 MIN | | 9.5 | 11:54:30 | 82.0 | 149.0 | 96.0 | 113.7 | 12.2 | | | |
| ESMOLOL 10 MIN | | 10.0 | 11:55:00 | 83.0 | 165.0 | 104.0 | 124.3 | 13.7 | | | |
| ESMOLOL 10.5 MIN | | 10.5 | 11:55:30 | 84.0 | 173.0 | 93.0 | 119.7 | 14.5 | | | |
| MAXIMUM (EFFICACY) | | | 11:55:30 | 84.0 | 173.0 | 104.0 | 124.3 | 14.5 | 11:55:30 | 11:55:30 | 11:55:00 |
| ISOFLURANE | 0.25 | | 11:55:30 | | | | | | | | |
| ** EFFICACY TIME ** | | | 11:55:30 | | | | | | | | |
| ESMOLOL 11 MIN | | 11.0 | 11:56:00 | 79.0 | 180.0 | 104.0 | 129.3 | 14.2 | | | |
| ESMOLOL 11.5 MIN | | 11.5 | 11:56:30 | 82.0 | 176.0 | 100.0 | 125.3 | 14.4 | | | |
| ESMOLOL 12 MIN | | 12.0 | 11:57:00 | 84.0 | 173.0 | 96.0 | 121.7 | 14.5 | | | |
| INFUSION 300 STOP | | | 11:57:00 | | | | | | | | |

• STARTED AFTER INTUBATION AND CONTINUED FOR APPROXIMATELY 3 MINUTES

CAROTID

CLINICAL OBSERVATIONS WITH REFERENCE TIMES INCLUDED, BY PATIENT
(HEART RATE, SYSTOLIC, DIASTOLIC, AND MEAN ARTERIAL BLOOD PRESSURE, AND RATE-PRESSURE PRODUCT)

----------PATIENT=617
TREATMENT=ESMOLOL----------

| PHASE | INHAL-ATION DOSE(%) | INFUSION TIME (MIN) | TIME | HEART RATE | SYSTOLIC BLOOD PRESSURE | DIASTOLIC BLOOD PRESSURE | MEAN ARTERIAL PRESSURE | RATE PRESSURE PRODUCT | TIME OF MAXIMUM HR | TIME OF MAXIMUM SBP | TIME OF MAXIMUM DBP |
|---|---|---|---|---|---|---|---|---|---|---|---|
| POST INF 2 MIN | | 2.0 | 11:59:00 | 85.0 | 173.0 | 84.0 | 113.7 | 14.7 | | | |
| MAXIMUM (ALL) | | | 11:59:00 | 85.0 | 180.0 | 104.0 | 129.3 | 14.7 | 11:59:00 | 11:56:00 | 11:55:00 |
| POST INF 5 MIN | | 5.0 | 12:02:00 | 76.0 | 151.0 | 79.0 | 103.0 | 11.5 | | | |
| ISOFLURANE | 1.00 | | 12:02:00 | | | | | | | | |
| POST INF 10 MIN | | 10.0 | 12:07:00 | 76.0 | 116.0 | 56.0 | 76.0 | 8.8 | | | |
| POST INF 15 MIN | | 15.0 | 12:12:00 | 77.0 | 114.0 | 64.0 | 80.7 | 8.8 | | | |
| INCISION | | | 12:15:00 | | | | | | | | |

PATIENT NUMBER/INITIALS: 619/

AGE/SEX: 51/M

DRUG GROUP: Esmolol

HISTORY:
1. Coronary artery bypass graft surgery x 2 (1980 and 1984)
2. Carotid endarterectomy (May 1984)
3. Colon resection for diverticulosis (1982)
4. Cervical laminectomy for degenerative arthritis (1978)
5. Average baseline: heart rate 94 bpm
   blood pressure 182/75 mm Hg

PRIOR MEDICATIONS:

Aspirin 60 mg p.o. q.d.

DETAILS: This patient had 1 mm horizontal ST-segment depression with biphasic T-waves throughout the five-minute baseline period. After the infusion of esmolol was started the T-waves became upright. After induction and immediately before intubation the ST-segment became upsloping. At two minutes after intubation, the ST-segment was less than 1 mm depressed. In the postinfusion follow-up period the ST-segment depression returned to a 1 mm depression.

**PATIENT NUMBER/INITIALS:** 619/

**OUTCOME:** Postop ECG unchanged from preop;
Uneventful postop course

CAROTID

CLINICAL OBSERVATIONS WITH REFERENCE TIMES INCLUDED, BY PATIENT
(HEART RATE, SYSTOLIC, DIASTOLIC, AND MEAN ARTERIAL BLOOD PRESSURE, AND RATE-PRESSURE PRODUCT)

----------PATIENT=619
TREATMENT=ESMOLOL----------

| PHASE | INHAL-ATION DOSE(%) | INFUSION TIME (MIN) | TIME | HEART RATE | SYSTOLIC BLOOD PRESSURE | DIASTOLIC BLOOD PRESSURE | MEAN ARTERIAL PRESSURE | RATE PRESSURE PRODUCT | TIME OF MAXIMUM HR | TIME OF MAXIMUM SBP | TIME OF MAXIMUM DBP |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 12L ECG, ST-SEGMENT DEPRESSION <1MM | | | | | | | | | | | |
| ** EFFICACY TIME ** | | | 7:41:00 | | | | | | | | |
| BASE -5 MIN | | -5.0 | 7:42:00 | 91.0 | 188.0 | 75.0 | 112.7 | 17.1 | | | |
| ST-SEGMENT DEPRESSION, 1MM | | | 7:42:00 | | | | | | | | |
| BASE -4 MIN | | -4.0 | 7:43:00 | 96.0 | 180.0 | 75.0 | 110.0 | 17.3 | | | |
| BASE -3 MIN | | -3.0 | 7:44:00 | 93.0 | 195.0 | 79.0 | 117.7 | 18.1 | | | |
| BASE -2 MIN | | -2.0 | 7:45:00 | 91.0 | 170.0 | 68.0 | 102.0 | 15.5 | | | |
| BASE -1 MIN | | -1.0 | 7:46:00 | 93.0 | 185.0 | 75.0 | 111.7 | 17.2 | | | |
| BASE 0 MIN | | 0.0 | 7:47:00 | 97.0 | 176.0 | 76.0 | 109.3 | 17.1 | | | |
| BASE AVERAGE | | | 7:47:00 | 93.5 | 187.3 | 74.7 | 110.6 | 17.0 | | | |
| LOAD DOSE START | | | 7:47:00 | | | | | | | | |
| ESMOLOL 1 MIN | | 1.0 | 7:48:00 | 98.0 | 205.0 | 90.0 | 128.3 | 20.1 | | | |
| ESMOLOL 2 MIN | | 2.0 | 7:49:00 | 90.0 | 195.0 | 82.0 | 119.7 | 17.5 | | | |
| ESMOLOL 3 MIN | | 3.0 | 7:50:00 | 87.0 | 196.0 | 80.0 | 118.7 | 17.1 | | | |
| ESMOLOL 4 MIN | | 4.0 | 7:51:00 | 87.0 | 195.0 | 80.0 | 118.3 | 17.0 | | | |
| INFUSION 300 START | | | 7:51:00 | | | | | | | | |
| ESMOLOL 5 MIN | | 5.0 | 7:52:00 | 88.0 | 189.0 | 76.0 | 113.7 | 16.6 | | | |
| INDUCTION | | | 7:52:00 | | | | | | | | |
| ESMOLOL 5.5 MIN | | 5.5 | 7:52:30 | 87.0 | 195.0 | 82.0 | 119.7 | 17.0 | | | |
| ESMOLOL 6 MIN | | 6.0 | 7:53:00 | 87.0 | 181.0 | 75.0 | 110.3 | 15.7 | | | |
| ESMOLOL 6.5 MIN | | 6.5 | 7:53:30 | 86.0 | 157.0 | 73.0 | 101.0 | 13.5 | | | |
| ESMOLOL 7 MIN | | 7.0 | 7:54:00 | 86.0 | 142.0 | 70.0 | 94.0 | 12.2 | | | |
| ST-SEGMENT IMPROVES | | | 7:54:00 | | | | | | | | |
| ESMOLOL 7.5 MIN | | 7.5 | 7:54:30 | 87.0 | 135.0 | 67.0 | 89.7 | 11.7 | | | |
| ESMOLOL 8 MIN | | 8.0 | 7:55:00 | 86.0 | 127.0 | 67.0 | 87.0 | 10.9 | | | |
| ESMOLOL 8.5 MIN | | 8.5 | 7:55:30 | 87.0 | 115.0 | 63.0 | 80.3 | 10.0 | | | |
| LARYNGOSCOPY START | | | 7:55:30 | | | | | | | | |
| ESMOLOL 9 MIN | | 9.0 | 7:56:00 | 83.0 | 107.0 | 55.0 | 72.3 | 8.9 | | | |
| END OF INTUBATION | | | 7:56:10 | | | | | | | | |
| ESMOLOL 9.5 MIN | | 9.5 | 7:56:30 | 88.0 | 157.0 | 86.0 | 109.0 | 13.8 | | | |
| ISOFLURANE | 0.30 | | 7:56:30 | | | | | | | | |
| ISOFLURANE | 2.00 | | 7:56:45 | | | | | | | | |
| ESMOLOL 10 MIN | | 10.0 | 7:57:00 | 91.0 | 191.0 | 103.0 | 132.3 | 17.4 | | | |
| MAXIMUM (ALL) | | | 7:57:00 | 91.0 | 215.0 | 113.0 | 147.0 | 19.6 | 7:57:00 | 7:59:00 | 7:59:00 |
| ESMOLOL 10.5 MIN | | 10.5 | 7:57:30 | 90.0 | 205.0 | 110.0 | 141.7 | 18.5 | | | |
| ESMOLOL 11 MIN | | 11.0 | 7:58:00 | 91.0 | 204.0 | 109.0 | 140.7 | 18.6 | | | |
| ESMOLOL 11.5 MIN | | 11.5 | 7:58:30 | 91.0 | 203.0 | 104.0 | 137.0 | 18.5 | | | |
| ST-SEGMENT IMPROVES, <1MM | | | 7:58:30 | | | | | | | | |
| ESMOLOL 12 MIN | | 12.0 | 7:59:00 | 91.0 | 215.0 | 113.0 | 147.0 | 19.6 | | | |
| INFUSION 300 STOP | | | 7:59:00 | | | | | | | | |

CAROTID

CLINICAL OBSERVATIONS WITH REFERENCE TIMES INCLUDED, BY PATIENT
(HEART RATE, SYSTOLIC, DIASTOLIC, AND MEAN ARTERIAL BLOOD PRESSURE, AND RATE-PRESSURE PRODUCT)

----------PATIENT=619
TREATMENT=ESMOLOL----------

| PHASE | INHAL-ATION DOSE(%) | INFUSION TIME (MIN) | TIME | HEART RATE | SYSTOLIC BLOOD PRESSURE | DIASTOLIC BLOOD PRESSURE | MEAN ARTERIAL PRESSURE | RATE PRESSURE PRODUCT | TIME OF MAXIMUM HR | TIME OF MAXIMUM SBP | TIME OF MAXIMUM DBP |
|---|---|---|---|---|---|---|---|---|---|---|---|
| POST INF 2 MIN | | 2.0 | 8:01:00 | 86.0 | 173.0 | 85.0 | 114.3 | 14.9 | | | |
| ST-SEGMENT WORSENS, 1MM | | | 8:01:00 | | | | | | | | |
| ISOFLURANE | 0.50 | | 8:01:45 | | | | | | | | |
| POST INF 5 MIN | | 5.0 | 8:04:00 | 86.0 | 135.0 | 65.0 | 88.3 | 11.6 | | | |
| ISOFLURANE | 0.00 | | 8:05:15 | | | | | | | | |
| ISOFLURANE | 0.50 | | 8:06:15 | | | | | | | | |
| ISOFLURANE | 0.30 | | 8:07:30 | | | | | | | | |
| POST INF 10 MIN | | 10.0 | 8:09:00 | 84.0 | 110.0 | 55.0 | 73.3 | 9.2 | | | |
| ISOFLURANE | 0.60 | | 8:11:15 | | | | | | | | |
| ISOFLURANE | 0.80 | | 8:12:30 | | | | | | | | |
| POST INF 15 MIN | | 15.0 | 8:14:00 | 84.0 | 130.0 | 60.0 | 83.3 | 10.9 | | | |
| ST-SEGMENT RETURNS TO BASELINE | | | 8:14:00 | | | | | | | | |
| INCISION | | | 8:14:30 | | | | | | | | |

PATIENT NUMBER/INITIALS: 624,

AGE/SEX: 71/M

DRUG GROUP: Esmolol

HISTORY:
1. Hypertension
2. Arteriosclerotic cardiovascular disease
3. Intermittent right bundle branch block
4. Left carotid artery stenosis
5. Lacunar infarction (April 1984)
6. Skin cancer
7. Average baseline: heart rate 72 bpm
   blood pressure 167/64 mm Hg

PRIOR MEDICATIONS:

1. Nifedipine 10 mg p.o. t.i.d.
2. Quinidine 200 mg p.o. q.i.d.

DETAILS: This patient had a 2.5 to 3.2 mm ST-segment depression during the five-minute baseline period. After starting the infusion the ST-segment depression was noted to be 2.9 mm until induction of anesthesia. The ST-segment depression improved from 2.9 mm depression to 2.0 mm depression until intubation at which time it dropped back to 2.9 mm depression. However within two minutes of intubation it had again improved to 2.0 mm depression. In the postinfusion period ST-segment depression was noted to be 1.9 to 2.0 mm depression.

PATIENT NUMBER/INITIALS: 624/

OUTCOME: ST-segment changes noted on postop ECG... clinically insignificant as judged by cardiology consultant;
Nitrate therapy initiated postop, however;
CPK normal;
No evidence of MI;
Occasional PVCs noted during first 24 hours postop, treated with quinidine

CAROTID

CLINICAL OBSERVATIONS WITH REFERENCE TIMES INCLUDED, BY PATIENT
(HEART RATE, SYSTOLIC, DIASTOLIC, AND MEAN ARTERIAL BLOOD PRESSURE, AND RATE-PRESSURE PRODUCT)

----------PATIENT=624
TREATMENT=ESMOLOL----------

| PHASE | INHAL-ATION DOSE(%) | INFUSION TIME (MIN) | TIME | HEART RA E | SYSTOLIC BLOOD PRESSURE | DIASTOLIC BLOOD PRESSURE | MEAN ARTERIAL PRESSURE | RATE PRESSURE PRODUCT | TIME OF MAXIMUM HR | TIME OF MAXIMUM SBP | TIME OF MAXIMUM DBP |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 12L ECG, STRAIN PATTERN TO ST-SEGMENT | | | | | | | | | | | |
| BASE -5 MIN | | -5.0 | 7:41:00 | 73.0 | 160.0 | 63.0 | 95.3 | 11.7 | | | |
| ST-SEGMENT DEPRESSION, 2.5MM | | | 7:41:00 | | | | | | | | |
| BASE -4 MIN | | -4.0 | 7:42:00 | 73.0 | 170.0 | 65.0 | 100.0 | 12.4 | | | |
| BASE -3 MIN | | -3.0 | 7:43:00 | 72.0 | 175.0 | 65.0 | 101.7 | 12.6 | | | |
| BASE -2 MIN | | -2.0 | 7:44:00 | 73.0 | 173.0 | 65.0 | 101.0 | 12.6 | | | |
| BASE -1 MIN | | -1.0 | 7:45:00 | 73.0 | 163.0 | 66.0 | 98.3 | 11.9 | | | |
| BASE 0 MIN | | 0.0 | 7:46:00 | 70.0 | 163.0 | 60.0 | 94.3 | 11.4 | | | |
| ST-SEGMENT WORSENS, 3.2MM | | | 7:46:00 | | | | | | | | |
| BASE AVERAGE | | | 7:46:00 | 72.3 | 167.3 | 64.0 | 98.4 | 12.1 | | | |
| LOAD DOSE START | | | 7:46:00 | | | | | | | | |
| ESMOLOL 1 MIN | | 1.0 | 7:47:00 | 67.0 | 170.0 | 60.0 | 96.7 | 11.4 | | | |
| ST-SEGMENT IMPROVES, 2.9MM | | | 7:47:00 | | | | | | | | |
| ESMOLOL 2 MIN | | 2.0 | 7:48:00 | 67.0 | 170.0 | 66.0 | 100.7 | 11.4 | | | |
| ESMOLOL 3 MIN | | 3.0 | 7:49:00 | 63.0 | 153.0 | 67.0 | 95.7 | 9.6 | | | |
| ESMOLOL 4 MIN | | 4.0 | 7:50:00 | 63.0 | 160.0 | 60.0 | 93.3 | 10.1 | | | |
| INFUSION 300 START | | | 7:50:00 | | | | | | | | |
| ESMOLOL 5 MIN | | 5.0 | 7:51:00 | 61.0 | 163.0 | 60.0 | 94.3 | 9.9 | | | |
| INDUCTION | | | 7:51:00 | | | | | | | | |
| ESMOLOL 5.5 MIN | | 5.5 | 7:51:30 | 61.0 | 160.0 | 68.0 | 98.7 | 9.8 | | | |
| ESMOLOL 6 MIN | | 6.0 | 7:52:00 | 64.0 | 155.0 | 70.0 | 98.3 | 9.9 | | | |
| ESMOLOL 6.5 MIN | | 6.5 | 7:52:30 | 59.0 | 142.0 | 68.0 | 92.7 | 8.4 | | | |
| ESMOLOL 7 MIN | | 7.0 | 7:53:00 | 58.0 | 142.0 | 65.0 | 90.7 | 8.2 | | | |
| ST-SEGMENT IMPROVES, 2.5MM | | | 7:53:00 | | | | | | | | |
| ESMOLOL 7.5 MIN | | 7.5 | 7:53:30 | 62.0 | 133.0 | 63.0 | 86.3 | 8.2 | | | |
| ESMOLOL 8 MIN | | 8.0 | 7:54:00 | 63.0 | 135.0 | 62.0 | 86.3 | 8.5 | | | |
| ESMOLOL 8.5 MIN | | 8.5 | 7:54:30 | 60.0 | 132.0 | 57.0 | 82.0 | 7.9 | | | |
| ESMOLOL 9 MIN | | 9.0 | 7:55:00 | 62.0 | 110.0 | 53.0 | 72.0 | 6.8 | | | |
| ST-SEGMENT IMPROVES, 2.0MM | | | 7:55:00 | | | | | | | | |
| LARYNGOSCOPY START | | | 7:55:09 | | | | | | | | |
| ESMOLOL 9.5 MIN | | 9.5 | 7:55:30 | 64.0 | 110.0 | 57.0 | 74.7 | 7.0 | | | |
| MAXIMUM (EFFICACY) | | | 7:55:30 | 64.0 | 114.0 | 57.0 | 74.7 | 7.1 | 7:55:30 | 7:56:30 | 7:55:30 |
| ST-SEGMENT WORSENS, 2.9MM | | | 7:55:30 | | | | | | | | |
| END OF INTUBATION | | | 7:55:32 | | | | | | | | |
| ESMOLOL 10 MIN | | 10.0 | 7:56:00 | 64.0 | 105.0 | 54.0 | 71.0 | 6.7 | | | |

CAROTID

CLINICAL OBSERVATIONS WITH REFERENCE TIMES INCLUDED, BY PATIENT
(HEART RATE, SYSTOLIC, DIASTOLIC, AND MEAN ARTERIAL BLOOD PRESSURE, AND RATE-PRESSURE PRODUCT)

PATIENT=624

TREATMENT=ESMOLOL

| PHASE | INHALATION DOSE(%) | INFUSION TIME (MIN) | TIME | HEART RATE | SYSTOLIC BLOOD PRESSURE | DIASTOLIC BLOOD PRESSURE | MEAN ARTERIAL PRESSURE | RATE PRESSURE PRODUCT | TIME OF MAXIMUM HR | TIME OF MAXIMUM SBP | TIME OF MAXIMUM DBP |
|---|---|---|---|---|---|---|---|---|---|---|---|
| ESMOLOL 10.5 MIN | | 10.5 | 7:56:30 | 62.0 | 114.0 | 55.0 | 74.7 | 7.1 | | | |
| ESMOLOL 11 MIN | | 11.0 | 7:57:00 | 64.0 | 110.0 | 54.0 | 72.7 | 7.0 | | | |
| *ST-SEGMENT IMPROVES, 2.0MM | | | 7:57:00 | | | | | | | | |
| ESMOLOL 11.5 MIN | | 11.5 | 7:57:03 | 61.0 | 109.0 | 55.0 | 73.0 | 6.6 | | | |
| ESMOLOL 12 MIN | | 12.0 | 7:58:00 | 59.0 | 109.0 | 52.0 | 71.0 | 6.4 | | | |
| INFUSION 300 STOP | | | 7:58:00 | | | | | | | | |
| POST INF 2 MIN | | 2.0 | 8:00:00 | 57.0 | 110.0 | 51.0 | 70.7 | 6.3 | | | |
| POST INF 5 MIN | | 5.0 | 8:03:00 | 63.0 | 115.0 | 60.0 | 78.3 | 7.2 | | | |
| POST INF 10 MIN | | 10.0 | 8:08:00 | 65.0 | 135.0 | 70.0 | 91.7 | 8.8 | | | |
| MAXIMUM (ALL) | | | 8:08:00 | 65.0 | 136.0 | 70.0 | 91.7 | 8.8 | 8:08:00 | 8:13:00 | 8:08:00 |
| ISOFLURANE | 0.50 | | 8:11:00 | | | | | | | | |
| POST INF 15 MIN | | 15.0 | 8:13:00 | 63.0 | 136.0 | 55.0 | 82.0 | 8.6 | | | |
| ** EFFICACY TIME ** | | | 8:13:00 | | | | | | | | |

* PERSISTS TO 8:13:00

Appendix 2E - Revised Efficacy and All Patients Data for Studies 51A, 51B and 49

IX. "Efficacy Patients" tables and "All Patient" tables and figures which include ten and 15 minute postinfusion observation for Studies #8052-83-49, 8052-84-51A, and 8052-84-51B.

A. Study 8052-84-51A

Table 11 - Efficacy Patients
HR
SBP

Table 12 - Efficacy Patients
DBP
MAP
RPP

B. Study 8052-84-51A

Table 25 - All Patients
HR
SBP

Table 26 - All Patients
DBP
MAP
RPP

C. Study 8052-84-51B

Table 11 - Efficacy Patients
HR
SBP

Table 12 - Efficacy Patients
DBP
MAP
RPP

D. Study 8052-84-51B

Table 27 - All Patients
HR
SBP

Table 28 - All Patients
DBP
MAP
RPP

E. Study 8052-83-49

Table 11 - Efficacy Patients
HR
SBP

Table 12 - Efficacy Patients
DBP
MAP
RPP

F. Study 8052-83-49

Table 27 - All Patients
HR
SBP

Table 28 - All Patients
DBP
MAP
RPP

Table 11

Heart Rate and Systolic Blood Pressure with Changes from Baseline, by Period, for "Efficacy Patients" Treated with Esmolol or Placebo[a]

| | | BASELINE | | | PREINDUCTION | | | PREINTUBATION | | | MAXIMUM | | | POST INF 2 | | | POST INF 6 | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | Mean ± SEM | | N | Mean ± SEM | | N | Mean ± SEM | | N[b] | Mean ± SEM | | N | Mean ± SEM | | N | Mean ± SEM | | N |
| Group | | | | | | | | | | | | | | | | | | | |
| HR (bpm) | Esmolol | 73.9 | 1.8 | 50 | 68.8 | 1.5 | 50 | 80.5 | 1.8 | 46 | 97.1 | 1.9 | 50 | 81.3 | 3.8 | 19 | 80.6 | 4.4 | 14 |
| | Placebo | 74.7 | 2.0 | 51 | 77.4 | 2.4 | 51 | 88.9 | 2.2 | 49 | 112.3 | 2.2 | 51 | 91.7 | 2.5 | 25 | 89.9 | 4.2 | 17 |
| HR Change | Esmolol | | | | -5.1[#] | 1.0 | 50 | 6.6[#] | 1.9 | 46 | 23.3 | 2.3 | 50 | 7.9 | 2.5 | 19 | 6.4 | 2.9 | 14 |
| | Placebo | | | | 2.7[#] | 1.1 | 51 | 13.8[#] | 1.6 | 49 | 37.5 | 2.2 | 51 | 15.6[#] | 3.4 | 25 | 13.2 | 5.0 | 17 |
| Comparison of Change[c] | | N.S. | | | P>E[**] | | | P>E[*] | | | P>E[**] | | | N.S. | | | N.S. | | |
| SBP (mmHg) | Esmolol | 131.8 | 2.4 | 50 | 127.0 | 2.3 | 50 | 124.8 | 2.8 | 43 | 157.9 | 3.0 | 50 | 110.9 | 4.3 | 19 | 103.5 | 5.5 | 14 |
| | Placebo | 128.5 | 2.2 | 51 | 128.3 | 2.3 | 51 | 121.9 | 2.3 | 48 | 168.7 | 3.4 | 51 | 118.6 | 2.7 | 25 | 113.6 | 2.9 | 17 |
| SBP Change | Esmolol | | | | -4.8[#] | 0.9 | 50 | -8.9[#] | 2.2 | 43 | 28.2 | 2.8 | 50 | -19.7[#] | 6.0 | 19 | -26.9[#] | 8.6 | 14 |
| | Placebo | | | | -0.2 | 1.0 | 51 | -6.4[#] | 2.0 | 48 | 40.2 | 2.8 | 51 | -11.7[#] | 2.4 | 25 | -19.2[#] | 4.1 | 17 |
| Comparison of Change[c] | | N.S. | | | P>E[*] | | | N.T. | | | P>E[**] | | | N.S. | | | N.S. | | |

[#] Indicates significant change from baseline ($p<0.05$). Maximum change from baseline was not tested for significance.
[a] Significant center by treatment interaction was detected for SBP at the preintubation period ($p<0.05$).
[b] Preintubation heart rates were not determined in Patients #101, 115, 511, and 513 in the esmolol group and in Patients #504 and 508 in the placebo group. In addition to these patients, SBP was not measured in Patients #154, 160 and 310 in the esmolol group and in Patient #126 in the placebo group.
[c] N.S. Indicates no significant difference between the esmolol and placebo treatment groups ($p\geq0.05$).
P = Placebo, E = Esmolol 300 mcg/kg/min, * $p<0.05$, ** $p<0.01$
N.T. Not tested because of significant center by treatment interaction.

Table 11 (continued)

New Table

Heart Rate and Systolic Blood Pressure with Changes from Baseline, at 10 and 15 Minutes Postinfusion, for "Efficacy Patients" Treated With Esmolol or Placebo

Study #8052-84-51A

| | | POST INF 10 | | | POST INF 15 | | |
|---|---|---|---|---|---|---|---|
| | | Mean ± SEM | | N | Mean ± SEM | | N |
| | Group | | | | | | |
| HR (bpm) | Esmolol | 75.8 | 5.6 | 8 | 67.5 | 1.2 | 4 |
| | Placebo | 87.5 | 6.7 | 10 | 82.8 | 5.5 | 6 |
| HR Change | Esmolol | 2.2 | 3.3 | 8 | 0.3 | 1.9 | 4 |
| | Placebo | 6.3 | 7.4 | 10 | 4.7 | 4.4 | 6 |
| Comparison of Change* | | N.T. | | | N.T. | | |
| SBP (mmHg) | Esmolol | 89.9 | 4.3 | 8 | 87.8 | 7.4 | 4 |
| | Placebo | 107.4 | 5.0 | 10 | 105.7 | 4.3 | 6 |
| SBP Change | Esmolol | -40.5# | 8.6 | 8 | -48.0 | 16.3 | 4 |
| | Placebo | -23.9# | 5.6 | 10 | -25.5# | 5.1 | 6 |
| Comparison of Change* | | N.T. | | | N.T. | | |

# Indicates significant change from baseline ($p<0.05$).

* N.T. Not tested due to small sample size.

Table 12

Diastolic Blood Pressure, Mean Arterial Blood Pressure, and Rate-Pressure Product with Changes from Baseline, by Period, for "Efficacy Patients" Treated with Esmolol or Placebo[a]

| | | BASELINE | | | PREINDUCTION | | | PREINTUBATION | | | MAXIMUM | | | POST INF 2 | | | POST INF 5 | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | Mean ± SEM | | N | Mean ± SEM | | N | Mean ± SEM | | N[b] | Mean ± SEM | | N | Mean ± SEM | | N | Mean ± SEM | | N |
| Group | | | | | | | | | | | | | | | | | | | |
| DBP (mmHg) | Esmolol | 78.5 | 1.7 | 50 | 77.3 | 2.0 | 50 | 81.2 | 2.7 | 43 | 111.0 | 2.6 | 50 | 87.8 | 4.3 | 19 | 82.5 | 4.7 | 14 |
| | Placebo | 76.8 | 1.4 | 51 | 76.0 | 1.4 | 51 | 75.1 | 1.9 | 48 | 114.2 | 2.5 | 51 | 71.6 | 2.6 | 25 | 73.5 | 2.9 | 17 |
| DBP Change | Esmolol | | | | -1.3 | 0.9 | 50 | 2.9 | 2.7 | 43 | 32.5 | 2.0 | 50 | -10.2* | 3.3 | 19 | -15.6* | 4.8 | 14 |
| | Placebo | | | | -0.8 | 1.2 | 51 | -1.7 | 1.6 | 48 | 37.4 | 2.0 | 51 | -7.9* | 2.3 | 25 | -8.0* | 3.6 | 17 |
| Comparison of Change[c] | | N.S. | | | N.S. | | | N.T. | | | N.S. | | | N.S. | | | N.S. | | |
| MAP (mmHg) | Esmolol | 98.3 | 1.8 | 50 | 93.9 | 2.0 | 50 | 95.7 | 2.6 | 43 | 125.9 | 2.6 | 50 | 82.2 | 4.1 | 19 | 78.2 | 4.8 | 14 |
| | Placebo | 94.0 | 1.6 | 51 | 93.4 | 1.5 | 51 | 90.7 | 1.9 | 48 | 131.2 | 2.7 | 51 | 87.3 | 2.5 | 25 | 86.9 | 2.7 | 17 |
| MAP Change | Esmolol | | | | -2.4* | 0.7 | 50 | -0.3 | 2.4 | 43 | 29.6 | 2.0 | 50 | -13.4* | 4.0 | 19 | -19.4* | 5.9 | 14 |
| | Placebo | | | | -0.8 | 0.9 | 51 | -3.3* | 1.5 | 48 | 37.2 | 2.1 | 51 | -9.2* | 2.1 | 25 | -11.7* | 3.4 | 17 |
| Comparison of Change[c] | | N.S. | | | N.S. | | | N.T. | | | P>E* | | | N.S. | | | N.S. | | |
| RPP | Esmolol | 9.8 | 0.3 | 50 | 8.8 | 0.3 | 50 | 10.0 | 0.3 | 43 | 14.3 | 0.5 | 50 | 9.2 | 0.7 | 19 | 8.5 | 0.8 | 14 |
| | Placebo | 9.6 | 0.3 | 51 | 9.9 | 0.3 | 51 | 10.8 | 0.3 | 48 | 18.0 | 0.8 | 51 | 10.8 | 0.3 | 25 | 10.3 | 0.7 | 17 |
| RPP Change | Esmolol | | | | -1.0* | 0.2 | 50 | 0.2 | 0.4 | 43 | 4.5 | 0.4 | 50 | -0.5* | 0.6 | 19 | -1.2* | 0.8 | 14 |
| | Placebo | | | | 0.3 | 0.2 | 51 | 1.2* | 0.3 | 48 | 8.4 | 0.5 | 51 | 0.9 | 0.5 | 25 | 0.1 | 0.9 | 17 |
| Comparison of Change[c] | | N.S. | | | P>E** | | | N.S. | | | P>E** | | | N.S. | | | N.S. | | |

* Indicates significant change from baseline ($p<0.05$). Maximum change from baseline was not tested for significance.

a Significant center by treatment interactions were found for both DBP and MAP at the preintubation period ($p<0.05$).

b Preintubation blood pressure was not determined in Patients #101, 115, 154, 160, 310, 511, and 513 in the esmolol group and Patients #126, 504 and 508 in the placebo group.

c N.S. Indicates no significant difference between the esmolol and placebo treatment groups ($p\geq0.05$).
P = Placebo, E = Esmolol 300 mcg/kg/min, * $p<0.05$, ** $p<0.01$
N.T. Not tested because of significant center by treatment interactions.

Table 12 (continued)

New Table

Diastolic and Mean Arterial Blood Pressures and Rate-Pressure Product with Changes from Baseline, at 10 and 15 Minutes Postinfusion, for "Efficacy Patients" Treated with Esmolol or Placebo

Study #8052-84-51A

| | | POST INF 10 | | | POST INF 15 | | |
|---|---|---|---|---|---|---|---|
| | | Mean ± SEM | | N | Mean ± SEM | | N |
| | Group | | | | | | |
| DBP (mmHg) | Esmolol | 56.4 | 4.4 | 8 | 51.2 | 5.4 | 4 |
| | Placebo | 73.0 | 4.4 | 10 | 63.2 | 3.2 | 6 |
| DBP Change | Esmolol | -24.5# | 4.6 | 8 | -30.2# | 7.1 | 4 |
| | Placebo | -8.6 | 4.3 | 10 | -18.2# | 4.5 | 6 |
| Comparison of Change[a] | | N.T. | | | N.T. | | |
| MAP (mmHg) | Esmolol | 67.5 | 4.2 | 8 | 63.4 | 5.9 | 4 |
| | Placebo | 84.5 | 3.8 | 10 | 77.3 | 2.9 | 6 |
| MAP Change | Esmolol | -29.9# | 5.8 | 8 | -36.2# | 9.6 | 4 |
| | Placebo | -13.7# | 4.1 | 10 | -20.6# | 4.4 | 6 |
| Comparison of Change[a] | | N.T. | | | N.T. | | |
| RPP | Esmolol | 6.8 | 0.6 | 8 | 5.9 | 0.5 | 4 |
| | Placebo | 9.6 | 1.1 | 10 | 8.8 | 0.7 | 6 |
| RPP Change | Esmolol | -2.8# | 0.5 | 8 | -3.2# | 0.9 | 4 |
| | Placebo | -1.1 | 1.2 | 10 | -1.5 | 0.6 | 6 |
| Comparison of Change[a] | | N.T. | | | N.T. | | |

# Indicates significant change from baseline ($p<0.05$).

[a] N.T. Not tested due to small sample size.

Study #8052-84-51A

TABLE 25

Heart Rate and Systolic Blood Pressure with Changes from Baseline, by Period, for "All Patients" Treated with Esmolol or Placebo[b]

| | | BASELINE | PREINDUCTION | PREINTUBATION | MAXIMUM | POST INF 2 | POST INF 5 |
|---|---|---|---|---|---|---|---|
| | | MEAN ± SEM N | MEAN ± SEM N | MEAN ± SEM N | MEAN ± SEM N | MEAN ± SEM N | MEAN ± SEM N |
| | Group | | | | | | |
| HR (bpm) | Esmolol | 73.9 1.8 58 | 69.7 1.6 57[c] | 81.5 1.9 53[c] | 97.2 1.9 57[c] | 75.8 1.7 57[c] | 72.8 1.7 56[c] |
| | Placebo | 74.9 1.9 54 | 77.8 2.4 54 | 88.8 2.1 52 | 113.1 2.1 53 | 86.8 1.9 53 | 82.0 2.2 51 |
| HR Change | Esmolol | | -4.4[a] 1.2 57 | 7.3[a] 1.9 53 | 23.1 2.1 57 | 1.7 2.0 57 | -1.6 1.9 56 |
| | Placebo | | 2.9[a] 1.1 54 | 13.5[a] 1.6 52 | 38.1 2.1 53 | 11.8[a] 2.1 53 | 6.6[a] 2.4 51 |
| Comparison of Change[b] | | N.S. | P>E** | P>E* | P>E** | P>E** | P>E* |
| SBP (mm Hg) | Esmolol | 132.3 2.2 58 | 127.4 2.2 57 | 126.5 2.8 49 | 160.4 2.8 57 | 107.1 3.1 57 | 100.4 2.7 56 |
| | Placebo | 128.7 2.1 54 | 128.4 2.2 54 | 122.5 2.2 51 | 167.8 3.3 53 | 116.7 2.0 53 | 107.6 2.2 50 |
| SBP Change | Esmolol | | -4.7[a] 0.9 57 | -6.0[a] 2.0 49 | 23.3 2.2 57 | -24.9[a] 3.3 57 | -31.8[a] 3.2 56 |
| | Placebo | | -0.4 1.0 54 | -8.1[a] 1.9 51 | 39.1 2.5 53 | -12.0[a] 1.7 53 | -20.1[a] 2.1 50 |
| Comparison of Change[b] | | N.S. | P>E** | N.T. | P>E** | P>E* | P>E* |

a Indicates significant change from baseline ($p<0.05$). Maximum change from baseline was not tested for significance.
a Significant center by treatment interactions were found for both DBP and MAP at the preintubation period ($p<0.05$).
b N.S. Inuicates no significant difference between the esmolol and placebo treatment groups ($p\geq0.05$).
P = Placebo, E = Esmolol 300 mcg/kg/min, * $p<0.05$, ** $p<0.01$
N.T. Not tested because of significant center by treatment interactions.
c Data not available for all patients.

Table 25 (continued)

New Table

Heart Rate and Systolic Blood Pressure with Changes from Baseline, at 10 and 15 Minutes Postinfusion, for "All Patients" Treated With Esmolol or Placebo

Study #8052-84-51A

| | | POST INF 10 | | | POST INF 15 | | |
|---|---|---|---|---|---|---|---|
| | | Mean ± | SEM | N | Mean ± | SEM | N |
| | Group | | | | | | |
| HR (bpm) | Esmolol | 75.0 | 2.1 | 49 | 75.9 | 2.0 | 44 |
| | Placebo | 80.0 | 2.3 | 46 | 78.8 | 2.4 | 39 |
| HR Change | Esmolol | 0.3 | 1.8 | 49 | 1.2 | 2.1 | 44 |
| | Placebo | 3.5 | 2.5 | 46 | 1.0 | 2.7 | 39 |
| Comparison of Change[a] | | | N.T. | | | N.S. | |
| SBP (mmHg) | Esmolol | 100.0 | 2.7 | 49 | 104.1 | 2.4 | 44 |
| | Placebo | 104.0 | 2.0 | 46 | 107.0 | 2.3 | 38 |
| SBP Change | Esmolol | -32.7# | 3.2 | 49 | -27.2# | 3.3 | 44 |
| | Placebo | -24.8# | 2.6 | 46 | -20.2# | 2.7 | 38 |
| Comparison of Change[a] | | | N.S. | | | N.S. | |

# Indicates significant change from baseline ($p<0.05$).

[a] N.T. Not tested due to significant center by treatment interaction.

N.S. Indicates no significant difference between the esmolol and placebo treatment groups ($p \geq 0.05$).

TABLE 26

Diastolic Blood Pressure, Mean Arterial Blood Pressure, and Rate-Pressure Product with Changes from Baseline, by Period, for "All Patients" Treated with Esmolol or Placebo[a]

| | | BASELINE | | | PREINDUCTION | | | PREINTUBATION | | | MAXIMUM | | | POST INF 2 | | | POST INF 5 | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | MEAN | ± SEM | N | MEAN | ± SEM | N | MEAN | ± SEM | N | MEAN | ± SEM | N | MEAN | ± SEM | N | MEAN | ± SEM | N |
| Group | | | | | | | | | | | | | | | | | | | |
| DBP (mm Hg) | Esmolol | 78.5 | 1.6 | 58 | 77.3 | 1.8 | 57[c] | 81.3 | 2.7 | 49[c] | 112.7 | 2.6 | 57[c] | 88.2 | 2.9 | 57[c] | 82.8 | 2.1 | 56[c] |
| | Placebo | 77.0 | 1.4 | 54 | 75.7 | 1.3 | 54 | 74.7 | 1.8 | 51 | 113.3 | 2.5 | 53 | 89.5 | 1.7 | 53 | 86.1 | 1.6 | 50 |
| DBP Change | Esmolol | | | | -1.3 | 0.8 | 57 | 2.8 | 2.5 | 49 | 34.1 | 1.9 | 57 | -10.4[a] | 2.5 | 57 | -16.2[a] | 1.8 | 56 |
| | Placebo | | | | -1.2 | 1.2 | 54 | -2.4 | 1.6 | 51 | 36.4 | 2.0 | 53 | -7.4[a] | 1.4 | 53 | -10.7[a] | 1.6 | 50 |
| Comparison of Change[b] | | N.S. | | | N.S. | | | N.T. | | | N.S. | | | N.S. | | | N.S. | | |
| MAP (mm Hg) | Esmolol | 96.4 | 1.7 | 58 | 94.0 | 1.9 | 57 | 96.4 | 2.6 | 49 | 127.8 | 2.6 | 57 | 81.2 | 2.9 | 57 | 75.2 | 2.2 | 56 |
| | Placebo | 94.2 | 1.5 | 54 | 93.3 | 1.4 | 54 | 90.6 | 1.8 | 51 | 130.2 | 2.7 | 53 | 85.2 | 1.7 | 53 | 79.9 | 1.8 | 50 |
| MAP Change | Esmolol | | | | -2.4[a] | 0.7 | 57 | -0.1 | 2.2 | 49 | 31.4 | 1.9 | 57 | -15.2[a] | 2.8 | 57 | -21.4[a] | 2.2 | 56 |
| | Placebo | | | | -1.0 | 0.9 | 54 | -3.6[a] | 1.5 | 51 | 36.1 | 2.1 | 53 | -9.0[a] | 1.3 | 53 | -13.8[a] | 1.6 | 50 |
| Comparison of Change[b] | | N.S. | | | N.S. | | | N.T. | | | N.S. | | | N.S. | | | N.S. | | |
| RPP | Esmolol | 9.8 | 0.3 | 58 | 8.9 | 0.3 | 57 | 10.2 | 0.3 | 49 | 14.6 | 0.5 | 57 | 8.2 | 0.4 | 57 | 7.4 | 0.3 | 56 |
| | Placebo | 9.6 | 0.3 | 54 | 10.0 | 0.3 | 54 | 10.9 | 0.3 | 51 | 17.9 | 0.6 | 53 | 10.1 | 0.3 | 53 | 9.0 | 0.4 | 50 |
| RPP Change | Esmolol | | | | -0.9[a] | 0.2 | 57 | 0.3 | 0.3 | 49 | 4.7 | 0.4 | 57 | -1.6[a] | 0.4 | 57 | -2.5[a] | 0.4 | 56 |
| | Placebo | | | | 0.3 | 0.2 | 54 | 1.2[a] | 0.3 | 51 | 8.3 | 0.5 | 53 | 0.5 | 0.3 | 53 | -0.7 | 0.4 | 50 |
| Comparison of Change[b] | | N.S. | | | P>E** | | | N.S. | | | P>E** | | | P>E** | | | P>E** | | |

[a] Indicates significant change from baseline ($p<0.05$). Maximum change from baseline was not tested for significance.
[a] Significant center by treatment interactions were found for both DBP and MAP at the preintubation period ($p<0.05$).
[b] N.S. Indicates no significant difference between the esmolol and placebo treatment groups ($p\geq0.05$).
P = Placebo, E = Esmolol 300 mcg/kg/min, * $p<0.05$, ** $p<0.01$
N.T. Not tested because of significant center by treatment interactions.
[c] Data not available for all patients.

Table 26 (continued)

New Table

Diastolic and Mean Arterial Blood Pressures and Rate-Pressure Product with Changes from Baseline, at 10 and 15 Minutes Postinfusion, for "All Patients" Treated with Esmolol or Placebo

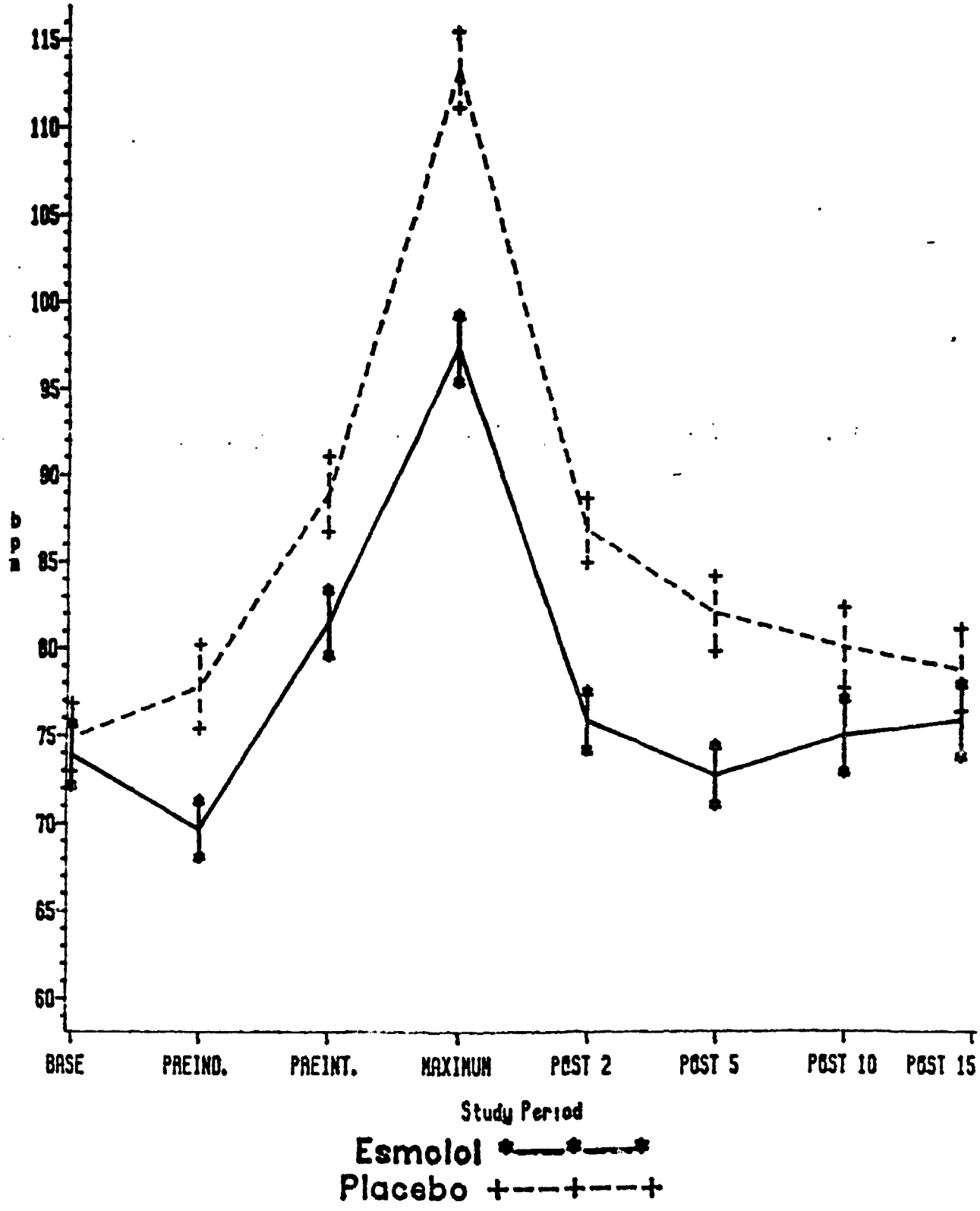
Study #8052-84-51A

| | | POST INF 10 | | | POST INF 15 | | |
|---|---|---|---|---|---|---|---|
| | | Mean ± SEM | | N | Mean ± SEM | | N |
| | Group | | | | | | |
| DBP (mmHg) | Esmolol | 64.0 | 1.9 | 49 | 67.5 | 2.4 | 44 |
| | Placebo | 66.8 | 1.5 | 46 | 68.7 | 2.0 | 38 |
| DBP Change | Esmolol | -15.6# | 1.9 | 49 | -12.4# | 2.3 | 44 |
| | Placebo | -10.8# | 1.6 | 46 | -8.4# | 2.1 | 38 |
| Comparison of Change[a] | | | N.S. | | | N.S. | |
| MAP (mmHg) | Esmolol | 76.0 | 2.1 | 49 | 79.7 | 2.4 | 44 |
| | Placebo | 79.2 | 1.5 | 46 | 81.5 | 2.0 | 38 |
| MAP Change | Esmolol | -21.3# | 2.2 | 49 | -17.3# | 2.5 | 44 |
| | Placebo | -15.5# | 1.8 | 46 | -12.3# | 2.2 | 38 |
| Comparison of Change[a] | | | N.S. | | | N.S. | |
| RPP | Esmolol | 7.6 | 0.3 | 49 | 8.0 | 0.4 | 44 |
| | Placebo | 8.4 | 0.3 | 46 | 8.5 | 0.3 | 38 |
| RPP Change | Esmolol | -2.4# | 0.4 | 49 | -1.9# | 0.4 | 44 |
| | Placebo | -1.5# | 0.4 | 46 | -1.4# | 0.4 | 38 |
| Comparison of Change[a] | | | N.S. | | | N.S. | |

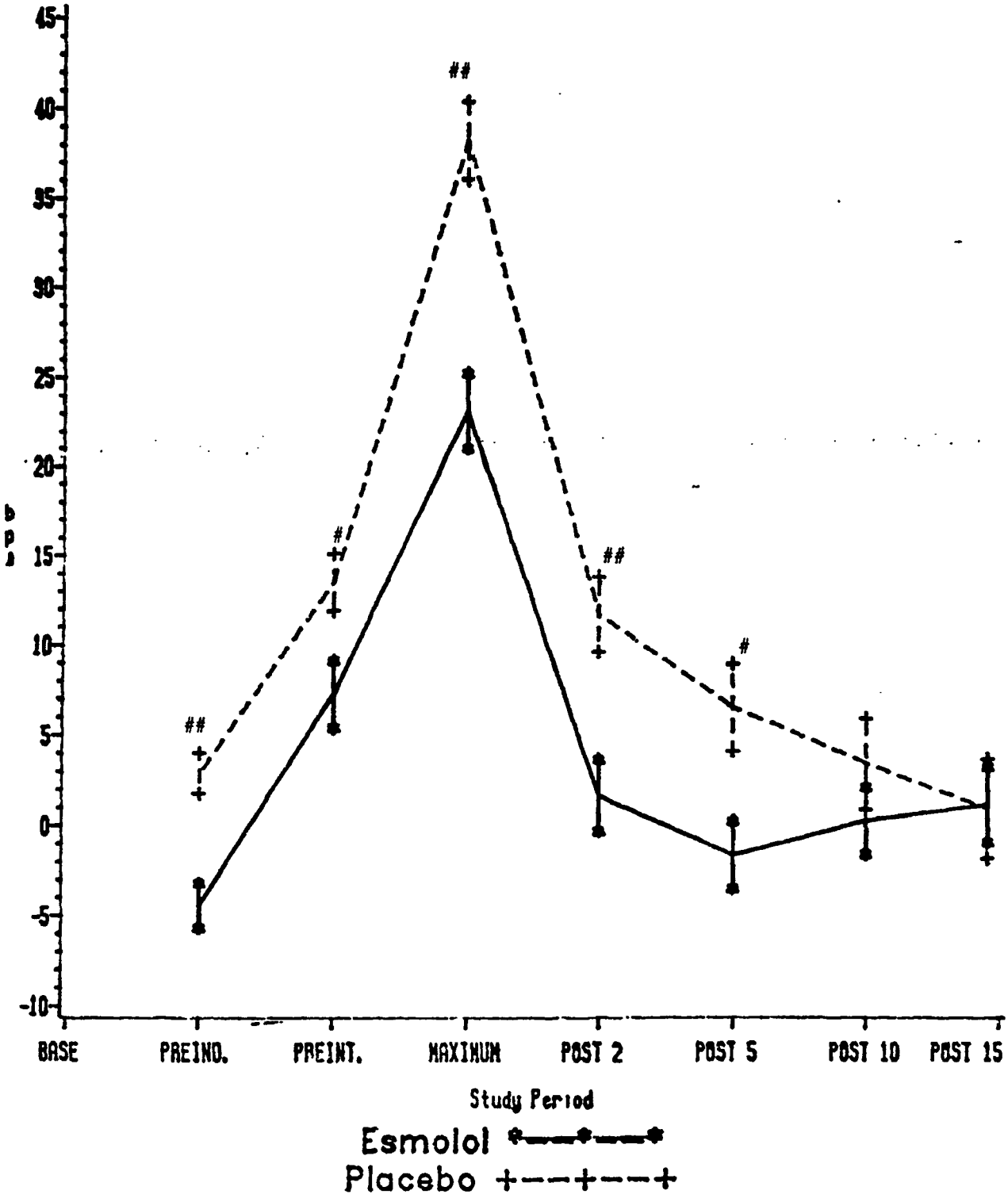
# Indicates significant change from baseline ($p<0.05$).

[a] N.S. Indicates no significant difference between the esmolol and placebo treatment groups ($p \geq 0.05$).

# *ASA I & II (8052-84-51A)*
## *Heart Rate for All Patients*



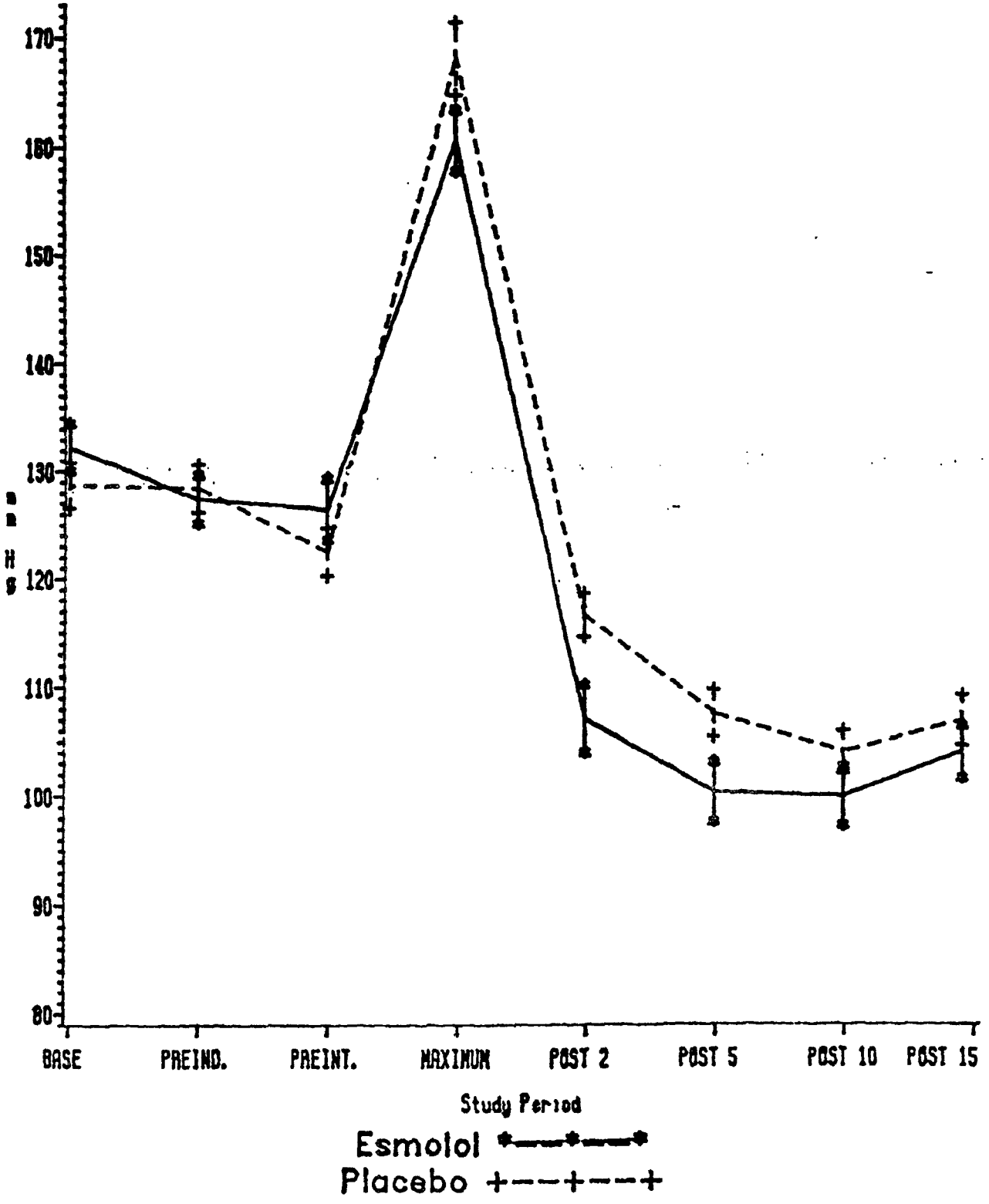
# *ASA I & II (8052-84-51A)*
# *Heart Rate Changes from Baseline for All Patients*



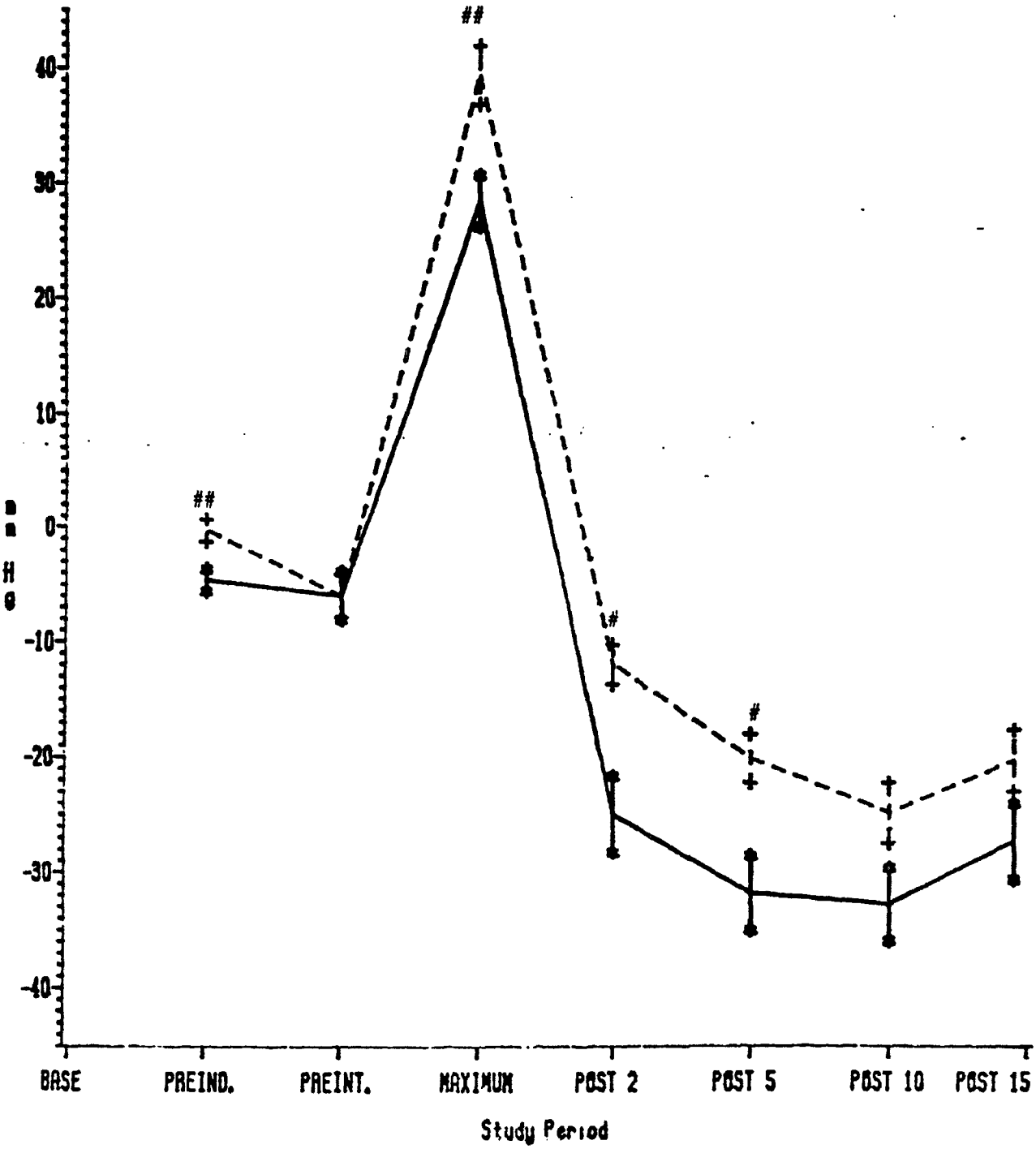

\# Significant difference between esmolol and placebo with respect to change from baseline ($p < 0.05$).

\## $p < 0.01$.

# *ASA I & II (8052-84-51A)*
## *Systolic Blood Pressure for All Patients*



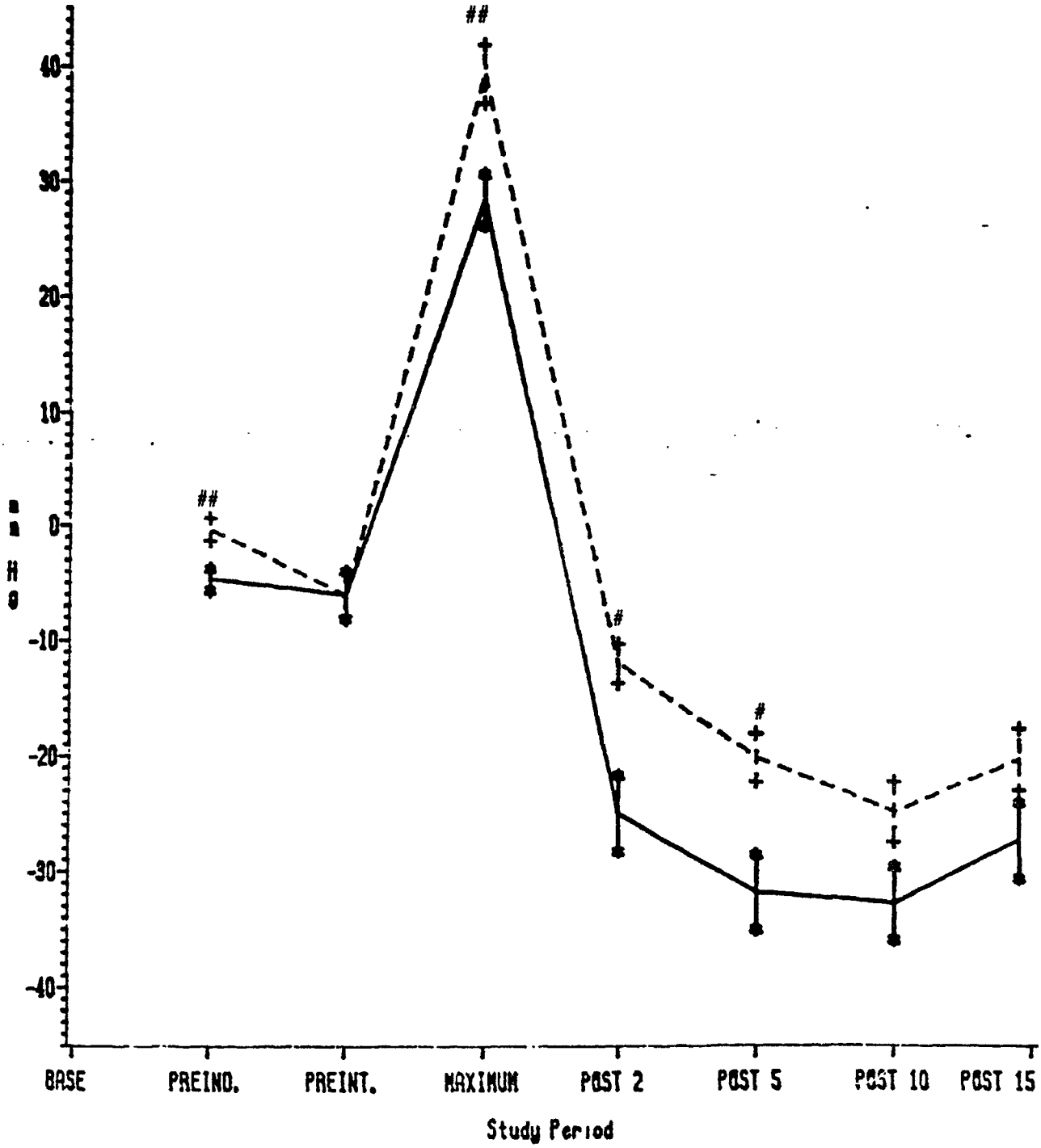
# *ASA I & II (8052-84-51A)*
## *Systolic Blood Pressure Changes from Baseline for All Patients*




\# Significant difference between esmolol and placebo with respect to change from baseline ($p < 0.05$).

\#\# $p < 0.01$

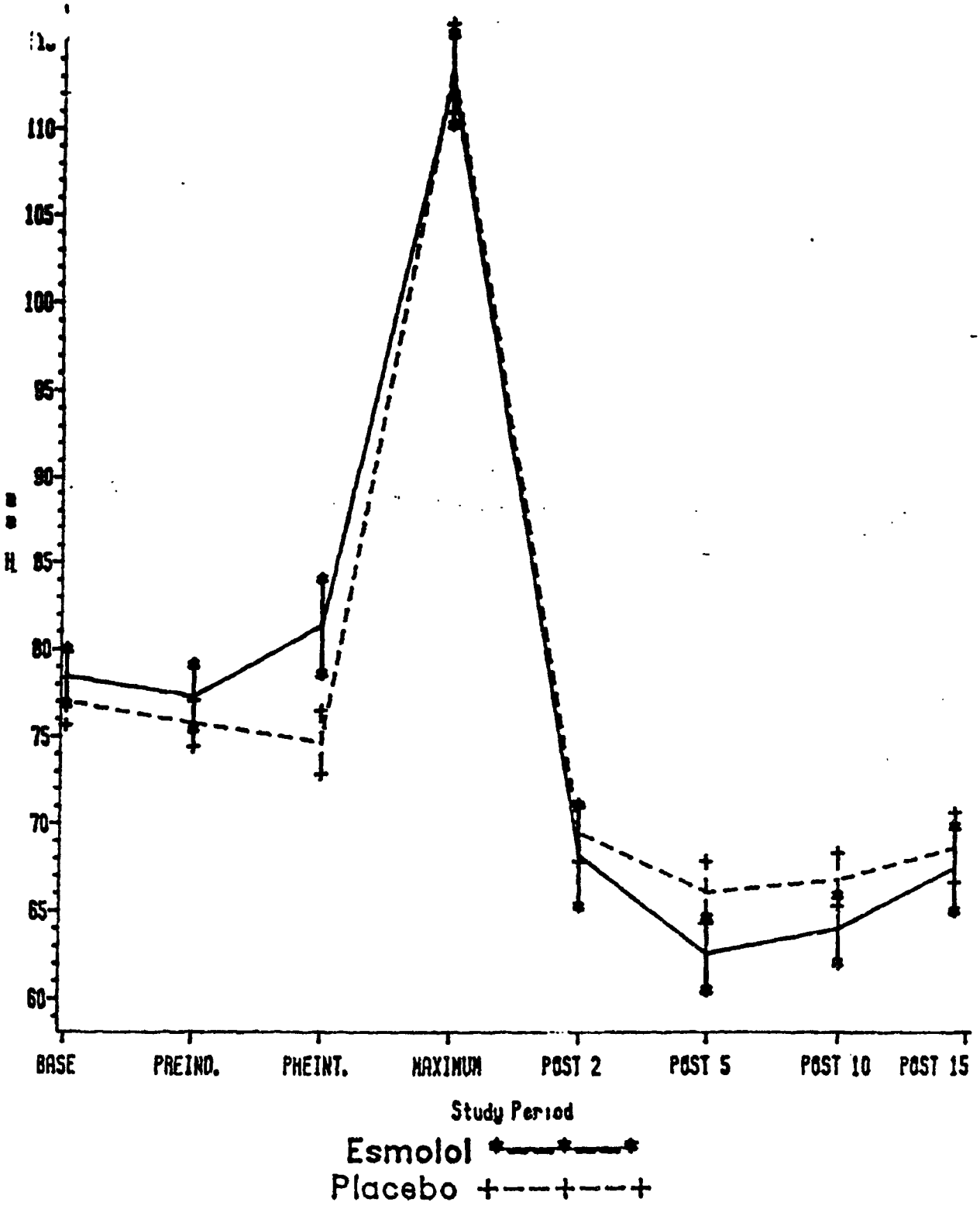
# *ASA I & II (8052-84-51A)*
## *Systolic Blood Pressure Changes from Baseline for All Patients*



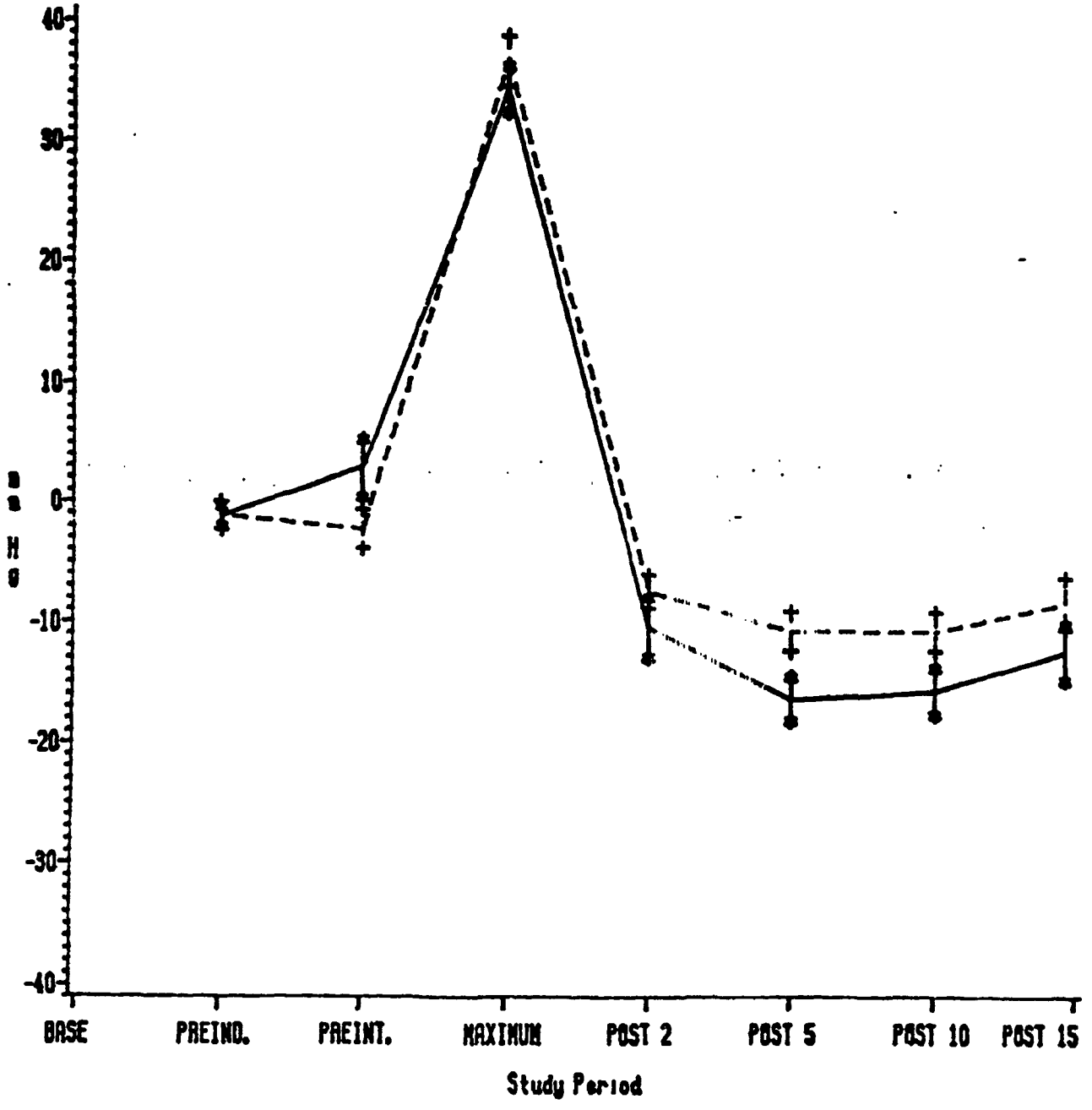

\# Significant difference between esmolol and placebo with respect to change from baseline ($p < 0.05$).

** $p < 0.01$

# *ASA I & .I (8052-84-51A)*
## *Diastolic Blood Pressure for All Patients*



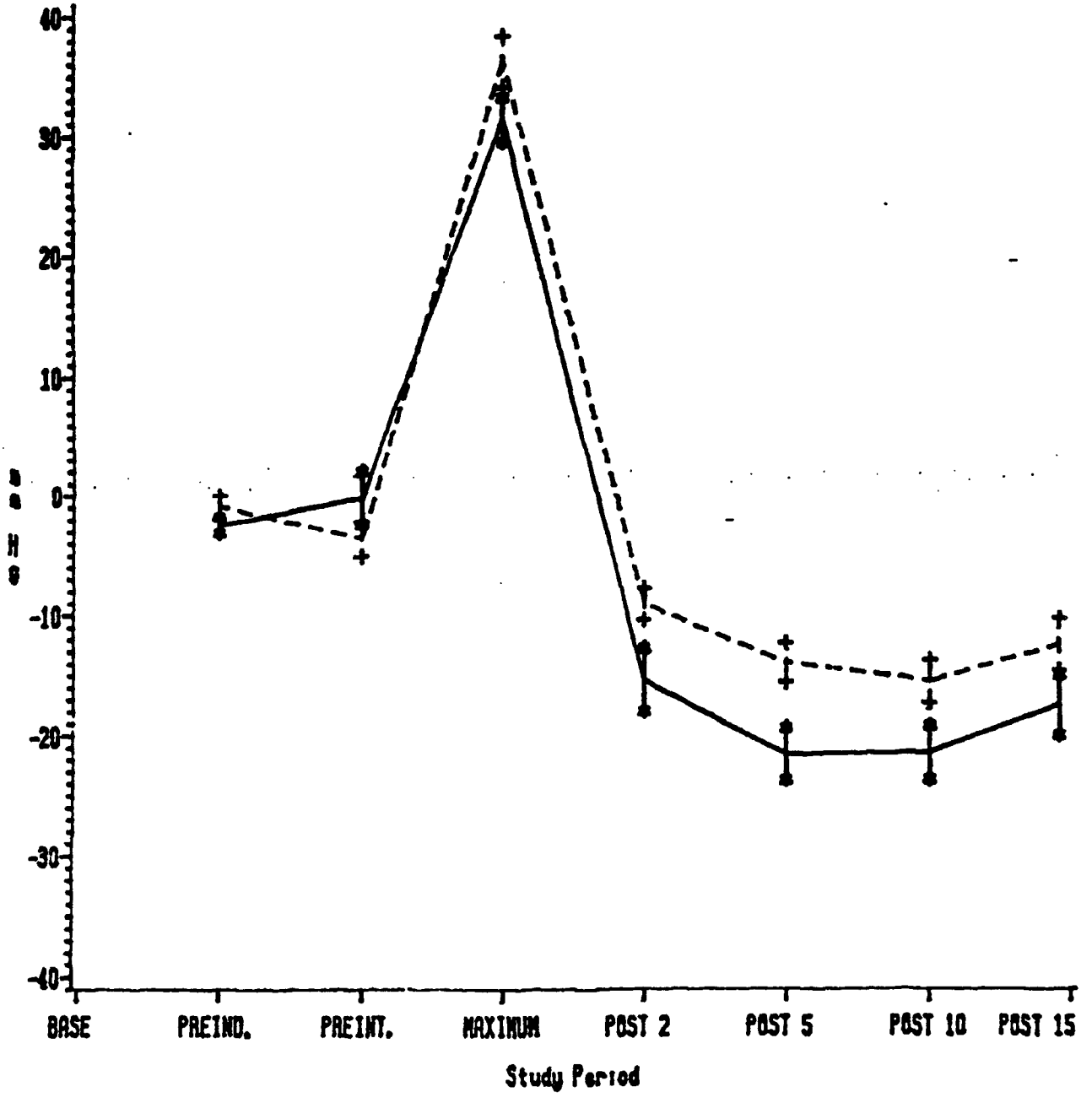
# *ASA I & II (8052-84-51A)*
# *Diastolic Blood Pressure Changes from Baseline for All Patients*




Esmolol *——*——*

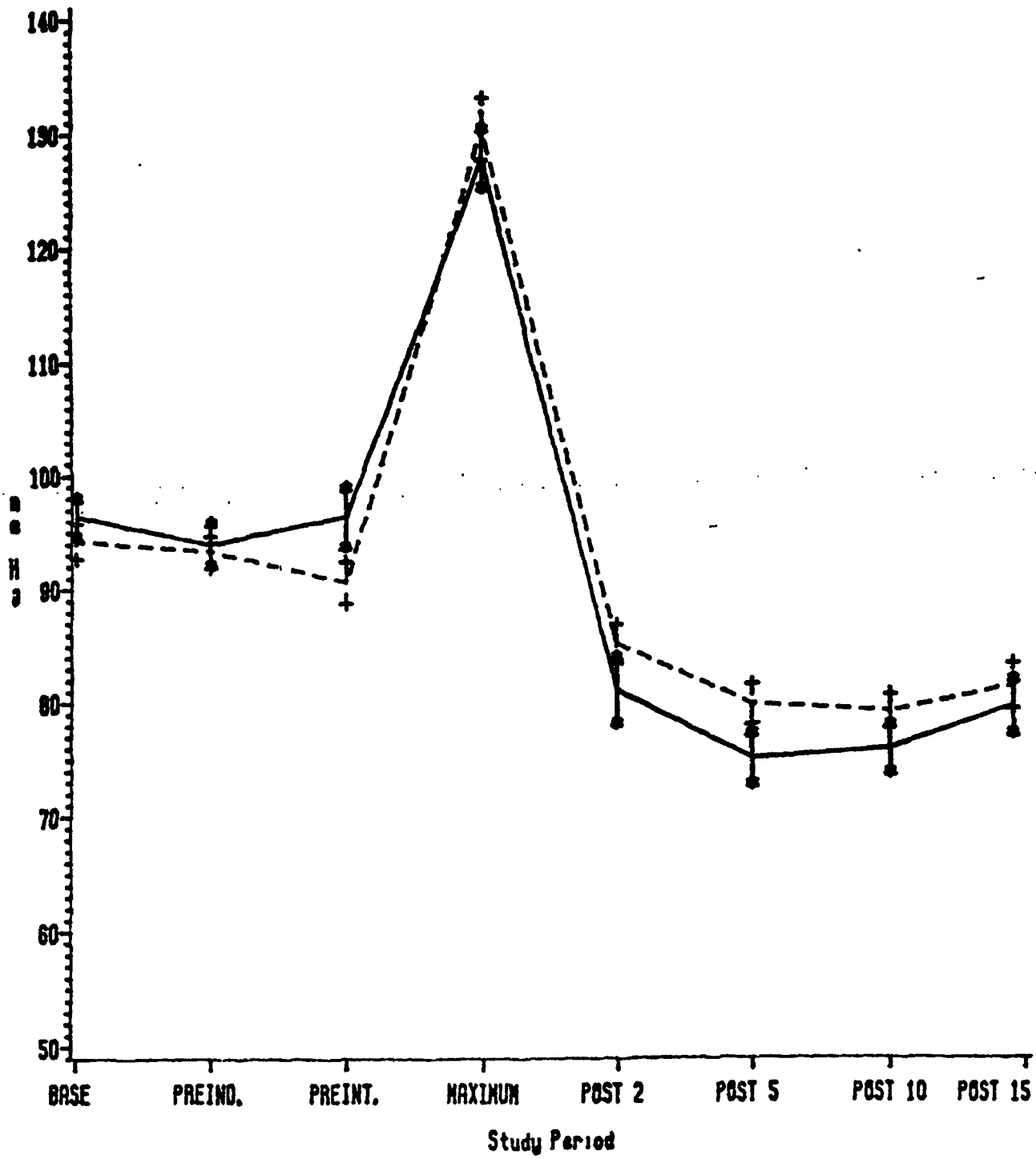
Placebo +——+——+

# *ASA I & II (8052-84-51A)*
## *Mean Arterial Blood Pressure Changes from Baseline for All Patients*

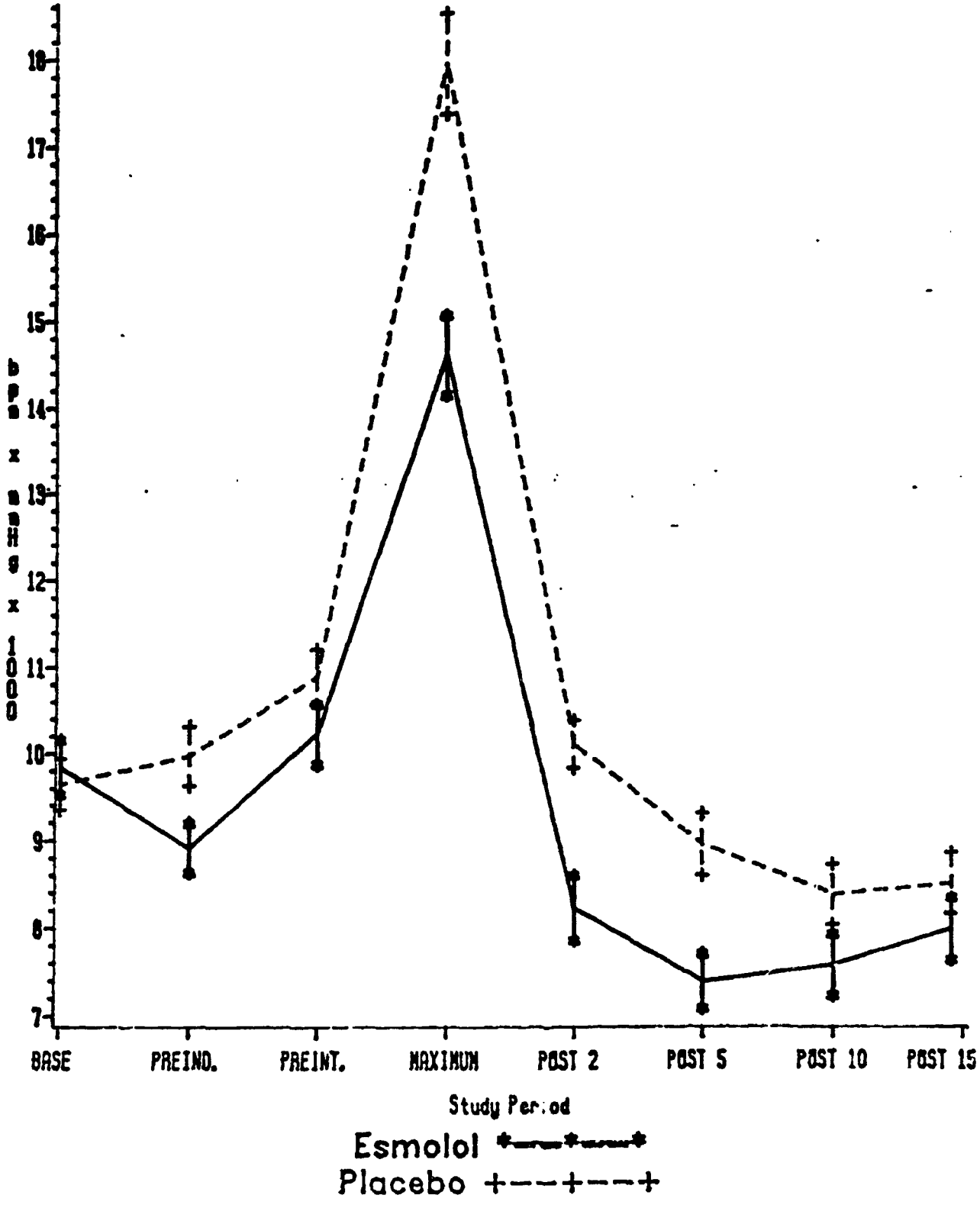



Esmolol
Placebo

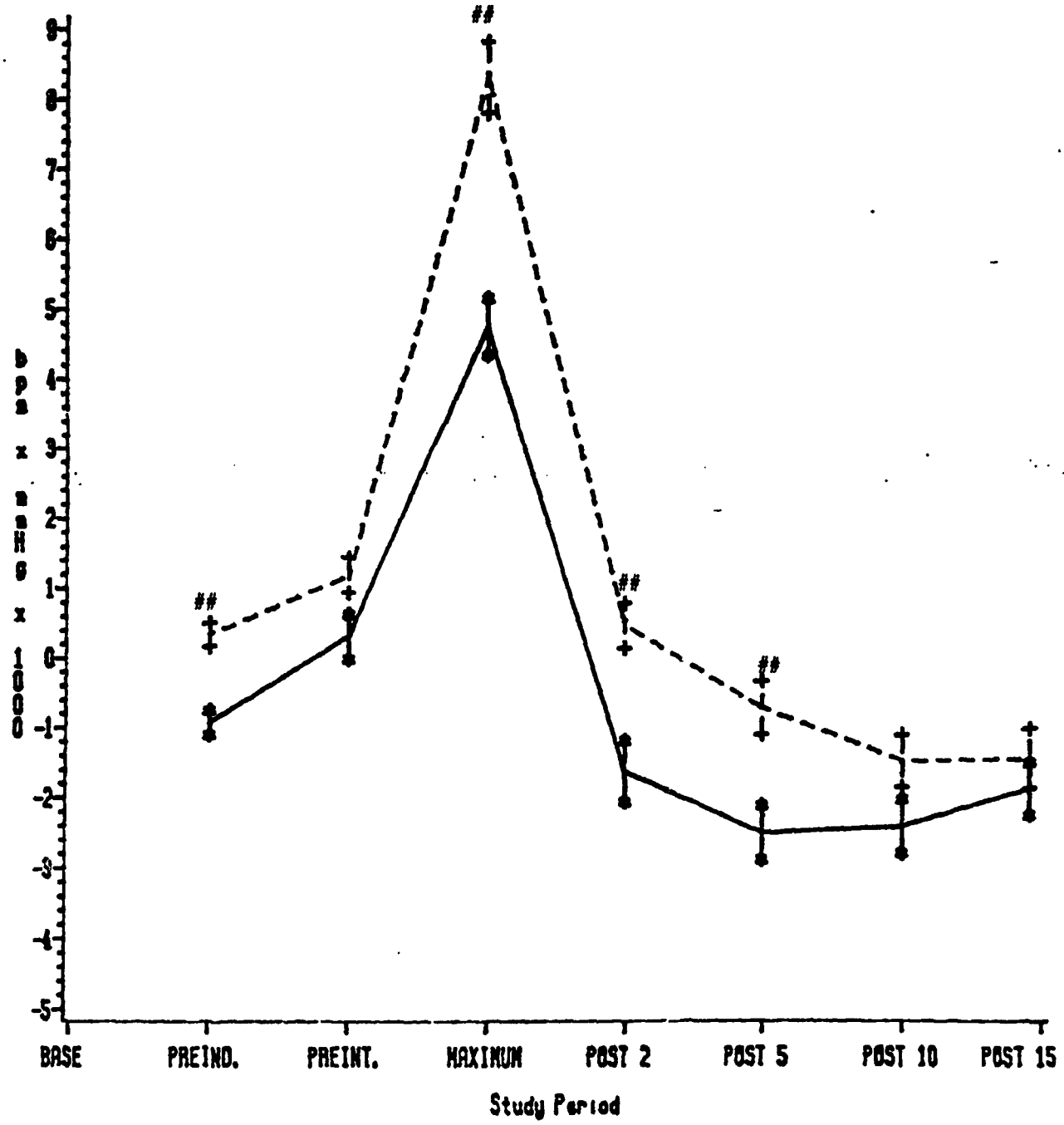
# *ASA I & II (8052-84-51A)*
## *Mean Arterial Blood Pressure for All Patients*



# *ASA I & II (8052-84-5A)*
# *Rate Pressure Product for All Patients*



# *ASA I & II (8052–84–51A)*
# *Rate Pressure Product Changes from Baseline for All Patients*




Esmolol *—*—*—*

Placebo +—+—+

## Significant difference between esmolol and placebo with respect to change from baseline ($p < 0.01$).

Table 11

Heart Rate and Systolic Blood Pressure with Changes from Baseline, by Period, for "Efficacy Patients" Treated with Esmolol or Placebo

| | | BASELINE | | | PREINDUCTION | | | PREINTUBATION | | | MAXIMUM | | | POST INF 2 | | | POST INF 5 | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | Mean ± SEM | | N | Mean ± SEM | | N | Mean ± SEM | | N[a] | Mean ± SEM | | N | Mean ± SEM | | N | Mean ± SEM | | N |
| Group | | | | | | | | | | | | | | | | | | | |
| HR (bpm) | Esmolol | 78.3 | 3.2 | 32 | 66.9 | 2.3 | 32 | 74.9 | 2.5 | 32 | 84.3 | 2.1 | 32 | 71.5 | 2.0 | 24 | 70.1 | 3.7 | 15 |
| | Placebo | 79.7 | 2.7 | 31 | 78.9 | 3.0 | 31 | 88.6 | 2.9 | 31 | 103.6 | 2.8 | 31 | 90.9 | 3.5 | 25 | 86.8 | 4.1 | 19 |
| HR Change | Esmolol | | | | -9.4# | 1.7 | 32 | -1.4 | 2.4 | 32 | 7.9 | 3.0 | 32 | -7.2# | 3.0 | 24 | -12.4# | 4.0 | 15 |
| | Placebo | | | | 0.8 | 1.4 | 31 | 8.9# | 2.4 | 31 | 23.9 | 2.7 | 31 | 10.6# | 2.5 | 25 | 3.6 | 2.8 | 19 |
| Comparison of Change[b] | | N.S. | | | P>E** | | | P>E** | | | P>E** | | | P>E** | | | P>E** | | |
| SBP (mmHg) | Esmolol | 144.8 | 3.8 | 32 | 139.3 | 3.8 | 32 | 129.5 | 5.0 | 31 | 184.2 | 5.0 | 32 | 129.4 | 4.8 | 24 | 119.1 | 6.1 | 15 |
| | Placebo | 139.0 | 4.6 | 31 | 145.6 | 6.5 | 31 | 141.5 | 7.6 | 31 | 184.5 | 6.6 | 31 | 148.8 | 8.6 | 25 | 129.0 | 7.8 | 19 |
| SBP Change | Esmolol | | | | -5.6# | 1.7 | 32 | -14.8# | 4.0 | 31 | 19.4 | 4.2 | 32 | -19.5# | 4.5 | 24 | -34.8# | 6.6 | 15 |
| | Placebo | | | | 6.7# | 2.6 | 31 | 2.5 | 5.5 | 31 | 45.5 | 4.7 | 31 | 7.1 | 6.8 | 25 | -13.6# | 5.9 | 19 |
| Comparison of Change[b] | | N.S. | | | P>E** | | | P>E* | | | P>E* | | | P>E* | | | N.S. | | |

# Indicates significant change from baseline ($p<0.05$). Maximum change from baseline was not tested for significance.
a Preintubation blood pressure was not determined in esmolol-treated Patient #425.
b N.S. indicates no significant difference between the esmolol and placebo treatment groups ($p\geq0.05$).
P = Placebo, E = Esmolol 300 mcg/kg/min, * $p<0.05$, ** $p<0.01$





Study #8052-84-51B

Table 11 (continued)

New Table

Heart Rate and Systolic Blood Pressure with Changes from Baseline, at 10 and 15 Minutes Postinfusion, for "Efficacy Patients" Treated with Esmolol or Placebo

Study #8052-84-518

| | | POST INF 10 | | | POST INF 15 | | |
|---|---|---|---|---|---|---|---|
| | | Mean ± SEM | | N | Mean ± SEM | | N |
| | Group | | | | | | |
| HR (bpm) | Esmolol | 71.4 | 5.3 | 10 | 75.3 | 6.4 | 7 |
| | Placebo | 81.7 | 4.3 | 10 | 83.6 | 6.5 | 5 |
| HR Change | Esmolol | -9.7# | 2.6 | 10 | -11.6# | 3.8 | 7 |
| | Placebo | 2.8 | 2.2 | 10 | -0.7 | 3.7 | 5 |
| Comparison of Change[a] | | P>E* | | | N.T. | | |
| SBP (mmHg) | Esmolol | 108.8 | 6.0 | 10 | 104.6 | 5.8 | 7 |
| | Placebo | 121.1 | 7.7 | 10 | 117.2 | 14.3 | 5 |
| SBP Change | Esmolol | -46.6# | 7.4 | 10 | -57.1# | 6.8 | 7 |
| | Placebo | -25.4# | 6.5 | 10 | -26.9# | 6.3 | 5 |
| Comparison of Change[a] | | N.S. | | | N.T. | | |

# Indicates significant change from baseline ($p<0.05$).

[a] N.T. Not tested due to small sample size.
N.S. Indicates no significant difference between the esmolol and placebo treatment groups ($p\geq0.05$).
P = Placebo, E = Esmolol 300 mcg/kg/min, *$p<0.05$.

Study #8052-84-518

Table 12

Diastolic Blood Pressure, Mean Arterial Blood Pressure, and Rate-Pressure Product with Changes from Baseline, by Period, for "Efficacy Patients" Treated with Esmolol or Placebo

| | | BASELINE | | | PREINDUCTION | | | PREINTUBATION | | | MAXIMUM | | | POST INF 2 | | | POST INF 5 | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | Mean ± SEM | | N | Mean ± SEM | | N | Mean ± SEM | | N[a] | Mean ± SEM | | N | Mean ± SEM | | N | Mean ± SEM | | N |
| Group | | | | | | | | | | | | | | | | | | | |
| DBP (mmHg) | Esmolol | 77.3 | 2.5 | 32 | 78.3 | 2.3 | 32 | 81.3 | 3.9 | 31 | 105.8 | 3.7 | 32 | 79.5 | 3.7 | 24 | 71.7 | 4.6 | 15 |
| | Placebo | 77.9 | 2.4 | 31 | 77.3 | 2.7 | 31 | 81.7 | 3.8 | 31 | 108.6 | 3.2 | 31 | 84.6 | 3.2 | 25 | 75.2 | 4.0 | 19 |
| DBP Change | Esmolol | | | | -1.1 | 1.8 | 32 | 4.4 | 3.7 | 31 | 28.5 | 3.4 | 32 | -2.3 | 3.5 | 24 | -10.2 | 4.9 | 15 |
| | Placebo | | | | -0.5 | 1.2 | 31 | 3.9 | 3.1 | 31 | 30.7 | 2.9 | 31 | 4.3 | 2.8 | 25 | -6.8 | 3.4 | 19 |
| Comparison of Change[b] | | N.S. | | | N.S. | | | N.S. | | | N.S. | | | P>E* | | | N.S. | | |
| MAP (mmHg) | Esmolol | 99.8 | 2.5 | 32 | 97.3 | 2.8 | 32 | 97.4 | .0 | 31 | 124.7 | 3.9 | 32 | 96.1 | 4.0 | 24 | 87.5 | 5.0 | 15 |
| | Placebo | 98.2 | 2.8 | 31 | 100.1 | 3.6 | 31 | 101.6 | 4.8 | 31 | 133.1 | 3.7 | 31 | 106.0 | 4.7 | 25 | 93.1 | 5.1 | 19 |
| MAP Change | Esmolol | | | | -2.6 | 1.8 | 32 | -2.0 | 3.6 | 31 | 24.8 | 3.5 | 32 | -8.0* | 3.7 | 24 | -18.4* | 5.2 | 15 |
| | Placebo | | | | 1.9 | 1.3 | 31 | 3.4 | 3.7 | 31 | 34.9 | 3.0 | 31 | 5.3 | 3.6 | 25 | -9.1* | 4.0 | 19 |
| Comparison of Change[b] | | N.S. | | | P>E* | | | N.S. | | | P>E* | | | P>E* | | | N.S. | | |
| RPP | Esmolol | 11.2 | 0.6 | | 9.4 | 0.4 | 32 | 9.9 | 0.6 | 31 | 13.3 | 0.6 | 32 | 9.3 | 0.5 | 24 | 8.4 | 0.7 | 15 |
| | Placebo | 11.1 | 0.6 | 31 | 11.7 | 0.9 | 31 | 12.[illegible] | .0 | 31 | 18.3 | 0.9 | 31 | 13.8 | 1.1 | 25 | 11.3 | 0.9 | 19 |
| RPP Change | Esmolol | | | | -1.8* | 0.3 | 32 | -1.4* | 0.6 | 31 | 2.1 | 0.7 | 32 | -2.4* | 0.7 | 24 | -4.2* | 1.0 | 15 |
| | Placebo | | | | 0.6 | 0.4 | 31 | 1.7* | 0.8 | 31 | 7.2 | 0.6 | 31 | 2.3* | 0.8 | 25 | -0.6 | 0.7 | 19 |
| Comparison of Change[b] | | N.S. | | | P>E** | | | P>E** | | | P>E** | | | P>E** | | | P>E* | | |

= Indicates significant change from baseline ($p<0.05$). Maximum change from baseline was not tested for significance.

[a] Preintubation blood pressure was not determined in esmolol-treated Patient #425.

[b] N.S. Indicates no significant difference between the esmolol and placebo treatment groups ($p \geq 0.05$).
P = Placebo, E = Esmolol 300 mcg/kg/min, * $p<0.05$, ** $p<0.01$

Table 12 (continued)

New Table

Diastolic and Mean Arterial Blood Pressures and Rate-Pressure Product from Baseline, at 10 and 15 Minutes Postinfusion, for "Efficacy Patients" Treated with Esmolol or Placebo

Study #8052-84-518

| | | POST INF 10 | | | POST INF 15 | | |
|---|---|---|---|---|---|---|---|
| | | Mean ± SEM | | N | Mean ± SEM | | N |
| | Group | | | | | | |
| DBP (mmHg) | Esmolol | 67.4 | 5.3 | 10 | 65.6 | 6.3 | 7 |
| | Placebo | 72.7 | 5.3 | 10 | 68.8 | 9.5 | 5 |
| DBP Change | Esmolol | -12.3# | 3.9 | 10 | -14.6# | 2.6 | 7 |
| | Placebo | -12.6# | 4.4 | 10 | -18.9# | 5.9 | 5 |
| Comparison of Change[a] | | | N.S. | | | N.T. | |
| MAP (mmHg) | Esmolol | 81.2 | 5.4 | 10 | 78.6 | 5.7 | 7 |
| | Placebo | 88.8 | 5.9 | 10 | 84.9 | 10.9 | 5 |
| MAP Change | Esmolol | -23.7# | 4.6 | 10 | -28.8# | 3.5 | 7 |
| | Placebo | -16.8# | 4.6 | 10 | -21.5# | 5.7 | 5 |
| Comparison of Change[a] | | | N.S. | | | N.T. | |
| RPP | Esmolol | 7.9 | 1.0 | 10 | 7.9 | 0.9 | 7 |
| | Placebo | 10.1 | 1.1 | 10 | 10.1 | 1.9 | 5 |
| RPP Change | Esmolol | -4.7# | 0.7 | 10 | -6.0# | 0.8 | 7 |
| | Placebo | -1.6 | 0.8 | 10 | -2.2 | 0.9 | 5 |
| Comparison of Change[a] | | | P>E* | | | N.T. | |

# Indicates significant change from baseline ($p<0.05$).

[a] N.T. Not tested due to small sample size.
N.S. Indicates no significant difference between the esmolol and placebo treatment groups ($p\geq0.05$).
P = Placebo, E = Esmolol 300 mcg/kg/min, * $p<0.05$.

TABLE 27

Heart Rate and Systolic Blood Pressure with Changes from Baseline, by Period, for "All Patients" Treated with Esmolol or Placebo

| | | BASELINE | PREINDUCTION | PREINTUBATION | MAXIMUM | POST INF 2 | POST INF 5 |
|---|---|---|---|---|---|---|---|
| | | MEAN ± SEM N | MEAN ± SEM N | MEAN ± SEM N[a] | MEAN ± SEM N | MEAN ± SEM N | MEAN ± SEM N |
| | Group | | | | | | |
| HR (bpm) | Esmolol | 75.3 2.9 36 | 66.2 2.1 36 | 74.6 2.3 36 | 84.4 2.0 36 | 73.5 1.9 36 | 70.4 2.2 36 |
| | Placebo | 78.8 2.5 37 | 78.5 2.6 37 | 89.4 2.6 37 | 104.4 2.9 37 | 91.5 2.5 37 | 86.1 2.8 37 |
| HR Change | Esmolol | | -9.1[@] 1.8 36 | -0.8 2.2 36 | 9.0[@] 2.6 36 | -1.8 2.4 36 | -4.8 2.6 36 |
| | Placebo | | -0.4 1.2 37 | 10.6[@] 2.2 37 | 25.6[@] 2.4 37 | 12.7[@] 2.1 37 | 7.3[@] 2.4 37 |
| Comparison of Change[b] | | N.S. | P>E** | P>E** | P>E** | P>E** | P>E** |
| SBP (mm Hg) | Esmolol | 143.8 3.4 36 | 138.0 3.5 36 | 130.0 5.2 35 | 164.5 4.3 36 | 131.2 4.7 36 | 116.0 4.1 36 |
| | Placebo | 138.3 4.1 37 | 143.9 5.6 37 | 142.9 6.6 37 | 183.2 6.1 37 | 142.2 6.3 37 | 122.2 4.8 37 |
| SBP Change | Esmolol | | -5.8[@] 1.5 36 | -13.4[@] 4.3 35 | 20.8[@] 3.6 36 | -12.7[@] 4.3 36 | -27.9[@] 4.7 3v |
| | Placebo | | 5.6[@] 2.3 37 | 4.6 4.8 37 | 44.9[@] 4.5 37 | 3.9 4.9 37 | -16.1[@] 4.2 37 |
| Comparison of Change[b] | | N.S. | P>E** | P>E** | P>E** | P>E* | N.S. |

[@] Indicates significant change from baseline ($p<0.05$). Maximum change from baseline was not tested for significance.
[a] Preintubation blood pressure was not determined in esmolol-treated Patient #425.
[b] N.S. Indicates no significant difference between the esmolol and placebo treatment groups ($p\geq0.05$).
P = Placebo, E = Esmolol 300 mcg/kg/min, * $p<0.05$, ** $p<0.01$

Table 27

Heart Rate and Systolic Blood Pressure with Changes from Baseline, by Period, for "All Patients" Treated with Esmolol or Placebo

| | | BASELINE | PREINDUCTION | PREINTUBATION | MAXIMUM | POST INF 2 | POST INF 5 |
|---|---|---|---|---|---|---|---|
| | | MEAN ± SEM N | MEAN ± SEM N | MEAN ± SEM N | MEAN ± SEM N | MEAN ± SEM N[b] | MEAN ± SEM N[b] |
| Group | | | | | | | |
| HR (bpm) | Esmolol | 75.3 2.3 37 | 66.6 2.0 37 | 74.0 2.2 37 | 85.4 2.5 37 | 70.6 2.1 37 | 71.1 1.8 37 |
| | Placebo | 79.0 2.2 37 | 76.1 2.2 37 | 88.3 2.4 37 | 106.7 2.4 37 | 88.8 2.6 36 | 84.8 2.6 36 |
| HR Change | Esmolol | | -8.7# 1.0 37 | -1.3 1.9 37 | 10.0 2.4 37 | -4.7# 1.9 37 | -4.2# 1.7 37 |
| | Placebo | | -1.0 1.1 37 | 9.3# 1.7 37 | 27.7 2.4 37 | 9.9# 3.1 36 | 5.9 2.9 36 |
| Comparison of Change[a] | | N.S. | P>E** | P>E** | P>E** | P>E** | P>E** |
| SBP (mm Hg) | Esmolol | 181.9 4.4 37 | 176.8 5.3 37 | 143.3 4.6 37 | 187.1 4.4 37 | 138.4 5.3 37 | 124.9 4.1 37 |
| | Placebo | 170.8 4.3 37 | 173.4 4.2 37 | 151.6 5.7 37 | 217.8 5.1 37 | 141.8 7.0 37 | 131.8 5.2 37 |
| SBP Change | Esmolol | | -5.3 5.0 37 | -38.6# 4.7 37 | 5.1 5.3 37 | -43.8# 5.7 37 | -57.0# 4.7 37 |
| | Placebo | | 2.6 2.2 37 | -19.2# 5.3 37 | 47.0 5.0 37 | -28.9# 7.3 37 | -39.0# 5.3 37 |
| Comparison of Change[a] | | N.S. | N.S. | P>E** | P>E** | N.S. | P>E* |

\# Indicates significant change from baseline ($p<0.05$). Maximum change from baseline was not tested for significance.

a N.S. Indicates no significant difference between the esmolol and placebo treatment groups (actual values used for baseline comparisons, change from baseline used for comparison at subsequent periods, $p \geq 0.05$).
P = Placebo, E = Esmolol 300 mcg/kg/min, * $p<0.05$, ** $p<0.01$

b POST INF 2 & 5 HR was not retrievable for Patient #607.

Table 27 (continued)

New Table

Heart Rate and Systolic Blood Pressure with Changes from Baseline, at 10 and 15 Minutes Postinfusion, for "All Patients" Treated With Esmolol or Placebo

Study #8052-84-518

| | | POST INF 10 | | | POST INF 15 | | |
|---|---|---|---|---|---|---|---|
| | | Mean ± SEM | | N | Mean ± SEM | | N |
| | Group | | | | | | |
| HR (bpm) | Esmolol | 67.8 | 2.5 | 33 | 70.2 | 3.7 | 21 |
| | Placebo | 82.2 | 2.9 | 32 | 78.3 | 3.4 | 19 |
| HR Change | Esmolol | -7.8# | 2.0 | 33 | -8.1# | 2.3 | 21 |
| | Placebo | 3.4 | 2.3 | 32 | -1.9 | 2.5 | 19 |
| Comparison of Change@ | | | P>E** | | | N.S. | |
| SBP (mmHg) | Esmolol | 103.5 | 3.2 | 33 | 105.0 | 4.9 | 21 |
| | Placebo | 107.6 | 3.7 | 32 | 107.6 | 4.6 | 19 |
| SBP Change | Esmolol | -42.0# | 3.9 | 33 | -45.7# | 5.6 | 21 |
| | Placebo | -31.0# | 3.9 | 32 | -39.4# | 3.3 | 19 |
| Comparison of Change@ | | | N.S. | | | N.S. | |

# Indicates significant change from baseline ($p<0.05$).

@ N.S. Indicates no significant difference between the esmolol and placebo treatment groups ($p\geq0.05$).
P = Placebo, E = Esmolol 300 mcg/kg/min, * $p<0.05$, ** $p<0.01$.

TABLE 28

Diastolic Blood Pressure, Mean Arterial Blood Pressure, and Rate-Pressure Product with Changes from Baseline, by Period, for "All Patients" Treated with Esmolol or Placebo

| | | BASELINE | PREINDUCTION | PREINTUBATION | MAXIMUM | POST INF 2 | POST INF 5 |
|---|---|---|---|---|---|---|---|
| | | MEAN ± SEM N | MEAN ± SEM N | MEAN ± SEM N[a] | MEAN ± SEM N | MEAN ± SEM N | MEAN ± SEM N |
| Group | | | | | | | |
| DBP (mm Hg) | Esmolol | 77.8 2.3 36 | 76.7 2.1 36 | 82.2 3.9 35 | 106.3 3.4 36 | 81.0 3.4 36 | 71.4 3.0 36 |
| | Placebo | 77.9 2.3 37 | 77.3 2.6 37 | 83.8 3.6 37 | 109.8 2.8 37 | 82.9 2.9 37 | 73.1 3.1 37 |
| DBP Change | Esmolol | | -1.1 1.6 36 | 4.8 3.7 35 | 28.5# 3.1 36 | 3.2 3.2 36 | -6.5# 3.1 36 |
| | Placebo | | -0.7 1.1 37 | 5.8# 2.8 37 | 31.8# 2.4 37 | 5.0# 1.9 37 | -4.8 2.5 37 |
| Comparison of Change[b] | | N.S. | N.S. | N.S. | N.S. | N.S. | N.S. |
| MAP (mm Hg) | Esmolol | 99.8 2.3 36 | 97.1 2.4 36 | 98.2 4.1 35 | 124.9 3.5 36 | 97.7 3.8 36 | 88.2 3.3 36 |
| | Placebo | 98.1 2.6 37 | 99.5 3.3 37 | 103.5 4.3 37 | 133.3 3.4 37 | 102.7 3.7 37 | 89.5 3.5 37 |
| MAP Change | Esmolol | | -2.7 1.4 36 | -1.2 3.7 35 | 25.1# 3.2 36 | -2.1 3.4 36 | -13.6# 3.5 36 |
| | Placebo | | 1.4 1.2 37 | 5.4 3.3 37 | 35.2# 2.7 37 | 4.6 2.7 37 | -8.6# 2.9 37 |
| Comparison of Change[b] | | N.S. | P>E* | N.S. | P>E* | N.S. | N.S. |
| RPP | Esmolol | 11.0 0.6 36 | 9.2 0.4 36 | 9.8 0.5 35 | 13.2 0.6 36 | 9.7 0.5 36 | 8.3 0.4 36 |
| | Placebo | 11.0 0.5 37 | 11.5 0.7 37 | 13.0 0.9 37 | 18.1 0.8 37 | 13.2 0.8 37 | 10.8 0.6 37 |
| RPP Change | Esmolol | | -1.8# 0.3 36 | -1.2# 0.6 35 | 2.3# 0.6 36 | -1.3# 0.6 36 | -2.7# 0.6 36 |
| | Placebo | | 0.5 0.4 37 | 2.1# 0.7 37 | 7.1# 0.6 37 | 2.2# 0.6 37 | -0.3 0.8 37 |
| Comparison of Change[b] | | N.S. | P>E** | P>E** | P>E** | P>E** | P>E** |

\# Indicates significant change from baseline ($p<0.05$). Maximum change from baseline was not tested for significance.

a Preintubation blood pressure was not determined in esmolol-treated Patient #425.

b N.S. Indicates no significant difference between the esmolol and placebo treatment groups ($p\geq0.05$).
P = Placebo, E = Esmolol 300 mcg/kg/min, * $p<0.05$, ** $p<0.01$

Table 28 (continued)

New Table

Diastolic and Mean Arterial Blood Pressures and Rate-Pressure Product with Changes from Baseline, at 10 and 15 Minutes Postinfusion, for "All Patients" Treated with Esmolol or Placebo

Study #8052-84-518

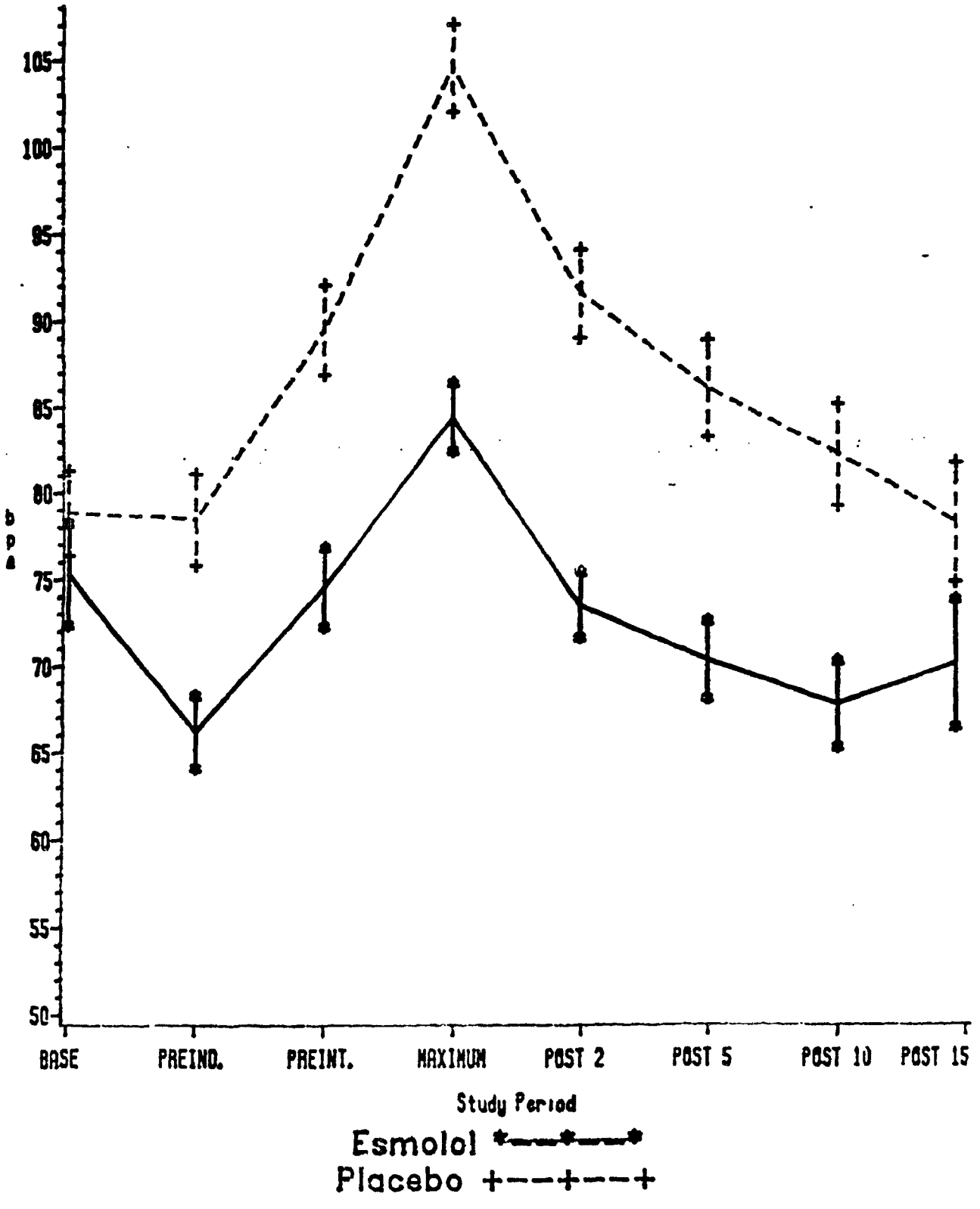
| | | POST INF 10 | | | POST INF 15 | | |
|---|---|---|---|---|---|---|---|
| | | Mean ± SEM | | N | Mean ± SEM | | N |
| | Group | | | | | | |
| DBP (mmHg) | Esmolol | 63.8 | 2.2 | 33 | 64.7 | 2.9 | 21 |
| | Placebo | 64.5 | 2.6 | 32 | 60.9 | 3.5 | 19 |
| DBP Change | Esmolol | -14.6# | 2.3 | 33 | -15.2# | 3.2 | 21 |
| | Placebo | -12.7# | 2.4 | 32 | -19.8# | 3.0 | 19 |
| Comparison of Change[a] | | | N.S. | | | N.S. | |
| MAP (mmHg) | Esmolol | 77.0 | 2.4 | 33 | 78.2 | 3.4 | 21 |
| | Placebo | 78.8 | 2.8 | 32 | 76.5 | 3.7 | 19 |
| MAP Change | Esmolol | -23.7# | 2.6 | 33 | -25.4# | 3.7 | 21 |
| | Placebo | -18.8# | 2.7 | 32 | -26.3# | 2.8 | 19 |
| Comparison of Change[a] | | | N.S. | | | N.S. | |
| RPP | Esmolol | 7.2 | 0.5 | 33 | 7.6 | 0.7 | 21 |
| | Placebo | 8.9 | 0.5 | 32 | 8.6 | 0.7 | 19 |
| RPP Change | Esmolol | -4.0# | 0.5 | 33 | -4.3# | 0.6 | 21 |
| | Placebo | -2.0# | 0.5 | 32 | -3.3# | 0.5 | 19 |
| Comparison of Change[a] | | | P>E** | | | N.S. | |

# Indicates significant change from baseline ($p<0.05$).

a N.S. Indicates no significant difference between the esmolol and placebo treatment groups ($p\geq0.05$).
P = Placebo, E = Esmolol 300 mcg/kg/min, * $p<0.05$, ** $p<0.01$.

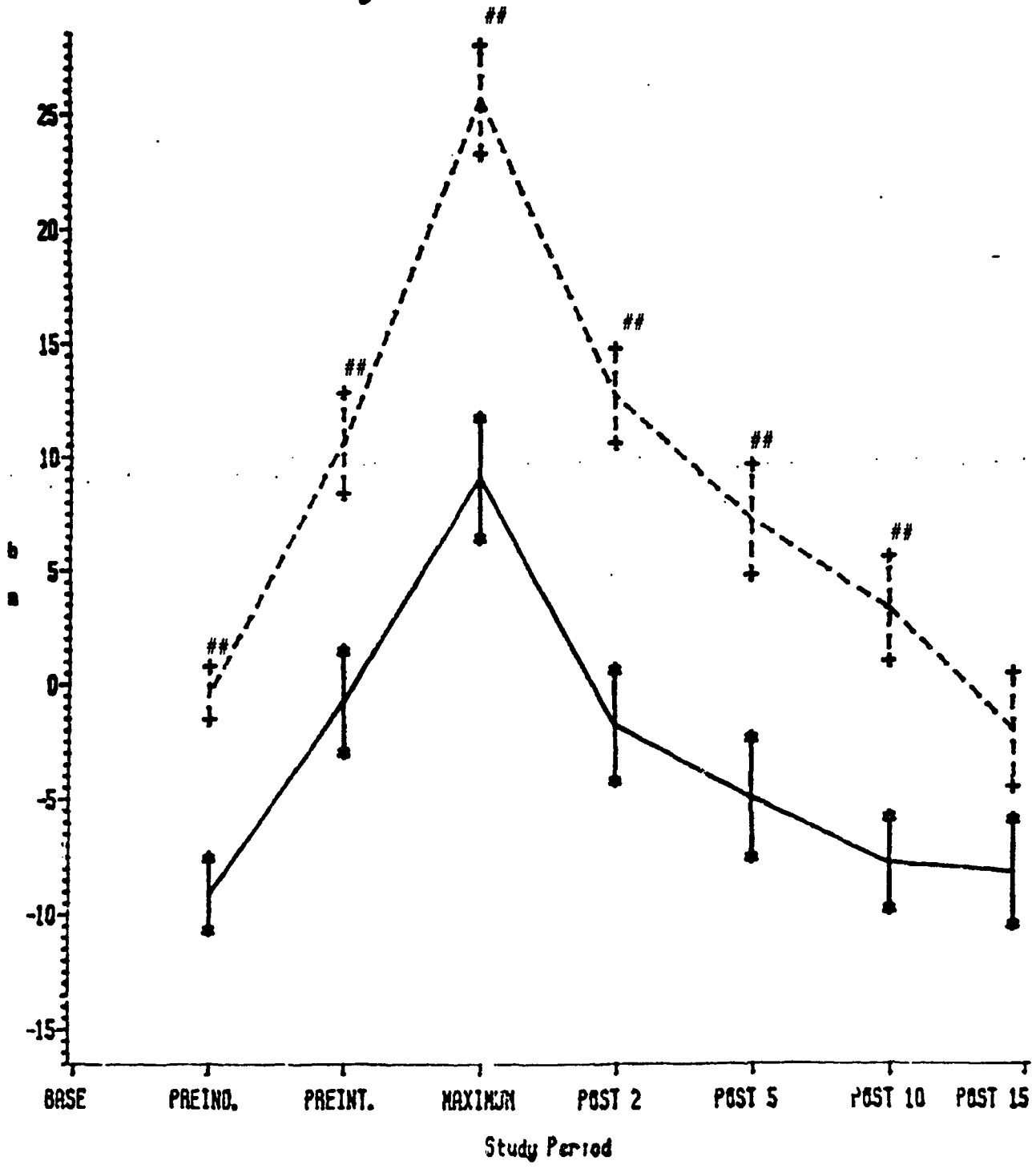
Study #8052-84-518

# *ASA III & IV (8052-84-51B)*
## *Heart Rate for All Patients*




to change from baseline ($p < 0.01$).

# *ASA III & IV (8052-84-51B)*
# *Heart Rate Changes from Baseline for All Patients*




## Significant difference between esmolol and placebo with respect to change from baseline ($p < 0.01$).

Table 11

Heart Rate and Systolic Blood Pressure with Changes from Baseline, by Period, for "Efficacy Patients" Treated with Esmolol or Placebo

| | | BASELINE | | | PREINDUCTION | | | PREINTUBATION | | | MAXIMUM | | | POST INF 2 | | | POST INF 5 | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | Mean ± SEM | | N | Mean ± SEM | | N | Mean ± SEM | | N | Mean ± SEM | | N | Mean ± SEM | | N | Mean ± SEM | | N |
| Group | | | | | | | | | | | | | | | | | | | |
| HR (bpm) | Esmolol | 74.4 | 2.3 | 32 | 66.0 | 1.8 | 32 | 73.1 | 1.9 | 32 | 82.3 | 2.1 | 32 | 72.1 | 4.9 | 8 | 75.8 | 5.5 | 4 |
| | Placebo | 80.0 | 2.8 | 30 | 78.2 | 2.6 | 30 | 88.3 | 2.8 | 30 | 104.2 | 3.2 | 30 | 98.5 | 2.7 | 4 | 94.0 | 5.5 | 3 |
| HR Change | Esmolol | | | | -8.4* | 1.1 | 32 | -1.3 | 2.1 | 32 | 7.9 | 2.5 | 32 | -7.7* | 3.0 | 8 | -9.0* | 1.8 | 4 |
| | Placebo | | | | -1.8 | 1.2 | 30 | 8.3* | 2.0 | 30 | 24.2 | 3.2 | 30 | 4.6 | 7.8 | 4 | 3.1 | 11.1 | 3 |
| Comparison of Change[a] | | N.S. | | | P>E** | | | P>E** | | | P>E** | | | N.S. | | | N.S. | | |
| SBP (mmHg) | Esmolol | 184.3 | 4.8 | 32 | 174.0 | 4.4 | 32 | 144.8 | 5.0 | 32 | 185.8 | 4.9 | 32 | 127.9 | 7.5 | 8 | 110.5 | 4.4 | 4 |
| | Placebo | 168.7 | 5.1 | 30 | 170.1 | 4.9 | 30 | 146.8 | 8.1 | 30 | 214.1 | 5.3 | 30 | 148.0 | 22.7 | 4 | 124.0 | 14.5 | 3 |
| SBP Change | Esmolol | | | | -10.3* | 2.4 | 32 | -39.5* | 4.8 | 32 | 1.5 | 8.8 | 32 | -48.7* | 12.3 | 8 | -73.7* | 15.5 | 4 |
| | Placebo | | | | 1.4 | 2.8 | 30 | -21.9* | 5.8 | 30 | 45.4 | 5.5 | 30 | -13.3 | 16.8 | 4 | -28.8 | 9.7 | 3 |
| Comparison of Change[a] | | N.S. | | | P>E** | | | P>E* | | | P>E** | | | N.S. | | | N.S. | | |

* Indicates significant change from baseline ($p<0.05$). Maximum change from baseline was not tested for significance.
[a] N.S. Indicates no significant difference between the esmolol and placebo treatment groups (actual values used for baseline comparison, change from baseline used for comparison at subsequent periods, $p \geq 0.05$).
P = Placebo, E = Esmolol, 300 mcg/kg/min, * $p<0.05$, ** $p<0.01$.

Table 11 (continued)

New Table

Heart Rate and Systolic Blood Pressure with Changes from Baseline, at 10 and 15 Minutes Postinfusion, for "Efficacy Patients" Treated With Esmolol or Placebo

Study #8052-83-49

| | | POST INF 10 | | | POST INF 15 | | |
|---|---|---|---|---|---|---|---|
| | | Mean ± SEM | | N | Mean ± SEM | | N |
| | Group | | | | | | |
| HR (bpm) | Esmolol | 67.5 | 2.5 | 2 | 62.5 | 0.5 | 2 |
| | Placebo | 114.0 | - | 1 | 105.0 | - | 1 |
| HR Change | Esmolol | -15.7 | 8.3 | 2 | -20.7 | 11.3 | 2 |
| | Placebo | 33.5 | - | 1 | 24.5 | - | 1 |
| Comparison of Change[a] | | N.T. | | | N.T. | | |
| SBP (mmHg) | Esmolol | 110.0 | 25.0 | 2 | 142.0 | 6.0 | 2 |
| | Placebo | 140.0 | - | 1 | 123.0 | - | 1 |
| SBP Change | Esmolol | -80.4 | 48.1 | 2 | -48.4 | 17.1 | 2 |
| | Placebo | -15.7 | - | 1 | -32.7 | - | 1 |
| Comparison of Change[a] | | N.T. | | | N.T. | | |

[a] N.T. Not tested due to small sample size.

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Table 12

Diastolic Blood Pressure, Mean Arterial Blood Pressure, and Rate-Pressure Product with Changes from Baseline, by Period, for "Efficacy Patients" Treated with Esmolol or Placebo

| | | BASELINE | | | PREINDUCTION | | | PREINTUBATION | | | MAXIMUM | | | POST INF 2 | | | POST INF 9 | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | Mean ± SEM | | N | Mean ± SEM | | N | Mean ± SEM | | N[b] | Mean ± SEM | | N | Mean ± SEM | | N | Mean ± SEM | | N |
| Group | | | | | | | | | | | | | | | | | | | |
| DBP (mm Hg) | Esmolol | 78.8 | 2.5 | 32 | 78.0 | 2.0 | 32 | 76.5 | 3.3 | 32 | 100.4 | 3.2 | 32 | 84.0 | 4.2 | 8 | 82.2 | 9.2 | 4 |
| | Placebo | 73.7 | 2.2 | 30 | 74.3 | 2.5 | 30 | 74.6 | 3.5 | 29 | 111.2 | 3.8 | 30 | 85.0 | 10.8 | 4 | 68.7 | 9.4 | 3 |
| DBP Change | Esmolol | | | | -0.9 | 1.1 | 32 | -2.4 | 2.9 | 32 | 21.5 | 3.0 | 32 | -9.7 | 5.3 | 8 | -10.7 | 8.6 | 4 |
| | Placebo | | | | 0.7 | 1.5 | 30 | 0.6 | 3.1 | 29 | 37.5 | 2.8 | 30 | 7.8 | 12.2 | 4 | -6.3 | 13.3 | 3 |
| Comparison of Change[a] | | N.S. | | | N.S. | | | N.S. | | | P>E** | | | N.S | | | N.S. | | |
| MAP (mm Hg) | Esmolol | 114.0 | 2.9 | 32 | 110.0 | 2.8 | 32 | 99.3 | 3.6 | 32 | 128.0 | 3.5 | 32 | 85.3 | 4.7 | 8 | 71.7 | 7.1 | 4 |
| | Placebo | 105.3 | 2.8 | 30 | 106.3 | 3.0 | 30 | 99.5 | 4.1 | 29 | 144.5 | 3.9 | 30 | 108.0 | 14.2 | 4 | 87.1 | 11.1 | 3 |
| MAP Change | Esmolol | | | | -4.0# | 1.3 | 32 | -14.7# | 3.5 | 32 | 14.0 | 3.8 | 32 | -22.7# | 7.8 | 8 | -37.7# | 11.0 | 4 |
| | Placebo | | | | 0.9 | 1.7 | 30 | -6.5 | 3.9 | 29 | 39.2 | 3.5 | 30 | 0.8 | 13.6 | 4 | -13.8 | 12.1 | 3 |
| Comparison of Change[a] | | N.S. | | | P>E* | | | N.S. | | | P>E** | | | N.S. | | | N.S. | | |
| RPP | Esmolol | 13.8 | 0.8 | 32 | 11.5 | 0.5 | 32 | 10.6 | 0.5 | 32 | 14.7 | 0.7 | 32 | 9.2 | 0.8 | 8 | 8.4 | 0.8 | 4 |
| | Placebo | 13.5 | 0.6 | 30 | 13.3 | 0.6 | 30 | 13.1 | 0.8 | 30 | 22.2 | 1.0 | 30 | 14.1 | 1.9 | 4 | 11.6 | 1.3 | 3 |
| RPP Change | Esmolol | | | | -2.3# | 0.3 | 32 | -3.2# | 0.6 | 32 | 1.0 | 0.8 | 32 | -5.1# | 1.6 | 8 | -7.3# | 1.4 | 4 |
| | Placebo | | | | -0.2 | 0.4 | 30 | -0.4 | 0.7 | 30 | 8.7 | 1.0 | 30 | -1.6 | 2.6 | 4 | -2.2 | 2.7 | 3 |
| Comparison of Change[a] | | N.S. | | | P>E** | | | P>E** | | | P>E** | | | N.S. | | | N.S. | | |

\# Indicates significant change from baseline ($p<0.05$). Maximum change from baseline was not tested for significance.

a N.S. Indicates no significant difference between the esmolol and placebo treatment groups (actual values used for baseline comparisons, change from baseline used for comparison at subsequent periods, $p \geq 0.05$)
P = Placebo, E = Esmolol 300 mcg/kg/min, * $p<0.05$, ** $p<0.01$

b Preintubation DBP was not retrievable for Patient #226.